TACTILE PROCESSING AND VIBROTACTILE DISCRIMINATION CAPACITY IN CHILDREN WITH TOURETTE SYNDROME

by

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B.S., Physics, Boğaziçi University, 2014

Submitted to the Institute of Biomedical Engineering
in partial fulfillment of the requirements
for the degree of
Master of Science
in
Biomedical Engineering

Boğaziçi University
2019

ACKNOWLEDGMENTS

This study received support from Boğaziçi University's BAP project no: 6747S. I would also like to thank to specialist psychiatrist Dr. Hilal Doktur and Assoc. Prof. Dr. Canan Tanıdır from Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery who conducted the clinical assessments, to Dr. Bige Akar who guided me on the statistical analyses, and to my thesis advisor Prof. Dr. Burak Güçlü.

ACADEMIC ETHICS AND INTEGRITY STATEMENT

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ABSTRACT

TACTILE PROCESSING AND VIBROTACTILE DISCRIMINATION CAPACITY IN CHILDREN WITH TOURETTE SYNDROME

Tourette Syndrome (TS) is a childhood-onset developmental psychiatric disorder. Pediatric patients are diagnosed with TS if they show multiple motor tics and at least one vocal tic for at least one year. The tic severity is known to be reduced in most of the cases as the patient progress into adulthood which suggests a cerebral adaptation over time. The pathology of TS is not clear; however, neurotransmission deficits, especially of γ-aminobutyric acid (GABA), and structural alterations in the cerebral structures are believed to be play a role in disorder's occurrence. Existing literature suggests the tics to arise from hyperexcitability due to GABAergic dysfunction, and the adaptive somatosensory mechanisms in TS to be disrupted. This study aimed to extend the GABAergic adaptive dysfunction in TS hypothesis by assessing the detection and difference thresholds through a psychophysical vibrotactile battery. Thirty TS children (7 female, 23 male) and 25 healthy controls (7 female, 18 male) participated in the experiments. Vibrotactile stimuli were generated by a portable device and applied to the fingertips of the subjects. The vibrotactile battery consisted of Choice Reaction Time (cRT, amplitude: 200 μm, Static Detection Threshold (DT_s), Dynamic Detection Threshold (DT_c , amplitude ramp: 2 μm/s), Amplitude Discrimination (AD, standard stimuli: 50, 100, 200 μm), and Amplitude Discrimination with single-site adaptation (cAD, the same standards, adapting stimuli: 100, 300 μm, adaptation duration: 1 s) measurements. The analyses showed that both groups produced comparable detection thresholds. Amplitude discrimination tasks produced further support for the GABAergic adaptive dysfunction in TS hypothesis, since in the baseline AD tasks TS group produced significantly higher difference thresholds, and in the cAD tasks control group closed the gap by showing a more prominent adaptation.

Keywords: Tactile processing, Amplitude discrimination, Tourette Syndrome.

ÖZET

TOURETTE SENDROMLU ÇOCUKLARDA DOKUNMA DUYUSUNUN VE TİTREŞİMSEL AYIRT ETME ÖZELLİĞİNİN İNCELENMESİ

Tourette Sendromu (TS) çocuklukta ortaya çıkan gelişimsel bir psikiyatrik bozukluktur. TS tanısı birden çok motor tikin en az bir vokal tik eşliğinde, en az bir yıl süresince görülmesi durumunda konulur. Tourette Sendromu'nun patolojisi net olarak bilinmemekte ancak başta γ-aminobütrik asit (GABA) olmak üzere nörotransmisyon bozukluklarından ve beyin yapılarındaki bozukluklardan kaynaklandığı düşünülmektedir. Literatür tiklerin Tourette Sendromu'nda görülen GABA bağlantılı bozukluklardan kaynaklanabileceğini ve TS hastalarında dokunma duyusu bağlantılı adaptasyon mekanizmalarında bozulmaların mevcut olabileceğini öne sürmektedir. Bu çalışmada TS hastalarında GABA bağlantılı adaptasyon bozuklukları olduğu hipotezi, algılama eşiklerinin ve genlik ayırt etme yetkinliklerinin psikofiziksel bir test bataryası aracılığıyla ölçülmesiyle incelendi. Çalışmada 30 TS hastası (7 kız, 23 erkek) ve 25 sağlıklı (7 kız, 18 erkek) çocuk yer aldı. Katılımcıların parmak uçlarına verilen titreşimsel uyaranlar taşınabilir bir cihaz aracılığıyla üretildi. Test bataryasında Seçim Tepki Zamanı (cRT, genlik: 200 μm), Statik Algılama Eşiği (DT_s), Dinamik Algılama Eşiği (DT_c , genlik artış hızı: 2 μm/s), Genlik Ayırt Etme (AD, standart uyaranlar: 50, 100, 200 μm) ve tek bölge adaptasyonuyla Genlik Ayırt Etme (cAD, aynı standart uyaranlar, maske uyaranları: 100, 300 μm) ölçümleri yer almıştır. Her iki grupta da eşik altı uyarandan kaynaklı adaptasyon gözlemlendi. Analizlerde AD testlerinde TS grubunun fark eşiklerinin sağlıklı kontrollerin fark eşiklerine kıyasla anlamlı derece yüksek olduğu da bulunmuştur. Ayrıca adaptasyon uyaranının mevcut olduğu cAD testlerinde iki grubun fark eşiklerinin benzer olması normal çocuklarda adaptasyonun daha fazla olduğuna işaret etmektedir. Bu durum TS hastalarında GABA bağlantılı adaptasyon bozukluklarının gözlemlendiği hipotezini destekler niteliktedir.

Anahtar Sözcükler: Tourette Sendromu, Dokunma duyusu, Genlik ayırt etme.

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Δ	Difference
γ	Gamma

LIST OF ABBREVIATIONS

2AFC	Two-Alternative Forced Choice
A	Adapting Stimulus
ACA	Anterior Cingulate Cortex
AD	Amplitude Discrimination
AD_d	Paired Change in Difference Threshold due to Adaptation
ADHD	Attention Deficit/Hyperactivity Disorder
cAD	Amplitude Discrimination with Single-Site Adaptation
CMA	Cingulate Motor Area
cRT	Choice Reaction Time
CSTC	Cortico-Striato-Thalamo-Cortical
DLPFC	Dorsolateral Prefrontal Cortex
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DT_c	Dynamic Detection Threshold
DT_d	Change in Detection Threshold due to Adaptation
DT_s	Static Detection Threshold
EEG	Electroencephalogram
FA	Fractional Anisotopy
FEF	Frontal Eye Field
FLT3	FMS-like Tyrosine Kinase 3
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GPi	Internal Segment of the Globus Pallidus
HRT	Habit Reversal Therapy
ITI	Inter-Trial Interval
JND	Just-Noticeable Difference
LOFC	Lateral Orbitofrontal Cortex
M1	Primary Motor Cortex
MD	Mediodorsal Nucleus of Thalamus

MDpl	Paralaminar Part of the Mediodorsal Nucleus of Thalamus
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRS	Magnetic Resonance Spectroscopy
NMDA	N-Methyl-D-Aspartate
NP1	Non-Pacinian 1
OCD	Obsessive-Compulsive Disorder
PMC	Premotor Cortex
PMU	Premonitory Urge
PSE	Point of Subjective Equality
PUTS	Premonitory Urge for Tics Scale
S	Standard Stimulus
SEF	Supplementary Eye Field
SLITRK1	Slit and Trk-like 1
SMA	Supplementary Motor Area
SNr	Substantia Nigra Pars Reticulata
SP	Sensory Phenomena
STI	Structural Tensor Imaging
T	Test Stimulus
TIE	Touch Inventory for Elementary-School-Aged Children
TS	Tourette Syndrome
USP-SPS	The University of Sao Paulo Sensory Phenomena Scale
VAmc	Magnocellular Part of the Ventral Anterior Nucleus of Thalamus
VApc	Parvocellular Part of the Ventral Anterior Nucleus of Thalamus
VLm	Medial Part of the Ventrolateral Nucleus of Thalamus
VLo	Pars Oralis Ventrolateral Nucleus of Thalamus
YGTSS	The Yale Global Tic Severity Scale

1. INTRODUCTION AND BACKGROUND

Tourette Syndrome is a common childhood-onset psychiatric disorder which drastically affects the patients' quality of life, yet its underlying mechanisms are still far from being understood. Psychophysical studies have proven to provide enlightenment regarding neural mechanisms both in healthy and psychiatrically compromised subjects [1, 2, 3] and Tourette Syndrome is not an exception [4]. Hence, a psychophysical study investigating the somatosensory processing in children with Tourette Syndrome can help researchers understand the neural mechanisms of the disorder better.

1.1 Processing of the Somatosensory Information

Three major functions of the somatosensory system are proprioception which enables us to have a conscious awareness of our posture and body movements, interoception which allows us - mostly unconsciously - to process information regarding our body's internal state and exteroception which allows us to process information from the external world regarding thermal sensations, pain (nociception) and the sense of touch [5] which will be the main concern of this thesis from now onward.

1.1.1 Dorsal Root Ganglion Neurons

Tactile sensations mentioned above are mediated by sensory neurons called dorsal root ganglion neurons which relay a variety of sensory information to the brain, with the help of their morphologically and molecularly specified terminal endings that are selective to a single somatosensory modality. Dorsal root ganglion cells, which are also known as posterior root ganglion or spinal ganglion, are pseudo-unipolar cells whose cell bodies lie in a ganglion on the dorsal root of a spinal nerve (Figure 1.1) [5]. Their axons (called primary afferent fibers) branch in two; one of them projecting to the periphery, innervating either the skin, joint capsules, muscles or viscera, and the

other one projecting to the central nervous system [5].

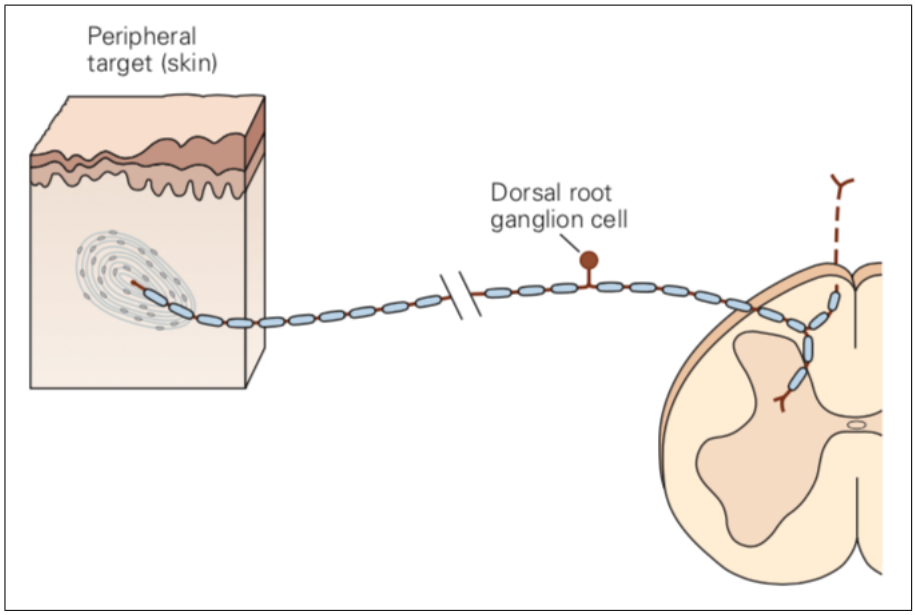

Figure 1.1 A dorsal root ganglion neuron.

1.1.2 Mechanoreceptors

Peripheral branches of the dorsal root ganglion cells contain mechanoreceptors which are sensitive to the physical deformation of the tissue they reside in. The deformation of the tissue causes depolarization in the sensory neuron and this information is transduced into electrical signal which is relayed to the central nervous system [5].

There are 8 types of mechanoreceptors in the skin that mediates touch and 4 of them exist in the glabrous skin of the hands: Meissner corpuscles, Merkel cells, Pacinian corpuscles, and Ruffini endings. Predominantly the Meissner corpuscles which are sensitive to flutter range of 2 to 40 Hz frequency are of interest for this study because these mechanoreceptors has the highest density in the glabrous pads of the finger tips, and all the stimuli in this study (which are explained in detail in the upcoming text) had a flutter range of 25 Hz frequency to which the Meissner corpuscles has high sensitivity [6]. However, the Pacinian corpuscles which are sensitive to vibration frequency of 5 to 1,000 Hz (best response to 200 Hz), along with Merkel cells which detects edges and points with a frequency range of 0 to 100 Hz, and Ruffini endings which are sensitive

to skin stretch may contribute to the relayed somatosensory information, although this contribution is not expected to be significant in case of the delivered stimuli for this study [5].

1.1.3 Sensory Pathway (for Touch)

Tactile signals are conveyed to the spinal cord and brain stem by the dorsal root ganglion cells which innervate the spinal gray matter before crossing the midline in the medulla and ascending in the medial lemniscus toward thalamus which is the relay station for all sensory information (except for olfaction). Somatosensory information from the periphery terminate in the ventral posterior lateral and medial nuclei of thalamus (Figure 1.2) [5] where it is determined which sensory information reaches the cortex, depending on factors such as attention or arousal [5].

1.2 Tourette Syndrome

1.2.1 Description of the Tourette Syndrome

Tourette Syndrome (TS) - also known as Gilles de la Tourette Syndrome - is a common polygenic neuropsychiatric disorder with pediatric onset, which is characterized by repetitive, stereotyped tics of motor and vocal origin; such as blinking, coughing, facial and/or abdominal movements, together with at least a phonetic tic [7, 8]. In the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), tics are defined as "sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations, generally preceded by an urge" [9]. In up to 25% of healthy children transient tics may be observed [7]. If one or more motor tics or vocal tics persevere with daily appearances longer than a year before the age of 18, the patient is diagnosed with chronic (persistent) motor or vocal tic disorder. In the same scenario, if the tics last less than 12 months, the patient is diagnosed with provisional tic disorder [9, 7].

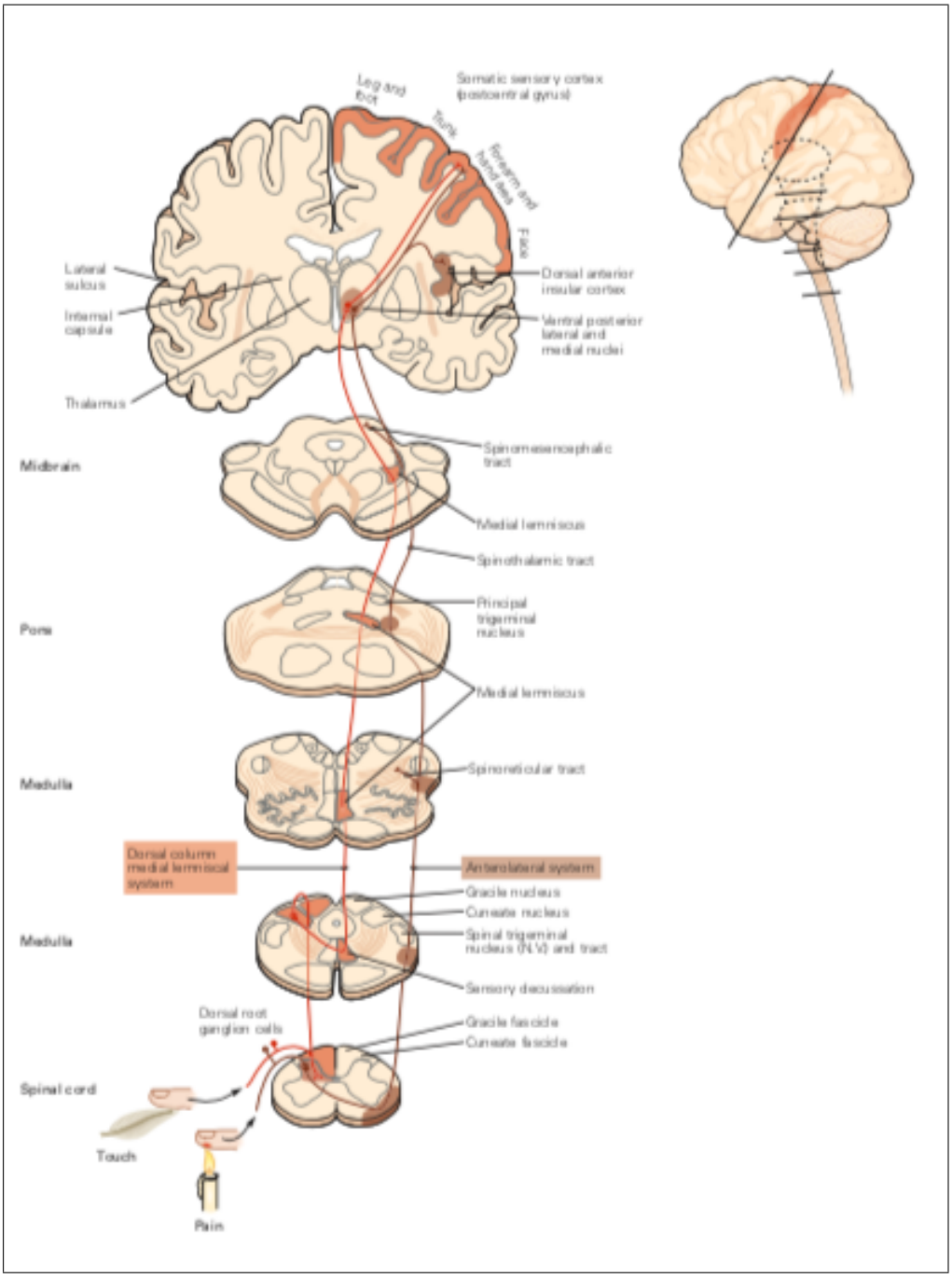

Figure 1.2 Somatosensory relay pathways.

In order the tics to be related to Tourette Syndrome, a patient must have multiple motor tics along with at least one vocal tic with the onset before the age of 18 years and the tics must last for at least one year even if they may wax and wane in frequency [9, 7]. The waxing and waning of the tics is not predictable and over time one tic may replace another [7]. Tics are either categorized as simple or complex motor/vocal tics. Tics such as blinking, shoulder shrugging, sniffing, and throat clearing are considered as simple motor or vocal tics since they have short durations in milliseconds range [9]. Complex motor and vocal tics include obscene gestures, imitation of another person's movements, repeating the last heard word or uttering socially inappropriate words and they may look like purposeful acts [9]. Occasionally tics may become linked in a way that one tic is rapidly followed by another and then another, forming a repertoire unique to each patient [7].

The Yale Global Tic Severity Scale (YGTSS), which was also used in this study, is a validated clinical instrument to evaluate the tics in five dimensions: number, complexity, intensity, frequency, and interference of vocal and motor tics for patients with tic disorders such as TS. It is in the form of a semi-structured six-point ordinal scale interview and is completed by an experienced clinician with one or multiple informants. The clinician then rates the severity of both motor and vocal tics, hence revealing the anatomical distribution and specific character of the tics for a patient in the five dimensions mentioned above [10].

1.2.2 Sensory phenomena

A high ratio of patients with TS, along with numerous patients with obsessive-compulsive disorder (OCD), report to have subjective sensory experiences which are categorized under three main titles: Premonitory urges, sensory tics and sensory hypersensitivity [11]. "Sensory tics" are defined as generalized somatic sensations in muscles, bones and joints which lead to voluntary movements that relieve the patients from these sensations [11]. In contrast to a sensory tic, "a premonitory urge" (PMU) is reported as a less generalized somatic sensation prior to tics which is a sensory build

up component, "an uncontrollable urge", from which the patient is relieved if he/she performs the tic [12, 9, 7]. Premonitory Urges are reported by more than 80% of TS patients over age 9 [13, 14, 15] and they may occur in a specific body region which is usually about the same area of the tic it precedes or may be experienced as an overall bodily sensation [12, 3, 14, 16]. After their development, PMUs strengthen the tics through negative reinforcement, increasing the probability of tics' future occurrence [13]. The patients who experience "sensory hypersensitivity" show heightened sensitivity to a variety of sensory modalities such as loud noises, bright lights and discomfort due to a contact with a material [17]. Sensory hypersensitivity may also be accompanied by obsessive-type thoughts (e.g. "Something is not just right") however they are associated with anxious arousal, whereas sensory phenomena (SP) are associated with somatic discomfort and muscular tension [13].

A number of standardized assessments allow researchers to quantify the behavioral correlate regarding the measurement for sensory phenomena and sensory sensitivity. The "Premonitory Urge for Tics Scale (PUTS)" is a brief self-report four-point ordinal scale questionnaire from which the total PMU score for a subject is calculated by summing the scores of all items [18]. The University of Sao Paulo Sensory Phenomena Scale (USP - SPS) is another valid instrument to assess the presence and severity of the SP where subjects are presented a checklist of a wide range of SP which they mark both for their current experiences and the peak time of their SP. The USP - SPS results are a combination of three ordinal scales with six anchor points regarding frequency of SP, stress caused by SP, and degree of their interference to patients' functioning [15]. The "Sensory Profile", which was conducted in this study as well, is a five-point Likert scale where parents report the percentage of time the children engage in the listed activities and provides a measure of children's responses regarding daily sensory experiences [19, 20]. Another more specified questionnaire which was also used in this study is the "Touch Inventory for Elementary-School-Aged Children" (TIE). TIE is a 26-item screening scale that is specifically designed as a standardized assessment for tactile defensiveness in children. It is suitable for children as young as age 6, hence providing a means for quantifying a tactile defensiveness score through self-reports from younger children [21].

These sensory phenomena distinguishes tic disorders from purely involuntary movement disorders, as it is possible for some patients to suppress their tics with a premonitory urge at the cost of an accumulating inner tension [7]. Thence, understanding the mechanisms of these sensory phenomena that are observed in many patients with TS, stands promising to shed more light on both neurobiological and behavioral factors which constitute the pathology of TS, along with its genetic variables. Hence studies with sensory foci [3, 2, 22, 23], including this one, may provide the missing links to constitute bases for future studies on the way to completely determining the etiology and mechanisms of TS and its comorbid disorders.

1.2.3 Prevalence & Comorbidities

The overall prevalence of Tourette Syndrome is estimated to be around 1% around the world [24]. Studies reveal a variation in TS prevalence within a range of 0.3% to 5.7% and the disorder is reported more frequently in white populations and considerably less commonly in sub-Saharan black African, Afro-Caribbean and African-American populations [25]. Male to female ratio varies from 2:1 to 10:1 in different studies, however general consensus is that TS shows a male predominance with a ratio around 3:1 to 4:1 [7, 26, 27, 28].

Typical age for onset of tics is 4 to 6 years and the motor tics tend to precede the vocal tics [7]. Tics peak in severity when the patient is 10 - 12 years old and tic severity declines throughout the adolescence and diminishes in adulthood for the majority of patients [7, 9, 27].

Up to 85% of the TS patients have one or more comorbid mental health or neurodevelopmental disorder [7]. The most common comorbidities of Tourette Syndrome are Attention Deficit/Hyperactivity Disorder (ADHD) and obsessive-compulsive disorder, both of which can be observed in approximately 30% to 60% of the TS patients [9, 29, 30, 7, 31]. Other common comorbidities of TS include autistic spectrum disorder (5%-15%), learning disorders, externalizing disorders (i.e. conduct disorder and

oppositional defiant disorder), sensory processing difficulties, anxiety, and depression. The ratio of TS patients without any comorbidities is shown to be around 10% [32, 7].

1.2.4 Pathophysiology of Tourette Syndrome

Although the exact mechanism of the syndrome is not clear, it is mostly thought to be a developmental disorder of neurotransmission with genetic predisposition (American Psychiatric Association, 2013). Studies on TS mainly focuses on volumetric changes and functional alterations in the basal ganglia, particularly the caudate nucleus, cortico-striato-thalamo-cortical network (CSTC), and the inferior prefrontal cortex [29, 33, 22]. As a neurodevelopmental disorder without an exact cause, Tourette Syndrome is evaluated from multiple aspects.

Existing literature regarding the inheritance and genetic factors of TS derives data from candidate genes studies, linkage studies, segregation analyses and family studies [34, 29, 31, 35, 36]. Several studies showed the morbidity risk of TS among relatives to be within the range of 9.8% to 15% and the rate of other tic disorders to be between 15% to 20% [35]. A genetic-epidemiological adult twins study with a sample size of 8323 monozygotic and dizygotic twins and their first-degree family members (n=7164, siblings and parents) showed a more moderate, yet a significant heritability of TS and other tic disorders within the range of 0.3% to 4.5% (Zilhao et al., 2017). Existing data on TS suggest a complex polygenic inheritance and linkage. The gene on chromosome 13 which encodes Slit and Trk-like 1 (SLITRK1) takes part in neurite outgrowth in response to guidance cues. SLITRK1 is the first gene to be associated with TS and SLITRK1 mRNA can be detected in a number of regions, including the ones such as thalamus, subthalamus, globus pallidus, striatum, developing neocortical plate and subplate zone which are put under the spotlights in TS studies [34]. Another more recent study which conducted a genome-wide association analysis, genetic enrichment analysis and gene-based association on 4,819 TS patients identified rs2504235, a genome-wide significant locus within FLT3 on chromosome 13 [36]. The same study indicated TS heritability to be 92.4% through analyzing the genetic variance

spanning the evolutionarily conserved regions and located the TS associated genes to be preferentially expressed in dorsolateral prefrontal cortex [36]. Current knowledge on the genetic determinants of TS emphasize the effect of a modulation in gene expression through non-coding variants, within the cortico-striatal circuits in particular [34, 31, 36].

Biochemically, focus in the literature has been mostly on abnormalities in neurotransmitter function for dopamine, and GABA through analyzing the change in their levels during tics and resting state. Presynaptic dopamine activity was found to be significantly higher in caudate nucleus in patients with Tourette Syndrome [37, 38] and several other studies have shown that elevated intrasynaptic dopamine release [39] and an increase in dopamine receptor reuptake sites were correlated with Tourette Syndrome. Singer et al. (2002) has shown that levels of intrasynaptic dopamine release were similar to the healthy controls when tics were not present, but they were elevated from baseline during tics; which can be an explanation for the normal functionality of patients with Tourette Syndrome when tics are not present [39]. A contradictory result is achieved from a biogenic amine metabolism study which analyzed cerebrospinal fluid samples from which the baseline homovanillic acid levels were shown to be significantly lower in TS patients. As homovanillic acid levels correlate with cerebral dopamine levels and administration of haloperidol, a dopamine receptor blocking agent, is found to be effective for bringing the homovanillic acid levels closer to the normal range in TS patients; an increased sensitivity of dopamine receptors which results in a reduction in dopamine release into the synaptic cleft due to stronger than normal negative feedback to the presynaptic neuron is suspected in TS [40, 38]. Gamma aminobutyric acid (GABA) is the main inhibitor of synaptic transmission in the central nervous system and a GABA-edited MRS study showed GABA concentrations to be reduced in the primary sensorimotor cortex, and be inversely correlated to tic severity in patients with Tourette Syndrome [4]. An ultra-high-field (7T) magnetic resonance spectroscopy (MRS) study showed a positive correlation of tic severity with GABA concentration within the supplementary motor area (SMA), an area which is found to be linked with the generation of motor tics in TS. SMA GABA concentrations were also found to be positively correlated with the fractional anisotropy values within a corpus callosal

region which projects to SMA and be inversely correlated with cortical excitability within the sensorimotor cortex [41]. These alterations in GABA content raise questions regarding the regulation of motor and sensory relays in TS, hence making tasks such as amplitude discrimination and tactile detection functional measures of probable atypical sensory processing for patients with TS.

The main focus of neuroanatomical studies on TS has been on the prefrontal cortex, motor cortex and the basal ganglia structures [42, 33, 38]. In a neuroanatomic study with a sample size of 155 children with TS, high-resolution magnetic resonance images of cortical and CSTC circuitry-associated white matter portions were acquired. The study found that patients with Tourette Syndrome had larger dorsal prefrontal and parietooccipital regions and smaller inferior occipital regions compared to healthy controls [43]. Another MRI study suggested investigating the cortical thickness to be more reliable due to low variety in cytoarchitectural grey matter structures to understand the brain morphology for the TS. The results showed significant cortical thinning in the somatosensory-motor and fronto-parietal cortices. Additionally, a decrement in the fronto-parietal thickness and a decrement in pre-central cortex thickness in male TS patients were found to be correlated with age. Male TS subjects were also found to have a thinner cortex in the fronto-parietal regions compared to female TS subjects [44].

In a volumetric magnetic resonance imaging (MRI) study of the basal ganglia and lateral ventricles, even though there were no significant size differences found in caudate nucleus, putamen and the globus pallidus; there found to be a significant difference in putamen and lenticular symmetry in children with TS when compared with the healthy controls. Moreover, a within group comparison for TS group among children with and without comorbid ADHD showed a significant difference in left globus pallidus volumes, where the left globus pallidus volumes of the TS patients with comorbid ADHD were significantly smaller than both pure TS group and the healthy control group. These changes in symmetries are speculated to indicate an atrophy/hypoplasia in the regions rather than an atrophy of their contralateral structures. Another important result of the study was the observation of a shift in putamen symmetry as

healthy male right handed control group showed a predominance of left putamen and this predominance was not observed in TS group, hence supporting the hypothesis of TS being a developmental abnormality [45].

In another study by Peterson et al. (2003) basal ganglia volumes, in particular caudate nucleus and lenticular nucleus volumes were reported to be significantly reduced in children with TS [46]. In a high-resolution MRI study, this volume reduction in caudate nucleus was confirmed and found to be inversely correlated with the severity of tic symptoms in children with Tourette Syndrome [47]. A multimodal neuroimaging study in which diffusion tensor imaging and alpha-[11C]methyl-L-tryptophan positron emission tomography were performed, targeted thalamus, caudate nucleus and lentiform nucleus in children with TS. In the caudate nucleus of children with TS an asymmetric immature microstructure, which was associated with an abnormal increment in serotonin synthesis, was considered to indicate higher than normal cortical disinhibition and serotonin synthesis due to abnormal connectivity in CSTC network [48].

Abnormal structural connectivity in CSTC pathway was investigated in detail in a study conducted on adult TS patients. The data acquired from a 3T magnetic resonance imaging scanner showed white matter abnormalities in neural pathways in between the cerebral cortex, basal ganglia and thalamus. Especially thalamus and striatum had abnormally high connectivity with sensory cortices and primary motor cortex, along with the supplementary motor area, the parietal cortex and several other cerebral regions. In the same study, CSTC pathways in TS population were found to show a reduced radial diffusivity and an increased fractional anisotropy (FA) which, along with the above results, indicate extensive structural abnormalities in CSTC white matter pathways, hence providing additional evidence for abnormal cerebral development hypothesis for TS [49]. A widespread structural connectivity deficit for TS was confirmed by a structural tensor imaging (STI) study with a main focus on intrahemispheric white matter connectivity for the cortico-subcortical networks that take part in motor control, which showed a reduced connectivity in the frontal cortico-cortical circuits and in between putamen and the supplementary motor areas [50]. A cohort

study with mean follow-up interval of 7.5 years investigated the relation between the change in structural connectivity with tic remission in adult TS patients through adulthood. Resting-state functional magnetic resonance imaging (fMRI) data suggested a change in immature cerebral network over time where a significantly higher connectivity between striatum, midcingulate cortex, and ipsilateral anterior cortex was observed and as local connections showed an increased connectivity, long range connectivity was found to be decreased [51]. Structural white matter abnormality was found in the somatosensory pathways as well. A study of diffusion tensor MRI which targeted the whole brain derived data from adult pure TS patients and a reduced branching in somatosensory pathways which were identified by probabilistic tractography to be in the ipsilateral cerebello-thalamo-cortical and transcallosal pathways of the somatosensory system innervating this particular subcortical region was observed. The results showed a negative correlation between tic severity and fractional anisotropy, hence suggesting the existence of an adaptive reorganization for the somatosensory processing in adult TS patients [52].

Functional neuroimaging studies, using modalities such as fMRI [53], cerebral metabolic activity detection by resting cerebral blood flow [54], and EEG [23] have shown that patients with tic spectrum disorders had increased primary sensorimotor cortex activity, as would be expected from increased motor functions during tics. Other than that, there were no differences observed between subjects with TS and healthy subjects in terms of the functionality of the primary sensorimotor cortex. A contradictory result was acquired from a study which analyzed the neural activation during stimulus driven execution and inhibition of mentally prepared movements. The data acquired from structural diffusion tensor imaging and event-related fMRI showed a reduced task-related activation in the left primary motor cortex and secondary motor areas during execution trials, however this was not observed during the inhibition trials. Moreover, a decreased co-activation between the left primary sensorimotor area, ipsilateral cerebellar regions and contralateral sensorimotor area was observed in patients with TS. These results indicate a link between the decrement in sensorimotor cortical activation while performing a task and a reduced co-activation between the sensorimotor cortex and other cerebral regions which take part in motor processing [55]. In

a multimodal neuroimaging study, GABA 1H magnetic resonance spectroscopy and fMRI were performed on adult TS patients. Data from fMRI showed an increased functional connectivity between the sensorimotor cortex and anterior insula, the insular part which is thought to integrate information regarding the internal state of an organism with the ongoing sensory input and is thought to be involved in processing urges and bodily sensations, hence suggesting an increased bodily awareness which may give rise to the sensory phenomena in TS. GABA 1H magnetic resonance spectroscopy produced data regarding the beta band activity, a cerebral rhythm linked to motor functions which is thought play a role in endogenous top-down processing for the maintenance of the sensorimotor set in presence of a disruptive stimulus. In healthy people, beta band activity is found to be correlated with GABAergic increase and it was reconfirmed for the control group in this study as well. Interestingly, even though the beta band base power and GABA content in TS were comparable to that of the control group, they were found to be negatively correlated; implying an impairment in the GABAergic interneuron system which disrupts the modulation of the beta oscillations in sensorimotor network, and/or a receptor level deficit in GABA binding in the sensorimotor network [16].

1.2.5 Treatment

Due to phenotypic variability throughout the TS population, pharmacological treatment is customized for each patient, generally modified with respect to the comorbid disorders, and treatment may not be needed for some patients if the intervention of the disorder does not affect patient's functionality in daily life [33, 38]. For the time being there is no treatment that completely eliminates tics, however neuroleptic drugs constitute the current standard to treat tic disorders and pharmacological approaches such as Dopamine D2 Receptor Antagonist Therapy shows reduction up to 50% to 80% in tic severity in patients with TS [56]. Habit reversal therapy (HRT) is constituted by various components such as relaxation training, competing response training, and awareness training through self-monitoring, and it provides an efficient non-pharmacological method for tic suppression after which patients benefit an 18.3%

to 37-5% reduction in tic severity scores [57].

1.2.6 Anatomy of the Basal Ganglia and the Cortico-Striato-Thalamo-Cortical Pathway

Volumetric changes and structural asymmetries in the basal ganglia, and a widespread abnormal connectivity in the cortico-striato-thalamo-cortical (CSTC) pathway are widely accepted to play a role in the pathology of Tourette Syndrome [32, 58, 44, 49]. Hence, their anatomical and physiological comprehension is critical to develop an understanding on the disorder.

Four main structures comprise the basal ganglia: substantia nigra, subthalamic nucleus, globus pallidus, and the striatum. The substantia nigra contains the pars reticulata and pars compacta nuclei. Pars reticulata is a major basal ganglionic output nucleus and pars compacta has strong dopaminergic projections to other basal ganglionic structures, especially to the striatum. The striatum is the major input structure of the basal ganglia, since it receives projections from the cerebral cortex, thalamus, and brain stem. The striatum is divided by the internal capsule into the putamen and the caudate nucleus. The globus pallidus is comprised of two different nuclei of different functions and connectivity. The external segment of the globus pallidus takes part in the intrinsic circuitry, whereas the internal segment serves as a major basal ganglionic output structure and it can be considered as a single output structure with the pars reticulata of the substantia nigra. The subthalamic nucleus lies between the substantia nigra and the thalamus. It is a small nucleus and it projects to the substantia nigra pars reticulata, and to both segments of the globus pallidus. The subthalamic nucleus receives projections from the cerebral cortex, brain stem, thalamus, and the external segment of the globus pallidus. The cortical projection to the subthalamic nucleus and related subthalamopallidal projections form a hyperdirect pathway [5].

The most common neurons in the striatum are the GABAergic medium spiny neurons whose activity is modulated by other neurotransmitters, especially by the

dopaminergic input from the ventral tegmental area and the substantia nigra pars compacta. Both the external and the internal segment of the globus pallidus contain large GABAergic neurons which receive projections from the striatum. Similar to the internal segment of the globus pallidus, the substantia nigra pars reticulata contains GABAergic neurons which intertwine with the dopaminergic neurons of the substantia nigra pars compacta. The subthalamic nucleus differentiates from the other basal ganglia structures as its projection neurons are glutamatergic [5].

Cortico-striato-thalamo-cortical (CSTC) circuit can be considered as a partially closed circuitry which takes part in skelemotor, oculomotor, limbic and associative (prefrontal) functions (Figure 1.3) [5]. Cerebral cortex regions project topographically to the striatum, which in turn projects to other basal ganglionic regions following the same trend, constituting functional domains throughout the basal ganglia, thalamus, and back in the cortex. These projections were shown to be converging within each circuitry structure, terminating on a much smaller number of neurons on each following circuit element. CSTC pathway is known to participate in a variety of motor behaviors and the main functions executed through these circuits are reinforcement learning, action selection, movement preparation, movement execution, and control of the movement parameters [5]. Moreover, thalamo cortical layer 4 GABAergic interneurons are shown to mediate feedforward inhibitory mechanisms by suppressing the spike generation in spiny neurons, and take part in the sensory gating process which filters the sensory input based on the selective attention and is shown to be abnormal in a variety of psychiatric disorders [30, 3, 59, 4, 60].

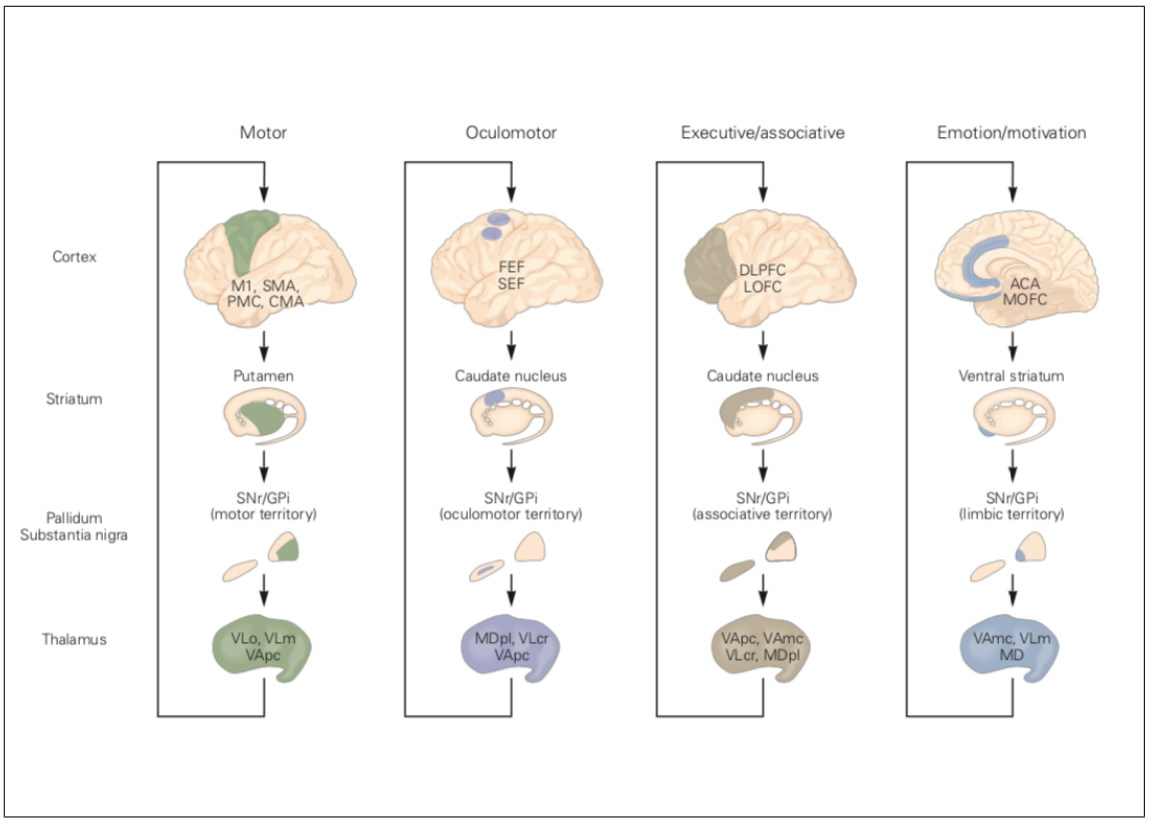

Figure 1.3 Anatomy of the cortico-striato-thalamo-cortical circuits.

1.3 Psychophysical Background and the Psychophysical Methods

1.3.1 Definition & Methods

Psychophysics, founded by German physiologist, physicist and philosopher Gustav Theodor Fechner in mid-nineteenth century, is the science which aims to establish quantitative rules to understand the human and animal sensory responses to physical and chemical sensory stimuli [61]. Psychophysical studies are often conducted in tandem with the physiological studies as psychophysics aims to understand what sensory systems do and physiology aims to understand how they do it.

Briefly stated, a psychophysical experiment has five main components: Stimulus, Task, Method, Analysis and Measure. Forms of the stimuli and the tasks are tailored according to the specific sensory function and the investigated question. There is a

variety of methods which can be adopted in psychophysical studies. Two-alternative forced choice (2AFC) method which obliges the subject to make a choice between two presented stimuli in a trial and staircase (adaptive) method in which the upcoming stimuli are adjusted according to the subject's former answers are two examples which were also used in this study and are explained in detail in the upcoming text. Analysis refers to the conversion of the collected data into measurements (e.g. taking the average of a group's data) and the measure is the investigated final product (e.g. a detection threshold). The term "procedure" is also commonly used, and it may refer to either a task, method, analysis or a combination of them. Psychophysical procedures tend to be classified through dichotomies such as "performance" versus "appearance", "threshold" versus "suprathreshold", "forced-choice" versus "non-forced-choice", "detection" versus "discrimination", and "criterion-dependent" versus "criterion-free" [62]. "Performance" tasks measure how good do subjects perform at a certain task in the sense of perception limits. "Appearance" tasks do not measure the performance of a subject, but measures the apparent magnitude of a certain stimulus dimension where there is not a correct nor incorrect answer in its trials [62]. The tasks which were adopted in this study fall under the category of "performance". "Threshold" is defined as the stimulus magnitude at which a subject perceives a new stimulus state and can be either an absolute or a difference threshold. As "absolute threshold" stands for the stimulus magnitude which can be just differentiated from its null (e.g. Dynamic Detection Threshold task used in this study), a "difference threshold" stands for the magnitude of stimulus difference necessary to make two suprathreshold stimuli just discriminable (e.g. Amplitude Discrimination tasks used in this study). "Suprathreshold" tasks can be either defined as non-threshold tasks or as the tasks in which all the applied stimuli are of a magnitude above their corresponding detection thresholds [62]. All of the tasks adopted for this study fall under the "threshold" category, except for the Choice Reaction Time task which falls under the "suprathreshold" category. In a "forced choice" task subjects are presented with two or more different stimuli among which there is one correct answer and the subjects are asked to make a goal related choice (e.g. Amplitude Discrimination tasks in this study). If a task does not require subjects to make a choice among different stimuli, that task is considered as a "non-forced choice" task (e.g. Choice Reaction Time and Dynamic Detection Threshold tasks in this study) [62].

"Detection" tasks are used to measure the thresholds to detect the presence of a stimulus in comparison to a null stimulus (e.g. Static and Dynamic Detection Threshold tasks in this study). "Discrimination" tasks refer to the tasks in which neither of the discriminated stimuli is a null stimulus (e.g. Amplitude Discrimination tasks in this study) [62]. "Criterion-dependent" tasks are the ones which do not present a correct answer in its trials and can be biased by a subject's perception of the task, independent of the actual strength of the internal signal (e.g. Dynamic Detection Threshold task in this study). Whereas, in the "criterion-free" tasks a correct answer is presented among the compared stimuli in each trial (e.g. Static Detection Threshold and Amplitude Discrimination tasks used in this study) [62]. Figure 1.4 represents a classification schema for the aforementioned psychophysical experiments [62].

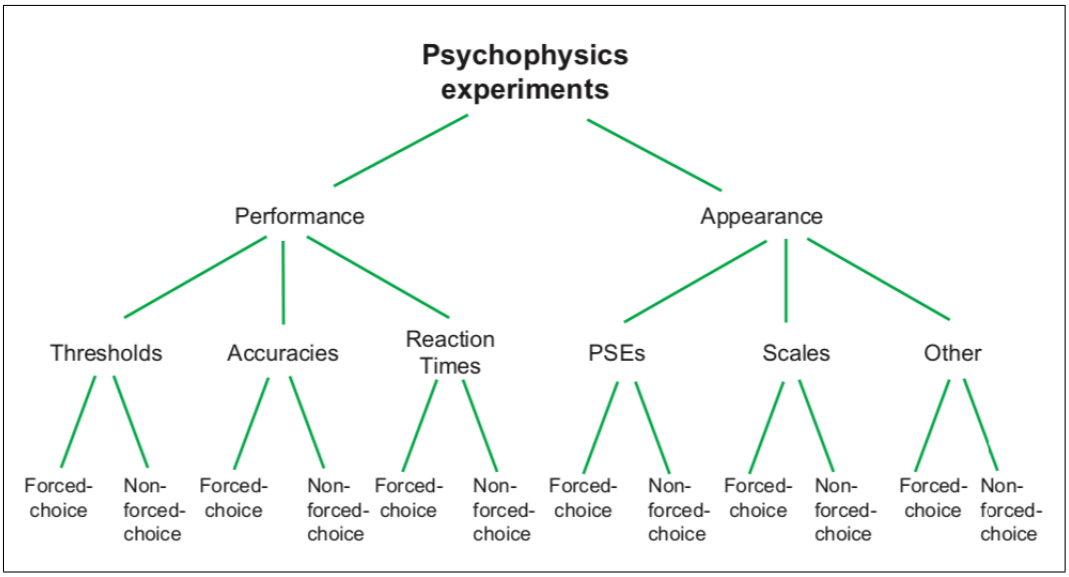

Figure 1.4 Classification schema of psychophysical experiments.

1.3.2 Psychometric Function

Psychometric function is a probabilistic tool which is used to define a mathematical relationship between the intensity of a sensation felt by a subject (or a subject group), and the actual amplitude of a stimulus (Figure 1.5) [5]. It plots the percentage of times a subject detects a stimulus as a function of stimulus amplitudes and the threshold is generally set to the stimulus amplitude which is detected on 50% of the

trials but can be adjusted according to the specific requirements of different studies. It is important to note that psychometric curves are affected by individual subjects' internal criteria in psychophysical tasks depending on how strict they personally approach to the task, as well as by subjects' physical and mental status during the task. Hence taking multiple measurements from a subject for the same task and/or taking the population means provide better threshold estimates, avoiding such bias in psychophysical experiments [62, 5].

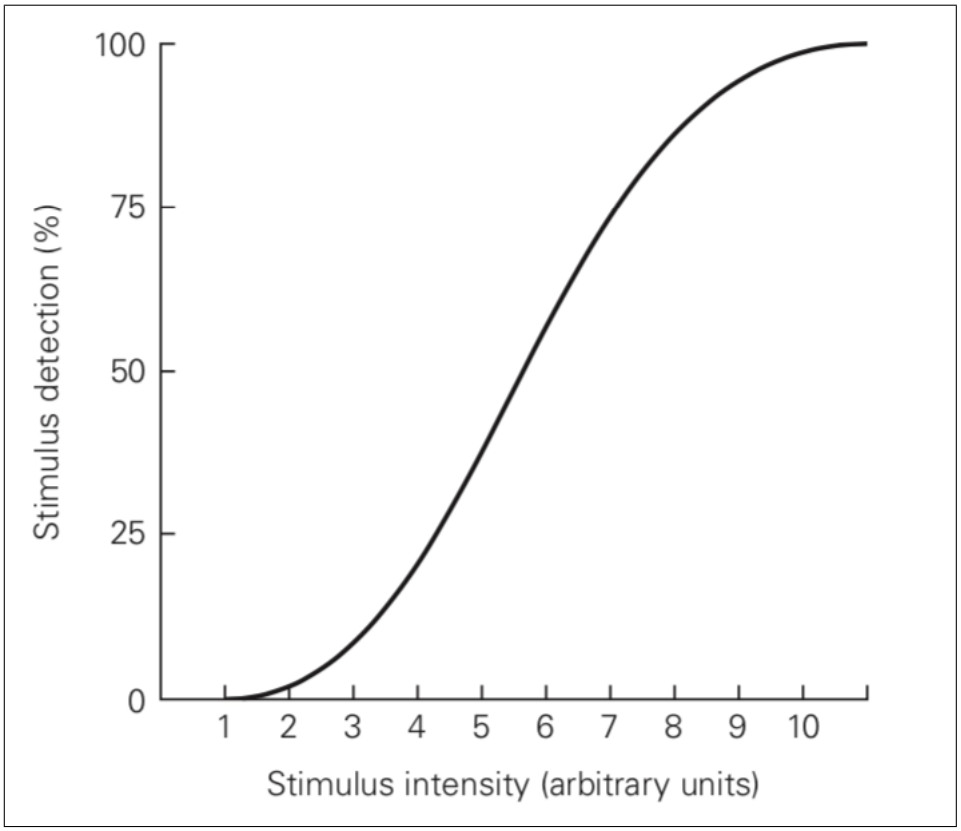

Figure 1.5 The Psychometric Function.

1.3.3 Weber's Law & Difference Limen

In 1834, Ernst Weber showed that the sensitivity of a sensory system to differences in intensity depends on the absolute strength of the compared stimuli [5]. In other words, it was found that as the intensity of the reference stimulus increased, subjects needed a larger difference in the intensity of a test stimulus in order to be able to perceive a difference between the compared stimuli [1]. This minimum difference in

magnitude which is necessary for a subject to discriminate between a standard stimulus (reference stimulus) and a test stimulus is called difference limen, difference threshold or just-noticeable difference (JND) [1].

Progressing from Weber's findings, physicist Gustav Theodor Fechner produced a formula to quantify the intensity of sensations in order to predict the relationship between the stimulus magnitude and sensory discrimination [5]. This formula which is now known as Weber's Law is as follows:

$$\Delta S = K.S \tag{1.1}$$

ΔS stands for the difference limen (also known as difference threshold or JND), S is the strength of the standard stimulus, and K is a constant called Weber fraction. Studies have shown that this fraction tends to be constant for a range of stimulus intensities in most of the senses including weight, brightness and sound frequency [63, 64, 65], making Weber's fraction a functional measure to assess psychiatrically compromised subjects' sensory processing by comparing their sensory discrimination performances to that of healthy subjects.

1.3.4 Psychophysical Studies on the Somatosensory System

Psychophysical studies provide answers to questions such as "How do sensory systems work?", "Under which circumstances do psychophysical laws hold true?", and "What kind of sensory dysfunctions are observed in certain disorders?". These answers in turn provide complementary data to physiological and anatomical studies, allowing science to understand the neural sensory mechanisms in healthy populations, as well as the underlying pathologies of health disorders.

As the skin is the biggest organ of human body, it is not surprising that somatosensory system attracts high academic interest. A study conducted by Francisco et al. (2008) investigated whether the vibrotactile amplitude discrimination capacity parallels the magnitude changes of the evoked activity in the somatosensory cortex in

healthy subjects, through a set of vibrotactile batteries and by comparing their data with that of Simons et al. (2005) who had analyzed the amplitude dependency of the primary somatosensory cortex response to flutter stimulation in squirrel monkeys. Combined results showed, for a wide range of standard stimuli (50 μm - 800 μm), that the ability to perceive the differences in vibrotactile stimuli changes systematically in relation to increasing stimulus magnitudes in a near linear fashion (R=0.9977) and follow the Weber's Law, hence suggesting the vibrotactile amplitude discrimination capacity to be an indicator of neural health [1, 66]. Several other studies adopted psychophysical methods to investigate the alterations in tactile processing in psychiatrically compromised populations. A study conducted on autistic children by Güçlü et al. (2007) showed a stronger than normal sensitivity to touch in autistic population which may originate due to an emotional modulation of the sensory response, instead of a perceptual sensory problem [2]. Another study by Güçlü et al. (2015) investigated the tactile processing in children with OCD. The study showed OCD group to have an altered somatosensory processing at suprathreshold levels, as the OCD subjects performed significantly worse in the Amplitude Discrimination task compared to the healthy controls. This reduced discriminative capacity was more prominent in the young males and the young OCD subjects showed reduced adaptation as well [3]. In the study by Belluscio et al. (2011) tactile thresholds of TS patients were measured by using a geometric series of VonFrey monofilaments ranging from 2 to 0.008 g. Tactile thresholds were obtained from two different skin regions, one being the most active tic and premonitory urge region of each patient and the other being the left peroneal region which was reported rarely to be a tic site, in order to investigate the possibility of unique alterations in tic regions. In the study TS group showed an increased sensitivity to weaker stimuli but not to stronger stimuli when compared to the healthy controls, which may suggest altered sensory gating in patients with TS. In the same study, both groups produced comparable detection thresholds, however the majority of the TS patients were reported to perceive themselves to have heightened sensitivity to external stimuli [67].

1.4 Aim

This master's thesis study aimed to investigate the somatosensory processing, vibrotactile adaptation and the validity of Weber's Law in children with Tourette Syndrome by using a set of vibrotactile test batteries. First, the altered feedforward inhibitory mechanisms in TS were observed by comparing the dynamic and static detection thresholds of healthy children and children with TS [4]. Then, the discriminative capacities of children with TS were assessed by producing difference limen values for three conditions in amplitude discrimination (AD) tasks and later on by applying two masking stimuli with different amplitudes, prior to each AD condition. These difference limen values allowed us to investigate whether Weber's Law holds true for a psychiatrically compromised population as TS patients. To the best of my knowledge, this is the first study to address this question in TS patients and it provides valuable information for future studies which would aim modeling sensory processing in patients with psychiatric disorders.

Hence, the ultimate aim of this thesis is shedding more light on the underlying neural mechanisms of Tourette Syndrome which may provide a foundation for developing methods to alleviate its symptoms.

2. Material & Methods

2.1 Participants

Thirty (7 female, 23 male) children and adolescents with Tourette Syndrome within the range of 8 - 17 years of age and twenty-five (7 female, 18 male) age- and sex-matched healthy controls were recruited for this study (p=0.76). Participation in the study was voluntary and there weren't any incentives except for a free-of-charge medical examination. All subjects were recruited in between February 2018 and July 2018. The study is approved by the Medical Ethics Committee of Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery. Parents of the subjects were asked to sign a consent form for the participation of their children in the study and the subjects who were older than 12 years were asked to sign their own consent forms as well.

2.2 Inclusion and Exclusion Criteria

Participants for the TS group was invited from Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery's database based on their Tourette Syndrome diagnoses according to the DSM-V criteria. TS group participants were included in the study regardless of their current therapy modality. TS subjects with comorbid ADHD, OCD, and generalized anxiety disorder were included in the study, however TS subjects with autism, conduct disorder, childhood schizophrenia or psychosis, major depression, or bipolar disorder and children with poor school performance and task performance were not included in the study [3, 68, 46, 4]. Healthy control subjects were recruited by invitation and they were assessed by a specialist psychiatrist for any undiagnosed condition which might have made them unsuitable for the control group [3].

2.3 Clinical Assessment

All subjects were recruited by specialist psychiatrists Dr. Hilal Doktur, Dr. Deniz Yıldız, and Assoc. Prof. Dr. Canan Tanıdır, from Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital through a clinical assessment in which subjects' diagnoses, age, sex, therapy modality and history, family history and handedness were recorded. Psychiatric comorbidities were determined according to the DSM-V criteria during the clinical assessment through interviews with the subjects and their parents. Tic severity for the TS group was assessed with the Yale Global Tic Severity Scale [10] and to quantify subjects' sensitivity to sensory stimuli, Sensory Profile [19, 20] and the Touch Inventory for Elementary-School-Aged Children [21] questionnaires were conducted both for TS and control group participants [3, 2].

The Yale Global Tic Severity Scale (YGTSS) is a clinical rating instrument which allows researchers and clinicians to evaluate the vocal and motor tics for a patient in five dimensions: number, complexity, intensity, frequency, and interference. It is a six-point ordinal scale interview, generally addressed to the subject by a clinician, which involves descriptive statements and detailed examples for motor and vocal tics. Subjects, and their caregivers, then affirm or decline the existence of the described condition based on both subject's current and past personal experiences, hence producing a comparable motor tic score, vocal tic score, impairment score and a total score. Tic scores are calculated as the sum of number, complexity, intensity, frequency, and interference scores for their corresponding tic modality, impairment score is appointed by the clinician who rates the effects of tics on a subject's daily life among YGTSS impairment score options, and total YGTSS score is calculated as the sum of motor tic, vocal tic and impairment scores for each subject [10].

The Sensory Profile is a standardized questionnaire which allows researchers and clinicians to assess a subject's response to daily sensory events through a total of 125 items under eight categories: Touch, Body Position, Movement, Taste/Smell, Visual, Auditory, Activity Level, and Emotional/Social. Every item is rated by subjects' caregivers based on subjects' daily sensory experiences through a five-point Likert

scale where the caregiver reports the percentage of time the child engages in the listed activities [20].

The Touch Inventory for Elementary-School-Aged Children (TIE) is a 26-item standardized screening scale for tactile defensiveness in children, during which an examiner addresses questions to a pediatric subject regarding common daily experiences where subjects are asked to answer either "no", "a little" or "a lot", producing a comparable total tactile defensiveness score for each subject [21].

2.4 Tactile Measurements

2.4.1 Apparatus

Tasks were carried out with a Cortical Metrics CM-4 stimulator (CM-4; Cortical Metrics, Chapel Hill, NC, USA) that is specifically designed to deliver vibrotactile stimuli to the glabrous pads of fingers [68]. CM-4 stimulator is a portable device and consists of two parts: the main body and a detachable head unit (Figure 2.1). Head unit is where the subjects rest their hands on and it has four discs for four digits (D2: the index, D3: middle, D4: ring, D5: little finger). Cortical CM-4 stimulator is specifically designed to be able to deliver simultaneous stimuli at the digit tips which ensure that the stimuli are delivered in a well-controlled and synchronized manner and its head unit allows an ergonomic hand placement. Device's prototypes are used in a variety of studies such as demonstrations of Weber's Law [1, 69], an assessment of temporal order judgements (TOJ) in healthy subjects [70], the impact of an NMDA receptor blocker on somatosensory adaptation [71], and measurements of amplitude discriminative capacities [2, 3, 70]; similar to this study.

The head unit contains four collateral cylindrical disks with a diameter of 130 mm and a depth of 11 mm, each disk containing an optical position sensor and a voice coil actuator [68]. Each voice coil actuator is attached to a plastic probe of 5 mm diameter which protrudes through a hole of 7 mm diameter on the side of each

Figure 2.1 Cortical Metrics CM-4 Device.

cylindrical disk where the subjects place their fingertips. Each disk's position, hence of the probes', can be arranged independently according to the finger lengths of individual digits which makes the CM-4 Cortical Metrics device functionally usable on both adult and pediatric subjects. Subjects place the glabrous pads of their fingertips on these probes where the positions of each vibrating tip are determined by optical displacement sensors. These non-contacting optical position sensors are also utilized to drive the tips to contact the skin with independent contact forces at the beginning of each battery. The device has its custom software which allows making changes in stimuli properties (i.e. amplitude, frequency, duration, number of trials, inter trial interval etc.) and it can be run with any computer with Microsoft XP or a later version.

2.4.2 Tactile Stimuli and Psychophysical Procedures

The tactile stimuli were sinusoidal mechanical vibrations, produced by the Cortical Metrics device (described above). Stimuli were applied to the glabrous pads of the fingertips of the subjects' digits D2 and D3 of their non-dominant hands. Then the subjects were asked to make a decision regarding the specific task by pressing the

buttons of a Bluetooth mouse. All stimuli had a frequency of 25 Hz, hence primarily stimulating the NP1 psychophysical channels which are sensitive to stimuli of a flutter range of 2 to 40 Hz. Associated dominating receptors in NP1 channels are called Meissner corpuscles and they are shown to be dense in concentration in the fingertips [5]. Digits D2 and D3 were chosen as they are processed more collaterally compared to the other digits in the somatotopic arrangement of the primary somatosensory cortex, hence reducing the effect of spatial cortical differences [72, 73] and also for the abundant existing neurophysiological information for their somatotopic region due to studies in primates [72, 1, 74, 75].

Each experiment was constituted of twelve protocols that last 36 minutes if performed without a break. These protocols are as follows, similar to that of Güçlü et al. (2015).

- **Choice Reaction Time (cRT)**: The main purpose of this protocol was getting subjects familiar with the device and training them for the upcoming tasks. A single-cycle (duration: 0.5 s) sinusoidal wave (amplitude: 200 μm) was applied either to digit D2 or D3 as a two-alternative forced choice (2AFC) task. The subjects were then asked to press the button which corresponded to the site where they felt the stronger stimulus (if the left hand is the non-dominant hand: left mouse button for D3 and right mouse button for D2, the opposite buttons if the right hand is the non-dominant hand). There were 10 trials in this task and the reaction time was calculated by taking the average of the median 5 reaction-time values (towards the higher end) regardless of correct/incorrect trials [3]. This task also provided a mean two-alternative forced choice (2AFC) reaction-time value for each subject, which was later used for correction for the dynamic detection threshold task

- **Dynamic Detection Threshold (DT_c)**: In this task, a dynamically increasing stimulus was randomly applied to either the digit D2 or D3, increasing in amplitude from zero at a rate of 2 μm/s). Subjects were asked to press the correct mouse button corresponding to the digit where they feel the stimulus the

moment they perceive it and the final value was recorded. This final value was corrected for each subject by subtracting the amplitude rise for subject's average reaction time which were calculated in the Choice Reaction Time task. DT_c task was constituted of 7 trials with 5-second inter-trial intervals (ITI) and the final DT_c value for each subject was calculated by taking the mean of the 7 trials.

- **Static Detection Threshold (DT_s)**: This task was produced by modifying a 2AFC amplitude discrimination task in which both D2 and D3 digits were simultaneously stimulated by 25 Hz vibrations for 0.5 s. In the task, only one of the digits was stimulated by a stimulus of 0.5 μm intensity which was the standard stimulus and the other digit was stimulated by the test stimulus of 20 μm initial intensity. Subjects were asked to press the button which corresponded to the site where they felt the stronger stimulus. The amplitude of the test stimulus was then modified in a stepwise fashion according to the subject's answers. In the first 15 trials, each correct answer reduced the intensity of the test stimulus by 1 μm and each wrong answer increased it by 1 μm. In the last 15 trials, this rule was modified such that two consecutive correct answers reduced the intensity of the test stimulus by 0.5 μm and each wrong answer increased it by 0.5 μm. After 30 trials were completed, the average of the final five values were calculated and corrected by adding the intensity of the standard stimulus (0.5 μm) to calculate the static detection threshold for each subject. Only the data which showed ± 1 step convergence in the last 6 trials were analyzed and the data which did not show convergence were discarded.

- **Amplitude Discrimination (AD)**: This task was a 2AFC task in which both digits (D2 and D3) were simultaneously stimulated by 25 Hz vibrations for 0.5 s, as explained above. There were three conditions of amplitude discrimination tasks with varying intensities of test and standard stimuli and varying step sizes. Each task had 20 trials and there were a 3 second ITI in between each trial. In the first AD task, the standard stimulus and test stimulus had an amplitude of 50 μm and 150 μm respectively. The test stimulus was modified in a staircase fashion (as explained in DT_s). In the first 10 trials, each correct answer

reduced the intensity of the test stimulus by 10 μm (step size 1) and each wrong answer increased it by 10 μm. In the last 10 trials, two consecutive correct answers reduced the intensity of the test stimulus by 2 μm and each wrong answer increased it by 2 μm (step size 2). In the second AD task, the standard stimulus and test stimulus had an amplitude of 100 μm and 200 μm respectively. The same staircase rule was applied to the test stimulus with a step size of 15 μm (step size 1) in the first 10 trials and a step size of 3 μm (step size 2) for the last 10 trials. And in the third and final AD task, the standard stimulus and test stimulus had an amplitude of 200 μm and 450 μm respectively. The same staircase rule was applied with a step size of 25 μm (step size 1) in the first 10 trials and a step size of 5 μm (step size 2) in the last 10 trials. The step size 1 to step size 2 ratio was arranged to be 5:1 in order to make a 'fine-tuning' for the detection thresholds, hence the difference thresholds. The first, larger step size made the subject quickly approach to the expected threshold value and the second, smaller step size allowed subjects to approach to a true threshold value more precisely. And only the data which showed a ± 11 step convergence in the last 6 trials were analyzed and the data which did not show convergence were discarded.

- **Amplitude Discrimination with single site adaptation (cAD)**: These tasks were similar to that of amplitude discrimination tasks (explained above) but an adapting stimulus was randomly applied to one of the digits (D2 and D3) of the subject prior to the simultaneous stimuli (Figure 2.2). Random application of the adapting stimulus doubled the number of trials that is normally required to achieve the investigated difference threshold value but it also prevented providing a cue to the subjects which was observed in an earlier study [3]. Each adapting stimulus had a frequency of 25 Hz and was presented 0.25 s prior to either the test or standard stimulus for a duration of 1 s. The intensity of the adapting stimulus was either 100 μm or 300 μm, and both intensities were presented before each of the three amplitude discrimination steps, hence constituting six cAD tasks in total for each experimental battery. Only the data with ± 11 step convergence in the last 6 trials were analyzed and the data which did not show convergence

were discarded.

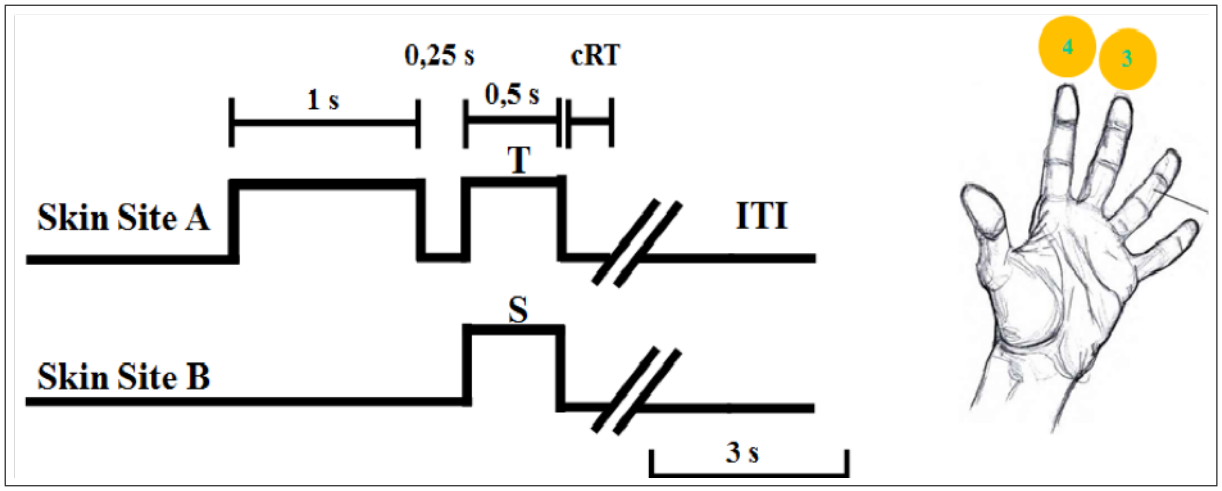

Figure 2.2 cAD Procedure. Adapting stimulus is randomly applied either prior to the test stimulus or the standard stimulus. (**A**: Adapting stimulus, **T**: Test stimulus, **S**: Standard Stimulus, **ITI**: Inter-trial interval)

2.4.3 Weber Fraction Calculation

Weber fraction for each task was calculated by taking the mean of the corresponding groups' Weber fractions for an AD or a cAD task and each subject's Weber fraction was calculated by dividing the JNDs of each subject with the corresponding tasks' standard stimulus as stated in the Weber's Law:

$$\Delta S = K.S \tag{2.1}$$

K stands for a constant called Weber fraction which corresponds to the ratio of the difference threshold (JND) ΔS to a standard stimulus S.

2.5 Statistical Analyses

Statistical analyses were performed in MS Excel 2017 and MATLAB 2018b (MathWorks, Natick, MA, USA) on all collected variables. Outliers were discarded by

using Peirce's criterion [76]. The means and standard deviations for each task, along with their corresponding one tailed t-test and p values were calculated for between group analyses.

3. Results

3.1 Participant Demographics

For the TS group 30 children and adolescents with Tourette Syndrome (7 female and 23 male) with a mean age of 13.2 ±1 2.5 years and 25 (7 female, 18 male) age- and sex-matched healthy controls with a mean age of 13.0 ±1 2.4 years were recruited for this study. One-tailed t tests and Fisher's exact tests were performed for the between group analyses. The mean ages were statistically comparable between the groups (p=0.67). Ninety-six percent of the TS group and 91% of the control group participants were right-handed. TS group exhibited 84% ADHD and 55% OCD comorbidity, whereas control group exhibited 8% ADHD comorbidity and none of the control group subjects had comorbid OCD. Fifty-six percent of the TS group subjects was on medication for ADHD and/or OCD, and 8% of the control group was using medication for ADHD. Forty-six percent of the TS group participants reported to experience sensory phenomena, whereas none of the control group participants reported to experience any type of sensory phenomena. Seventy-one percent of the TS group participants had an at least a first or second degree relative with a psychiatric disorder and none of the control group participants reported to have a close relative with a psychiatric disorder. Clinical and demographic characteristics for each group are listed in Table 3.1.

3.2 Clinical Assessment Data

Questionnaires and clinical interviews were conducted to assess the tic severity in the TS group (YGTSS), and sensory sensitivity for both TS and control group (Sensory Profile and Touch Inventory for Elementary-School-Aged Children). One-tailed t tests were performed for the between group analyses (Table 3.2).

Table 3.1
Clinical and demographical characteristics for the TS and control groups.

	TS Group N=30	Control Group N=25	Test Statistic	p
Mean Age ±SD (years)	13.0 ±2.4	13.2 ±2.5	t test	0.76
Sex (% female)	23	28	Fisher's exact	0.76
Handedness (% right-handed)	96	92	Fisher's exact	0.59
ADHD (% with ADHD comorbidity)	84	8	Fisher's exact	<0.001
OCD (% with OCD comorbidity)	55	0	Fisher's exact	<0.001
Sensory phenomena (% present)	46	0	Fisher's exact	<0.001
Medication (% medicated)	56	8	Fisher's exact	<0.001
Psychiatric illness in family history (% present)	71	0	Fisher's exact	<0.001

3.2.1 Yale Global Tic Severity Scale Data

To assess tic severity in TS group, Yale Global Tic Severity Scale (YGTSS) was used. Maximum motor tic score and maximum vocal tic score are each 25 and the maximum impairment score is 50 in YGTSS, hence the maximum YGTSS score is 100 and it is calculated as the sum of these three scores [10]. Two out of 30 subjects were not included to the YGTSS analysis as they did not participate in the questionnaire. One-tailed t tests were performed for the between group analyses. For the TS group in this study; mean motor tic score was 10.25 ± 4.78 (n=28), mean vocal tic score was 5.92 ± 5.94 (n=28), mean impairment score was 22.14 ± 9.29 (n=28), and the mean total YGTSS score was 38.32 ± 17.82 (n=28). (Table 3.2)

3.2.2 Sensory Profile Data

Sensory Profile was used to quantify the sensitivity of each subject to common sensory stimuli in both the TS group and the healthy control group. If a subject was reported to show a higher percentage of occurrence for a certain Sensory Profile questionnaire item than the generally accepted rate of occurrence for that item, reported by

Table 3.2
Questionnaire scores for TS and control groups. Sensory Profile positive scores represent the mean number of questionnaire items which were observed more than the normally accepted occurrence rate for the corresponding group.

	TS Group N=30	Control Group N=25	Test Statistic	p
Touch Inventory (Raw Scores)	45.1±8.7	39.9 ±6.4	t test	**0.03**
Sensory Profile (Positive Scores)				
Touch	10.66±5.94	10.63 ±6.84	t test	0.98
Emotional/Social	12.80 ±5.00	14.42 ±6.68	t test	0.33
Total	56.03 ±25.24	63.31 ±29.40	t test	0.36
Yale Global Tic Severity Score				
Motor Tic Score	10.25 ±4.78			
Vocal Tic Score	5.92 ±5.94			
Impairment Score	22.14 ±9.29			
Total Score	38.32 ±17.82			

Dunn (1994), the result for that item was assigned as a "positive score", or a "negative score" in the contrary scenario (W. Dunn, 1994). The ratio of occurrences for each item was appointed by the subjects from a 5-item Likert scale where subjects ranked the occurrence for each item from "1" (100%, Always) to "5" (0%, Never). The Sensory Profile data are presented as positive scores in this study and one-tailed t tests were performed for the between group analyses [2, 3]. Positive Touch score for the TS group was 10.66 ± 5.94 (n=30) and 10.63 ± 6.84 (n=19) for the control group and there was no statistically significant difference between the groups (p=0.98). Positive Emotional score for the TS group was 12.8 ± 5.0 (n=30) and 14.42 ± 6.68 (n=19) for the control group, and the between group comparison did not show a statistically significant difference (p=0.33). Total positive Sensory Profile score was 56.03 ± 25.24 (n=30) for the TS group and 63.31 ± 29.4 (n=19) for the control group, which again did not show a statistically significant difference between the groups (p=0.36). (Table 3.2)

3.2.3 Touch Inventory for Elementary-School-Aged Children Data

To measure the tactile defensiveness in both TS and health control subjects, the Touch Inventory for Elementary-School-Aged Children (TIE) was used [21]. The data for TIE are presented as the mean total raw scores in this study [2, 3]. The mean total raw TIE score for the TS group was 45.1 ± 8.7 (n=28) and 39.9 ± 6.4 (n=18) for the control group. Between group comparison with one-tailed t test revealed a statistically significant difference in TIE raw scores among the TS and healthy control (p=0.03). (Table 3.2)

3.3 Psychophysical Data

Psychophysical data from the tactile task batteries were acquired through the custom CM-4 Cortical Matrix software (CM-4; Cortical Metrics, Chapel Hill, NC, USA). All the measurements were taken from either the index finger (D2) or middle finger (D3) of the subjects' non-dominant hands. All the stimuli were delivered as sinusoidal waves of 25Hz frequency. The stimuli were delivered in a random manner to avoid any cues which could bias the subjects. One complete tactile battery consisted of twelve protocols which lasted approximately one hour, which varied for each subject depending on the subject's performance and the given breaks. Subjects were free to quit the experiment when they were tired, as the staircase rule could not be satisfied without the attention of subjects, which in turn produced missing data. Only the data which satisfied the corresponding rules were used in the analyses and the rest were discarded. The tactile battery consisted of Choice Reaction Time (cRT), Dynamic Detection Threshold (DT_c, Static Detection Threshold (DT_s, Amplitude Discrimination (AD) and Amplitude Discrimination with single site adaptation (cAD) tasks. Three different standard stimuli were used to determine the discriminative capacities as difference thresholds for each subject with the AD tasks, and the effects of two different masking stimuli for each of the AD conditions were measured to investigate the tactile adaptation capacities and the applicability of the Weber's Law with the cAD tasks in both groups [1, 2, 3]. All between group comparisons were performed through

one-tailed t tests and the results are presented as group mean ± standard deviation (SD). The tactile battery results are summarized in Table 3.3 and Table 3.4.

3.3.1 Choice Reaction Time Results (cRT)

Mean two-alternative forced choice reaction time for the TS group was 900.6 ± 312.9-ms (n=30) and 795.6 ± 245.4-ms (n=25) for the healthy controls. Mean Choice Reaction Time values for TS and control group did not reveal a statistically significant between group difference (p=0.17). The mean cRT value of each subject was also used as the mean two-alternative forced choice (2AFC) reaction time for the corresponding subject to correct that subject's DT_c value [3]. (Table 3.3)

3.3.2 Detection Threshold Results (DT_s , DT_c , DT_d)

Mean Static Detection Threshold (DT_s) was 6.8 ± 2.2 μm for the TS group (n=27) and 7.4 ± 2.0 μm (n=22) for the control group. There was no a statistically significant between group difference for the DT_s (p=0.35). Mean Dynamic Detection Threshold values were corrected for each subject's 2AFC reaction time by subtracting the increment in stimulus amplitude (2 μm/s) which corresponds to each subject's 2AFC reaction time before calculating the group means. Mean Dynamic Detection Threshold (DT_c) was 11.1 ± 3.4 μm (n=30) for the TS group and 10.5 ± 3.3 μm (n=24) for the control group. Between group comparison did not show a statistically significant difference (p=0.47). Changes in detection thresholds due to adaptation (DT_d) were calculated by subtracting the DT_s values of each subjects from that subject's DT_c values. Mean change in detection thresholds for the TS group was 3.80 ± 3.96 μm (n=26) and 3.44 ± 2.97 μm (n=21) for the healthy controls. Between group comparison for the mean change in detection thresholds did not show a statistical difference (p=0.73) (Table 3.3, Figure 3.1).

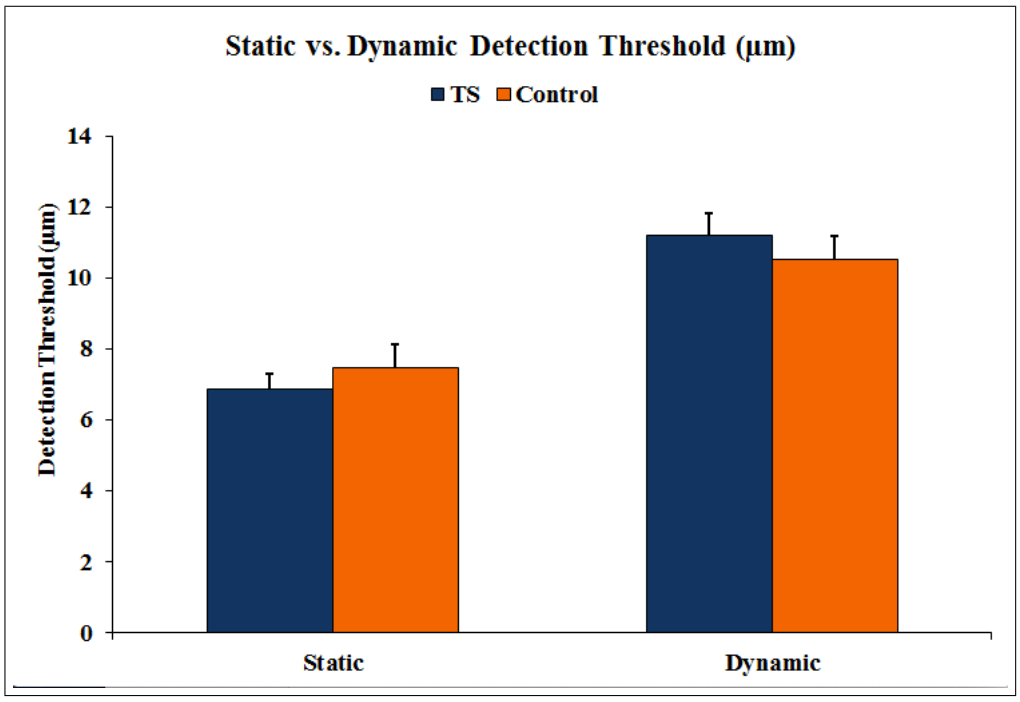

Figure 3.1 Detection Thresholds for the TS and Control Group. Blue columns represent the TS group and orange columns represent the healthy controls. Error bars are the standard error of the means. There was no statistically significant between group difference for the detection threshold tasks.

3.3.3 Amplitude Discrimination Results (AD & cAD)

Discriminative capacities of the subjects were measured as difference thresholds (difference limens) through Amplitude Discrimination (AD) and Amplitude Discrimination with single-site adaptation (cAD) tasks in three steps. Each step had a different standard stimulus amplitude and each standard stimulus amplitude was assessed for three conditions: Baseline (no masking), 100 μm-masking, and 300 μm-masking. Missing data resulted from non-convergent staircases or omission of outliers. (Table 3.3, Figure 3.2)

- **Baseline Amplitude Discrimination (AD) Results**: AD tasks constituted the baseline condition for the amplitude discrimination steps in both groups as there was no prior adaptive masking stimulus applied before the test stimuli. Missing data resulted from non-convergent staircases or omission of outliers.

  In the first AD step which had a standard stimulus of 50 μm and a test stimulus of

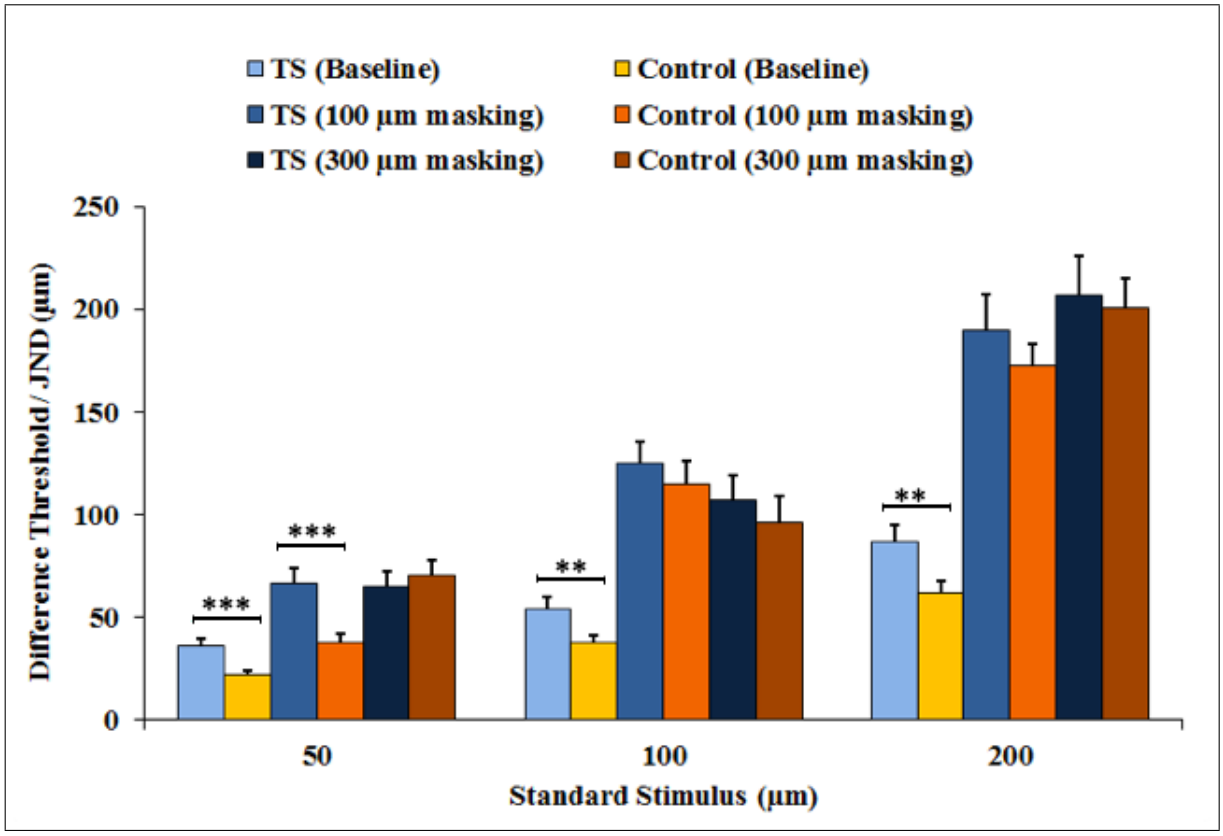

Figure 3.2 Just Noticeable Differences in Amplitude Discrimination and Amplitude Discrimination with Single-site Adaptation Tasks for TS and Control groups. Blue columns represent the TS group and orange columns represent the healthy controls. Error bars are the standard error of the means. Statistically significant differences are marked with asterisk signs (**; $p<0.01$, ***; $p<0.001$).

150 μm, the mean difference threshold of the TS group was 36.2 ± 16.4 μm (n=24) and 21.8 ± 8.7 μm (n=22) for the control group. Between group comparison revealed a statistically significant difference in the mean difference thresholds for the 50 μm baseline AD condition where TS group produced significantly higher difference thresholds (p=0.0007). (Table 3.3, Figure 3.2)

In the second AD step which had a standard stimulus of 100 μm and a test stimulus of 200 μm, the mean difference threshold of the TS group was 54.0 ± 29.8 μm (n=29) and 38.0 ± 13.5 μm (n=21) for the control group. There was a statistically significant between group difference in the mean difference threshold values for the 100 μm baseline AD condition as well (p=0.0026). (Table 3.3, Figure 3.2)

In the third AD step which had a standard stimulus of 200 μm and a test stimulus of 450 μm, the mean difference threshold of the TS group was 86.6 ± 42.9 μm (n=28) and 61.7 ± 27.2 μm (n=19) for the control group. There was a statistically significant between group difference in the mean difference threshold values for the 200 μm baseline AD condition as well (p=0.03). (Table 3.3, Figure 3.2)

- **Amplitude Discrimination with single-site adaptation (cAD) Results**: Amplitude Discrimination with single site adaptation (cAD) tasks constituted the 100 μm-masking and 300 μm-masking conditions for the amplitude discrimination steps where a random adaptive masking stimulus 0.25 s prior to either the test stimulus or the standard stimulus was applied for a duration of 1 s. Missing data resulted from non-convergent staircases or omission of outliers.

  cAD tasks with 100 μm masking stimulus constituted the second condition for each amplitude discrimination step. In the first amplitude discrimination step which had a standard stimulus of 50 μm and a test stimulus of 150 μm, the mean difference threshold of the TS group was 66. ± 38.4 μm (n=26) and 37.9 ± 19.4 μm (n=21) for the control group when the 100 μm adaptive masking stimulus was applied. Difference threshold values showed a statistically significant between group difference for the cAD task with 50 μm standard stimulus and 100 μm masking stimulus (p=0.0033). (Table 3.3, Figure 3.2)

  In the second amplitude discrimination step which had a standard stimulus of 100

μm and a test stimulus of 200 μm, the mean difference threshold of the TS group was 125.2 ± 55.6 μm (n=28) and 114.9 ± 52.3 μm (n=23) for the control group when the 100 μm adaptive masking stimulus was applied. Difference threshold values did not show a statistically significant between group difference for the cAD task with 100 μm standard stimulus and 100 μm masking stimulus (p=0.49). (Table 3.3, Figure 3.2)

In the third amplitude discrimination step which had a standard stimulus of 200 μm and a test stimulus of 450 μm, the mean difference threshold of the TS group was 189.5 ± 89.2 μm (n=20) and 172.9 ± 44.0 μm (n=26) for the control group when the 100 μm adaptive masking stimulus was applied. Difference threshold values did not show a statistically significant between group difference for the cAD task with 200 μm standard stimulus and 100 μm masking stimulus (p=0.45). (Table 3.3, Figure 3.2)

cAD tasks with 300 μm masking stimulus constituted the third condition for each amplitude discrimination step. In the first amplitude discrimination step which had a standard stimulus of 50 μm and a test stimulus of 150 μm, the mean difference threshold of the TS group was 64.9 ± 34.9 μm (n=23) and 70.7 ± 30.5 μm (n=20) for the control group when the 300 μm adaptive masking stimulus was applied. Difference threshold values did not show a statistically significant between group difference for the cAD task with 50 μm standard stimulus and 300 μm masking stimulus (p=0.56). (Table 3.3, Figure 3.2)

In the second amplitude discrimination step which had a standard stimulus of 100 μm and a test stimulus of 200 μm, the mean difference threshold of the TS group was 106.8 ± 58.2 μm (n=22) and 96.3 ± 60.9 μm (n=23) for the control group when the 300 μm adaptive masking stimulus was applied. Difference threshold values did not show a statistically significant between group difference for the cAD task with 100 μm standard stimulus and 300 μm masking stimulus (p=0.55). (Table 3.3, Figure 3.2)

In the third amplitude discrimination step which had a standard stimulus of 200 μm and a test stimulus of 450 μm, the mean difference threshold of the TS group was 206.6 ± 95.0 μm (n=24) and 200.3 ± 64.7 μm (n=19) for the control group

when the 300 μm adaptive masking stimulus was applied. Difference threshold values did not show a statistically significant between group difference for the cAD task with 200 μm standard stimulus and 300 μm masking stimulus (p=0.80). (Table 3.3, Figure 3.2)

- **Paired Changes in Difference Thresholds due to adaptation (AD_d)**
  Results: Paired changes in difference thresholds (AD_d) due to adaptation were calculated by subtracting the baseline difference threshold (AD) value of a subject from that subject's 100 μm and 300 μm cAD difference threshold values. Missing data resulted from non-convergent staircases or omission of outliers. (Table 3.4, Figure 3.3)

  In the first amplitude discrimination step where the standard stimulus was 50 μm and the test stimulus was 150 μm, the mean paired change in the JNDs for the TS group was 29.3 $\pm$ 38.5 μm (n=21) and 19.1 $\pm$ 21.9 μm (n=18) for the control group when the masking stimulus had an amplitude of 100 μm. Between group comparison did not reveal a statistically significant difference for the 100 μm masking condition in the first step for AD_d (p=0.32). For the 300 μm masking condition, the mean paired change in the JNDs for the TS group was 32.2 $\pm$ 40.5 μm (n=20) and 55.8 $\pm$ 27.7 μm (n=17) for the control group in the first step. Between group comparison revealed a quasi-significant statistical difference for the 300 μm masking condition of the first step for the paired change group means (p=0.050). (Table 3.4, Figure 3.3)

  In the second amplitude discrimination step where the standard stimulus was 100 μm and the test stimulus was 200 μm, the mean paired change in the JNDs for the TS group was 70.2 $\pm$ 42.3 μm (n=27) and 77.59 $\pm$ 43.2 μm (n=19) for the control group when the masking stimulus had an amplitude of 100 μm. Between group comparison did not reveal a statistically significant difference for the 100 μm masking condition in the second step for AD_d (p=0.56). For the 300 μm masking condition, the mean paired change in the JNDs for the TS group was 53.5 $\pm$ 49.5 μm (n=21) and 60.8 $\pm$ 58.0 μm (n=19) for the control group in the second step. Between group comparison did not reveal a statistically significant difference for the 300 μm masking condition in the second step for

AD_d (p=0.67). (Table 3.4, Figure 3.3)

In the third amplitude discrimination step where the standard stimulus was 200 μm and the test stimulus was 450 μm, the mean paired change in the JNDs for the TS group was 106.1 ± 92.0 μm (n=24) and 114.3 ± 50.0 μm (n=16) for the control group when the masking stimulus had an amplitude of 100 μm. Between group comparison did not reveal a statistically significant difference for the 100 μm masking condition in the third step for AD_d (p=0.74). For the 300 μm masking condition, the mean paired change in the JNDs for the TS group was 113.8 ± 94.1 μm (n=22) and 145.5 ± 60.2 μm (n=16) for the control group in the third step. Between group comparison did not reveal a statistically significant difference for the 300 μm masking condition in the third step for AD_d (p=0.24). (Table 3.4, Figure 3.3)

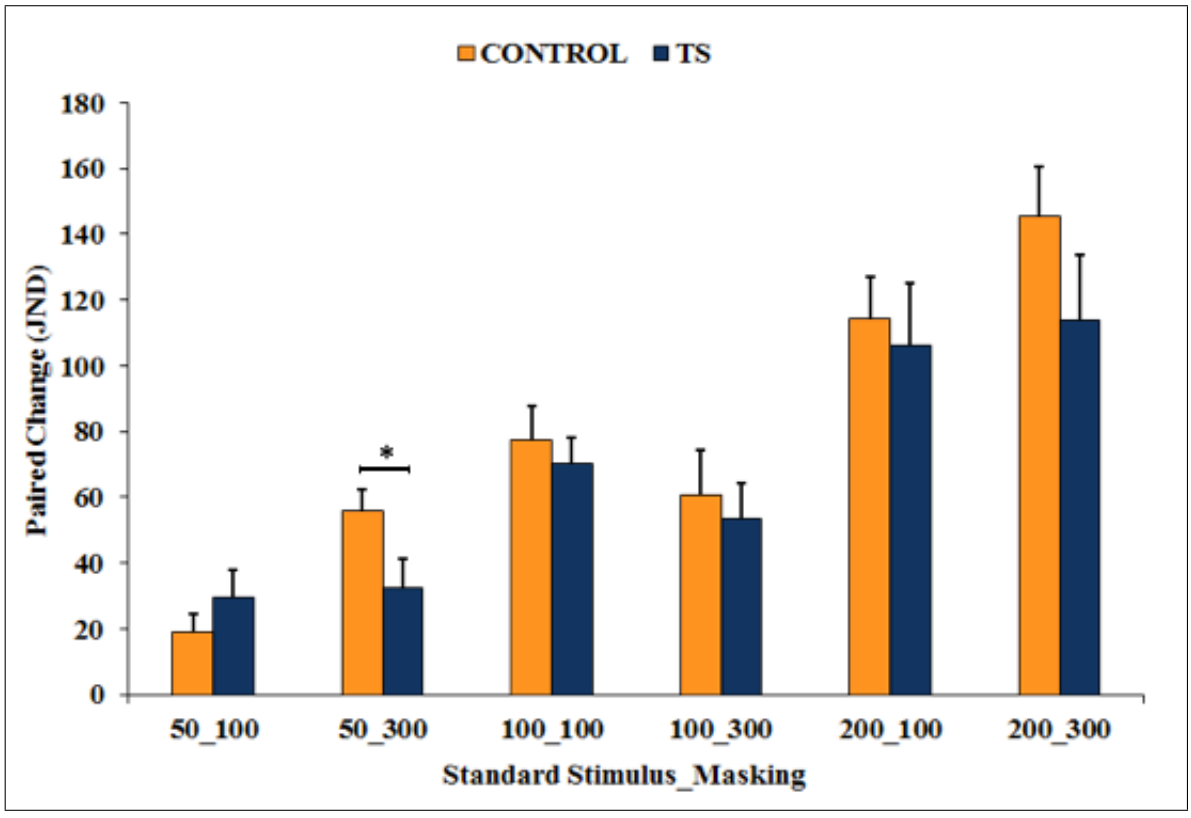

Figure 3.3 Paired changes in difference thresholds due to adaptation (AD_d) for TS and Control groups. Blue columns represent the TS group and orange columns represent the control group. Error bars are the standard error of the means. Statistically significant difference is marked with asterisk sign. (*; p<0.05)

3.3.4 Weber Fraction Results

Weber fractions here are given as the ratio of a subject's difference threshold (JND) in an AD or cAD task to that task's standard stimulus, which was either 50 μm, 100 μm or 200 μm as stated above. Missing data resulted from non-convergent staircases or omission of outliers. Results are listed as mean Weber fraction ± standard deviation in Table 3.5 and plotted in Figure 11 for the TS group and in Figure 12 for the control group.

In the first amplitude discrimination step where the standard stimulus was 50 μm and the test stimulus was 150 μm, the group mean of the Weber fraction values was 0.72 ± 0.33 (n=24) for the TS group and 0.44 ± 0.17 (n=22) for the healthy controls in the baseline condition. Mean Weber fraction values showed a statistically significant between group difference for the 50 μm baseline condition (**p=0.0009**). (Table 3.5, Figure 3.4, Figure 3.5)

When the 100 μm masking stimulus was presented in the first amplitude discrimination step, the group mean of the Weber fraction values was 1.37 ± 0.76 (n=25) for the TS group and 0.76 ± 0.39 (n=21) for the healthy controls. Mean Weber fraction values showed a statistically significant between group difference in the first step for the 100 μm masking condition as well (**p=0.0018**). ((Table 3.5, Figure 3.4, Figure 3.5)

When the 300 μm masking stimulus was presented in the first amplitude discrimination step, the group mean of the Weber fraction values was 1.30 ± 0.70 (n=23) for the TS group and 1.42 ± 0.61 (n=20) for the healthy controls. Between group comparison of the Weber fraction group mean values did not reveal a statistically significant difference for the 300 μm masking condition in the first step (p=0.55). (Table 3.5, Figure 3.4, Figure 3.5)

In the second amplitude discrimination step where the standard stimulus was 100 μm and the test stimulus was 200 μm, the group mean of the Weber fraction values

was 0.54 ± 0.30 (n=29) for the TS group and 0.38 ± 0.14 (n=21) for the healthy controls in the baseline condition. Mean Weber fraction values showed a statistically significant between group difference for the 100 μm baseline condition as well (**p=0.02**). (Table 3.5, Figure 3.4, Figure 3.5)

When the 100 μm masking stimulus was presented in the second amplitude discrimination step, the group mean of the Weber fraction values was 1.25 ± 0.56 (n=28) for the TS group and 1.15 ± 0.52 (n=23) for the healthy controls. Mean Weber fraction values did not show a statistically significant between group difference in the second step for the 100 μm masking condition (p=0.51). (Table 3.5, Figure 3.4, Figure 3.5)

When the 300 μm masking stimulus was presented in the second amplitude discrimination step, the group mean of the Weber fraction values was 1.07 ± 0.58 (n=22) for the TS group and 0.96 ± 0.61 (n=23) for the healthy controls. Between group comparison of the Weber fraction group mean values did not reveal a statistically significant difference for the 300 μm masking condition in the second step (p=0.53). (Table 3.5, Figure 3.4, Figure 3.5)

In the third amplitude discrimination step where the standard stimulus was 200 μm and the test stimulus was 450 μm, the group mean of the Weber fraction values was 0.43 ± 0.21 (n=28) for the TS group and 0.31 ± 0.14 (n=19) for the healthy controls in the baseline condition. Mean Weber fraction values showed a statistically significant between group difference for the 200 μm baseline condition as well (**p=0.03**). (Table 3.5, Figure 3.4, Figure 3.5)

When the 100 μm masking stimulus was presented in the third amplitude discrimination step, the group mean of the Weber fraction values was 0.95 ± 0.45 (n=26) for the TS group and 0.86 ± 0.22 (n=20) for the healthy controls. Mean Weber fraction values did not show a statistically significant between group difference in the third step for the 100 μm masking condition (p=0.41). (Table 3.5, Figure 3.4, Figure 3.5)

When the 300 μm masking stimulus was presented in the third amplitude discrimination step, the group mean of the Weber fraction values was 1.03 ± 0.48 (n=24) for the TS group and 1.00 ± 0.32 (n=19) for the healthy controls. Between group comparison of the Weber fraction group mean values did not reveal a statistically significant difference for the 300 μm masking condition in the third step (p=0.81). (Table 3.5, Figure 3.4, Figure 3.5)

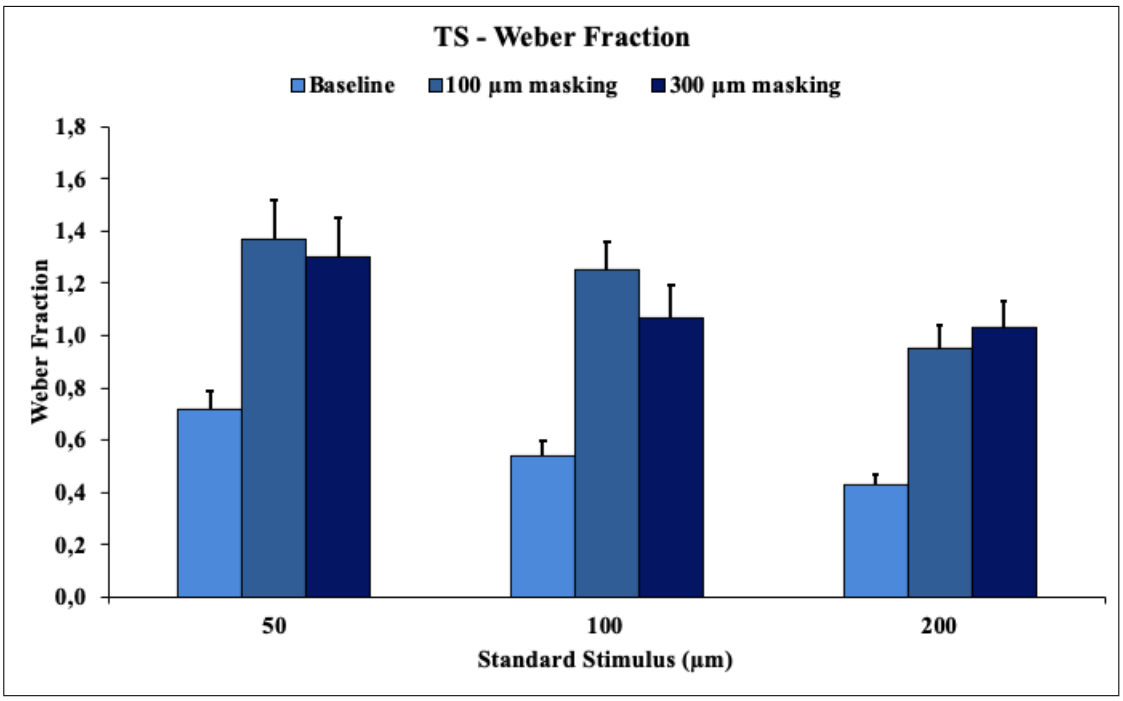

Figure 3.4 Mean Weber fraction values for the Tourette group. Error bars are the standard error of the means.

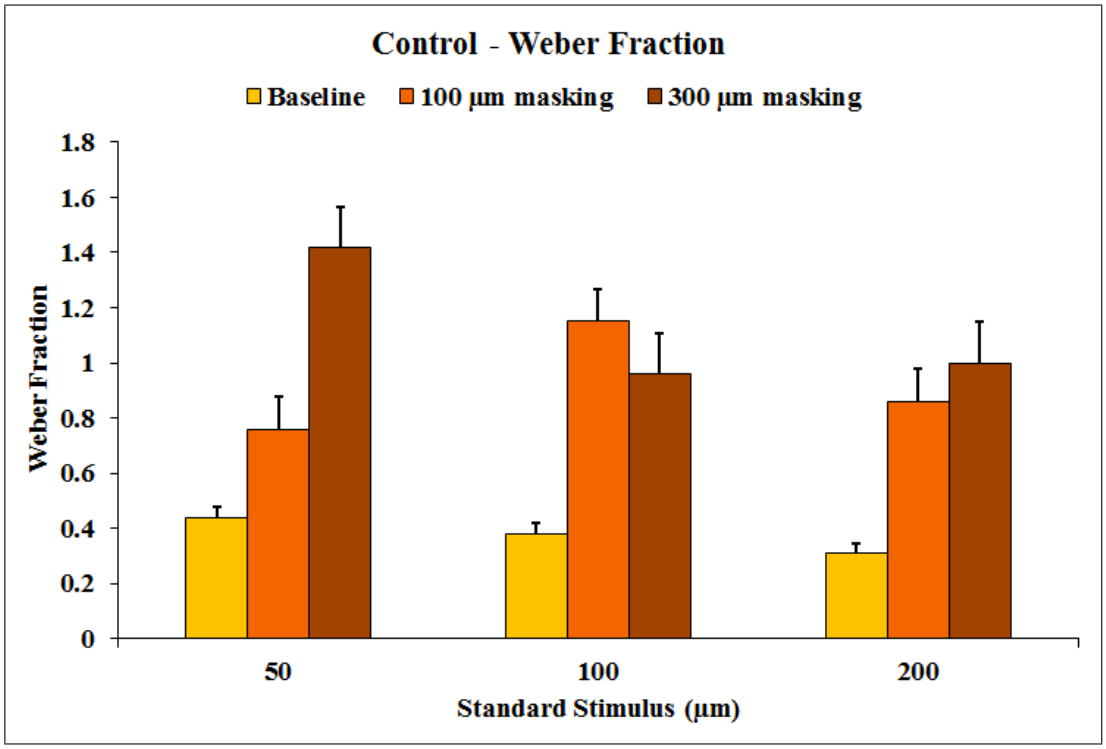

Figure 3.5 Mean Weber fraction values for the control group. Error bars are the standard error of the means.

Table 3.3
Psychophysical test battery results for TS group and the control group. The results are given as means and standard deviations. TS: Tourette Syndrome group, cRT: Choice Reaction Time, DT_c : Dynamic Detection Threshold (corrected for cRT), DT_s : Static Detection Threshold (corrected for the standard stimulus), DT_d : Change in the Detection Threshold due to adaptation, JND: Just Noticeable Difference, AD: JND in Amplitude Discrimination, cAD: JND in Amplitude Discrimination with single-site adaptaion.

	TS Group N=30	Control Group N=25	Test Statistic	p
Choice Reaction Time cRT (ms)	795.6 ±245.4	900.6 ±312.9	t test	0.17
Detection Thresholds				
DT_c (μm	10.5 ±3.3	11.1 ±3.4	t test	0.47
DT_s (μm)	7.4 ±2.0	6.8 ±2.2	t test	0.35
DT_d (μm)	3.44 ±2.97	3.80 ±3.96	t test	0.73
JNDs in AD & cAD Tasks				
AD (μm; std=50 μm)	21.8 ±8.7	36.2 ±16.4	t test	**0.0007**
cAD (μm) (std=50 μm, mask=100μm)	37.9 ±19.4	66.6 ±38.4	t test	**0.0033**
cAD (μm) (std=50 μm, mask=300μm)	70.7 ±30.5	64.9 ±34.9	t test	0.56
AD (μm; std=100 μm)	38.0 ±13.5	54.0 ±29.8	t test	**0.026**
cAD (μm) (std=100 μm, mask=100μm)	114.9 ±52.3	125.2 ±55.6	t test	0.49
cAD (μm) (std=100 μm, mask=300μm)	96.3 ±60.9	106.8 ±58.2	t test	0.55
AD (μm; std=200 μm)	61.7 ±27.2	86.6 ±42.9	t test	**0.03**
cAD (μm) (std=200 μm, mask=100μm)	172.9 ±44.0	189.5 ±89.2	t test	0.45
cAD (μm) (std=200 μm, mask=300μm)	200.3 ±64.7	206.6 ±95.0	t test	0.80

Table 3.4
Psychophysical test battery results for TS group and the control group (continued). AD_d : Paired change in JND due to adaptation.

	TS Group N=30	Control Group N=25	Test Statistic	p
AD_d (μm) (std=50 μm, mask=100μm)	19.1 ±21.9	29.3 ±38.5	t test	0.32
AD_d (μm) (std=50 μm, mask=300μm)	55.8 ±27.7	32.2 ±40.5	t test	0.050
AD_d (μm) (std=100 μm, mask=100μm)	77.59 ±43.2	70.2 ±42.3	t test	0.56
AD_d (μm) (std=100 μm, mask=300μm)	60.8 ±58.0	53.5 ±49.5	t test	0.67
AD_d (μm) (std=200 μm, mask=100μm)	114.3 ±50.0	106.1 ±92.0	t test	0.74
AD_d (μm) (std=200 μm, mask=300μm)	145.5 ± 60.2	113.8 ±94.1	t test	0.24

Table 3.5
Weber fractions for the corresponding Amplitude Discrimination or Amplitude Discrimination with Single-site Adaptation tasks for TS and control groups. The results are given as group means and standard deviations. TS: Tourette Syndrome group, AD: Weber fraction in Amplitude Discrimination, cAD: Weber fraction in Amplitude Discrimination with single-site adaptation.

	TS Group N=30	Control Group N=25	Test Statistic	p
AD (μm; std=50 μm)	0.72 ±0.33	0.44 ±0.17	t test	**0.0009**
cAD (μm) (std=50 μm, mask=100μm)	1.37 ±0.76	0.76 ±0.39	t test	**0.0018**
cAD (μm) (std=50 μm, mask=300μm)	1.30 ±0.70	1.42 ±0.61	t test	0.55
AD (μm; std=100 μm)	0.54 ±0.30	0.38 ±0.14	t test	**0.02**
cAD (μm) (std=100 μm, mask=100μm)	1.25 ±0.56	1.15 ±0.52	t test	0.51
cAD (μm) (std=100 μm, mask=300μm)	1.07 ±0.58	0.96 ±0.61	t test	0.53
AD (μm; std=200 μm)	0.43 ±0.21	0.31 ±0.14	t test	**0.03**
cAD (μm) (std=200 μm, mask=100μm)	0.95 ±0.45	0.86 ±0.22	t test	0.41
cAD (μm) (std=200 μm, mask=300μm)	1.03 ±0.48	1.00 ±0.32	t test	0.81

4. CONCLUSION

4.1 Summary of the Main Findings

This study investigated sensory sensitivity and somatosensory processing in children with TS and their age- and sex-matched healthy controls in both behavioral and psychophysical dimensions.

In behavioral assessments through questionnaires, TS and the control group showed similar trends in overall sensory sensitivity (p=0.36), in sensitivity to sense of touch (p=0.98), and the emotional/social intervention of sensory stimuli in their daily lives (p=0.33); however TS group showed a significantly stronger tactile defensiveness in comparison to the healthy controls (p=**0.03**).

Both groups performed similar in the psychophysical assessments of the reaction times (p=0.17), had comparable detection thresholds (DT_s ; p=0.35, DT_c ; p=0.47) and showed comparable increments in detection thresholds due to adaptation (DT_d ; p=0.73).

In all of the baseline Amplitude Discrimination tasks Tourette group had significantly higher difference thresholds (50 μm; p=**0.0007**, 100 μm; p=**0.026**, 200 μm; p=**0.03**), yet in all Amplitude Discrimination with single-site adaptation tasks, TS and the control groups produced comparable difference thresholds (p>0.05), except for the 100 μm-masking condition in the first Amplitude Discrimination step which had a standard stimulus of 50 μm where TS group had again significantly higher difference thresholds (p=**0.0033**).

When the adaptive effect of the masking stimuli was analyzed by comparing the baseline conditions with the 100 μm- and 300 μm masking conditions of each corresponding Amplitude Discrimination step, there was no statistically significant between

group difference in the changes in difference thresholds due to adaptation ($p \geq 0.05$). However, in the first Amplitude Discrimination step which had a standard stimulus of 50 μm, when the 300 μm masking condition was compared with the baseline condition, between group comparison showed a marginally significant statistical difference in difference thresholds due to the adaptive effect of the 300 μm masking stimulus where the TS group had a higher increment when compared with healthy controls ($p=0.050$).

When the Weber fractions from each Amplitude Discrimination task were compared, TS group showed significantly higher Weber fractions in all of the baseline conditions when compared with the healthy controls (50 μm; p=**0.0009**, 100 μm; p=**0.02**, 200 μm; p=**0.03**) and also for the 100 μm masking condition in the first Amplitude Discrimination step which had a standard stimulus of 50 μm (p=**0.0018**). For both TS and the control group, the suggested constancy of Weber fraction was less prominent for the baseline Amplitude Discrimination conditions and more prominent for the Amplitude Discrimination with single-site adaptation conditions towards higher standard stimulus amplitudes, particularly in the second and third steps.

These results stand in favor of the reduced GABAergic adaptation in patients with TS hypothesis, as the TS group produced significantly larger difference thresholds in the baseline Amplitude Discrimination conditions, and even though both groups produced larger difference thresholds due to the adaptive effect of masking stimuli in the Amplitude Discrimination with single-site adaptation tasks, the effect of adaptation was more prominent in healthy controls, causing higher increments in healthy controls' difference thresholds which in turn closed the gap between the mean group difference thresholds in all but one cAD conditions ($p>0.05$). Interestingly, mean changes in difference thresholds due to adaptation did not show any statistically significant between group difference as one would expect from the presented AD and cAD results. This may be due to within group variances in TS group since the group had a broad age range and the influence of TS tend to lessen as the patients progress into adulthood, as well as other factors such as the comorbidities and medication status of the subjects.

4.2 Behavioral Responses of Children with Tourette Syndrome

The Tourette group in this study had a mean motor tic score of 10.25 ± 4.78 (out of 25), a mean vocal tic score of 5.92 ± 5.94 (out of 25), a mean impairment score of 22.14 ± 9.29 (out of 50) in YGTSS, and a mean total YGTSS score of 38.32 ± 17.82 (out of 100); hence showing 'mild' tic severity which signifies minor difficulties in daily life functioning [10]. Thomalla et al. (2009) found tic severity to be inversely correlated with regional fractional anisotropy in the somatosensory pathways in patients with TS, where fewer tics were thought to imply an alteration in white matter microstructure for the sake of an adaptive reorganization of the somatosensory processing [52].

Sensory Profile data showed no statistically significant difference between TS and health controls in neither overall sensory sensitivity (p=0.12), in sensitivity to sense of touch (0.84) nor in the emotional/social intervention of sensory stimuli in subjects' daily lives (p=0.11). However, another study in which a pure TS population was compared with a TS + ADHD population, found Sensory Profile scores to be significantly different across all sensory modalities, hence suggesting a strong effect of comorbid disorders on a subject's sensory sensitivity (Needham, 2013).

The Touch Inventory for Elementary-School-Aged Children (TIE) scores revealed a significantly stronger tactile defensiveness in TS group when compared with the healthy controls (p=0.03). In two other studies which also adopted TIE as a tactile defensiveness measure on psychiatrically compromised populations such as OCD [3], and autism [2] patients, there was no significant difference between the tested groups and healthy controls, which may suggest a higher sensitivity to tactile sensation in TS patients.

4.3 Psychophysical Comparisons

4.3.1 Choice Reaction Time Comparisons

Choice Reaction Time values which were obtained through a two-alternative forced choice reaction time task were higher for the TS group, however between group difference was not statistically significant (p=0.17) which suggests normal attention in children with TS. However, the mean choice reaction time values were at least 100-ms longer for both TS and healthy control subjects in this study when compared to two other studies which used the same device for the same task on TS [4] and OCD [3] patients and their age- and sex-matched healthy controls, in which psychiatrically compromised subjects produced comparable Choice Reaction Time values as well (p>0.05).

4.3.2 Static and Dynamic Detection Threshold Comparisons

Mean Static Detection Threshold (DT_s) values and mean Dynamic Detection Threshold (DT_d) values were comparable between the TS and control groups (DT_s ; p=0.35, DT_d ; p=0.47). Existing literature suggests the response of TS patients to weak sensory stimuli to be different when compared to that of the healthy subjects [67, 13], which may either cause TS patients to produce higher (static) detection thresholds [4] or may be an outcome of an altered central processing as perceived intensity, rather than enhanced peripheral detection [67]. TS group in this study had lower, yet statistically comparable Static Detection Threshold values (p=0.35) and is in favor of the latter suggestion which is further supported by our TIE data.

Even though an increment in detection thresholds due to feedforward inhibitory neural mechanisms were observed in both groups in the Dynamic Detection Threshold tasks and the TS group showed a slightly higher increment in detection thresholds, mean changes in detection thresholds were not found to be statistically significant between the groups (p=0.73). These results are contradictory to the results of the study by Puts et al. (2015) in which the same comparison was performed on a different set

of children with TS and their age- and sex-matched healthy controls. In the aforementioned study there was a statistically significant between group difference in the mean Static Detection Threshold values where TS group had higher detection thresholds ($p<0.05$) and the mean Dynamic Detection Threshold values were found to be comparable between the groups ($p=0.31$), hence suggesting a deficit in feedforward inhibitory adaptation mechanisms for the TS population [4].

4.3.3 Just Noticeable Difference Comparisons for Amplitude Discrimination Tasks

In all of the baseline Amplitude Discrimination tasks, TS group produced significantly higher difference thresholds (50 μm; p=**0.0009**, 100 μm; p=**0.02**, 200 μm; p=**0.03**). This condition repeated itself for the Amplitude Discrimination with single-site adaptation task which had a standard stimulus of 50 μm and a masking stimulus of 100 μm, in which TS group again had significantly higher difference thresholds (p=**0.0033**). However, in all other Amplitude Discrimination with single-site adaptation tasks both groups produced comparable difference thresholds ($p>0.05$). Even though both groups produced higher difference thresholds due to the adaptive effect of masking stimuli which were applied prior to the test stimuli, the increments in difference thresholds due to adaptation was higher for the healthy controls, closing the gap between the groups (Table 3). Puts et al. (2015) showed the difference thresholds in the baseline Amplitude Discrimination task with 100 μm- standard stimulus to be comparable in a different set of TS and healthy control participants ($p=0.68$), who produced significantly different JNDs in the Amplitude Discrimination with single-site adaptation task which had a standard stimulus of 100 μm and a masking stimulus of 100 μm amplitude ($p<0.02$). In the aforementioned study, healthy controls produced significantly higher difference thresholds due to the adaptive effect of the masking stimulus. Both results support the hypothesis of disrupted inhibitory and adaptive mechanisms in TS, implicating a GABAergic dysfunction [4].

Curiously, comparison of the mean changes in JNDs due to adaptation showed

no statistically significant difference between the groups ($p \geq 0.05$). This may be due to the within group variability in TS population which participated in this study. Especially the wide age range (8 - 17 years) since the TS symptoms are known to be reduced or diminished throughout the adolescence and during the adulthood which is thought to be due to cerebral adaptation, and the variability between the pure TS subjects and TS subjects with comorbid ADHD and/or OCD, may have caused TS group to produce comparable mean JNDs in this study [30, 7, 22, 27]. In the current study, adaptive effects of two different masking stimulus amplitudes (100 μm & 300 μm) were assessed, hypothesizing that stronger masking stimulus would produce a stronger adaptive change in the JNDs. Interestingly, both masking stimulus amplitudes produced similar increments in JNDs, and in the amplitude discrimination tasks which had a standard stimulus of 100 μm, a lower mean increment in difference thresholds was observed in both TS and healthy subjects when the stronger masking stimulus was applied. These results may indicate a saturation in tactile adaptation in both healthy and psychiatrically compromised populations and further research which assesses the effects of different masking stimulus amplitudes is required to investigate this hypothesis. (Table 3.3)

4.3.4 Weber Fractions and the Applicability of the Weber's Law

A Weber fraction is calculated by dividing a difference threshold by the corresponding task's standard stimulus and is suggested to be a constant for a range of stimulus intensities in a variety of sensory modalities [1, 63, 64, 65]. As the Weber fraction value correlates linearly with the standard stimulus amplitude, it can be used as a measure of neural health [1, 69]. Francisco et al. (2008) investigated the relationship between the difference threshold and standard stimulus amplitudes via a vibrotactile battery similar to the battery of this study in healthy adults and found a strong positive correlation between the two quantities ($R^2 = 0.99771$). Aforementioned study also showed that Weber fraction values tend to show a trend towards constancy at higher standard stimulus amplitudes (standard stimulus$\geq$300 μm, Weber fractions by Francisco et al. (2008) are expressed as % differences in Figure 4.1) [1]. The data

from this study also showed a reduction in Weber fraction values as the standard stimulus amplitude increased, however both groups produced larger Weber fractions in the baseline Amplitude Discrimination tasks in comparison to the data from Francisco et al. (2008), and in this study Weber fractions of the TS group were significantly larger than the healthy controls' Weber fraction values (Table 3.5). This may be due to the age difference between the subjects, as an adult population had participated in their study and this study was conducted on children and adolescents.

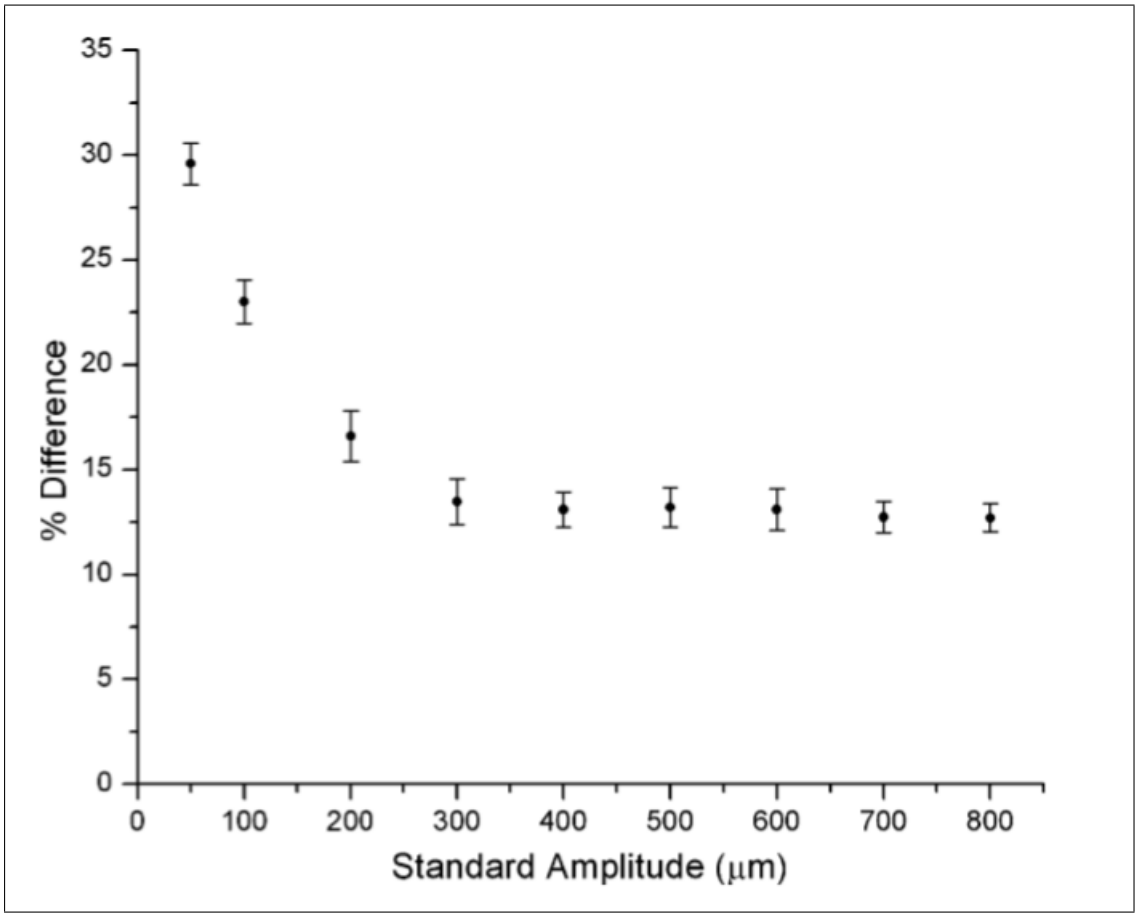

Figure 4.1 Weber fractions (as % difference) plotted against standard stimulus amplitudes by Francisco et al. (2008).

To the best of my knowledge, this is the first study to investigate the effect of different masking stimuli on Weber fractions in a psychiatrically compromised population. In the TS group both masking stimuli increased the Weber fraction values and their values decreased as the standard stimulus values increased similar to the aforementioned study. This pattern was not observed in the healthy controls and the effect of the masking stimuli on Weber fractions was irregular within the applied standard

stimulus range (Table 3.5). The adopted standard stimulus range may not be sufficient to demonstrate the constancy of Weber fraction if that trend can be more prominently observed for higher standard stimulus amplitudes for the tactile sense. Overall, these Weber fraction results may imply a higher than normal tactile sensitivity in TS as they performed better in the lower adaptation steps as well. Further research with a wider standard stimulus amplitude range with a more homogeneous patient group is required to clarify this hypothesis.

5. Limitations & Future Work

This study had a moderate sample size and a broad age range which may influence the investigated quantities since symptoms, hence the influence, of the Tourette Syndrome tend to decrease or diminish as the patients progress into adulthood. Apart from the age, factors such as comorbid disorders, gender, and medication status can also affect the questioned measures. Moreover, this study was a pediatric study and it was limited by the shorter attention span of children which produced some missing data. Also, only three standard stimulus amplitudes were investigated in this study since a study with more standard stimulus amplitudes would not be tolerable for pediatric subjects. Taking the skin decoupling which takes place for strong stimulus amplitudes and deforms the sinusoidal wave property of the stimuli, further research with a larger sample size is required to assess other standard stimulus amplitudes, along with the effects of different masking stimulus amplitudes, and within group variances is required to have a better understanding on the investigated qualities in this study.

5.1 List of publications produced from the thesis

1. Vibrotactile adaptation and Weber's Law in children with Tourette Syndrome, U. Eşen, H. Doktur, C. Tanıdır, M. Tommerdahl, B. Güçlü, *Society for Neuroscience, SfN, Neuroscience 2018 - Annual Meeting of Society for Neuroscience*, (San Diego, USA), 2018.

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