

Investigating sensory phenomena and
alterations in brain structure in
Tourette syndrome using a multi-
modality framework.

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T hesis abstract

Tourette syndrome (TS) is a childhood onset, hyperkinetic movement disorder, characterised by inappropriate motor tics and vocalisations. TS affects approximately 1% of children and adolescents aged 5-18 years, while rates are much lower in young adults. In addition to tics, patients report feelings of uncomfortable inner bodily and cognitive sensations termed premonitory sensory phenomena (PSP), which exacerbate during the inhibition of tics. Furthermore, patients with TS report having increased sensitivity to sensory inputs across all sensory modalities but in the absence of any differences in sensory thresholds measured using objective methods.

Most studies to date have measured affective touch thresholds in adult patients only, and therefore limited inference can be made in younger patients. In addition, the neural substrates of PSP are not well understood but possibly emerge due to improper sensorimotor gating mechanisms and altered function of cortico-basal ganglia circuits. The epicentre of this might also be the insular cortex, which is responsible for the detection, awareness and relaying information about sensory input to higher cortical areas.

The primary focus of this thesis is on sensory phenomena and the alteration in brain structure in young people with TS, and is laid out in 4 experimental chapters. Using a multi-modal framework this work had two aims. The first aim was to investigate if and why young patients with TS demonstrate sensory amplification to sensory input. To achieve this, I gathered data on tactile sensory thresholds using a set of Von Frey monofilaments and determined sensory thresholds using psychometric function fitting, and sensitivity and response bias using signal detection theory. Furthermore, I employed transcranial magnetic stimulation (TMS) to ascertain differences in cortical maps between patients and healthy volunteers. Using this data, I was able to make inference of the location, distance between and the size of several muscle

representations on the sensorimotor cortex and ask the question if any ‘remapping’ of these representations could explain perceived sensitivity to sensory inputs.

The second aim of this thesis was to investigate the relationship between PSP and brain structure. To achieve this, I first acquired data using diffusion tensor imaging (DTI) to make inferences on the structural connectivity of white matter. Secondly, I used high-resolution structural imaging to measure volume of cortical grey matter. Analyses were performed using whole-brain exploratory methods, network-based methods and pattern recognition methods. The results show marked differences on a global scale but also very specific and focal differences in key areas of the brain, which correlated with the frequency and severity of PSP in patients with TS.

This thesis concludes with a discussion, which summarises and integrates all results presented. The text is organised according to three major discussion points, and reviews similarities between the present results and the current knowledge of PSP in TS. Moreover, the chapter also briefly discusses the similarities between TS, and the symptoms and the neural substrates of individuals with sensory processing disorders.

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I think it is appropriate to end this with the chorus from an Icelandic song, which title translates to “The end of a journey”:

*“Sól slær silfri á voga, sjáið jökulinn loga.
Allt er bjart fyrir okkur tveim, því ég er kominn heim.
Að ferðalokum ég finn þig sem mér fangar höndum tveim.
Ég er kominn heim, já ég er kominn heim.”*

Name: Ferðalok, author: Óðinn Valdimarsson

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CHAPTER 1

Chapter One – A general introduction to Tourette syndrome and the associated sensory abnormalities

1.1 THESIS OVERVIEW AND INTRODUCTION

Hyperkinetic movement disorders are characterised by excessive, out-of-the-ordinary movements often observed in children with neurological disorders (Sanger et al., 2010). Most common movement disorders related to the term ‘hyperkinetic’ are dystonia, chorea, tremor, tics and stereotypies (Sanger et al., 2010). In school-aged children and adolescence, the prevalence of tics is thought to range between 16-21% (Cubo et al., 2011; Kurlan et al., 2002). Several subtypes of tic disorders have been described such as provisional tic disorders, persistent tic disorders and Tourette syndrome (TS) (APA, 2013). TS is of prime interest in this thesis. TS is commonly (as with other hyperkinetic movement disorders) associated with motor impairments, but in recent years significant interest has risen regarding the sensory aspects of the syndrome (Leckman, Walker, & Cohen, 1993; Patel, Jankovic, & Hallett, 2014; Ruhrman et al., 2017; Weisman et al., 2018).

In this thesis I focus specifically on these sensory aspects in TS. Even though sensory symptoms have been associated with TS for a long time (Patrick, 1905), this still remains a fairly underrepresented subject of study in the literature. Specifically, the occurrence and clinical characteristics as well as the neural correlates of sensory phenomena in TS remains relatively unknown.

The first aim of this thesis was to investigate *if* and *why* affective touch thresholds are altered in young people with TS. To date such questions have primarily been applied

in adult samples of patients while no study has investigated why patients report or show heightened sensitivity to sensory stimuli. These two questions are answered in Chapters 3 and 4. In Chapter 3 I investigate affective touch thresholds in patients and a group of healthy volunteers. Sensory thresholds were quantified using psychometric functions, while measures of sensitivity and response bias are calculated using signal detection theory. In Chapter 4 I employed *transcranial magnetic stimulation* (TMS) and a novel brain mapping technique to locate and outline muscle representations on the sensorimotor cortex (SM), and relate these measures to data on cortical inhibition, sensory amplification and interoceptive awareness.

The second aim of this thesis was to investigate the relationship between sensory phenomena and brain structure. Two studies were conducted and are presented in Chapters 5 and 6. These studies focus specifically on the structural connectivity of white matter (WM) and the volume of grey matter (GM). Structural connectivity was quantified using data from diffusion tensor imaging (DTI), and analysed using whole-brain tract-based spatial statistics (TBSS) and graph theory. The volume of GM was acquired using high-resolution structural neuroimaging measured at two different timepoints, spaced one year apart. The data was analysed using a whole-brain exploratory method and pattern recognition in the hope of identifying neuroimaging biomarkers which could give an indication of syndrome progression.

The thesis concludes with a discussion chapter which summarises and integrates all the results.

1.2 A BRIEF HISTORY OF TOURETTE SYNDROME AND ITS CLINICAL FEATURES

Jean Marc Itard, a French physician, was the first to describe a case of what is now known as TS (Itard, 1825). Itard described a female patient who presented symptoms of coprolalia (uttering of socially inappropriate vocalisation) in addition to multiple motor and vocal tics. This was further iterated by George Gilles de la Tourette in his seminal work “maladie des tics” in 1885, where he added that TS is a motor disorder, in addition to symptoms of impulsivity and echophenomena (Tourette, 1885).

According to the Diagnostic and Statistical Manual (DSM-5; APA, 2013) diagnosis of TS is given when the patient presents multiple motor and at least one vocal tic for a duration of one year, prior to the age of 18 years. TS is characterised by a waxing and waning course of symptoms, which is also taken into account during diagnosis (Leckman, 2002; Singer, 2005). Symptoms must also not be induced or brought about by an underlying illness or medication (APA, 2013). Few reliable biomarkers for clinical diagnosis of TS exist and consequently TS could be misdiagnosed, while many patients in the general public might never get a diagnosis (Robertson, 2008). The misdiagnosis might be due to the disorder's complicated and multifaceted clinical feature (Cavanna & Seri, 2013), while in some instances diagnosis is delayed due to the lack of knowledge of physicians on TS (Debes, Hjalgrim, & Skov, 2008).

1.2.1 Tics

Tics are recurrent and rigid voluntary motor movements or vocal outbursts that appear to serve no purpose or function but are often analogous to normal movement (e.g., eye-blinks) (Leckman, 2002; Robertson et al., 2017; Singer, 2005). Tics also occur in bouts, many times a day, with varying intervals. Patients often note that tics are exacerbated during stress, while also some tics can be quite forceful and cause injury (Robertson et al., 2017). Tics have also been known to subside during focused control such as when playing instruments or playing sports (Robertson et al., 2017).

Tics can be categorised as being either simple or complex (Jankovic, 2001; Tallur & Minns, 2010). *Simple motor* tics are short-lasting and often meaningless actions (e.g., twitch of a single muscle) where the most common simple tics are eye-blinks. Simple tics can be further described as clonic tics (sudden jolting movements), dystonic tics (abnormal postures) and tonic tics. *Complex motor* tics include excessive head shaking, throwing, jumping, kicking and making obscene gestures (copropraxia) or imitating gestures of others (echopraxia). Complex motor tics involve a group of muscles which appear to act in a coordinated pattern (Leckman, 2002). *Simple vocal* tics are short utterances (words, statements or sounds) such as sniffing and throat clearing. Lastly, coprolalia (shouting obscenities), echolalia (imitating sounds of others) and palilalia (repeating one's own words) are viewed as *complex vocal* tics. Importantly, complex

vocal tics are rare and only occur in approximately 10-15% of patients (Jankovic, 2001; Singer, 2005).

Appearance and severity of tics is highly variable across individuals. However, motor tics commonly emerge first around the age of ~5-7 years, while majority of patients get a confirmed clinical diagnosis prior to the age of 10 (Freeman et al., 2000; Robertson, 2012). Vocal tics usually follow the onset of motor tics by few years (Robertson, 2012; Singer, 2005). Tics are most commonly reported in the eyes, followed by the face and neck areas, and then upper and lower limbs (Ganos, Bongert, et al., 2015). Tics are consciously felt prior to execution, while the voluntariness of tics has been debated (Cavanna & Nani, 2013). One participant of mine gave me an excellent description of his tics capturing this notion nicely:

“My tic experience can be likened to a flickering lightbulb. This is how I feel my brain is doing. Each flicker of the lightbulb is like a signal, a signal telling me to execute a tic, and I can’t do anything to stop it... I want it to stop but I cannot control it!” Anonymous.

This description also gives rise to the notion that TS can be viewed as a disorder of impaired self-agency (which is the sensation of being in control of your actions and their consequences) (Farrer et al., 2003) or the feeling of lost control over self-generation actions (Delorme et al., 2016).

As noted above, tics are distinguishable from other similar hyperkinetic movements such as myoclonus, chorea, tremor or dystonia because of three important aspects (Sanger et al., 2010): (1) tics are experienced as (in)voluntary movements, (2) tics can be suppressed for several minutes, where tic suppression is most successful in areas where tics are uncommon (Ganos, Bongert, et al., 2015), and (3) tics are preceded by or associated with premonitory sensory phenomena (PSP). PSP, in addition to other sensory phenomena. This is described in detail in subsection 1.3.

Briefly, the externally apparent symptoms of TS (i.e., tics) are often socially debilitating and embarrassing for the patient, who is often forced to hide his/hers tics from the public and in the classroom. As such, TS can have a harmful impact on the patients everyday social interactions and functioning (Cath et al., 2011). Inhibiting the

externally apparent symptoms causes uncomfortable and often painful cognitive and bodily sensations, which build up until the patient is forced to “let go” and perform the tic(s), in which case they become more forceful than otherwise (Hollenbeck, 2003). These PSP have been likened to an itch or the irresistible and often uncomfortable feeling that precedes the onset of a sneeze or a yawn (Lang, 1991).

1.2.2 Prevalence and prognosis

Studies of children show that the prevalence of TS is between 0.1-1% in children, while rates are slightly lower in adolescents (Comings, Himes, & Comings, 1990; Nomoto & Machiyama, 1990; Robertson, 2012). TS has been described worldwide, in all social, cultural and racial groups, albeit to differing degrees (Robertson, 2008). Prevalence rates seem to be consistent across continents such as in Europe (Cubo et al., 2011; Kadesjö & Gillberg, 2000; Tallur & Minns, 2010), North America (Carter, Pauls, Leckman, & Cohen, 1994; Comings et al., 1990; Peterson, Pine, Cohen, & Brook, 2001) and Asia (Nomoto & Machiyama, 1990). In the UK specifically, it is estimated that TS is present in 0.46-1.85% of individuals aged between 5-18 years (Tallur & Minns, 2010). Consistent with the notion that TS is a childhood, neurodevelopmental disorder, the prevalence of TS in adults (18 years and older) is much lower and is estimated to be between 0.066% (Yang et al., 2016) to 0.077% (Schlander, Schwarz, Rothenberger, & Roessner, 2011) in Europeans and North Americans. It is important to note that the criteria for TS diagnosis has changed throughout the years with regular updates of diagnostic tools which might explain slight variation in prevalence estimations.

As noted above, tics wax and wane and even though the syndrome is highly variable between patients, common consensus exists that tics reach a peak in severity in late childhood or early adolescence (between ages 8-12 years) and decrease linearly with age (Leckman et al., 1998, see Figure 1.1).

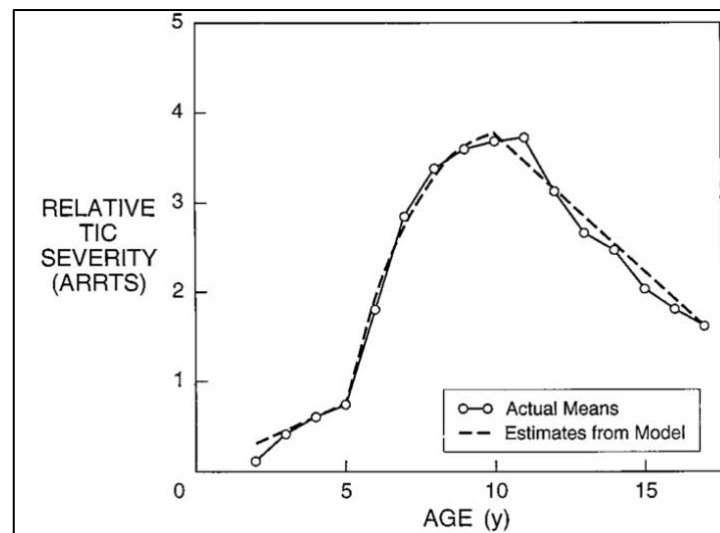


Figure 1.1. A mathematical model presented by Leckman and colleagues (1998) showing the progression of worst ever tic severity, peaking in late childhood and decreasing linearly with age. Figure is reproduced with permission from *Pediatrics journal*, volume 102, pages 14-19, Copyright © 1998 by the American Academy of Pediatrics.

As such, prognosis for individuals with TS is considered generally good. In one longitudinal study Leckman and others (1998) reported that nearly 50% of patients considered themselves largely tic-free by adulthood, while only 11% still presented marked or moderate severity of symptoms. This was further corroborated by Pappert and colleagues (2003) who compared video recordings of patients during neurological consultation in both childhood and adulthood. This study showed that half of patients who considered themselves as being tic free actually demonstrated clear tics on video recordings, indicating that perhaps patients become accustomed to their symptoms and wrongfully report their severity (Pappert et al., 2003). Nonetheless, the literature seems consistent on this decrease in tic frequency and severity into adulthood (see review by Hassan & Cavanna, 2012).

It is commonly acknowledged that TS affects males much more than females, and the gender ratio in children and adolescents is thought to be ~4:1 (Freeman et al., 2000). Conversely, by adulthood the gender ratio seems to be more comparable and is closer to a 1:1 ratio (Schlander et al., 2011; Yang et al., 2016). During adolescence, TS impairment is less severe in females, while by young adulthood the overall TS impairment is more likely to improve in males (Lichter & Finnegan, 2015). By contrast,

tic presence, distribution and severity seems to increase in females with age (Lichter & Finnegan, 2015). Thus, it appears as if symptoms are more persistent in females and increase in severity which might explain the reduced gender bias in TS in adulthood (Lichter & Finnegan, 2015; Schlander et al., 2011; Yang et al., 2016). However, it is unclear at this point why symptoms go into remission for some patients but not others. It is imperative to study this to improve both behavioural and pharmacological treatment. Clinicians are forced to rely on traditional and often out-dated diagnostic and prognostic tools whilst treating patients with TS. Recently, Hassan and Cavanna (2012) identified several variables which might be important predictors of increased and persistent presence of symptoms in TS including heightened tic severity, smaller volume of the caudate nucleus and poorer fine motor control in childhood. The use of pattern recognition or machine learning algorithms (see Chapter 6) has also recently come into vogue to predict disease outcome and remission of symptoms (see for example the study by Adaszewski, Dukart, Kherif, Frackowiak, & Draganski, 2013) and this might become important clinical tools which are able to identify and locate neurological biomarkers of perseverance of TS symptoms.

1.2.3 Comorbidities

TS is a heterogeneous disorder and it is generally accepted that ~90% of patients demonstrate symptoms of several other disorders, and consequently ~10% of patients are categorised as 'uncomplicated TS' (Debes, 2013; Eapen, Cavanna, & Robertson, 2016; Robertson, 2012; Robertson et al., 2017). The most common comorbidities with TS are attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder or behaviours (OCD/B) (Eapen et al., 2016). Frequency of these comorbidities in TS varies considerably depending on the sample studied, where ADHD is reported to occur in between 21-90% and OCD in 11-80% of patients (for reviews see Debes, 2013; Eapen et al., 2016). Other common comorbid conditions observed in patients include: autism spectrum disorders (ASD), anxiety and mood disorders, conduct and oppositional defiant disorders (CD/ODD), self-injurious behaviour (SIB) and academic learning disabilities such as dyslexia (Eapen et al., 2016; Freeman et al., 2000; Kadesjö & Gillberg, 2000). Greater prevalence of males is observed in nearly all comorbid

disorders such as ADHD and CD/ODD but not in OCD/B or anxiety disorders (Freeman et al., 2000). By contrast, females are more often diagnosed with SIB and 'uncomplicated TS' (Freeman et al., 2000). Comorbid conditions in TS can adversely affect the quality of life in patients and even delay diagnosis (Eapen et al., 2016).

1.2.4 Pathophysiology of TS

A general consensus exists that TS occurs as a result of disinhibition in key cortico-striato-thalamo-cortical (CSTC) circuits known to be particularly implicated in the initiation and selection of movement (Albin & Mink, 2006; G. E. Alexander, DeLong, & Strick, 1986; Leckman, Bloch, Smith, Larabi, & Hampson, 2010). Three parallel yet partially overlapping CSTC circuits have been particularly highlighted: the sensorimotor, associative (cognitive) and limbic (emotional) loops. These circuits are composed of anatomical and functional connections between cortical and subcortical areas and are maintained by excitatory (glutamatergic) and inhibitory (γ -amino-butyric acid- [GABA] ergic) neurotransmitters in addition to pathways with high affinity for dopamine (DA) receptors (Leckman et al., 2010). Alteration of these circuits is thought to result in a selection of cognitive, behavioural and movement disorders (Tremblay, Worbe, Thobois, Sgambato-Faure, & Féger, 2015). This is outlined below.

At the heart of these circuits are basal ganglia (BG) nuclei, which include the striatum (caudate nucleus and putamen [dorsal striatum] and the nucleus accumbens [ventral striatum]), substantia nigra (pars compacta [SNpc] and pars reticulata [SNpr]), the subthalamic nucleus (STN), and globus pallidus (interna [GPi] and externa [GPe]) (Albin & Mink, 2006; G. E. Alexander et al., 1986). Studies have primarily focused on the sensorimotor loop, which is believed to play a primary role in movement selection and execution (Tremblay et al., 2015).

1.2.4.1 The sensorimotor loop

Within the sensorimotor loop, primary motor and sensory motor cortices project to medium spiny neurons (MSNs) in the matrix (matrisomes) on the sensorimotor territory of the striatum (i.e., dorsal striatum) (Leckman et al., 2010). The MSNs in the

dorsolateral striatum and dorsomedial STN project to the GPi and SNpr, either directly or indirectly via the GPe (Bronfeld, Israelashvili, & Bar-Gad, 2013). The STN projects through excitatory pathways whereas the dorsal striatum projections are inhibitory (Bronfeld et al., 2013). The GPi and SNpr (forming the primary output nuclei of the BG complex) project to the brainstem and ventrolateral nucleus of the thalamus through inhibitory pathways, terminating in the cortex through excitatory pathways (Bronfeld et al., 2013; Leckman et al., 2010). Cortical activation is governed by these nuclei of the BG complex. Particularly, reduced activity of the GPi/SNpr results in lowered inhibition of the thalamus and cortex, and thus facilitates cortical activation. By contrast, increased activity of the same nuclei is thought to enhance cortical inhibition (Bronfeld et al., 2013). In non-pathological states, dormancy of the thalamus, which otherwise would result in inappropriate movements, is maintained by striatal neurons through tonic GABAergic inhibition (i.e., GABAergic interneurons) (Tepper & Bolam, 2004). Action selection is then dominated by activation of the striatal MSNs lowering inhibition of the pallido-thalamic output (Tremblay et al., 2015). As such, GABAergic inhibitory interneurons are particularly important for maintaining the excitatory/inhibitory balance of the brain. These inhibitory interneurons, in the striatum, are primarily parvalbumin and calretinin expressing type, covertly maintaining homeostasis of the BG complex (see Gernert et al., 2000; Rapanelli, Frick, & Pittenger, 2017).

In pathological states such as in TS, tics might be the result of altered release of DA within the striatum, leading to inappropriate activity of MSNs (Albin & Mink, 2006). The cause of this has been hypothesised to be due to reduced GABAergic inhibition (Leckman et al., 2010). In support, *ex vivo* studies have shown reduced and altered distribution of GABAergic inhibitory interneurons within nuclei of the BG complex (Kalanithi et al., 2005). The same group led by Dr. Flora Vaccarino, also reported reduced number of cholinergic interneurons in the dorsal striatum (Kataoka et al., 2010). Interestingly, this study also revealed a marked gradient of cholinergic interneurons in the striatum in normal controls, where most abundance is found in the associative territory, intermediate in the sensorimotor and lowest number of interneurons are found in the limbic region. Interestingly, this gradient was completely absent in TS patients (Kataoka et al., 2010).

Converging evidence for the occurrence of tics within the BG complex comes from animal models. Injection of bicuculline (a GABA_A antagonist) into the sensorimotor striatum results in aberrant DA release, causing increased striatal disinhibition (McCairn, Iriki, & Isoda, 2013). Based on time latencies, the authors observed a burst of activity (i.e., local field potentials) within the BG indicating an initiation of a tic, while bursts were also noted in the primary motor and cerebellar cortices during overt tic-like movements (McCairn et al., 2013). This indicates that the BG complex might be the driver of tics, whereas more motor control output centres are responsible for performing the tic. These findings have received some support from computational studies (Caligiore, et al. 2016). Neuroimaging studies of patients with TS have also provided supporting evidence for altered structural integrity of BG nuclei, although some contradictory results have been reported. This is reviewed below (although more comprehensive work is presented in Chapter 6).

Based their *ex vivo* work, Kalanithi and others (2005) reported (in addition to reduced number of GABAergic interneurons) reduced volume of the caudate and putamen. This corroborated previous result demonstrating smaller volume of the lenticular nucleus (i.e., Globus pallidus and putamen) in adult patients with TS (Peterson et al., 1993, 1992). Similarly, one study with ten sets of monozygotic twins (age range: 9-31) diagnosed with TS, where one twin had a more severe version of the syndrome, showed that increased severity of tics was associated with reduced volume of the right caudate and left lateral ventricle (Hyde et al., 1995). Conversely, Singer and colleagues (1993) reported no differences in the size of the caudate, putamen, globus pallidus or ventricles in a boys only sample. However, the authors did report significant asymmetries of the putamen and lenticular region, results that were found to be influenced by comorbid ADHD diagnosis. More recent studies have supported the notion of altered putamen volume in boys with TS (Kassubek, Juengling, & Ludolph, 2006; Ludolph et al., 2006; Roessner et al., 2011). Comparison of subgroups (i.e. complicated vs. uncomplicated TS) is often difficult due to small sample sizes. One large study including patients with TS and ADHD (ADHD n = 39, TS n = 47, control n = 55) found no differences in the shape or volume of basal ganglia nuclei in young patients

(age range: 8-12; Forde et al., 2016). These results confirm the importance of investigating large samples of patients and consider comorbid statuses.

Cortically, morphological studies have also demonstrated cortical thinning in several areas of the brain (Worbe, Gerardin, et al., 2010). Most interestingly, the study by Worbe and others (2010) showed a trend for cortical thinning based on tic severity and comorbidities, where thinning in motor and premotor regions, prefrontal and parietal regions, and limbic regions (e.g., anterior cingulate cortex [ACC]) was associated with *simple tics*, *complex tics* and *OCD*, respectively.

Most of research into TS has focused on the sensorimotor loop due to its prominent role in the generation of motor tics. However, it is important to emphasise the importance of the roles played by other CTSC loops due to their possible emergence in more complex symptoms and comorbidities. Below I present the ‘associative’ and ‘limbic’ loops, and later in this introductory chapter I will demonstrate how the sensory aspects of TS link well with the known pathology of TS.

1.2.4.2 *The associative and limbic loops*

The associative network is thought to initiate with input from prefrontal (e.g., dorsolateral prefrontal cortex [DLPFC]) and association cortices sending information to the association territory of the striatum (dorsomedial striatum), where MSNs project through inhibitory pathways to the ventromedial thalamus via the associative part of the pallidum (G. E. Alexander et al., 1986; Tremblay et al., 2015). Studies in non-human primates have confirmed the role of the associative striatum or GPe in the manifestation of hyperactivity symptoms akin to the ones demonstrated by patients with TS (Bronfeld et al., 2013; Grabli et al., 2004; Worbe et al., 2009, 2013). In adult patients, alteration in functional connectivity and cortical sulci changes of the associative network has been reported (Muellner et al., 2015; Worbe et al., 2012).

Within the ‘limbic loop’ striosomes on the limbic part of the striatum (i.e., ventral striatum) receive excitatory cortical efferents from orbitofrontal (OFC), cingulate and insular cortices (Crittenden & Graybiel, 2011). In turn, MSNs project to the ventral pallidum, and ventral tegmental area (VTA)/SNpc (Haber & Knutson, 2010). From there,

cortical afferents are projected to the prefrontal cortex (PFC) (Haber & Knutson, 2010). The cortical limbic areas have been implicated in reward and emotional or motivational processing, and thus the limbic circuit is often thought to play a role in goal-directed behaviour (Tremblay et al., 2015). The limbic territory of the striatum is thought to play an important role in emotional anticipation and behavioural avoidance of aversive events (Haber & Knutson, 2010). The ventral striatum includes the NAcc which has a critical role in reinforcement and habit-learning (Haber & Knutson, 2010) and thus possibly also in the reinforcement of the relationship between tics and the PSP. However, convincing evidence suggest that the neural substrates of reward prediction involves activity of the ventral striatum (S. R. Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011). This is discussed further, below in the relevant subchapter. In support, enhanced dopaminergic connectivity between the ventral (i.e., NAcc) and dorsal striatum is associated with the formation of habits (Everitt & Robbins, 2005; Graybiel, 2008). Similarly, the insular cortex plays an instrumental role in forming and relaying unpleasant somatosensory sensations (Craig, 2002; S. R. Jackson, Parkinson, Kim, et al., 2011). The role of the insular cortex in the emergence and maintenance of sensory phenomena in TS was nicely outlined in the work of Jackson and colleagues (2011). This framework is reviewed in subsection 1.3.2.

Work on animal models has supported the role for the limbic circuit in the appearance of more complex symptoms in TS. For example, disinhibition of the NAcc (the limbic territory of the striatum) induces complex tics (McCairn et al., 2016) and compulsive-like behaviours (Worbe et al., 2009) in monkeys. Furthermore, PET studies of adult patients with TS demonstrated reduced metabolic activity of the limbic areas including the orbitofrontal cortex (OFC), insula and ventral striatum (Braun et al., 1993). Neuroimaging studies of patients with TS, investigating WM microstructure, have reported altered water diffusion in limbic WM tracts such as the cingulum and uncinate fasciculus (Neuner et al., 2010).

1.3 SENSORY PHENOMENA IN TOURETTE SYNDROME

Somatosensation is thought to play a major role in disease progression and maintenance of symptoms in TS and has been implicated in the syndrome since the start of the 20th century, but are yet to be added to current diagnostic criteria for TS (APA, 2013; Cox, Seri, & Cavanna, 2018).

Patrick (1905) wrote:

“Convulsive tic may be said to be a habit spasm, a sort of motor expression of an imperative impulse...its original cause is generally sensory – some uncomfortable sensation which an attempt is made to relieve by a movement which finally becomes habitual” (Patrick, 1905, pp. 439-440).

Cogent evidence exists suggesting that hyperkinetic movement disorders such as TS and focal hand dystonia (FHD; a disorder characterised by dystonic postures and can affect, for example, muscles involved in writing [writer’s cramp] or fingers used to play musical instruments [musician’s dystonia]) are modulated by both internal and external sensory signals (Hallett, 1995; Patel et al., 2014). Moreover, it is widely recognised that abnormal sensorimotor integration alters the normal control of motor movements (Abbruzzese & Berardelli, 2003). Indeed, reduced sensory afferent inhibition (SAI; Orth, Amann, Robertson, & Rothwell, 2005) in patients with TS is an important physiological evidence of where increased sensory input alters motor output (Orth & Münchau, 2013).

In TS, sensory events can originate both internally or externally and these sensory aspects have collectively been termed ‘*sensory phenomena*’ (Prado, do Rosário, Shavitt, & Miguel, 2007). The term sensory phenomena can be thought of as an ‘umbrella’ term and encompasses several different aspects of sensation experienced by patients with TS which affects the somatosensory system. This system monitors the internal state of the body and responds to any changes to the external surface (Craig, 2002; Crossley & Cavanna, 2013; L. C. Miller, Murphy, & Buss, 1981). To provide consistency in the literature, Prado and others (2008) and Crossley and Cavanna (2013) suggest that the term *sensory phenomena* includes: the physical sensation (uncomfortable sensations

in the skin, muscles-joints, or body sensations), ‘just-right’ perceptions, premonitory urges (the most widely studied sensory experience in patients), sensory tics, feelings of discomfort, incompleteness, pressure, tension, tingling, warmth and increased energy.

In TS, sensory phenomena are thought to follow the onset of tics by about 3 years (Banaschewski, Woerner, & Rothenberger, 2003; Leckman et al., 1993). In adults, prevalence of sensory phenomena is high (97.2% of patients reported the presence of at least one type) and these can cause significant distress and affect the patient’s perceived health-related quality of life (Crossley & Cavanna, 2013). As noted before, the voluntariness of tics is debated, but some patients note that a tic is a voluntary response to an involuntary sensation, and that tics could be eradicated in the absence of these sensations (Kwak, Dat Vuong, & Jankovic, 2003; Leckman et al., 1993). Importantly, behavioural therapies in TS focus primarily on sensory phenomena and require the patient to use these to gain control over the tics (see McGuire et al., 2014).

As noted above, sensory phenomena encompass several terms or aspects, which have been studied in TS. These include: (1) sensory tics, and (2) premonitory urges, (3) ‘just-right’ or ‘not-just-right’ experiences, and (4) sensory experiences caused by exteroceptive stimuli. All aspects are covered in the text below.

1.3.1 Sensory tics

Interest in these sensory experiences are thought to have originated with Hugh T. Patrick in 1905. In his paper “Convulsive tics” Patrick identified the habit formation that occurs, and the significant role sensory aspects must play in the syndrome. Bliss (Bliss, 1980) then provided possibly the first introspective description of these sensory urges (Bliss being himself a sufferer of TS) and writes: “All of the TS actions are grotesque extensions of more or less ordinary bodily actions[...]what is basic to TS overt actions is the intolerable need to[...]gratify and terminate an almost intolerable urge.” (Bliss, 1980, pp. 1345). Here Bliss is describing his tics as the extreme version of normal, everyday behaviour, but while also indicating that suppressing your tics leads to the uncontrollable urge to move, which is often more forceful and prolonged than otherwise (Bliss, 1980; Bullen & Hemsley, 1983; Hollenbeck, 2003).

Based on this, Shapiro and others (1988) suggested the term “sensory tics”, which are not actual tics but is rather used to describe all somatic sensations in the joints, bones, muscles and other parts of the body, which force the patient to perform a voluntary response and relief the uncomfortable sensation (Cavanna, Black, Hallett, & Voon, 2017; Shapiro et al., 1988). Then, Eapen, Moriarty and Robertson (1994) suggested a distinction between *reflex tics* and sensory tics, stating that reflex tics occur in response to some externally produced stimuli (e.g., someone coughs around the patient), while sensory tics are in response to a stimulus arising from the soma (e.g., tingling or tightening sensation) or from stimuli from within the body (e.g., when the patient himself coughs). The *reflex tics* term has not really caught on; however, this distinction is somewhat supported by studies showing that patients subjectively perceive themselves as hypersensitive to external stimulation (e.g., Belluscio et al., 2011; Jewers, Staley, & Shady, 2013). This is discussed in detail below in subsection 1.4.1.

Systematic evaluation of sensory tics showed these to be quite prevalent in patients as 41% of the sample in the study by Kurlan, Lichter and Hewitt (Kurlan, Lichter, & Hewitt, 1989) reported symptoms indicative of sensory tics. Interestingly, in this study most patients noted the sensation increasing in severity during voluntary tic suppression. Moreover, all patients who reported the presence of these sensations were able to suppress their tics, while only 63% were able to suppress tics in the absence of sensory tics (Kurlan et al., 1989). This observation suggests that sensory phenomena might be an important aspect in the ability to suppress tics, which is a distinguishing feature of the syndrome.

The concept of a sensory tic was somewhat redefined by Chee and Sachdev (1997), who studied the frequency and characteristics of sensory tics in a large sample including patients with TS, OCD and neurologically healthy individuals. The authors defined sensory tics as (1) transient and recurrent, (2) felt on or close to the skin, (3) the patient could identify where on the body the sensation occurred, (4) sensed with or without a motor or vocal discharge and (5) not caused by other physical pathology. In this sense, Chee and Sachdev (1997) actually excluded the term “urges” from the concept since they believed an urge to represent a drive that preceded the behavioural

response, and consequently, an urge would be a cognitive rather than a sensory phenomenon. This has however been disproven, and the urge to act must be biological (S. R. Jackson, Parkinson, Kim, et al., 2011). Chee and Sachdev (1997) determined that 28% of TS patients presented sensory tics, while sensory tics were present in 10% of OCD patients and 8.9% in healthy controls. This prevalence is somewhat lower than previously reported by Kurlan, Lichter and Hewitt (1989). Most importantly, this study shows the prevalence of sensory experiences or tics in patients in the absence of the term “urges” (Chee & Sachdev, 1997).

1.3.2 Premonitory sensory phenomena (PSP)

In the literature, it is common for studies to discuss the covert sensory aspects of TS as ‘premonitory urges’ or simply ‘urges’, possibly due to the most commonly used clinical measure used (i.e., the PUTS scale). However, as I will show in Chapter 2, the questionnaire measures more than simply ‘urges’ and encompasses many aspects of sensory phenomena. Therefore, throughout this thesis I have decided to call this premonitory sensory phenomena (PSP) as I find this term more appropriate to describe the interoceptive feeling, related to the urge to tic.

Tics are distinguished from other similar hyperkinetic movements insofar as they are suppressible. However, tic suppression often leads to a prolonged bout of tics, which are often more forceful than otherwise and lead to a build-up of PSP (Hollenbeck, 2003). One of the earliest studies to systematically study PSP showed that 82% (22 out of 28) adult patients with TS reported experiencing PSP prior to both motor and vocal tics, while more than half of all subjects found the PSP more troublesome than the tics themselves (Cohen & Leckman, 1992). In a subsequent retrospective, cross-sectional study, Leckman, Walker and Cohen (1993) expanded upon this in a study of 101 patients and showed that patients found tics momentarily relieving of the uncomfortable sensation, which is in accord with the description by Bliss (Bliss, 1980). The study by Leckman, et al. (1993) was also the first to systematically record the location of the most prevalent urges (Figure 1.2). The study by Leckman, et al. (1993) remains the largest investigation of body regions affected by PSP, with other studies showing that the face/head and neck are the most affected followed by shoulders, arms

and legs (Ganos et al., 2012; Kwak et al., 2003; McGuire et al., 2016; Schunke et al., 2016). Figure 1.3 and Figure 1.4 capture the most prevalent types of PSP and body locations.

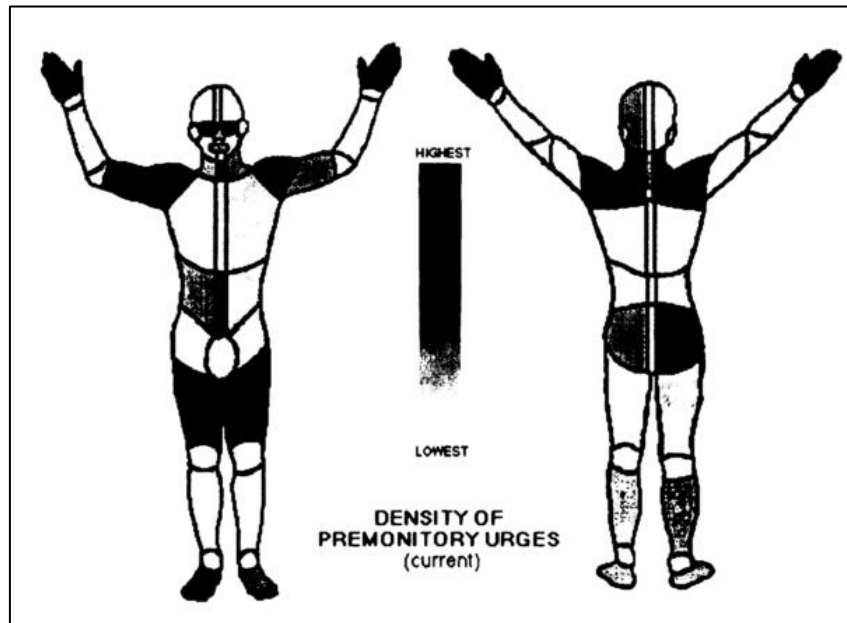


Figure 1.2. Spread and most common body regions affected by premonitory urges reported by adult patients with TS (Leckman et al., 1993). Figure is reprinted with permission from the American Journal of Psychiatry (Copyright, 1993). American Psychiatric Association.

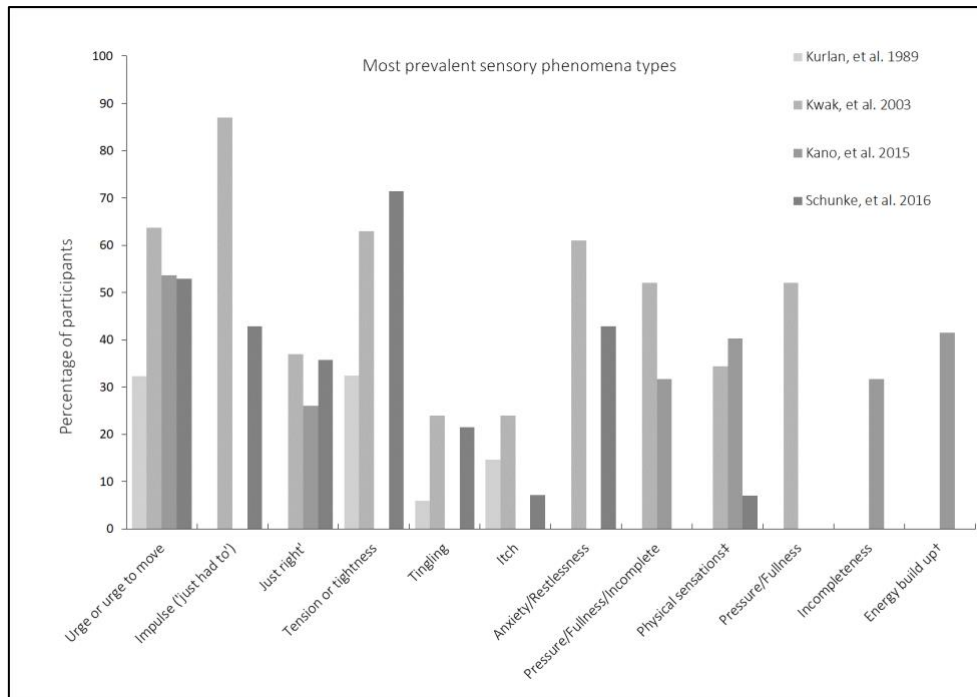


Figure 1.3. Overview of the most prevalent sensory phenomena type reported. ‡ Kano, et al. 2015 asked about physical sensations in general. Consequently, I collapsed reports on for example burning, aching, coldness and numbness reported by Kwak, et al. 2003 and Schunke, et al. 2016 as physical sensations. †Kano, et al. 2015 asked about energy build up which was not reported by others. I decided to include this as several participants report the build-up of energy as a sensory phenomenon.

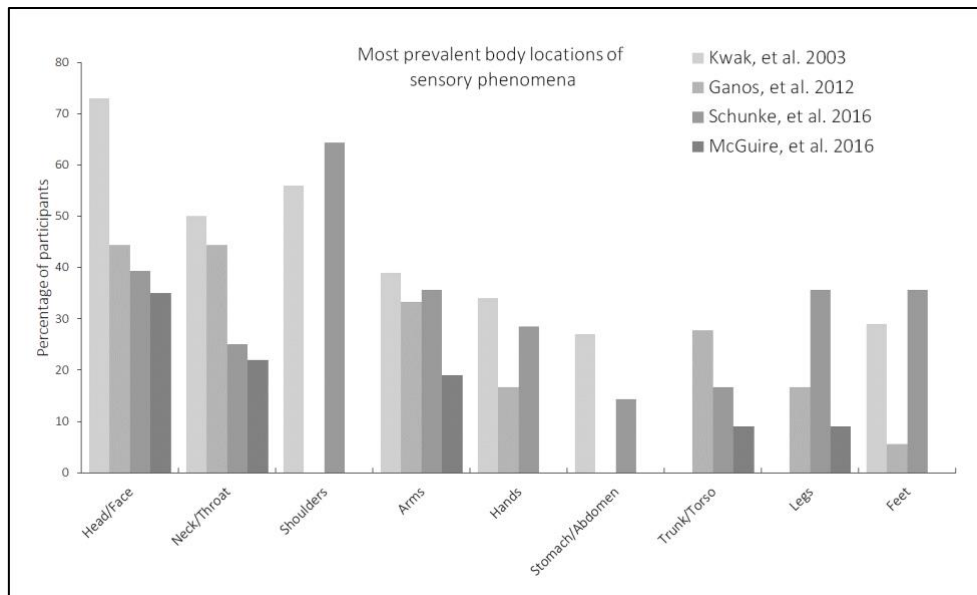


Figure 1.4. Overview of the most prevalent body locations for sensory phenomena reported. It is worth noting that Leckman, et al. 1993 did not report on percentages and were thus not included in this overview.

Interestingly, the study by Leckman and co-workers (1993) mentioned that most patients reported the onset of PSP approximately 3 years following the onset of tics, and that patients became first aware of these urges, on average, at the age of 10 years. Banachewski et al. (2003) studied these sensations in 254 children and adolescents to investigate the developmental aspects of PSP and how well younger patients can suppress their tics. Most interestingly, Banachewski et al's results showed that only 24% of children aged 8-10 years were aware of their PSP, while this percentage of awareness rose to 34% and 57% in patients aged 11-14 and 15-19 years, respectively. This indicates that there is a developmental trajectory of tic-urge fusion. To put it differently, younger children might not yet associate the strange sensory urges with the onset of their tics, but this is later developed as the child ages through negative reinforcement (Capriotti, Brandt, Turkel, Lee, & Woods, 2014). Others have interpreted these results as to show that there is a critical period where the child learns to distinguish between volitional movements initiated by oneself from involuntary movements (Draper, Jackson, Morgan, & Jackson, 2015) or other maturational processes, which are independent from the onset of tics (Cavanna et al., 2017).

Importantly, and as noted before, the relationship between PSP and tics remains somewhat unknown. Nonetheless, studies have shown that tic suppression is not solely reliant upon the awareness of PSP since 64% of young patients reported being able to suppress their tics, while only 37% reported being aware of PSP (Banachewski et al., 2003). This was further corroborated by Ganos and colleagues (2012) in a sample of adults with 'uncomplicated' TS, indicating that perhaps PSP are not a prerequisite to successful tic inhibition. Nonetheless, awareness of PSP might to some extent suppress imminent tics and awareness of PSP is a critical component in behavioural interventions such as the exposure and response prevention (Verdellen et al., 2008) and Habit Reversal Training (Himle, Woods, Piacentini, & Walkup, 2006) which have been shown to reduce tic severity. Such interventions focusing on the PSP have proven fruitful. In a recent study, urge-acceptance (where participants were asked to monitor their PSP while practicing the willingness to experience a PSP and not fight it) resulted in a significant decrease in both PSP frequency, intensity and discomfort due to urges in comparison to free-to-tic and tic-suppression (Gev et al., 2016). These results are in line

with the work of Himle and others (2007) who showed that urges increase significantly during tic-suppression and the work of Reese and others (2015) who proposed that mindfulness-based stress reduction therapy reduces tic severity and the associated impairment, with the effects lasting at least for 1 month.

Few pharmacological treatments have been employed to treat sensory aspects in TS. One method has, however, been proven fruitful in both TS and dystonia. Botulinum toxin types A and B (a neurotoxic protein and an acetylcholine antagonist) are known to relax contracted muscles and alter peripheral sensory input (Patel et al., 2014). This has proven fruitful in patients with FHD (Byrnes et al., 1998). Botulinum toxin has also been used successfully to reduce the intensity and frequency of tics and the PSP sensation (Jankovic, 1994; Kwak, Hanna, & Jankovic, 2000; Marras, Andrews, Sime, & Lang, 2001).

Until recently, there was no standardised clinical scale available to measure PSP in tic disorders. The Premonitory Urge for Tics Scale (PUTS; Woods, Piacentini, Himle, & Chang, 2005) was developed to measure the severity of premonitory urges in patients with tic disorders. The PUTS is further introduced and discussed in Chapter 2 subsection 2.1.2. The scale has been shown to correlate with tic severity in children (Draper et al., 2015) but not adults (Ganos et al., 2012; Gulisano, Cali, Palermo, Robertson, & Rizzo, 2015; but cf Brandt, et al. 2016). Furthermore, inferring on the relationship between PSP and tics and the properties of PSP in patients is not well captured by self-report measures. More recently, Brandt and others (2016) reported on the temporal relationship between PSP and tics in adults with TS (urge) and without TS (blink suppression) using a real-urge monitor. Results showed that tics and PSP are temporally related insofar as urges increase prior to tics and decrease following the execution of a tic. The findings indicate that the relationship between tics and PSP is strengthened through negative reinforcement as previously suggested (Capriotti et al., 2014; Himle et al., 2007).

The study by Brandt, et al. (2016) also shows great similarities in the urge to act between patients (tic suppression) and controls (blink suppression). The neural correlates of the urge to tic and urge to act (e.g., swallow or yawn) seem to overlap to great extent (S. R. Jackson, Parkinson, Kim, et al., 2011). In particular, Jackson and

others (2011) showed that the urge to act (such as swallowing and urinating) was associated with a rise in the fMRI BOLD response in the right insular and mid cingulate cortices, areas that overlapped with the physiological response during the urge to tic (during tic suppression). The pathophysiology of TS, and specifically sensory phenomena is detailed in subsection 1.5.

1.3.1 Just-right experiences

Sensory phenomena are quite common in OCD, a disorder often diagnosed in patients with TS (Ferrão et al., 2012). Majority of OCD patients in fact report at least one subtype of sensory phenomena preceding the onset of repetitive behaviours that characterise the disorders (Ferrão et al., 2012). Leckman, et al. (1994) introduced the term ‘just-right’ perception, which some patients with TS report in response to when something feels, looks or sounds not right. Also, sometimes tics are performed until the feeling is ‘just-right’ (Belluscio, Tinaz, & Hallett, 2011). Cavanna and Nani (2013) define these perceptions as “a force, triggered by visual, auditory, or tactile perceptions, as well as a feeling of imperfection about actions and intention, that leads to the individual performing compulsive acts until the actions are felt by the individual to be complete” (Cavanna & Nani, 2013, pp. 2; see also Helena S Prado et al., 2008). In their study, Leckman and colleagues (1994) showed that these ‘just-right’ feelings occur in 50% of patients and can cause disturbance. Also, several studies have shown these feelings are substantially more common in adult (Kwak et al., 2003; Neal & Cavanna, 2013a) and younger patients with TS+OCD (Worbe, Mallet, et al., 2010). Importantly, these ‘just-right’ feelings in TS patients can be distinguished from similar perceptions (i.e., obsessions) in OCD patients as these are not accompanied by feelings of anxiety in TS. Finally, these feelings are also easily distinguishable from other sensory phenomena (Leckman et al., 1994), however, more recent studies have shown a correlation between ‘just-right’ perceptions and other PSP (Brandt, Beck, Sajin, Anders, & Münchau, 2016; Kano et al., 2015).

1.4 ALTERED EXTEROCEPTIVE SENSORY PROCESSING IN TS

It is now clear that TS is also characterised by non-motor features such as abnormal internal bodily sensations which are related to the occurrence of tics. This has prompted some to suggest that hypersensitivity to stimuli should be considered the 'core' of TS and a prime contributor to symptoms of TS (Bullen & Hemsley, 1983).

Sensory processing is the way the nervous system receives, organises and makes sense of sensory stimuli from both within and outside our body, and occurs so that the individual can determine how to react to the demands of the environment (L. C. Miller et al., 1981). Ample evidence exists demonstrating that patients experience a general feeling of sensory amplification. As such, it is possible that some tics are futile reactions to external sensory stimulation and some have suggested this is repeated until the feeling is 'just-right' (Leckman et al., 1994; Weisman et al., 2018).

1.4.1 *Sensory amplification*

As noted above, some have suggested a category of tics termed *reflex tics* (Eapen et al., 1994). It has long been known that external sensory events can trigger tics, and tics can also be in the form of an imitation (echopraxia and echolalia; Gilles de la Tourette, 1885). *Exteroception* is one of the functions of the somatosensory system. Exteroception is the sense of our body's interaction with the external world and how external sensory input affects our body (Gardner & Johnson, 2013b). Exteroception conveys information on the sense of touch, including pressure, contact and stroking. Exteroception also governs the mode of thermal sensation (Gardner & Johnson, 2013b).

Few observational studies have reported patients feeling the irresistible need to tic in response to certain visual, auditory or tactile stimuli (Commander, Corbett, Prendergast, & Ridley, 1991; Eapen et al., 1994; Tijssen, Brown, Morris, & Lees, 1999). Reflex tics, however, give rise to the suggestion that patients with TS demonstrate abnormal sensorimotor gating and altered startle reflex has been suggested (Swerdlow,

2013). However, Tjissen and colleagues (1999) reported the observation of patients demonstrating tics in the absence of an exaggerated startle reflex.

In addition to exteroceptive stimuli which might trigger or induce the onset of tics, patients also describe the general feeling of amplification to external sensory stimuli (i.e., heightened exteroceptive awareness), across all sensory modalities (Belluscio, Jin, et al., 2011; Cohen & Leckman, 1992). For example, patients commonly complain of extreme irritation due to clothing tags, or that bright lights, loud noises and differences in heat/cold are bothersome (Belluscio, Jin, et al., 2011; Cohen & Leckman, 1992). Indeed, one study showed that patients report heightened sensitivity to external stimuli in at least one sensory modality such as olfactory (70%), tactile perception (65%), visual (55%) and gustatory (50%) (Belluscio, Jin, et al., 2011). Moreover, it appears that faint, repetitive or constant, and non-salient stimuli are most bothersome, whereas patients preferred more intense stimuli (Belluscio, Jin, et al., 2011). Contradictory to this, patients do not seem to demonstrate altered sensory thresholds, when using affective touch paradigms (Belluscio, Jin, et al., 2011; Schunke et al., 2016). This has led to the conclusion that self-evaluated sensory hypersensitivity is not due to a dysfunction of the peripheral nervous system, but rather how the stimuli is processed in the central nervous system. However, no study has assessed affective touch thresholds in children. Related to this, one study has assessed discriminative touch (the difference between affective and discriminative touch is introduced in Chapter 2) thresholds in children with TS (Puts et al., 2015).

The journey from sensory stimulation to realisation and action is complex. In the tactile sensory modality specifically touch input is conveyed by mechanoreceptors (i.e., low-threshold mechanoreceptors and C-tactile afferents [CT]) in the skin by dorsal root ganglion neurons (Gardner & Johnson, 2013b). The sensory information is then projected through the spinal cord dorsal horn through two major pathways: the *spinothalamic pathway* and the *dorsal-column medial-lemniscal (DCML) pathway* (Gardner & Johnson, 2013; See Figure 1.5|A). The spinothalamic pathway (or anterolateral system [ALS]) is split into two sections, the anterior part which processes crude touch and pressure, and the lateral part which processes pain and thermal sensations (Gardner & Johnson, 2013b). This direct ALS pathway is thought to relay

sensory information from the periphery to the cerebral cortex (Patestas & Gartner, 2016), which is then received by the ventral posterolateral (VPL) nucleus of the thalamus. The thalamus plays a putative role in relaying sensory input, through the internal capsule to the primary somatosensory cortex (Noback, Strominger, Demarest, & Ruggiero, 2005b). The DCML pathway also projects through the VPL and conveys information for fine touch and proprioception, and plays thus a major role in planning and executing movement (Noback et al., 2005b). The end-station for both pathways lies in the primary somatosensory cortex. In the case of CT afferents (unmyelinated fibers responding to tactile stimulation such as stroking and low force monofilaments), information is not processed in the somatosensory cortex, but rather in the anterior insular cortex (Cole & Sedgwick, 1992; Olausson et al., 2002; Vallbo, Olausson, & Wessberg, 1999).

The somatosensory cortex (S1) is located in the parietal lobe, adjacent to the primary motor cortex (M1), separated by the central sulcus. The somatosensory cortex function is to detect and process information coming in from the senses both with respect to the magnitude and location on the body (McGlone & Reilly, 2010). The function of the primary motor cortex is primarily motor output. Other motor areas of the brain facilitate communication between the two and as such both are often combined as the sensorimotor (SM) cortex; thus, sensation and movement are anatomically separated but functionally integrated. Each area is, however, organised somatotopically into what is called the motor and sensory homunculi (McGlone & Reilly, 2010). The somatotopy of the SM cortex is studied in Chapter 4.

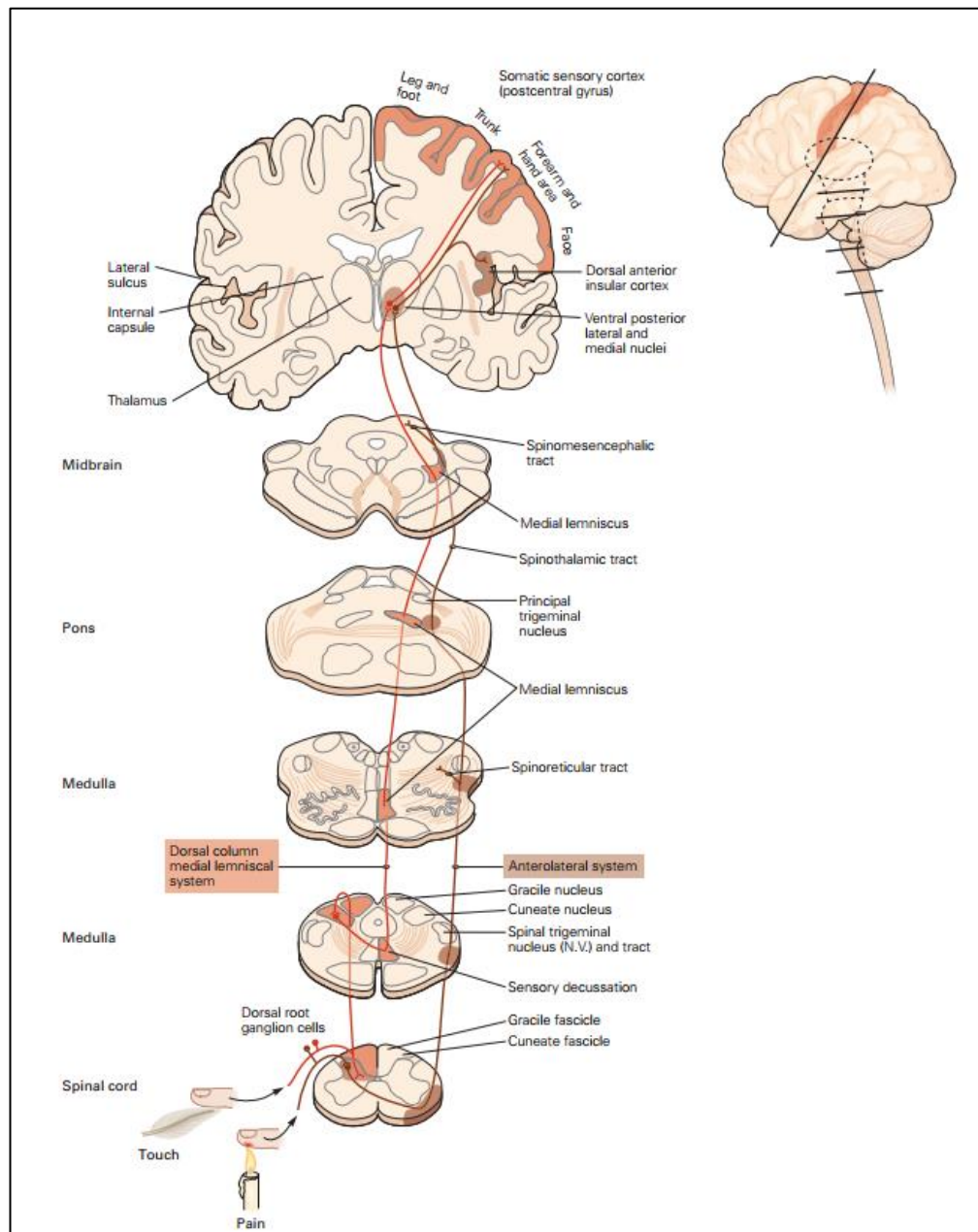


Figure 1.5. The dorsal-column medial lemniscal and spinothalamic pathways. The figure is reprinted with generous permission from McGraw-Hill Global Education Holdings, LLC. (Request ID: HIL988749907-2). The original figure appears in (Gardner & Johnson, 2013b) on page 493.

1.4.2 Sensorimotor gating

It is conceivable that heightened perception of sensory stimuli is due to faulty sensorimotor gating mechanisms (Houghton, Capriotti, Conelea, & Woods, 2014; Rajagopal, Seri And, & Cavanna, 2013). Sensorimotor gating is the process of allocating

neural resources during a standoff between sensory and cognitive information from the external world (Swerdlow, Braff, & Geyer, 2016). To put differently, the necessity to filter out irrelevant sensory stimuli to ensure correct behaviour and action to environmental demands is vital and is controlled by a gatekeeper. In TS for example, improper filtering of sensory information, due to aberrant sensorimotor gating, might induce sensory phenomena and subjective feeling states of sensory amplification (Rajagopal et al., 2013). It is possible that the 'gatekeeper' in this instance is the dorsal striatum, which is in line with the action-selection model of the BG complex, suggesting that the nuclei within the BG select a single response while inhibiting the emergence of other competing responses (Mink, 1996). Reduced sensorimotor gating has been reported in TS on subjective measures, where patients for example state feeling overwhelmed by sensory stimuli (Sutherland Owens, Miguel, & Swerdlow, 2011). This has also been shown in empirical studies where sensory stimulation increases reaction times in patients only (Panagopoulos, Greene, Campbell, & Black, 2013)

The startle reflex is perhaps the most widely studied phenomenon thought to be governed by this gating mechanism (Swerdlow et al., 2016). An operational measure of the sensorimotor gating is the pre-pulse inhibition (PPI). PPI is a measure of individuals' inhibition of the startle reflex and is a good indicator of sensorimotor gating. During such paradigms, a startle stimulus is preceded by (about 30-300 ms) a weaker ('prepulse') stimulus and this is thought to inhibit the normal startle reflex (Swerdlow, 2013). Some studies have noted altered startle reflex in TS (Gironell et al., 2000; S. J. Smith & Lees, 1989) but cf. (Sachdev, Chee, & Aniss, 1997). Employing the PPI paradigm, several studies have established altered inhibition of the startle reflex in TS, suggesting aberrant gating mechanisms (Buse, Beste, Herrmann, & Roessner, 2016; Castellanos et al., 1996; Swerdlow et al., 2001; Zebardast et al., 2013). PPI is thought to activate several cortical and subcortical structures, primarily thought to be involved in the 'limbic' circuit, and be governed by norepinephrine and dopamine substrates (Swerdlow, Bongiovanni, Tochen, & Shoemaker, 2006; Swerdlow et al., 2016). As such, several areas known to be aberrant in TS overlap well with the neural substrates of the PPI mechanisms. Consequently, PSP might emerge in TS due to faulty sensory gating (Rajagopal et al., 2013).

1.5 THE NEURAL SUBSTRATES OF SENSORY PHENOMENA

1.5.1 *Formation, maintenance and neural correlates of sensory phenomena*

According to some, during tic suppression the urge to act increases (Brandt, Beck, Sajin, Baaske, et al., 2016), which is also observed during suppression of natural bodily urges such as yawning, swallowing or urinating (Jackson, et al. 2011). Nonetheless, the formation of PSP remains somewhat unknown and limited evidence exists (Godar & Bortolato, 2017; Houghton et al., 2014). There is evidence that the formation of PSP occurs through inappropriate operation of the habit-learning system (Graybiel, 2008; S. R. Jackson, Parkinson, Kim, et al., 2011). Indeed, tics have been likened to habits and in the same way habits form through reinforcement, tics can be considered reinforced actions to PSP, possibly mediated by dopaminergic neurotransmission (Palmiter et al., 2011). Moreover, the neural correlates of habits and tics overlap substantially and both matrisomes and striosomes are thought to code for and act in accord with the salience of the incoming stimuli (Albin & Mink, 2006; Graybiel, 2008; Leckman et al., 2010). Empirical studies have also demonstrated different habit learning in patients compared to their peers (Delorme et al., 2015; Marsh et al., 2004).

Several structural and functional neuroimaging (for reviews see Cavanna et al., 2017; Cox et al., 2018; Ganos, Roessner, & Münchau, 2013), brain stimulation (Orth, 2009), computational (Conceição, Dias, Farinha, & Maia, 2017) and animal (McCairn & Isoda, 2013) studies have attempted to capture the pathological characteristics of PSP in TS. This is briefly reviewed below in addition to considering the key neurotransmitters involved.

1.5.2 *Neuroimaging evidence*

Neuroimaging studies of tic generation have provided some evidence for the neural correlates of PSP. In one such study, Bohlhalter and colleagues (2006) studied 10 adult patients under two different conditions: 'free-to-tic' or 'imitate-tic'. In the 'free-to-tic' condition, a significant rise in the fMRI BOLD response was noted 2 seconds prior to the onset of tics in several areas of the brain including the SMA and other pre-motor

areas, and the parietal operculum, insular cortex, ACC, thalamus, putamen and cerebellum bilaterally. According to the authors, stronger activation was noted at tic onset in the cerebellum, precentral gyrus, (M1), DLPFC, superior parietal lobules (SPL) and substantia nigra, while distinguished activity was noted in the ACC and SMA, suggesting these areas form the urge-tic network (Bohlhalter et al., 2006). These results have largely been replicated in subsequent studies (Neuner et al., 2014; Z. Wang et al., 2011), where one second before tic onset, a significant activation is noted in the ACC, putamen, insula, amygdala, cerebellum and occipital cortex. Using positron emission tomography (PET), there was an increased metabolic demand in several subcortical nuclei such as the thalamus, bilateral insula and cerebellum (specifically area VI) while contrasting tic generation to activity during sleep in patients (Lerner et al., 2007). Cortical activation was also noted in bilateral SMA, anterior cingulate, STG (superior temporal gyrus) and OFC (orbitofrontal cortex).

In relation to the clinical measure of PSP, Draper and colleagues (2015) reported significantly reduced GM thickness in both insular and SM cortices, which was inversely related to PUTS scores, indicating that patients whose GM thickness was most dissimilar to their peers had the highest frequency and severity of PSP. Similarly, in adults Draganski and others (2010) showed a positive correlation between PUTS scores and GM volume in left somatosensory and dorsal pre-motor cortices, and the right prefrontal cortex. In the same study, Draganski, et al. (2010) also reported significant correlation between PUTS and structural changes in the superior longitudinal fasciculus tract (a white matter tract within the SM cortex vital for regulating motor behaviour and somatosensory integration; Makris et al., 2005). Further involvement of the insular cortex in PSP was shown by Tinaz and co-workers (2015) who noted that the functional connectivity between right dorsal anterior insula and SMA was positively associated with PUTS scores.

In summary, studies focusing on the neural substrates of PSP in TS have identified primarily areas that overlap with the known anatomy of the limbic circuit (e.g., OFC, ACC, insula, thalamus, and cerebellum), suggesting a role for these areas in the generation of PSP. Indeed, it is well established that the insular cortex plays a key role in the suppression of natural bodily urges such as blinking (Lerner et al., 2009), yawning,

swallowing and urinating (S. R. Jackson, Parkinson, Kim, et al., 2011) and that the neural correlates of the ability to suppress these urges overlap greatly with the urge-tic network identified by the work of Bohlhalter, et al. (2006) as shown by a quantitative meta-analysis (S. R. Jackson, Parkinson, Kim, et al., 2011). Primarily, Jackson and others (2011) suggested that the secondary somatosensory cortex (within the parietal operculum), and the posterior and mid-insula are part of a neural network representing bodily sensations, while activity of the anterior insula is associated with the awareness of such sensations. Furthermore, the authors also suggest a network involving the mid- and anterior insula and the cingulate motor area to form a network responsible for the generation of an urge to act, selecting an action that is needed, predicting the most likely outcome of that action, decide if the action is in accord with what is requested (by the sensory input) and if the urge that arose has been satisfied. Finally, parts of this network then, if appropriate, generate the sense that the urge has been satisfied (S. R. Jackson, Parkinson, Kim, et al., 2011).

The thalamus has also been implicated in the generation and maintenance of PSP. Sensory information from the thalamus projects toward the cortex through thalamocortical connections within the internal capsule (Noback, Strominger, Demarest, & Ruggiero, 2005a). Using effective connectivity, Jackson and colleagues (2011) showed that the thalamus is intrinsically connected with the mid-cingulate and insular cortices. Importantly, their analysis showed that the anterior thalamus influenced the cingulate, and the two thus play a part in signalling information of emotional and visceral sensations, which might influence the selection of motor responses. Studies of GM morphology have also emphasised the possible alteration of the thalamic nuclei in TS (Greene et al., 2017; Lee et al., 2006; A. M. Miller et al., 2010). Studies of WM have also shown abnormal structural connectivity of the thalamus (Makki, Behen, Bhatt, Wilson, & Chugani, 2008) and that diffusion of a WM pathway from the hypothalamus to frontal cortex is associated with tic severity in very young patients (Y. Liu et al., 2013). Finally, subcortical sensory areas such as the thalamus and striatum are hyper-connected with the SMA and sensorimotor cortex, which is positively related to tic severity (Worbe et al., 2015). It is therefore possible that TS-related symptoms could be related to thalamic perturbations.

Lastly, I would like to discuss the SM cortex, as this is the focus of the study in Chapter 4. The SM cortex is the composite of the S1 and M1. In TS, WM connectivity between the two has been shown to be altered (Thomalla et al., 2009), while substantial thinning of the SM cortex has been reported in young (Draper et al., 2015; Sowell et al., 2008) and adult (K. Müller-Vahl et al., 2009; Worbe, Gerardin, et al., 2010) patients.

In OCD patients (in which sensory phenomena commonly occurs; Ferrão et al., 2012) one multi-centre study found that OCD with sensory phenomena was associated with increased GM volume in the SM cortex bilaterally in comparison to patients without sensory phenomena. Furthermore, in comparison to controls, patients with sensory phenomena showed significant volume increases in bilateral sensorimotor cortex, left posterior putamen, pallidum and thalamus, while no structural differences were observed between patients without sensory phenomena and controls (Subira, et al. 2015). These results indicate that the presence and the experience of sensory phenomena alone can alter GM volume.

1.5.3 Brain stimulation

Several studies have used brain stimulation and specifically transcranial magnetic stimulation (TMS; see subsection 2.3 in Chapter 2 for explanation on TMS) to study sensory-motor integration in TS. Primarily, it is possible to study the inhibitory effect of a sensory input on the motor output. One study showed that a SAI (short-interval afferent inhibition; applying a TMS pulse to the motor cortex preceded by few milliseconds by a median nerve stimulation, resulting in reduced motor output) was altered in adults with TS (i.e., in TS the TMS pulse after the median nerve stimulation produced greater motor output compared to controls) (Orth et al., 2005). Concomitant with the results of Bohlhalter and others (2006) implicating the SMA in the tic generation, high-frequency stimulation to the SMA in non-TS individuals induces echophenomena (Finis et al., 2012) and the urge to move or unusual sensations (Fried et al., 1991). Therefore, the SMA might be an important mediator between the uncomfortable urge to move and the initiation of movement (Rajagopal et al., 2013).

In patients with FHD, altered posture of limbs can be explained by somatotopic re-arrangement of the SM cortex (Byrnes et al., 1998; Elbert et al., 1994). TMS brain mapping studies have demonstrated that altered segregation of muscle representations might explain abnormal sensory discrimination in patients with dystonia. This is studied in Chapter 4.

1.5.4 Neurotransmitters

Animal models and in vivo work on humans have proven fruitful in elucidating the pathophysiology of TS and the possible role of several neurotransmitters (Draper et al., 2014; McCairn & Isoda, 2013).

1.5.4.1 Dopamine

The efficacy of dopamine antagonists such as risperidone and aripiprazole in ameliorating tics gives strong argument for the central role of dopamine in TS (Buse, Schoenefeld, Münchau, & Roessner, 2013). There might also be a critical role for dopaminergic processing in sensory processing, and this could play a role in the emergence and maintenance of PSP and abnormal sensory processing in TS (Cavanna & Seri, 2013; Rajagopal et al., 2013). Indeed, injection of dopamine agonists into the limbic (ventral) striatum results in marked deficit in sensorimotor gating, providing a causal link between the neurotransmitter and altered sensory processing in TS (McCairn & Isoda, 2013). Support for this comes from post-mortem studies demonstrating increased dopamine transporter, D1 and D2 receptor density, and α 2-adrenergic receptors in the M1, premotor cortex and SMA, DLPFC and OFC (Minzer, Lee, Hong, & Singer, 2004; Yoon, Gause, Leckman, & Singer, 2007) and increased dopamine uptake sites in the dorsal striatum (Singer, Hahn, & Moran, 1991). Caution must however be taken when interpreting these results since majority of these studies are conducted in adults, and secondary compensatory mechanisms cannot be excluded (K. R. Müller-Vahl, Loeber, Kotsiari, Müller-Engling, & Frieling, 2017).

Computational models have argued for the role of dopamine in the formation of PSP, suggesting that tics might be reinforced by positive prediction errors (the

difference between obtained and expected reinforcement) mediated by distinguishing the uncomfortable sensation arising due to PSP and signalled by phasic dopamine (Maia & Conceição, 2017). The insula is then placed as the epicentre of representing the aversiveness associated with PSP (Conceição et al., 2017). This is supported by evidence noting that cues predicting aversive outcome promote the release of DA into the core of the NAcc (Wenzel, Rauscher, Cheer, & Oleson, 2015), and that the termination of aversive stimuli results in release of phasic dopamine (Conceição et al., 2017).

Finally, animal models have also been used and suggest a role for the D1 receptor in sensory symptoms of TS, using the D1CT-7 model, where rodents demonstrate altered PPI (Godar et al., 2016) and impairments in sensorimotor integration (Fowler, Mosher, Godar, & Bortolato, 2017).

1.5.4.2 *Glutamate*

Glutamate is the brain's major excitatory neurotransmitter and the majority of synapses in the brain are glutamatergic (Udvardi, Nespoli, Rizzo, Hengerer, & Ludolph, 2013). *Ex vivo* studies have demonstrated reduced levels of glutamate in the direct projection pathways from the STN (Anderson et al., 1992b, 1992a). *In vivo* studies of glutamatergic neurotransmission in TS is lacking, but two recent studies employing magnetic resonance spectroscopy (MRS) have been published. One study of 37 adult patients showed reduced concentration of the glutamate and glutamine composite in the thalamus and striatum in patients, while an inverse relationship between thalamic glutamate concentration and PUTS scores was noted (Kanaan et al., 2016). As such, patients who are most dissimilar to their peers have greater frequency and severity of PSP. Also, in young patients aged 5-12 years increased glutamate levels in the premotor cortex but unaltered levels in the ventromedial prefrontal cortex, DLPFC, and striatum were found (Mahone, Puts, Edden, Ryan, & Singer, 2018). This indicates that striatal glutamate levels might decrease in adulthood due to compensatory mechanisms to gain control over tics. These results have been somewhat substantiated by studies on neurotransmitter levels taken from the serum (Janik, Kalbarczyk, Gutowicz, Barańczyk-Kuźma, & Kwieciński, 2010)

1.5.4.3 GABA

Conversely, γ -aminobutyric-acid (GABA) is the brain's major inhibitory neurotransmitter and is synthesized from glutamate by glutamate decarboxylase enzymes (Udvardi et al., 2013). In the brain, GABA_A (ionotropic) and GABA_B (metabotropic) receptors exist (Udvardi et al., 2013). It is generally accepted that excessive GABAergic signalling results in sedation, amnesia and ataxia (lack of voluntary coordination of muscle movements) (Xia & Shen, 2018). By contrast, heightened excitement, anxiety, agitation, and exaggerated responsiveness is observed during reduction of GABAergic signalling (Xia & Shen, 2018).

In vivo studies of patients with TS seem to show unaltered subcortical levels of GABA (Mahone et al., 2018; Naaijen et al., 2016). By contrast, GABA levels in cortical structures such as SMA (Draper et al., 2014), SM cortex (Puts et al., 2015) and ACC (Freed et al., 2016) is altered in young people with TS. A relationship between the GABAergic tone of the SM cortex and tactile thresholds has been suggested. Primarily, reduce vibrotactile discrimination thresholds are inversely related to SM (but not occipital) cortex GABA levels (Puts et al., 2015), whereas increased concentration of GABA is associated with greater perceptual acuity (Kolasinski et al., 2017).

Greater role of GABA in TS has been demonstrated using TMS, demonstrating altered GABA-mediated inhibition acting via the GABA_A receptor. This is more comprehensively introduced and discussed in Chapter 4.

1.5.4.4 Histamine

Recent years have seen a rise in interest in another neuromodulator. Histamine (HA) is synthesised by L-histidine (an amino acid) by L-histidin decarboxylase (HDC; an enzyme) and three receptors have been identified in the brain: H1, H2 and H3 (Udvardi et al., 2013). Early observations showed that symptoms of TS could emerge or become more pronounced after administration of antihistaminergic medication (Shafii, 1986).

Subcortically, the tuberomammillary nucleus (TMN; the posterior part of the hypothalamus) contains histaminergic neurons which project and innervate several

areas of the brain including the BG (see Bolam & Ellender, 2016). The BG is a known recipient of histaminergic projections and specifically, the striatum is known to express high density of HA receptors (Bolam & Ellender, 2016). Within the BG, HA has been shown to depolarise striatal MSNs and modulate glutamatergic afferents from cortex and thalamus to MSNs. As such, HA is well capable of directly affecting function of the striatum and BG output (Bolam & Ellender, 2016).

In the realm of TS, recent evidence suggests a role of HA. In particular, one study showed that tic disorders can emerge due to mutation of the HDC gene (Ercan-Sencicek et al., 2010). Furthermore, knockout animals of the HDC gene demonstrated marked reduction in HA concentration in hypothalamus, striatum and cortex, which potentially caused specific behaviours akin to the ones thought to characterise TS (Castellan Baldan et al., 2015). The study by Castellan Baldan and others (Castellan Baldan et al., 2015) also demonstrated that both knockout animals of the HDC gene and humans carrying HDC mutation showed marked deficits in PPI. Interestingly, both haloperidol (a D2 antagonist) and HA infusion resulted in reduced tic-like behaviours (Castellan Baldan et al., 2015). Similar results are observed in H3 receptor knockout animals (Vanhanen, Nuutinen, Tuominen, & Panula, 2016).

1.6 SUMMARY AND AIM

To recapitulate, tics are repetitive stereotyped movements and vocalisations and characterise TS. In addition to tics, patients present multiple comorbidities of which ADHD and OCD are most common. The prognosis of TS is thought to be generally good, and majority of patients find their symptoms to go into remission by adulthood. Symptoms of TS are thought to emerge due to disinhibition of several CSTC circuits including the sensorimotor, associative and limbic loops, where cortical structures project to the BG complex, which is thought to select an appropriate action dependent on the cortical input. Involved are also excitatory and inhibitory neurotransmitters. Another core feature of TS are uncomfortable cognitive and bodily sensations called PSP that are thought to precede the onset of tics and exacerbate during tic inhibition. The neural correlates of PSP are not well understood but are thought to originate due

to improper sensorimotor gating mechanisms, probably within the cortical-BG circuits, resulting in inappropriate or aberrant selection of appropriate actions. The heart of this is the insular cortex which might be responsible for the awareness and relaying of these interoceptive sensations. Additionally, patients often complain of extreme irritation due to exteroceptive stimuli in the absence of altered sensory detection thresholds. Again, it is possible that the insular cortex plays a major role in the subjective feelings of somatosensory amplification in TS. Importantly, myriad of studies has demonstrated altered GM volume and WM structural connectivity in TS, specifically of brain structures part of the sensorimotor and limbic circuits.

In this thesis, a specific emphasis is on the sensory phenomena in young patients with TS. In general, this thesis has two primary research aims: (1) investigate if and then why patients show altered sensory tactile thresholds and further clarify the suggestion that patients demonstrate altered central sensory processing and (2) if young patients with TS demonstrated altered WM diffusion and connectivity, and GM volume of key limbic circuit areas which then can be related to the frequency and severity of PSP. In the end, I will draw conclusion on my results, with the focus that perhaps TS is primarily a sensory disorder.

It is important to note that in this thesis I primarily focus on children and adolescents. Although studies of tic-persistent patients (in adulthood) are important, adult patients with TS only represent a small fraction of the total affected individuals with tic disorders (Leckman et al., 1998). Also, adult patients might demonstrate altered brain state, due to long-term compensatory brain re-organisation as a way to gain control of their tics, in addition to prolonged tic suppression and medication use (Eichele & Plessen, 2013; S. R. Jackson, Parkinson, Jung, et al., 2011). Furthermore, I have put no restriction on medication use or comorbid status as I feel this represents a broader sample of patients with TS. Importantly, in no situation was a patient asked to stop his medication intake prior to participation.

CHAPTER 2

Chapter Two – Methodological consideration. Clinical measures, psychophysics, brain stimulation and brain imaging.

In this chapter I will review key techniques used in this thesis. Prior to introducing each method, the appropriate chapter where the method is used is specified, and one can consider each section as a companion for the respective experimental chapter. First, I briefly introduce the primary clinical measures and questionnaires I used, and specifically the Premonitory Urge for Tics Scale. Subsequently, I will introduce psychophysics and the von Frey monofilaments to test tactile sensitivity. Finally, sections on TMS and MRI follow which were used in this thesis to investigate brain structure.

2.1 PARTICIPANTS AND CLINICAL MEASUREMENTS

2.1.1 *Participants*

All participants who participated in my studies presented in this thesis were from the greater United Kingdom. All patients had confirmed diagnosis of Tourette syndrome except two who participated in the study presented in Chapter 4. One had a diagnosis of a chronic tic disorder and the other had never formally been diagnosed, but symptoms of TS were confirmed in an interview. Patients were mostly children and adolescents who were part of a cohort participating in a longitudinal brain imaging study. Data from this longitudinal study is presented in part in chapters 5 and 6. I

declare that much of the data presented in Chapter 5 was collected by myself (about 50%). Data presented in Chapter 6 was mostly collected by other researchers (within the same lab) than me.

In some cases, young adults were also recruited to participate (in Chapter 4). Participants without TS were always age and gender matched to their respective patient with TS. All studies had an approval from appropriate local ethic committees and written informed consent was collected from all participants, or their parents or guardians. Also, participants always completed health and safety questionnaires (i.e., MRI safety and TMS safety questionnaires) to ascertain if the methods used were suitable for the participant.

Of note, throughout this thesis I have tried to keep consistency in all figures where the TS groups are always coded in magenta ● control groups always in blue ● while general colours are usually a combination of grey ● and cyan ●.

It is also important to note that in all studies (except the study presented in Chapter 4), patients were screened for symptoms of attention-deficit hyperactivity disorder (ADHD) using the Conners-3 self-report measure (Conners, 2008); obsessive-compulsive behaviour (OCB) using Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997); and autism spectrum disorders (ASD) using Social Communication Questionnaire (SCQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999) by a trained clinical research nurse. Also, IQ estimates were obtained from each participant using the vocabulary and matrix reasoning sub-tests from the Wechsler's Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). In all instances, exclusion criteria were as follows: (1) IQ below 70, (2) diagnosis of anxiety, depression or any other form of psychiatric disorder, and learning and sight disabilities, and (3) when a participant had any contraindication to either TMS or MRI such as pacemakers, aneurysm clips or any other ferromagnetic metal in the body or head.

2.1.2 *Premonitory urge for tics scale (PUTS)*

It has become a standard practice in research of patients with tic disorders to measure PSP qualitatively using clinical psychometric instruments. To date one is

prominently used and is called the Premonitory Urge for Tics Scale (PUTS; Woods, Piacentini, Himle, & Chang, 2005). The PUTS is a self-report measure where items assess the intensity and frequency of the PSP and the relationship between PSP and tics (Brandt, Beck, Sajin, Anders, et al., 2016; Woods et al., 2005). Each item is scored from 1 ("Not at all true") to 4 ("Very much true") and asks questions such as "Right before I tic, I feel like my insides are itchy" or "Right before I do a tic, I feel like there is energy in my body that needs to get out" or "I have these feelings almost all the time before I do a tic". Originally a 10-item measure, the authors recommend only to score 9 items due to lack of correlation of the 10th item with the rest (Woods et al., 2005). The 9-items are thus scored and added to generate a total score (with 9 being the lowest score and 36 being the highest possible score). It is thus important to note that in all studies presented in this thesis, the 9 item PUTS scale was used.

Scores on the PUTS of 12.5 – 25.5 indicate medium frequency, 25-30.5 high frequency, and scores 31 and higher indicating extremely high frequency of sensory urges in patients (Reese et al., 2014). In the original publication, the PUTS scale was assessed in 42 young patients (ages 8-16 years) with tic disorders (Woods et al., 2005). The scale demonstrated high internal consistency (Cronbach's alpha = 0.81) and good temporal stability, where results showed that the test-retest reliability at 1 week was $r = 0.79$ and $r = 0.86$ at two-week intervals. Furthermore, Woods and colleagues (2005) also measured the concurrent validity and showed that across the entire sample, PUTS scores correlated significantly with complexity, interference and the global severity scales of the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). Results were, however, much less reliable in a sub-sample of participants aged ≤ 10 years (Woods et al., 2005). In a large sample of adolescents, young and older adults, Reese, et al. (2014) showed very similar results noting good internal consistency (Cronbach's alpha = 0.83), and adequate temporal stability with $r = 0.79$ when the scale was administered at 2 weeks post baseline.

Originally, the PUTS was developed as a single-dimension scale (Woods et al., 2005). It is possible however that the PUTS measures more than one dimension. Indeed, Brandt, et al. (2016) showed that the PUTS might actually measure 3 prime factors: 'quality of PSP', 'overall intensity of PSP', and 'The perceived control over tics and urges'.

Importantly, the study by Brandt, et al. (2016) shows that the PUTS also measures the severity and frequency of PSP. The authors noted a good convergent validity of the scale comparing it to a real-urge monitor, which measures the intensity and frequency of PSP in patients online (Brandt, Beck, Sajin, Anders, et al., 2016; Brandt, Beck, Sajin, Baaske, et al., 2016). Conversely, the study by Brandt, et al. showed bad discriminant validity of the PUTS, since it correlated significantly with the Y-BOCS. This indicates that the PUTS does not discriminate well with urges observed in TS and OCD (Brandt, Beck, Sajin, Anders, et al., 2016; Kano et al., 2015). Note, however, that only the 10-item PUTS correlated with the Y-BOCS, not the 9-item version (Brandt, Beck, Sajin, Anders, et al., 2016). It is also clear that PUTS does not measure any aspects of external sensory sensitivity since no correlation has been found between PUTS scores and a comprehensive battery of sensory testing (Schunke et al., 2016).

Some have even suggested alteration to the PUTS scale, and even created an individualized scale, which measures the presence, frequency, intensity and body region of PSP (McGuire et al., 2016).

2.1.3 Assessment of tic severity

Current symptoms of TS are assessed using the YGTSS (Leckman et al., 1989) for all participants, in all studies presented in this thesis. The YGTSS is a semi-structured clinician-rated measure, which assesses the nature of motor and vocal tics present over the past two weeks. The YGTSS consists of three subscales: Impairment rating, motor tic rating and vocal tic rating. Subjects are questioned on each subscale and encouraged to describe tics specifically regarding the frequency and intensity of their tics. Both motor and vocal tics are scored based on their number, frequency, intensity, complexity and interference, rated on an ordinal scale from 0-5 (thus a maximum score is 25). The overall tic severity score ranges from 0-50. Moreover, impairment is also measured as the distress caused by symptoms on social, academic and occupational day to day functioning, and is taken into consideration (Storch et al., 2005). Impairment is scored on the scale of 0-50. Therefore, the minimum score is 0 and maximum being 100. The YGTSS is almost used exclusively since it has shown to outperform any other

rating measure in terms of internal consistency, stability and discriminant validity (Storch et al., 2005).

2.1.4 *Measuring somatosensory sensitivity, amplification and interoceptive awareness*

In Chapter 4 I qualitatively measured participants' somatosensory sensitivity, amplification and interoceptive awareness for the purpose of relating these to cortical organisation. These three aspects are measured using three separate questionnaires:

The Adult/Adolescent sensory profile [AASP] (C. Brown, Tollefson, Cromwell, & Fillion, 2001) is a 60-item self-report measure and probe for the behavioural response to sensory stimuli. The AASP includes four quadrants, *low registration, sensory sensitivity, sensation seeking and sensation avoiding* and assesses specific sensory types (Dunn, 1997). The scale shows good internal consistency (Cronbach's alpha = 0.64 – 0.78).

The *somatosensory amplification scale [SAS]* is a 10-item self-report questionnaire where responders rate how much each statement is characteristic of them in general on a scale of 1-5 (Barsky, Wyshak, & Klerman, 1990). Higher scores indicate greater symptom amplification. The SAS asks questions such as "When someone else coughs, it makes me cough too" or "Sudden loud noises really bother me". Higher scores indicate a greater tendency to amplify normal body sensations. The scale has also been shown to be effective in assessing psychosomatic phenomena (Nakao & Barsky, 2007). The SAS shows good test-retest reliability (0.79) and good internal consistency (Cronbach's alpha = 0.82) (Barsky et al., 1990).

Finally, to assess the levels of interoceptive awareness, participants completed the Multidimensional Assessment of Interoceptive Awareness [MAIA] (Mehling et al., 2012). The MAIA is an instrument designed to assess interoceptive awareness, consisting of 32-items and eight subcomponents. Each statement is rated on a scale from 0-5 with some questions needing reversed scoring. The MAIA consists of eight sub-scales, tapping into 5 domains of interoceptive awareness and mindfulness (Mehling et al., 2012); Awareness of body sensation, emotional reaction and

attentional response to sensations, the capacity to regulate attention during multiple sensory stimulation, the awareness of mind-body integration and trusting bodily sensations. The MAIA also shows good internal consistency (Cronbach's alpha range = 0.66-0.87).

2.2 PSYCHOPHYSICS

The origin of psychophysics can be traced back to the mid-1800s and is today the pillar of several psychological research domains. Two different types of sensory thresholds based on the work of Gustav Fechner and Ernst Heinrich Weber are primarily used: the *difference threshold* (which is the smallest amount of difference between two stimuli that a person can reliably detect) and the *absolute threshold* (which is the smallest amount of stimulus intensity one can perceive) (F A A Kingdom & Prins, 2011). Work using psychophysics has several advantages. For example, today the methods are computer controlled and avoids the pitfalls of operator bias. Methods can also be used to assess a range of sensory modalities (vision, touch, smell, etc.), while data can be acquired rapidly where one can make general inference on sensory processing (Gardner & Johnson, 2013a). By contrast, psychophysics also carries some disadvantages. For example, stimulus parameters must be carefully controlled and monitored, requiring calibration of the testing equipment which must be maintained to keep level playing fields between participants. Moreover, careful experimental protocol development is essential to avoid learning effects (F A A Kingdom & Prins, 2011).

Psychophysical methods are used in Chapter 3, where I introduce a study to measure and compare tactile sensory thresholds in young participants using a simple Yes-No paradigm. In his seminal work, Fechner described three different types of methods to measure the absolute threshold: *the method of limits*, *the method of adjustment* and *the method of constant stimuli*. The study in Chapter 3 used the method of limits and this is briefly described in text below.

To measure a sensory threshold, a study design must include a range of stimulus intensities. As such, all intensities are introduced to the participant and his

performance is recorded. The stimulus intensities are determined prior to study initiation and are presented in either an ascending (starting with the most salient stimulus) or descending (starting with the lowest stimulus intensity) order. Subsequently, the stimulus intensity is decreased, or increased, until a sensory threshold can be determined. Importantly, during each stimulus presentation, the participant is required to indicate if the stimulus was perceived or not. The primary advantage of this method is that it requires relatively few presentations of each stimulus, compared to for example the method of constant stimuli, and is thus quick to administer (F A A Kingdom & Prins, 2011). Even if few trials are needed, this method is not less sensitive than other alternatives and might be more preferable when quick verbal responses are needed, specifically in the case of children (F A A Kingdom & Prins, 2011).

When the method of limits is used, one variation of the method is to implement the “staircase method” (or 'Up/Down' method; Dixon & Mood, 1948). During a staircase procedure, the stimulus intensity changes in a stepwise fashion depending on the participant's performance. When the participant perceives the stimulus, the intensity of the stimulus is taken down by one level but moved up if not. This continues until sufficient amount of ‘changes’ or ‘reversals’ have occurred. Most often, changes in levels are monitored by a computer which tracks the participant's performance. Another variation of the method of limits is to implement a ‘forced-choice procedure’ (Blackwell, 1952). An example of this is where two or more stimulus alternatives are presented during a trial, where one alternative contains the true signal. When only one outcome is possible the design is termed a 1-alternative forced-choice (1AFC). Commonly, the staircase and forced-choice procedures are used in combination.

2.2.1 *von Frey monofilaments*

To put this into perspective, one example of a detection experiment, implementing the staircase and the force-choice procedures is presented in Chapter 3. Let's say we are interested in testing a participant's sensitivity to mechanical (or affective) touch. First, a range of stimulus intensities are chosen *a priori* and labelled 1-5. These stimuli are then presented in an ascending order starting with the most salient stimulus

intensity (e.g., intensity 5). During each trial, two possibilities exist, either a touch occurs with a specific pressure intensity or no touch occurs. If the participant perceives the stimulus on M number of trials, using the staircase procedure we present the next, less salient, stimulus intensity (e.g., intensity 4) and so on until a tactile sensory threshold can be determined.

In the nineteenth century, Austrian-German physiologist Maximilian Ruppert Franz von Frey developed a specific type of esthesiometer consisting of various calibrated monofilaments (see Figure 2.1). Nowadays we refer to these monofilaments as the von Frey monofilament test. These monofilaments can determine an individual threshold for force detection and can produce the sensation of touch or even pain, but are thought of as a non-invasive psychophysical approach to characterise somatosensory sensitivity (Bradman, Ferrini, Salio, & Merighi, 2015; Yarnitsky & Pud, 2004).



Figure 2.1. An example of a von Frey monofilament.

The monofilament kit consists of 20 calibrated nylon filaments and are mounted at a 90-degree angle on a plastic bar. These monofilaments are capable of delivering forces to the skin ranging from 0.008 – 447 g (or 1.89 - >6.13 target force according to Bradman, et al. 2015, or 0.08 – 4383 milli Newton [mN]). Once bent, the force generated by the monofilaments is constant, regardless of degree of bending.

2.3 TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a type of a non-invasive brain stimulation (NIBS) technique which works via principles of electromagnetic induction (Hallett, 2000). TMS produces a current which easily penetrates both the scalp and the skull (the skull has low impedance and thus offers little resistance) and induces a depolarisation of neurones or their axons (Hallett, 2000). TMS is applicable to a wide range of experimental research and has been used in studies where the aim is to temporarily produce transient functional lesions in the brain to assess the behavioural consequences (e.g., Siebner & Rothwell, 2003). However, commonly, and most relevant to this thesis, TMS can be used to study structure and function of the SM cortex.

A critical advantage of stimulating the SM cortex is the production of a brief, cortically driven muscle contraction termed motor evoked potential (MEP) which can be measured using electromyography (EMG) (Hallett, 2000). When delivered at a critical intensity (i.e., above an individual motor threshold), and producing MEPs, TMS is thought to primarily activate, both directly and trans-synaptically, pyramidal tract neurones, which project monosynaptically to alpha motoneurones (Di Lazzaro, Ziemann, & Lemon, 2008; Rothwell, Thompson, Day, Boyd, & Marsden, 1991). TMS is regarded as a safe technique, while minimal adverse events have been reported in the literature (Rossi et al., 2009). Importantly, TMS is safe to use in children and adolescents, where the most common complaints of adverse events include headaches and scalp discomfort (Krishnan, Santos, Peterson, & Ehinger, 2015). Importantly, Krishnan and colleagues (2015) suggest that if safety guidelines are followed, TMS is considered a very safe brain stimulation modality for use in sensitive clinical populations.

Depending on the stimulation parameters TMS can be used to investigate changes in cortical excitability, trans-callosal communication or to induce neuroplasticity (see Siebner & Rothwell, 2003). Two of these variants are discussed below, single-pulse TMS (spTMS) to measure corticospinal excitability (CSE) and paired-pulse TMS (ppTMS) to

measure cortical inhibition. These parameters are employed in the study presented in Chapter 4.

2.3.1 Single-pulse TMS & sensorimotor cortex mapping

Single TMS pulse is thought to produce a strong and synchronised depolarization of multiple corticospinal cells and/or interneurons (Di Lazzaro & Ziemann, 2013). Single-pulse TMS (spTMS) can be used to assess changes in corticomotor and cortico-cortical connections (Siebner & Rothwell, 2003). Primarily, in Chapter 4 I employ spTMS to assess the location and distribution of muscle representations on the SM cortex, in a process termed TMS mapping (Wassermann, McShane, Hallett, & Cohen, 1992; Wilson, Thickbroom, & Mastaglia, 1993). As such, spTMS is used to assess individual cortical excitability.

TMS is an appealing method since, in the realm of research, TMS can be used to individually tailor the experimental protocol. This is achieved by identifying a motor threshold at rest (rMT), when there are no visible artefacts in the EMG recording prior to a TMS pulse. rMT can be considered as a general measure of cortical excitability, and most likely depends on ion channel conduction (Ziemann, Lönnecker, Steinhoff, & Paulus, 1996). Studies have also demonstrated a role for glutamatergic neurotransmission, since cortical excitability can be altered through the administration of ketamine (a NMDA receptor antagonist) (Di Lazzaro et al., 2003). As such, TMS stimulates excitatory (glutamatergic) cortico-cortical fibers, which synapse on corticospinal tracts (the corticospinal tract [CST] is a major WM pathway projecting from the SM cortex and terminates in motor neurons and interneurons on the spinal cord, sub-serving all major motor control functions; Kalaska & Rizzolatti, 2013) (Di Lazzaro & Ziemann, 2013). MTs are determined from targeted area of the cortex, and motor outputs are recorded from muscle(s) of interest. The most common targeted muscles are the first dorsal interosseous (FDI), abductor pollicis brevis (APB) and the abductor digiti minimi (ADM), since all represent a large section of the SM cortex and are easily located using TMS. Most are then used as motor 'hotspots' for cortical motor output (Shahana & Gilbert, 2013). The rMT can be used as an indication of the

excitability of corticospinal projections from the primary motor cortex of the motor 'hotspot' (Di Lazzaro & Ziemann, 2013).

MTs are usually identified through a trial-and-error procedure (Rossini et al., 1994). TMS pulses are systematically delivered to a pre-defined area (e.g., FDI) of the cortex, starting with a supra- or sub-threshold pulse intensity and the intensity is adjusted accordingly in a step-wise fashion. The MT is then recorded as the pulse intensity (often reported as the percentage of maximum stimulator output [MSO]) yielding a peak-to-peak MEP amplitude between 50-100 μ V in >5 out of 10 trials (Groppa et al., 2012; Rossini et al., 1994). Determining the MT is the simplest way of assessing individual CSE, reflecting stimulation of the CST. As noted above, spTMS can also be used to make inferences on SM cortical organisation.

Neurologist John Hughlings Jackson was perhaps the first to demonstrate that motor maps exist on the cortex (Kalaska & Rizzolatti, 2013). In his heyday, Jackson showed that specific areas of the cerebral cortex had causal roles in motor movement in humans (Kalaska & Rizzolatti, 2013). Subsequently, motor mapping studies determined that cortical areas responsible for controlling muscles of the finger, hand and distal arm were concentrated at a central cone of the motor cortex, while more proximal arm muscles are found in a horseshoe-shaped ring at the central core (Kalaska & Rizzolatti, 2013).

As previously stated, TMS can be used to construct and make inference of the gross somatotopy of the motor homunculus (Siebner & Rothwell, 2003). As such, TMS-generated cortical representations (also known as a motor maps) is defined as the area of the motor cortex, eliciting MEPs in a targeted muscle after repeatedly stimulating a predefined area of the cortex at constant intensity (Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998). Motor maps can therefore be considered to be related to the origin and spatial distribution of the pyramidal tract neurones (Di Lazzaro et al., 2008; Rothwell et al., 1991). Once MEPs have been collected, the position or coordinates of the TMS location on the scalp and the MEPs are synchronized (either on- or offline) to create topographical maps of motor representations, where stimulus position is placed on the x- and y-axes, and MEP amplitude on the z-axis (van de Ruit, Perenboom, & Grey, 2015; Wassermann et al., 1992; Wilson et al., 1993). Figure 2.2 is an example of this.

These maps therefore represent CSE across the SM cortex of the targeted muscle(s), and can be reliably related to the somatotopy of the SM cortex in an individual (Wassermann et al., 1992; Wilson et al., 1993).

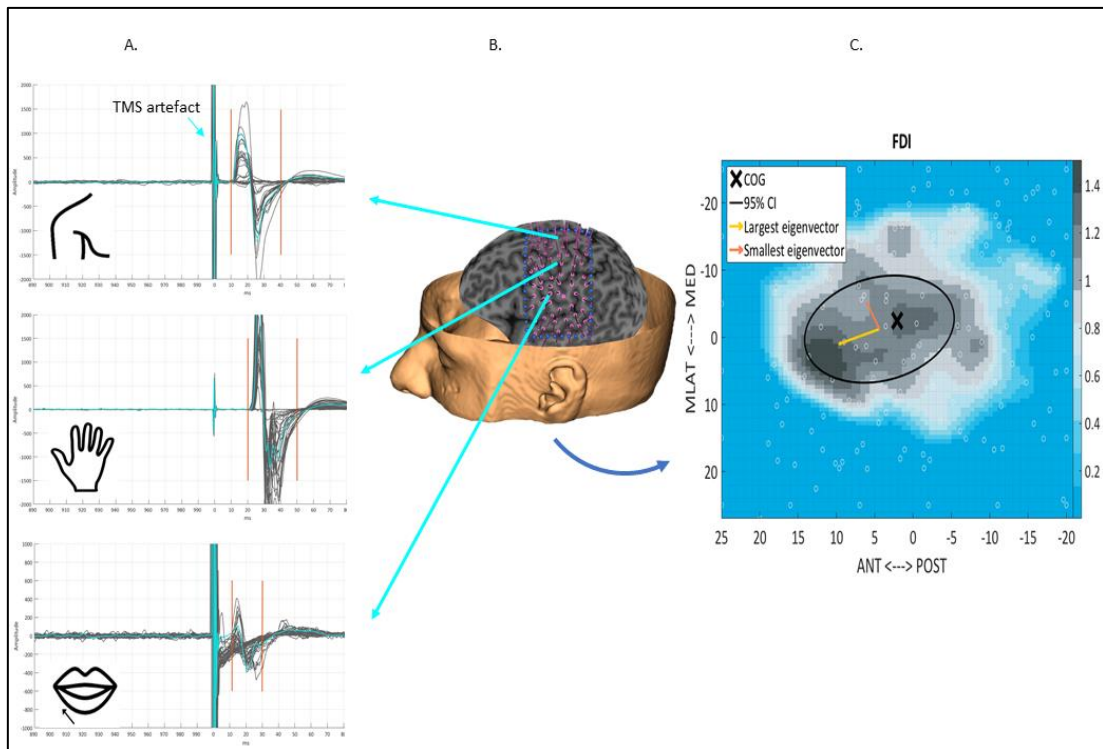


Figure 2.2. Figure depicting how a cortical motor map can be constructed. A: MEP amplitudes are recorded from different muscles of interest and synchronised with TMS stimulation locations (B). C: From MEP amplitudes and stimulation locations a 2-dimensional contour plot is constructed. LAT = lateral, MED = medial, ANT = anterior, POST = posterior.

In addition to simply probing for location and outline of motor representations, TMS generated maps can also be used to make inference on the effect of learning or re-learning a motor skill. This is primarily thought to reflect the effect of neuroplasticity on cortical organisation (Feldman & Brecht, 2005; Siebner & Rothwell, 2003). In many ways, motor learning, sensory stimulation and sensory de-afferentation can induce neuroplasticity and TMS mapping can be used to measure the extent of changes in cortical organisation (Donoghue, 1995; Feldman & Brecht, 2005; Hamdy, Rothwell, et al., 1998; Pons et al., 1991; X. Wang, Merzenich, Sameshima, & Jenkins, 1995). Also, cortical re-organisation can be observed using TMS maps following brain infarcts (Hamdy, Aziz, et al., 1998). As such, TMS generated cortical maps can easily be implemented into clinical populations and even in clinical practice. In fact, the most

common usage of TMS mapping in clinical work is pre-operative motor mapping (Krieg et al., 2017). Neuroplasticity and TMS mapping are discussed further in Chapter 4.

SM cortical mapping using TMS like the methods used by Hamdy and colleagues (1998) has recently come into vogue due to technological advances and immediate availability of TMS equipped with a neuronavigation system (which utilises frameless stereoscopy; see more detail below). Such cortical neuronavigated TMS (nTMS) maps have been used to localise and outline motor representations more efficiently and reliably (van de Ruit & Grey, 2016; van de Ruit et al., 2015). The neuronavigation system (i.e., image-guided frameless stereotaxy) allows easy tracking of the coil and the participants head with the use of an infra-red camera and spherical reflector trackers, mounted on the coil and the participant's forehead. Importantly, TMS mapping in conjunction with a neuronavigation system have been shown to improve quality of MEPs (Julkunen et al., 2009). Employing neuronavigation one can get better estimation of the position, orientation and the angle of the TMS coil over the targeted region on the scalp (Julkunen et al., 2009; Ruohonen & Karhu, 2010). The BrainSight neuronavigation coordination system is akin to the Cartesian system, where location of the coil on the scalp is given in X Y Z space, whereas coordinates of the coil are given as direction cosines and track the pitch, roll and yaw of the coil position, thereby determining the orientation of each stimulation. The output from BrainSight is shown in Equation 2.1.

$$BrainSight = \begin{bmatrix} X_{scalp} & X \bullet x & X \bullet y & X \bullet z \\ Y_{scalp} & Y \bullet x & Y \bullet y & Y \bullet z \\ Z_{scalp} & Z \bullet x & Z \bullet y & Z \bullet z \end{bmatrix}$$

Equation 2.1. BrainSight coordinate system, consisting of TMS coil position and orientation in space. The coordinate system is adapted from van de Ruit, et al. (2015).

Commonly, TMS cortical maps are created by locating muscles of the upper extremities such as the hand, bicep or shoulder (van de Ruit et al., 2015; Wassermann et al., 1992; Wilson et al., 1993). Recently, however, two studies showed the feasibility

of mapping facial muscles (Säisänen et al., 2015; Weiss et al., 2013). Stimulating facial muscles is inherently difficult, due to several impediments such as the danger of artefacts contaminating the EMG signal (e.g., peripheral nerve stimulation), rendering it difficult to distinguish the true MEP. Some upper facial muscles (e.g., orbicularis oculi) are innervated bilaterally, which again could contaminate the EMG signal (Cruccu, Berardelli, Inghilleri, & Manfredi, 1990; Paradiso, Cunic, Gunraj, & Chen, 2005). Finally, the resting motor threshold of facial muscles is high, whereas the MEP amplitude is low (Paradiso et al., 2005; Säisänen et al., 2015; Weiss et al., 2013). These issues can be avoided with appropriate methods such as with proper coil orientation (Dubach, Guggisberg, Rösler, Hess, & Mathis, 2004). Also, MEPs have a very discrete shape and are easily distinguishable from artefacts. Moreover, MEPs from facial muscles such as the orbicularis oculi can be distinguished from the blink reflex based on the latency of the cortical MEP (Säisänen et al., 2015).

Using a nTMS mapping procedure, Saisanen and colleagues (2015) successfully located and outlined six facial muscles including the eyes (orbicularis oculi), lips (orbicularis oris) and jaw (masseter) in healthy participants. As expected, lower facial muscle representations mapped onto the precentral gyrus, but the total area of MEPs extended beyond and into the ventral premotor cortex and the postcentral gyrus. The study by Saisanen, et al. showed that latency for facial muscles, ranging between ~11-20 ms, was much shorter than what is commonly observed in upper extremities.

In addition to the issue of mapping facial muscle representations, collecting nTMS maps can be time consuming. However, more recently one group based in Birmingham UK, headed by Michael J. Grey, proposed an alternative method of acquiring TMS maps more rapidly and efficiently (see van de Ruit et al., 2015). The authors used a method termed '*pseudorandom walk method*', where MEPs are sampled randomly across the SM cortex. Offline, a map is constructed by synchronising MEPs with coordinate location of the stimulating TMS coil, combined with a sophisticated mathematical approach. Using this method, there is no need to place the TMS coil in pre-defined positions and consequently acquisition time can be reduced. In two studies by Grey's group, the pseudorandom walk method was compared with the more traditional grid-based methods, by mapping the hand muscle (van de Ruit & Grey, 2016; van de Ruit et

al., 2015). In the context of the study in Chapter 4, two important findings were reported: (1) only time spent collecting a map differed, while both accuracy and reliability were unaltered and (2) different stimulation intensities affected the size of the motor maps obtained, but not the shape or the location of the targeted muscle (van de Ruit & Grey, 2016; van de Ruit et al., 2015). Importantly, this pseudorandom walk method might be considered more ideal to use in patient populations, where time-consuming protocols are discouraged, especially in patient populations who might otherwise have difficulty remaining still for more lengthy research protocols. The *pseudorandom walk method* is employed in the study presented in Chapter 4.

2.3.2 Paired-pulse TMS

In contrast to spTMS where a single pulse is delivered in isolation, paired-pulse TMS (ppTMS) is a popular method of assessing intracortical inhibitory mechanisms (see Figure 2.3). Using two, separate but connected TMS machines, two TMS pulses (one-sub threshold [conditioning stimulus] and another supra-threshold [test stimulus]) are delivered in close synchrony (usually 1-5 ms) (Kujirai et al., 1993). As a consequence, one can observe a decrease in MEP amplitude compared to if the same supra-threshold pulse was delivered alone, thought to occur due to the conditioning effects of the preceding pulse. This is termed short-interval intracortical inhibition (SICI) and is one method of quantifying the output of either inhibitory or excitatory interneuronal circuits in the motor cortex (Shahana & Gilbert, 2013). SICI has been extensively investigated in movement disorders, including TS (Berardelli et al., 2008; Ziemann, Paulus, & Rothenberger, 1997).



Figure 2.3. The figure depicts the MEP resulting from a single pulse TMS (left) and paired-pulse TMS paradigm (right). The consequence of the preceding (by 3 ms in this case) sub-threshold conditioning pulse is clear in the reduced MEP amplitude.

The inhibitory potential of the conditioning stimulus is not yet fully understood. However, many believe that it activates low-threshold inhibitory (GABAergic) circuits and this results in a synaptic inhibition of the corticospinal cells which are stimulated by the subsequent test stimulus (Di Lazzaro & Ziemann, 2013; Petersen, Butler, Taylor, & Gandevia, 2010). The characteristics of the inhibition produced by the conditioning pulse has been studied in pharmacological studies (see Ziemann et al., 2015). In particular, SICI is thought to be dependent upon GABA_A receptors. Several studies have demonstrated that administration of Benzodiazepines (positive modulators of GABA_A) cause greater cortical inhibition. Similar effects are observed during administration of dopamine agonists (i.e., increased SICI), while dopamine antagonists decreased the SICI effect (Ziemann et al., 2015). This is perhaps not surprising since both dopamine and GABA are known to interact in the primary motor cortex (Lindenbach et al., 2016).

In most SICI protocols, several conditioning stimulus intensities are used intermixed with the test stimulus alone. Magnitude of inhibition is then determined by the ratio between the amplitudes of the two. SICI is employed and studied in TS in Chapter 4.

2.4 MAGNETIC RESONANCE IMAGING

The study of brain structure and function has been an area of interest since Gall and Spurzheim coined the term 'phrenology' and hypothesised that the brain consisted of 27 functionally distinct organs (Young, 1968). Fast forwarding past the discovery of X-rays by Conrad Roentgen and the development of the computed tomography scanner, magnetic resonance imaging (MRI) is one of the fastest growing field in neuroscience research today. The popularity of MR imaging results from its ability to acquire high-resolution images of the brain and other organs non-invasively. The MRI relies on the properties of nuclear magnetic resonance, which measures the electromagnetic radiation when nuclei are influenced by a magnetic field (Jezzard & Clare, 2001). When placed in an external magnetic field, hydrogen atoms in our body (which have magnetic properties) resonate at a frequency detectable by radio frequency coils (Jezzard & Clare, 2001). MRI scanners can have different magnetic field strengths, with 3 and 7 Tesla being the most common. All imaging studies presented in this thesis were collected on a 3T Philipps MRI scanner at the Sir Peter Mansfield Imaging Centre in Nottingham. More detailed description of MRI principles is generally beyond the scope of this thesis and rather I will describe two methods employed in this thesis to make inferences on WM diffusion and connectivity using diffusion tensor imaging (DTI) and GM volume (voxel-based morphometry [VBM]) from structural MRI (sMRI). Before, I think it is important to mention that during brain imaging analyses, the brain is always split into voxels (3D pixels) often with resolution of 1-3 mm. Each voxel is thought to include neural cell bodies, axons, dendrites, glia and blood vessels (Paus, 2005).

2.4.1 *Diffusion Tensor Imaging*

MR imaging can be used to measure the diffusion of water molecules in tissue. The word diffusion refers to the process where molecules interact due to their kinetic energy of random motion and in an isotropic environment (e.g., inside a glass of water) water molecules diffuse randomly according to Brownian motion (Le Bihan, 2003). Water molecule diffusion in the brain can be anisotropic or isotropic, and this can be

used to infer on the microscopic details of tissue (Le Bihan, 2003). Anisotropic diffusion occurs due to the architectural properties of the tissue itself (i.e., anatomical boundaries). For example, inside an axon, water molecules have low probability of crossing the neurones membrane (Le Bihan, 2003). These properties can be measured and quantified by DTI, and as such DTI allows the characterisation of the magnitude, direction and orientation of the diffusion of water in both normal and diseased brain *in vivo* (Basser, Mattiello, & Le Bihan, 1994; Le Bihan, 2003). Fundamentally, the DTI signal is primarily modulated by myelin in WM and in turn DTI itself can be used to surmise on different properties of WM tracts such as the density and myelination (A. L. Alexander, Lee, Lazar, & Field, 2007; Assaf & Pasternak, 2008). As is depicted in Figure 2.4, diffusion in tissue varies with direction and is least restricted parallel to the orientation of the fibres, while being much more restricted perpendicular to them (Nucifora, Verma, Lee, & Melhem, 2007).

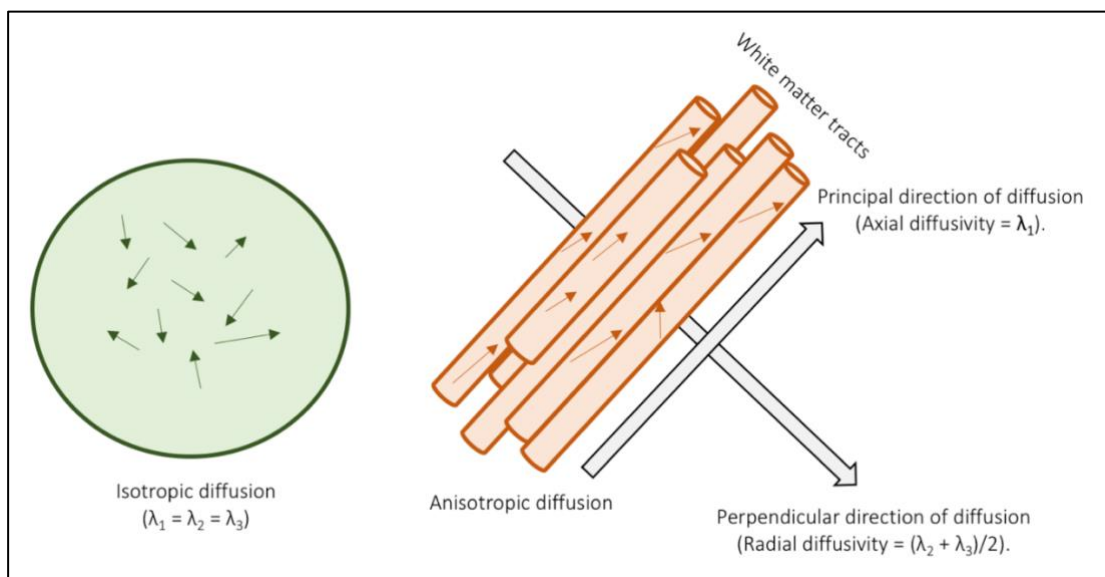


Figure 2.4. Diffusion can be either isotropic or anisotropic. Isotropic diffusion (left) refers to the sort of diffusion which has the same properties in all directions (freely moving). Anisotropic diffusion (right) is not isotropic, rather is diffusion with different properties in different directions.

In this thesis, I primarily focus on brain structure, where description of DTI can be considered a functional imaging technique. However, Symms and others (2004) argue

that diffusion MR imaging should rather be considered as a technique measuring the structural integrity of the brain, since different metrics (discussed below) measure the structural integrity of WM fibre tracts.

During diffusion imaging, we can combine direction and the amount of diffusion and compute diffusion tensors, which are then fitted to each voxel of the brain. Each tensor is defined by six parameters. These are three eigenvalues (λ_1 [longest axes], λ_2 [middle axes], λ_3 [shortest axes]) which define the shape of the tensor, and three eigenvectors (V_1 , V_2 and V_3) which define the orientation of axes (A. L. Alexander et al., 2007). These six parameters are summarised in a 3x3 diffusion tensor D :

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

Equation 2.2. The diffusion tensor D defined by six parameters (see text for explanation).

The diagonal elements of the diffusion tensor D represent the diffusion along the x, y, and z axes (effectively (λ_1 , λ_2 , λ_3) and the off diagonal represent the correlation between the diffusion in perpendicular directions (A. L. Alexander et al., 2007; Basser et al., 1994). Based on the information about different directions of travel, we can construct several DTI metrics or scalars: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). The most commonly reported metric is FA. FA is a measure of the main direction of diffusion and is calculated as the fraction of all eigenvalues (Basser & Pierpaoli, 1996). FA can range from 0 – 1, where 0 indicates unrestricted diffusion (See Figure 2.4|left [all eigenvalues are similar and the diffusion is considered isotropic]). The closer FA is to 1, diffusion of water molecules becomes more restricted (See Figure 2.4|right [in this case one eigenvalue predominates and the tensor will have a cigar-shape]). Changes in FA can be attributed to several causes. Density of axon bundles and extent of myelination have been hypothesised to influence regional FA (reviewed in Beaulieu, 2009). It is most safe to assume that changes in FA potentially reflect differences in some aspects of connectivity, but cannot ascertain the specific type of change (e.g., aspect or direction

of change (A. L. Alexander et al., 2007; Jones, Knosche, & Turner, 2013). Some have argued, based on animal models that FA can be an indication of density of axons, (Song et al., 2002). FA tends to be high in areas on WM with high proportion of myelination but low in others such as in ventricles which are largely filled with CSF (Beaulieu, 2009).

MD is the mean of all eigenvalues ($(\lambda_1+\lambda_2+\lambda_3)/3$) and is a measure of overall diffusion without making a distinction in what direction. The first eigenvalue (λ_1) is used to represent AD (diffusion parallel to the principal axis of the tensor), while RD (diffusion perpendicular to the principal axis of the tensor) is the average of the second and third eigenvalues ($(\lambda_2+\lambda_3)/2$). Limited work on humans using a model of callosotomy suggest that AD is governed by the integrity of axons, whilst RD is modulated by myelin in WM (Concha, Gross, Wheatley, & Beaulieu, 2006; Song et al., 2005; Tyszka, Readhead, Bearer, Pautler, & Jackobs, 2006). However, what these scalars exactly measure is currently unknown, and several factors must be considered prior to interpretation. For example, interpretation can differ based on the targeted sample of participants (e.g., type of underlying condition). In Chapter 5 I employ two methods to analyse DTI data: TBSS and probabilistic tractography. This is introduced below.

Tract-based spatial statistics (TBSS) is a whole-brain non-hypothesis driven approach to determine the characteristics of diffusion of water molecules in the brain (S. M. Smith et al., 2006). One of the advantages of this approach is that it is fully automated and operator-independent, hence there is little danger of an operator bias. TBSS projects volumetric data onto a white matter skeleton (see Figure 5.1 in Chapter 5). This method gains statistical power due to dimensionality reduction and thus circumvents the partial volume effect (PVE; S. M. Smith et al., 2006). TBSS is an attractive method due to its power in adjusting for image misalignment and renders data smoothing unnecessary. Several studies have demonstrated altered WM diffusion of key WM tracts connecting cortical and BG structures (Govindan, Makki, Wilson, Behen, & Chugani, 2010) and increased diffusion in bilateral S1 in TS (Draganski et al., 2010) using TBSS.

As noted above, FA is the most commonly reported measure of water diffusion. However, it is important to note that measures of diffusion such as FA can be distorted due to crossing fibers in the brain. Several well characterised WM pathways such as the

uncinate fasciculus (a WM pathway connecting several GM structures part of the limbic circuit) are particularly loaded with such crossing fibers, and consequently FA will be low in these tracts (A. L. Alexander et al., 2007). Measures of water diffusion can also be distorted due to the PVE, where voxels contain high amount of both GM and WM. Water diffusion is much lower in GM compared to WM.

The FA maps used in TBSS, can also be used to make inferences on WM structural connectivity of GM structures. This is called tractography and can be thought of as a 3D re-construction of the WM pathways in the brain (A. L. Alexander et al., 2007). A key step in tractography is to select a “seed area” from which to start the search for a tract, and move in small steps to trace the tract until the tracker hits a voxel below a specific diffusion value or until hitting a bend beyond the *a priori* chosen degree termination criteria (Behrens, Johansen-Berg, et al., 2003). Using this method, one can realistically re-construct the WM pathways of the brain such as the corticospinal tract, internal capsule and the anterior thalamic radiation, and make inferences on differences in structural connectivity both between and within groups. Two variants of tractography exist: *deterministic* and *probabilistic*. In Chapter 5 I employed probabilistic tractography, which searches for the most probable orientation of the fibre tract at each voxel of the brain through numerous iterations based on the data (Behrens, Johansen-Berg, et al., 2003). The advantage of this method is that it can reliably represent uncertainty in the data (Behrens, et al. 2003) and reliably reconstruct crossing fibers and thus terminates the search quickly once the degree of bending criteria is violated (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). The disadvantage of this method compared to its counterpart (deterministic) is that it is very computationally heavy and time consuming. Using tractography, Worbe and colleagues (2015) for example showed that adult patients with TS show enhanced structural connectivity between several cortical regions and the striatum and thalamus, primarily within the left hemisphere. Moreover, this study also showed hyperconnectivity between the thalamus and putamen in patients, which correlated positively with tic severity scores (such that greater connectivity between the two nuclei is associated with greater severity of tics) (Worbe et al., 2015).

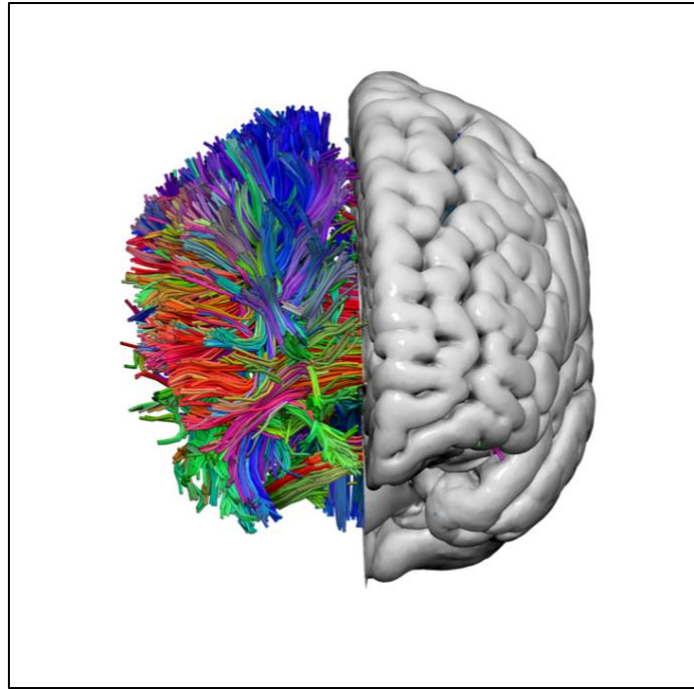


Figure 2.5. This figure depicts the major WM tracts in the brain and also gives an indication of directionality, which then makes inference on water diffusion possible. Red = left-right, green = posterior-anterior, blue = inferior-superior. The figure is created using SurfIce rendering program by Chris Rorden at McCausland Centre for Brain Imaging.

2.4.2 Structural MRI

Structural MRI (sMRI) are detailed anatomical images of the brain. sMRI images can be used to investigate either whole brain or region-specific volume, density or magnitude, non-invasively. sMRI images provide a good contrast between GM and WM, which is imperative to study various conditions affecting the CNS such as demyelinating diseases or neurodevelopmental disorders such as TS to assess GM volume or thickness. The sMRI images used in Chapters 5 and 6 are T1-weighted images of the brain, acquired using the ‘magnetization-prepared rapid gradient-echo’ (MPRAGE). These images provide excellent contrast between GM and WM since WM has shorter relaxation time and will appear brighter on the images than GM (Paus, 2005). This generates the possibility of separating the two and in the case of the study in Chapter 6, separate GM from WM and study GM alone. Below I introduced two computational analyses of sMRI images: VBM and pattern recognition (i.e., machine learning).

2.4.3 *Voxel-based morphometry*

The combination of structural MRI and computational morphometry have proven fruitful in describing differences in local composition of brain tissue (Mechelli, Price, Friston, & Ashburner, 2005), specifically in individuals with movement disorders (Whitwell & Josephs, 2007). One way of achieving such results is to use voxel-based morphometry (VBM). VBM is an automated, operator independent, imaging analysis technique. VBM brings about the possibility to compare segments of the brain using structural sMRI scans, both between and within groups of subjects (Ashburner & Friston, 2000). This imaging analysis technique is popular, mainly due to its simple application and the derived results are biologically plausible (Whitwell & Josephs, 2007), where the aim is to localise changes or differences in GM (or WM) while controlling for any differences in gross anatomy and position (Mechelli et al., 2005).

Prior to statistical analysis between- or within groups, several preprocessing steps are taken which include image segmentation, normalisation and smoothing of the images (Mechelli et al., 2005). During segmentation, the raw brain images are separated into GM, WM and CSF using tissue probability maps, which are based on signal intensities. Following, the normalisation step registers the individual images to a standardised template (e.g., MNI) and resamples the images to a 1 or 1.5 mm resolution. This is important to prevent the occurrence of PVE. Finally, the images are smoothed using a Gaussian kernel (most often an 8- or 12-mm full-width half maximum [FWHM] kernel). This step is important for several reasons (Ashburner & Friston, 2000) since smoothing: (1) ensures symmetry of tissue in each voxel from neighbouring voxels, (2) renders the data more normally distributed and aids in statistical validity, and (3) compensates for the inexact nature of the normalisation step. Smoothing also aids in reducing the number of statistical comparisons, and thus consequently reduces the amount of multiple comparisons (Ashburner & Friston, 2000; Mechelli et al., 2005). Finally, to correct for the confounding effect of variable brain sizes of participants in a study, it is imperative to compute the total intracranial volume (TIV) which is the sum of all three tissue classes. Subsequently, this variable is inputted as a nuisance variable in any statistical analyses. Some have, however, criticised the technique since it might possess reduced effectiveness to detect spatially complex and subtle group differences

(Davatzikos, 2004). Therefore, a more sensitive approach could be necessary to detect such subtle group differences of maturing individuals such as those with and without TS. VBM is applied as a technique in Chapter 6 to investigate the long-term effects of having TS on brain GM volume. Also, the relationship between change in volume and the presence and frequency of PSP is investigated.

2.4.4 *Machine learning*

Statistical analysis of VBM data using standard software packages such as SPM or FSL represents a univariate approach of identifying GM volume differences in participants. Multivariate pattern recognition (PR) techniques (also known as machine learning) are nascent way of analysing sMRI data and have been proven successful in labelling individual brains according to diagnostic status (i.e., the machine assigns a subject [or a brain] into one of two or more classes). For example, PR methods have been used to correctly label (or predict) individual brains such as in the case of children and adults using fMRI (Dosenbach et al., 2011). Moreover, PR methods have been used to distinguish patients from cognitively normal individuals (Kloppel et al., 2012) or predict changes in GM volume using structural MRI in postpartum mothers (Hoekzema et al., 2017) with high accuracy. PR methods have also been successfully applied to longitudinal brain imaging datasets. For example, one study recently demonstrated the ability of PR to classify converters and non-converters to Alzheimer's disease correctly, when investigating patients with mild cognitive impairment (Adaszewski et al., 2013). As such, a specific 'brain state' can be used for the prognosis of neurodegenerative diseases. Therefore, this versatile method might be well suited to study TS-related changes in GM volume, measured at several timepoints. This is exactly what will be done and shown in Chapter 6.

The advantage of multivariate methods in comparison to univariate, is that the former considers information of all *features* (in this case brain regions) as opposed to considering features as independent (as in the case of the univariate approach). In the context of brain imaging, PR automatically searches for patterns in a whole-brain multidimensional data and PR can describe potential neuroimaging biomarkers, and as

such might become a valuable clinical diagnostic tool by individualising clinical treatment (Kloppel et al., 2012; Mwangi, Ebmeier, Matthews, & Douglas Steele, 2012).

Prior to any mathematical computations, all data is pooled and divided into two separate datasets, one that is used for training and one that is used for testing. The pipeline of PR occurs in two stages. First, the machine attempts to learn characteristic patterns in the data while membership labels (i.e., patients/controls) is known. This is called the *training stage*. Next, the dataset for testing is presented, while labels are obscured. Here the algorithm uses knowledge from the training stage to classify this newly, never before seen data. This is known as the *test stage*. Commonly, this process is repeated multiple times as ‘cross-validation’. The most basic and commonly used form of cross-validation is called the leave-one-out (LOOCV), where each datapoint is used in the test stage one (commonly used in brain imaging where datapoints are small; Kloppel et al., 2012). For the purpose of this thesis and the study presented in Chapter 6, a single subject is removed from the pool of subjects, then a classifiers accuracy is estimated by its ability to predict this subject’s correct group label. Performance of the classifier is reported as mean accuracy, sensitivity and specificity:

$$Accuracy = \frac{TP + TN}{TN + FN + FP + TP}$$

$$Sensitivity = \frac{TP}{TP + FN}$$

$$Specificity = \frac{TN}{TN + FP}$$

where TP = true positive (number of subjects correctly classified), TN = true negative (number of controls correctly classified), FP = false positive (number of normal controls classified as patients), and FN = false negative (number of patients classified as normal controls). Results can also be portrayed as a confusion matrix or in a contingency table. When performance of the algorithm exceeds the expectation by chance we can reject the null hypothesis stating that the data holds no information about the label being predicted (Schrouff et al., 2013).

In this final paragraph I will discuss a specific type of ‘machine’ which is subsequently implemented in Chapter 6. To classify, several machines or classifiers can

be used such as support vector machine (SVM), which is perhaps the most common machine used. Using SVM, the machine classifies data into groups by searching for a hyperplane which can be drawn to separate the data (Mwangi et al., 2012). Recently however, studies have started to use different type of machines such as multiple-kernel learning (MKL; Gönen & Alpaydın, 2011), and this has been applied in TS (Wen, Liu, Rekik, Wang, Zhang, et al., 2017). MKL uses multiple kernels rather than relying on a single kernel as SVM does, and this can often lead to a much better solution of the data. This has the advantage of determining the contribution of each area of interest (e.g., using an atlas) to the discrimination (or decision function) (Gönen & Alpaydın, 2011). As such, greater and more in-depth details are attained using MKL machine. Imagine the problem depicted in Figure 2.6|left, here there is little possibility of drawing a best line to separate the two groups. Using MKL, we project the data from original space to higher dimension (Figure 2.6|right) and now it is possible to find the best hyperplane, resulting in better classification. MKL has been shown to outperform (i.e., increased classification accuracy and enhanced interpretability) other classification techniques, specifically when using sMRI (Hinrichs, Singh, Xu, & Johnson, 2011).

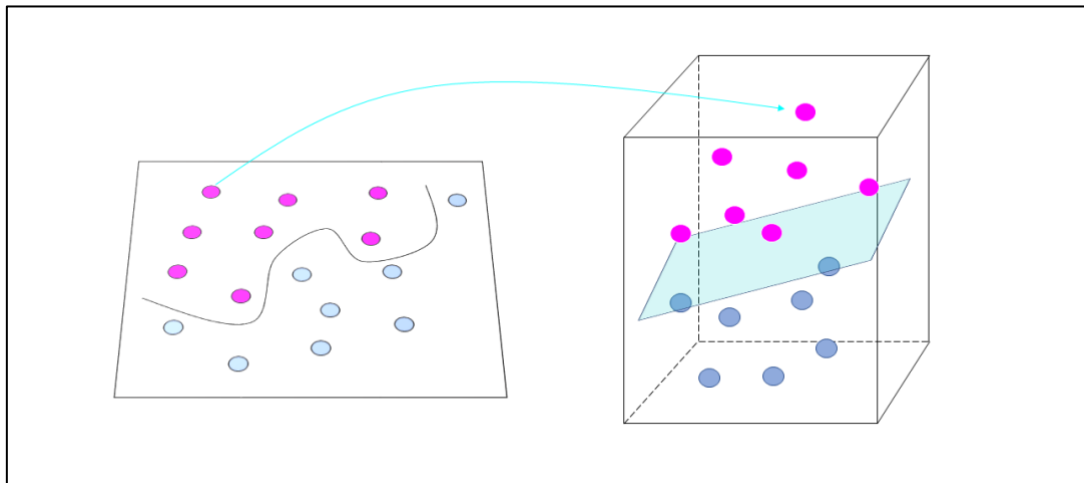


Figure 2.6. An example of a problem solved using MKL.

CHAPTER 3

Chapter Three – Quantifying tactile sensitivity in Tourette syndrome using tactile force detection

Patients with Tourette syndrome (TS) often report increased sensitivity to external stimulation, as measured by self-evaluation questionnaires. Empirical studies to date have not been able to clarify the perceived sensory hypersensitivity in patients with TS using tactile, auditory, thermal, or olfactory behavioural quantitative measures. In this study, 36 participants participated, of which 20 were young patients with TS. Tactile force detection thresholds were acquired using a set of von Frey monofilaments from two separate skin locations, the hand and cheek. Individual sensory thresholds were calculated, in addition to a sensitivity index (d') and a response bias (Criterion c). Results showed no significant differences in tactile force detection thresholds or the sensitivity index between the two groups on either skin location. Importantly, there was a trend for a difference in the response bias. Results suggest unaltered sensory thresholds and sensitivity in TS, but a potential for distorted perception of sensory stimuli. The results are partly discussed in the realm of predictive coding model of perception. These models view the top-down influence of expectation on bottom-up sensory processing as separate entities. Evidence so far seems to indicate that sensory input is not altered but rather interpreted much differently by the TS brain, giving rise to self-evaluated sense of sensory hypersensitivity.

Keywords: *Tactile force detection threshold, von Frey monofilaments, psychometric function, Signal detection theory, d-prime, response bias.*

3.1 INTRODUCTION

Our activities of daily living are largely mediated by our ability to process sensory information, like vision and the perception of touch. Imagine feeling the sharpness of a prickle on the stem of a rose, or the warmth of a cup of coffee on a cold Monday morning. These mechanical tactile forces impinged upon our skin are mediated by specific touch receptors and we have little difficulty telling these different types of stimuli apart (i.e., sting of a prickle or the heat of a coffee). What is more, neurologically healthy individuals waste little energy ignoring the constant sensation of certain stimuli such as the fabric of our socks pressing against our leg, or the clothing tag rubbing against our neck. By contrast, majority of patients with TS report these sensations as extremely irritating and disturbing, and report heightened sensory sensitivity on self-evaluation measures across all sensory modalities (Belluscio, Jin, et al., 2011; Cohen & Leckman, 1992; Jewers et al., 2013; Kane, 1994; Ludlow & Wilkins, 2016). Additionally, several studies also report a surge in tic frequency as a response to certain auditory, visual, and tactile external sensory events (Commander et al., 1991; Eapen et al., 1994; Neal & Cavanna, 2013b; Tijssen et al., 1999; Webber, Johnson, & Storch, 2014). These are sometimes referred to as *reflex tics* (Commander et al., 1991; Eapen et al., 1994; Tijssen et al., 1999). However, these reports have not been substantiated fully.

In this brief introductory text, I have introduced the potential internal conflict that occurs in the sensory perception in patients with TS to external sensory stimuli. Below I will review the current literature where sensory detection is tested empirically in patients.

3.1.1 *Sensory thresholds in TS*

Patients with TS display augmented sensation characterized by, but not limited to, gentle, innocuous external sensory stimuli that affects their activities of daily living. The measurement of actual sensory thresholds has been done in few studies. Belluscio et al. (2011) measured tactile sensitivity using a set of monofilaments on two separate skin locations, one on the lower leg, and one on the site of the most active tic and

sensory urges as described by patients. The authors reported no significant differences in tactile force detection thresholds between adult patients with TS and a matched group of control participants. Belluscio and colleagues (2011) interpreted these findings as to indicate that self-evaluated sensory hypersensitivity in TS is not due to dysfunction in the periphery and the input of sensory stimulation, but rather how the sensory stimulation is processed in the central nervous system. This study is however limited by rather crude measures of sensory thresholds and variability of skin locations between participants.

Schunke and colleagues (2016) followed up on this few years later with a more comprehensive sensory testing, establishing 13 different sensory parameters. In this study, they tested 14 adult patients with TS, without any clinically defined comorbid disorders (uncomplicated TS). Even though all patients reported the presence of PSP (self-evaluated level of somatosensation was not assessed) no difference was found regarding sensory threshold on any sensory parameter measured. Moreover, sensory thresholds did not correlate with the frequency of PU. The authors note that it is important to keep in mind that sensory phenomena are described as internal bodily sensations, while here they measured exteroceptive sensitivity. Nonetheless, the study is limited by the fact that sensory thresholds were only measured from one skin location (the hand) and the number of participants is rather low.

Another study, by Puts and colleagues (2015), studied vibrotactile sensory detection using a battery of tests in young patients with TS. First, no significant differences were observed on a simple reaction time task, indicating that simply pressing a button is not slowed in patients, and that baseline amplitude discrimination thresholds are unaffected in TS. However, when a weak stimulus is applied to one of two fingers and the task is to indicate which finger was stimulated, children with TS demonstrate significantly higher static detection thresholds. Conversely, a sub-threshold stimulation in a dynamic paradigm had a significant effect on performance in the control group, while no such effect was observed in the TS groups, and vibrotactile thresholds are statistically equal. Most importantly, a preceding adaptive stimulus has no effect on performance in TS, this causes detrimental effects in the control group, indicating no adaptation effects in the TS group. This is the first time a study has shown

altered discrimination touch thresholds in children with TS. The lack of adaption effect in TS (i.e., the process of sensory adjustment to incoming sensory stimuli) is not surprising since many studies have suggested dysfunctional sensorimotor gating mechanisms in TS (Buse et al., 2016; Castellanos et al., 1996; Rajagopal et al., 2013; Sutherland Owens et al., 2011; Swerdlow et al., 2001).

Finally, Kessler (2002) conducted a study assessing thermal dysregulation in TS. Although this study is very subjective, it did demonstrate a difference in the sensitivity for temperature changes between patients and controls. Moreover, patients had the tendency to judge temperatures differently, indicating a potential dysfunctional internal thermostatic mechanism. Also, and perhaps more importantly, body temperature was found to be abnormal in patients with TS, irrespective of sex, age or the presence of comorbid disorders. Greater body temperature fluctuation between morning, afternoon and evening is also found in TS, beyond what is considered normal. Finally, atypical circadian body temperature cycle is found to be abnormal, where body temperature tends to drop in the afternoon as opposed to rise. Kessler (2002) suggested TS might be presented with idiopathic hypothalamic disorder, consistent with previous preliminary results showing significant relationship between core body temperature and tic severity (Scahill et al., 2001). Nonetheless, the study by Kessler (2002) is limited by its observational status and needs to be interpreted with caution. Also, thermal thresholds were assessed in the study by Schunke and colleagues (2016) which showed no differences regarding hot and cold sensations. However, it might be interesting to study further the irregular body temperature and dysregulation in TS as Kessler showed.

Based on these reports, patients with TS might be demonstrating classical symptoms of sensory modulation disorder (SMD; the inability to properly process sensory input and generate an appropriate response to those inputs, severely affecting ones' activities of daily living). Indeed, one recent observational study demonstrated that the prevalence of SMD is six times higher in TS than in healthy children (see Ruhrman et al., 2017). Sensory inputs are thought to be processed abnormally in TS, manifest themselves as PU, and are inappropriately coupled with motor or vocal tics (Ruhrman et al., 2017).

3.1.2 *The perception of touch*

The perception of touch as a sensory input arises from the skin and can be categorized as either 'Discriminative touch' or 'Affective touch'. This is one of several cutaneous senses (McGlone & Reilly, 2010). Our skin is subdivided into three categories: (1) the glabrous skin (the thicker, non-hairy skin on the palm of the hand); (2) the hairy skin (this covers the greatest proportion of the skin on our body); and (3) the mucocutaneous skin (the skin on our lips). Touch sensations can arise from all three categories of our skin and is mediated by four, functionally distinct low-threshold mechanoreceptors (LTMs; Johansson & Vallbo, 1979a, 1979b). These LTMs are all myelinated A β fiber group receptors and innervate primarily the glabrous skin. These myelinated afferents give rise to sensations of the tactile touch since they are all activated by weak, innocuous stimuli (Abraira & Ginty, 2013).

Another type of mechanoreceptors solely found in the hairy skin are low-threshold mechanosensitive fibers. In humans, they are termed C-tactile afferents (CT; for a comprehensive review see McGlone, Wessberg, & Olausson, 2014). These CT's are unmyelinated fibers responding to tactile stimulation such as stroking and low force monofilaments (Cole & Sedgwick, 1992). CT afferents are characterized by being small but abundant in the skin. They also show both moderately sustained discharge during continuous stimulation as well as long post-stimulus discharge (McGlone et al., 2014). CT afferents respond to skin indentation in the range of 0.3-2.5 millinewton (mN; Vallbo, Olausson, & Wessberg, 1999). Some types of A β fiber type receptors are found in hairy skin, in addition to CT afferents. Thus, CT afferent receptor stimulation is always coupled with A β stimulation. Tactile detection has been shown to depend on CT afferents in the hairy skin, since patients lacking A β fiber type receptors detected tactile force stimulation (Cole et al., 2006; Vallbo et al., 1999).

3.2 SUMMARY, AIM AND HYPOTHESES

In summary, patients with TS display greater self-perceived hypersensitivity across all sensory domains which is not reflected in lowered sensory thresholds. This warrants

a further investigation. The aim of this study was to assess tactile force detection thresholds in young patients with TS using von Frey monofilaments. To address shortcomings of previous studies in the field, I evaluated sensory thresholds using classical psychophysics. Based on previous studies, I hypothesize to see lower sensory detection thresholds in TS and possibly altered perception of sensory input due to dysfunctional sensory gating mechanisms and altered function of the insular cortex in TS.

3.3 METHODOLOGY

3.3.1 *Participants*

In total, 20 patients with confirmed diagnosis of TS (2 females, mean age: 14.1 ± 1 SD: 2.41, age range: 10.4 – 19.1) were recruited as part of ongoing studies in our lab. Sixteen age and gender matched typically developing individuals (1 female, mean age: 14.5 ± 1 SD: 2.8, age range: 10.2 – 19.6) also participated in this study.

Six patients with TS had confirmed comorbidities (2 ASD, 3 OCD, 1 anxiety disorder). Also, nine patients were medicated (clonidine, aripiprazole, melatonin, sertraline, haloperidol and citalopram) on the day of testing. Two patients (10%) and two healthy volunteers (12.5%) were left-handed (when asked which hand is the dominant one). Patient specific characteristics including mean tic severity and frequency of PSP is shown in

Table 3.1. This study was approved by an appropriate local ethical review committee.

Table 3.1. Patient specific characteristics taking part in the study on tactile force detection.

Yale Global Tic Severity scale (YGTSS)											
TS ID	Age	Sex	Handedness	WASI	PUTS	Impairment	Motor	Vocal	Global	Comorbidity	Medication
TS001	18.03	M	R	103	10	0	12	11	23	None	None
TS002	19.12	M	R	110	16	30	22	18	70	None	Citalopram
TS003	14.09	M	R	123	21	20	23	20	63	None	Sertraline, Haloperidol
TS004	16.81	M	R	118	27	10	13	11	34	None	Clonidine
TS005	11.00	M	R	99	9	5	14	5	24	None	None
TS006	15.17	M	R	102	28	25	21	17	63	OCD	Melatonin
TS007	13.47	M	R	133	12	0	9	4	13	None	None
TS008	14.61	M	R	118	21	30	19	18	67	OCD	None
TS009	13.59	F	R	89	20	20	14	8	42	OCD	Melatonin
TS010	12.35	M	R	124	16	10	13	7	30	None	None
TS011	13.78	M	R	119	23	5	15	10	30	None	None
TS012	13.00	M	L	109	25	30	20	21	71	None	Clonidine
TS013	11.18	M	R	88	24	30	20	17	67	Anxiety	Clonidine and Aripiprazole
TS014	11.12	M	R	135	17	5	12	8	25	None	None
TS015	14.97	M	R	96	21	5	12	14	31	ASD	None
TS016	17.70	F	R	116	16	10	5	10	25	ASD	Clonidine
TS017	13.50	M	R	115	31	20	12	8	40	None	Clonidine and Aripiprazole
TS018	14.27	M	R	112	28	10	21	13	44	None	None
TS019	13.19	M	R	111	18	20	12	9	41	None	None
TS020	10.42	M	R	110	13	10	9	0	19	None	None
Average	14.1	-	-	111.5	19.8	14.8	14.9	11.5	41.1	-	-

Greyed out area indicates the two patients whose data was excluded from the study. WASI: Wechsler's Abbreviated Scale of Intelligence. PUTS: Premonitory Urge for Tics Scale. OCD: Obsessive compulsive disorder. ASD: Autism spectrum disorder.

3.3.2 Tactile force detection threshold assessment

Absolute tactile force detection thresholds were assessed using a set of Jamar 'von Frey' monofilaments (single-touch stimuli [Sammons Preston], see section 2.2.1 in Chapter 2 for a description of the monofilaments) in a 1-alternative forced-choice (1AFC) paradigm, by the *method of limits*; also implementing the staircase method where an automated tracking of responses determined when to change stimulus intensity. Specifically, stimulus intensity was changed based on performance in cumulative percentages, as opposed to the traditional ratio between correct and incorrect responses. The aim of the study was to assess perceived increase in magnitude of sensation, thus I opted for using five monofilaments capable of delivering the lowest intensities available, with target forces measured 1.89, 2.34, 2.62, 2.88 and 3.20 according to Bradman, et al. (2015). The procedure is detailed in Section 3.3.2.1 below.

Tactile force detection thresholds were acquired from two separate spatial locations: (1) 1 cm inferior of the zygomatic cheekbone, and (2) the palm of the hand (midpoint of the flexor pollicis brevis). Please refer to Figure 3.1 as a reference depicting these two locations. First, the cheek was chosen specifically as it is easily accessible, avoiding discomfort for the participant. The cheek is part of the hairy skin and thus contains both A β and CT afferent fiber types. Also, the cheek is an uncommon area of PSP in TS (Leckman et al., 1993). Second, the palm of the hand was chosen as it is a relatively common area of PSP in TS, especially the 'just-right' perceptions (Leckman et al., 1993, 1994). The palm is glabrous skin and contains thus solely A β fiber type receptors. That is, the palm is completely devoid of CT afferents (McGlone et al., 2014). Finally, one study showed that tactile thresholds are significantly different between the glabrous and hairy skin (Ackerley, Carlsson, Wester, Olausson, & Backlund Wasling, 2014). The order of touch sites was randomized across participants.

3.3.2.1 Procedure

Participants were sat next to the experimenter with their eyes closed, and with either the palm of the dominant hand or corresponding cheek in plain view. Next, in half of the trials, the von Frey monofilament was manually lowered onto the surface of the skin, until the skin was sufficiently blenched, and the monofilament appropriately buckled. The filament was kept constantly bent for approximately 1.5 s and then gradually removed. During each presentation of the monofilaments caution was taken to ensure that no hairs on the skin were touched, or the sides of the monofilament touched or stroked the skin (Bradman et al., 2015). If so, the trial was discarded and a new trial was randomly generated. Trials were generated by an in-house custom written script running on Matlab (R2014a, The Mathworks). Trials were pseudorandomized with half being “touch” trials and half “no touch” trials. This way each trial had equal probability of being presented. This was made clear to the participants at the start of the session. In a binary decision process, following each trial, the participant was asked to respond with either “touch” or “no touch”. Equivalent of saying “yes I felt the stimuli” or “no I did not feel the stimuli”. A guess was requested in case the participant was unsure.

In a descending order, the most salient monofilament was used first (Target force: 3.20) and depending on the participants’ performance, the task got more difficult (i.e., the monofilaments got thinner and more difficult to detect). Only one stimulus is presented per trial, thus 1AFC.

Participant responses were recorded using the same script which generated the trials. Intensity of monofilaments presented was calculated by the script as well, based on performance (the adapted up/down method). After eight trials, if performance was $\geq 75\%$ correct, a lighter more difficult to detect monofilament was presented. If performance, however, was $\leq 50\%$ (under chance performance), a more intense and easier to detect monofilament was used. The experimental block was stopped when either eight ‘changes’ of intensity had occurred or after 80 trials in total.

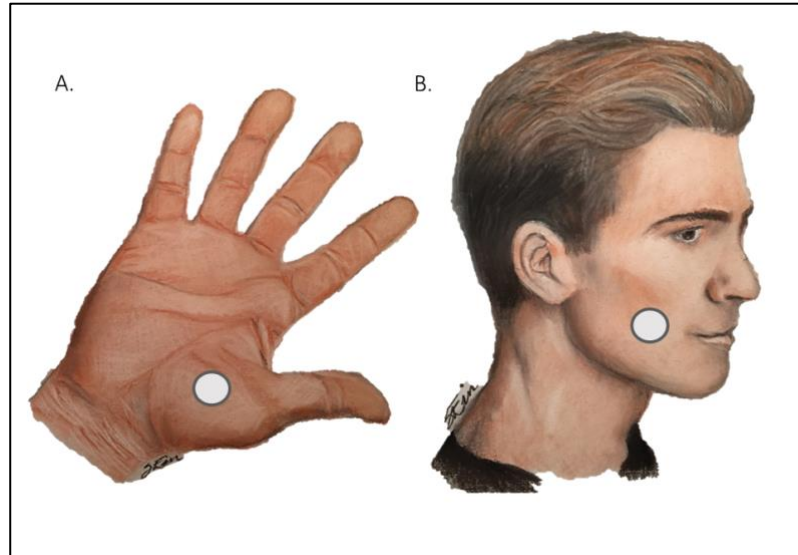


Figure 3.1. Skin locations used in the study to measure tactile force detection thresholds marked with a grey circle. A: Palm of the hand and B: 1 cm inferior of the zygomatic cheek bone.

3.3.3 Data analysis

3.3.3.1 Psychometric function fitting

For each participant, I fitted a sigmoidal logistic function using the maximum likelihood estimation (MLE; Wichmann & Hill, 2001b) to his/hers proportion of correct detection responses of *touch trials only* against stimulus intensity, using Palamedes toolbox (Prins & Kingdom, 2009) for Matlab. Each function was defined by four parameters: threshold α (proportion of correct responses), the slope β (the slope of the curve), guess rate γ and lapse rate λ (Wichmann & Hill, 2001a). Two parameters (threshold and slope) were fixed while others were set as free parameters. Each function estimated the participant's tactile force detection threshold (i.e., sensory threshold) at the 75% point of the psychometric function. Each function was estimated with $N_{bootstrap} = 500$ iterations to estimate the error of the two outcomes from a randomly generated hypothetical data simulated by the real data. At each iteration a function is fitted to this hypothetical data. Finally, I ran a goodness-of-fit measure to ascertain that the function fit well to the real data. A more detailed description of how to derive a psychometric function is explained in Appendix 1 subsection 9.1.

3.3.3.2 *Signal detection analysis*

The same data was also analysed using SDT methods. I calculated the adjusted proportion of Hits (pHit) and proportion of false alarms (pFA; Stanislaw & Todorov, 1999). This adjustment is important to avoid the problem of dividing by zero or in the case of an infinite values when calculating d' (dee-prime) and the response criterion c . Increasing d' indicates better ability to detect the tactile stimulus from noise, whereas decreasing d' is suggestive of greater difficulty distinguishing signal from noise. A positive response bias c indicates a bias towards responding “no” (i.e., a more conservative criterion used) and a negative response bias c is indicative of a participant with bias towards replying “yes” (i.e., a more liberal criterion used). pHit, pFA, d' and c were calculated for each participant. A more detailed description of signal detection theory is explained in Appendix 1 subsection 9.2.

3.3.4 *Statistical analysis*

Prior to any statistical comparison of tactile thresholds or SDT measures I assessed if age or IQ were significant predictors. This was accomplished using multiple or multivariate linear regression. Tactile force detection thresholds on cheek and hand were analysed separately since post-processing of the data revealed that majority of participants demonstrated floor effects in the cheek condition. That is, the force generated by the thinnest monofilament was detected 100%. This resulted in exclusion of participants from one condition (cheek) but not the other (hand). Differences between groups in thresholds were assessed using one-tailed independent sample t -test. I chose one-tailed tests because as my hypothesis clearly states, I assume that patients will demonstrate significantly *lower* tactile thresholds. SDT measures were analysed using mixed model ANOVA with factor *Group* as a between-subject variable and *Location* (Hand v Cheek) as a within-subject variable. Main effects of Location and Group, as well as the interaction and effect sizes are reported. In separate analyses, I assessed the relationship between frequency of PSP and tactile force detection thresholds and SDT measures using Pearson correlation coefficient. Statistical

significance was thresholded at $\alpha < 0.05$. Statistical analysis was accomplished using SPSS and Matlab.

3.4 RESULTS

Prior to statistical analysis, two patients with TS had to be excluded due to revised experimental protocol rendering their data incompatible with the rest. Therefore, data from 34 participants (18 TS and 16 CS) was used for statistical analysis.

All patients reported the presence of sensory phenomena as measured by the PUTS scale (PUTS $M = 19.8 \pm 1$ SD: 6.3, min = 9, max = 31). A two-tailed two-sample t-test showed that *age* was not significantly different between the two groups (CS $M = 14.5 \pm 2.8$, range = 10.2 – 19.6, TS $M = 14.1 \pm 2.4$, range = 10.4 – 19.1), $t(32) = 0.576$, $p = 0.568$. This was also true when the two excluded participants were included in the sample. In addition, WASI was not significantly different between the groups (CS $M = 115.8 \pm 8.2$, range = 97 – 129, TS $M = 111.5 \pm 12.8$, range = 88 – 135), $t(32) = -0.9196$, $p = 0.364$, which was also true when including the excluded participants.

3.4.1 Psychometric function fitting

Fitting of the data using a logistic psychometric function for one patient and one control participant is depicted in Figure 3.2. Such a plot was produced for all participants. The goodness-of-fit measure showed that the function did not fit well for some participants. The reasons were primarily: (1) the goodness-of-fit value was below 0.05 (F A A Kingdom & Prins, 2011), (2) not enough data was acquired for a specific stimulus intensity or (3) the participant found the task too easy and hit floor effect. The goodness-of-fit values and figures of the fit were explored and used as a basis for exclusion of participants in either or both conditions. Figure 3.2 also shows an example of a bad fit for participants. Prior to statistical analysis of thresholds, I noticed that I would have to exclude many participants from the cheek condition but no participant from the hand condition.

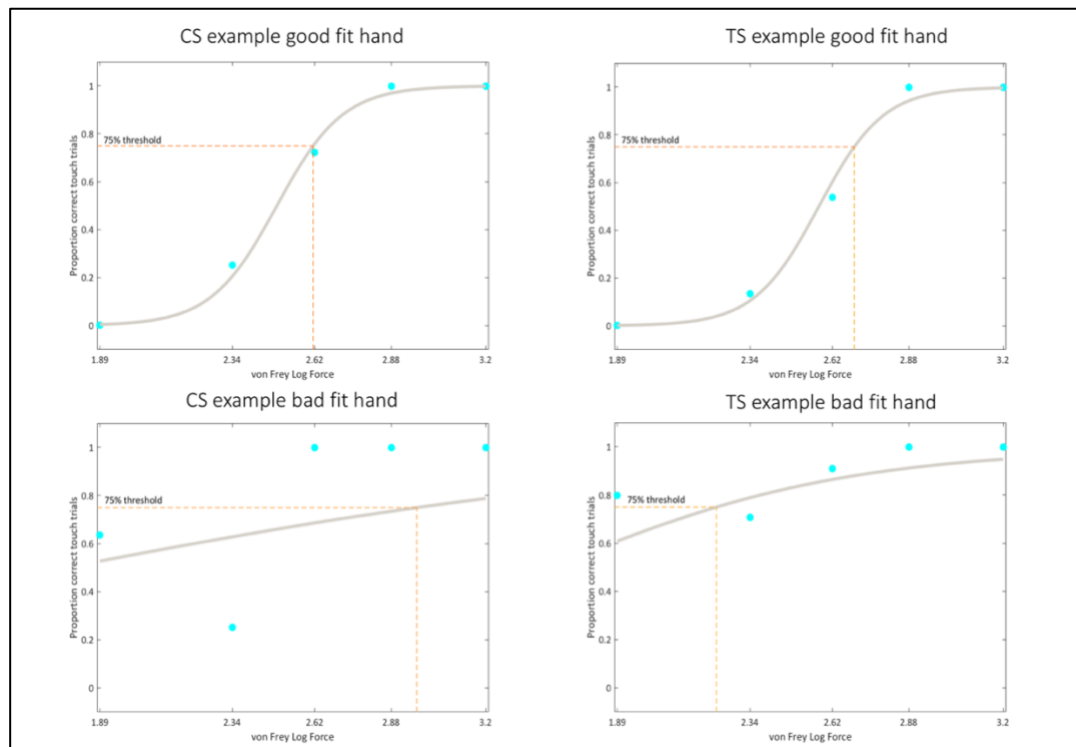


Figure 3.2. An example of the psychometric function fitting. First column: Examples of a good fit and a bad fit for two CS. Second column: Example of a good fit and a bad fit for two TS.

3.4.1.1 Hand condition

Multiple regression to test the effects of age and IQ on tactile force detection threshold showed no effect of the two predictors (see Figure 3.3), $F(2, 31) = 0.61$, $p = 0.55$, $R^2 = 0.04$, $\text{Adj. } R^2 = 0$. This indicates that neither age or IQ are significant predictors of tactile thresholds. Unstandardised (B), standardised (Beta), t-stats and p-values are shown in Table 3.2. Durbin-Watson test of independence of residuals showed that residuals from the regression were uncorrelated (Durbin-Watson statistic= 2.01, $p = 0.873$). Similarly, Cook's distance showed no case to be particularly influential since Cook's $d < 1$, indicating that no single case is overly influential on the model's ability to predict all cases).

Table 3.2. *Coefficients of the regression analysis in the hand condition using age and IQ measure as predictors and tactile force detection threshold as outcome.*

Threshold hand					
Predictor	B	SE B	Beta	t-value	p-value
Constant	2.866	0.515	-	5.569	< 0.01
Age	0.006	0.016	0.069	0.384	0.704
WASI	-0.004	0.004	-0.170	-0.949	0.350

B: Unstandardized regression coefficients, SE B: Standard error of regression coefficients, WASI: Wechsler's Abbreviated Scale of Intelligence.

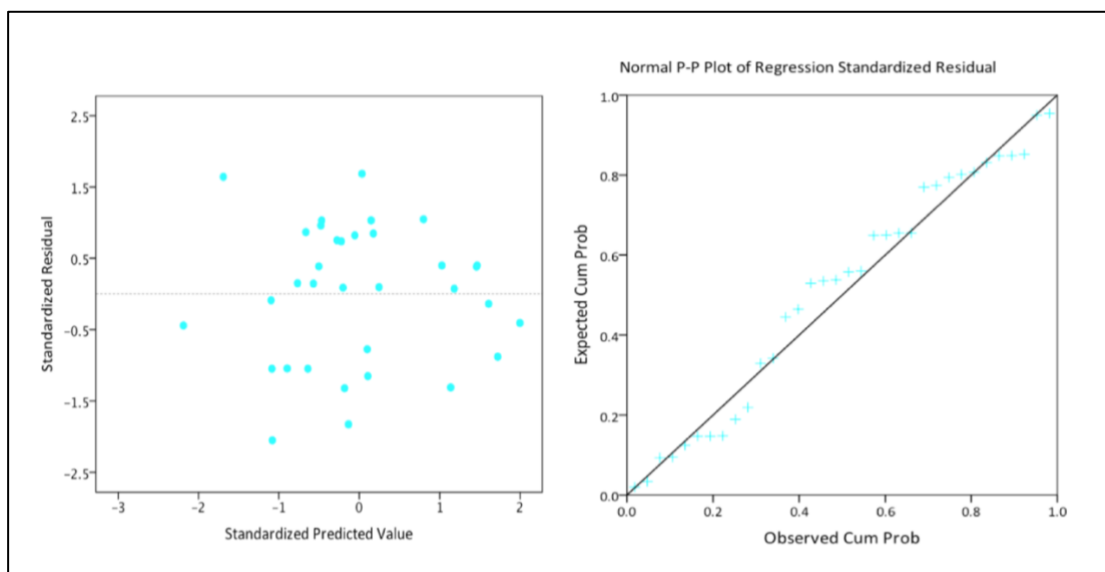


Figure 3.3. Age and IQ regression analysis in the **hand condition**. Left: Plot of standardized predicted values with standardized residuals. Right: Normal P-P plot of residuals.

Test of significant group differences of tactile thresholds showed that patients with TS did **not** display *lower* tactile force detection thresholds: $t(32) = 1.23$, $p = 0.89$, effect size $d = 0.42$. I performed a power analysis using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) both to estimate the sample size needed with the error probability α (type I error rate) = 0.05, power (1- β error probability) = 0.80 and the observed effect size and to ascertain the necessary population effect size d (Cohen's d 0.2, 0.5 and 0.8 are small, medium and large effects, respectively). The sample size needed is $N = 142$. For the data to achieve power of 0.8 (80%) with $\alpha = 0.05$, $N_{TS} = 18$ and $N_{CS} = 16$, the necessary effect size d needed is 0.85. Please find statistic descriptives for all comparisons in Table 3.4.

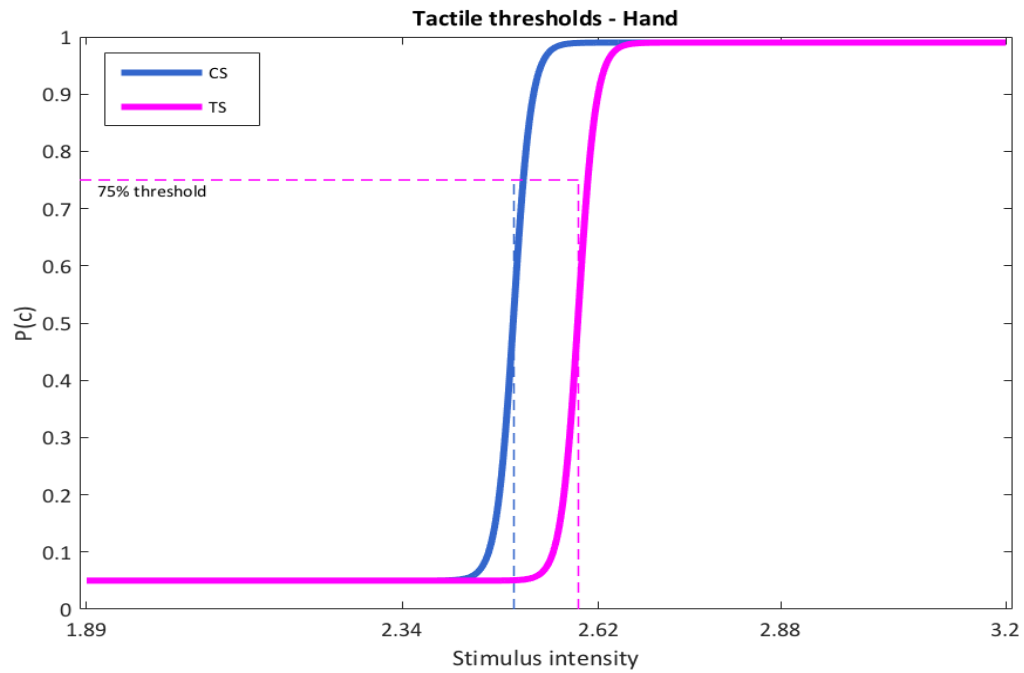


Figure 3.4. Group average psychometric functions with reference to group tactile thresholds in the hand condition.

3.4.1.2 Cheek condition

Based on the exclusion criteria I decided to exclude 13 participants (5 patients and 8 controls). As in the hand condition I ran the same regression analysis to ascertain whether age or IQ had significant effects on tactile force detection thresholds. A multiple linear regression analysis showed that neither age or IQ were significant predictors of tactile force detection thresholds (see Figure 3.5); $F(2, 17) = 1.41$, $p = 0.27$, $R^2 = 0.14$, Adj. $R^2 = 0.04$. Coefficients, t-stats and p-values for each predictor is shown in Table 3.3. Durbin-Watson test of independence of residuals showed that residuals from the regression were uncorrelated (Durbin-Watson statistic= 1.16, $p = 0.352$). Similarly, Cook's d was normal.

Table 3.3. Coefficients of the regression analysis in the cheek condition using age and IQ measure as predictors and tactile force detection threshold as outcome.

Threshold cheek					
Predictor	B	SE B	Beta	t-value	p-value
Constant	1.546	0.635	-	2.433	0.026
Age	0.018	0.029	0.143	0.622	0.542
WASI	0.006	0.003	0.384	1.674	0.111

B: Unstandardized regression coefficients, SE B: Standard error of regression coefficients, WASI: Wechsler's Abbreviated Scale of Intelligence.

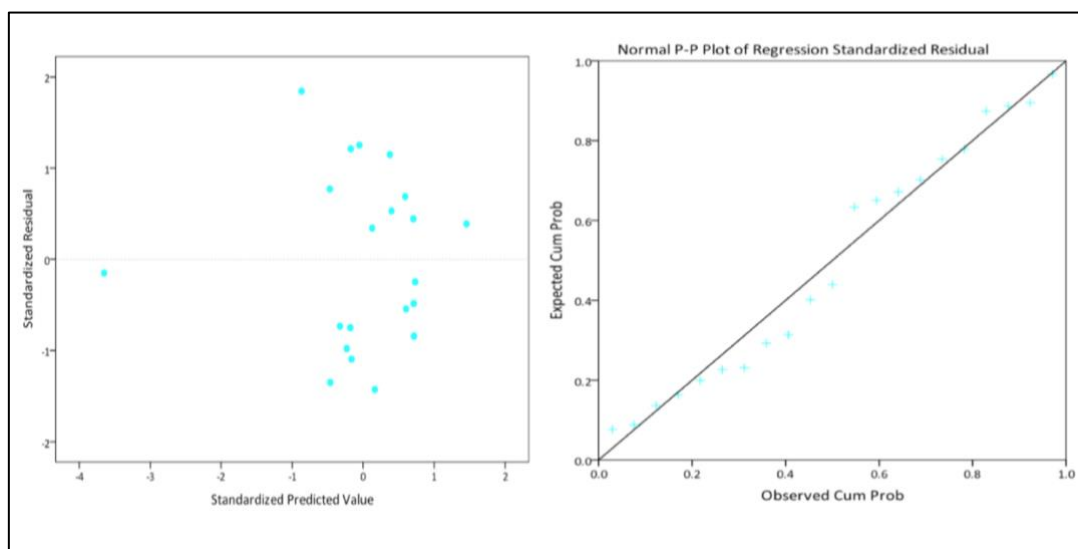


Figure 3.5. Age and IQ regression analysis in the **cheek condition**. Left: Plot of standardized predicted values with standardized residuals. Right: Normal P-P plot of residuals.

Statistical comparison of group means showed that patients with TS did **not** display lower tactile force detection thresholds $t(19) = -0.21$, $p = 0.42$, $d = 0.49$. With the observed effects, a power analysis showed that the projected sample size needed is $N = 102$.

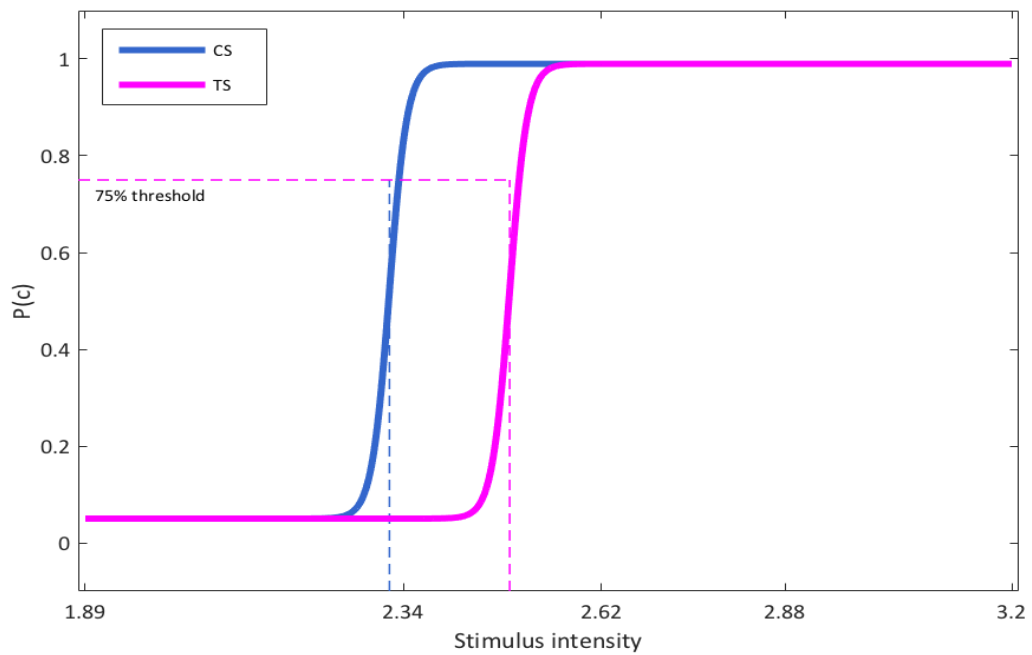


Figure 3.6. Group average psychometric functions with reference to group tactile thresholds in the cheek condition.

3.4.2 Signal detection

The data presented here was collected using the method of limits, with variable stimulus intensities. Within the realm of SDT, data from different intensities cannot be pooled or collapsed together. Thus, for this analysis I specifically focus only on data derived from monofilaments capable of delivering a force of 0.02 g. This decision is supported by two facts: (1) most number of trials were collected using this particular monofilament (as controlled by the participants' performance) and (2) thresholds determined by the PF show that the 75% threshold lies, on average, just above this detection for both groups (see Table 3.4 for descriptives). To put differently, all participants could detect this stimulus with a proportion correct above the liberal threshold of 75% and thus participants' actual sensitivity and criterion can be measured using this stimulus level only.

Table 3.4. Means (± 1 SD) standard deviation for assessment of tactile force detection in patients and control participants.

	PF		Signal detection							
	Threshold		pHits		pFA		d' (dee-prime)		C	
	Hand	Cheek	Hand	Cheek	Hand	Cheek	Hand	Cheek	Hand	Cheek
CS	2.50 (0.24)	2.33 (2.44)	0.52 (0.26)	0.71 (0.27)	0.14 (0.11)	0.24 (0.15)	1.23 (0.79)	1.32 (0.63)	0.55 (0.49)	0.12 (0.50)
TS	2.59 (0.19)	2.49 (0.41)	0.43 (0.21)	0.65 (0.22)	0.09 (0.06)	0.16 (0.09)	1.18 (0.64)	1.49 (0.53)	0.78 (0.36)	0.31 (0.48)

I used a multivariate multiple linear regression with SDT measures from the hand as outcomes, and age and IQ as predictors. The overall model was non-significant, $F(8, 56) = 0.991$, $p = 0.453$, Wilk's $\lambda = 0.767$. Regression coefficients, t-statistics and p-values are shown in Table 3.5.

Table 3.5. Multiple regression run for assessing influence of covariates for SDT analysis in the hand condition. The table displays regression coefficients, SE of B, t-statistic and p-values.

pHit				
Predictor	B	SE B	t-value	p-value
Constant	-0.1322	0.5347	-0.247	0.8064
Age	-0.0122	0.0162	-0.753	0.4570
WASI	0.0068	0.0039	1.767	0.0870
pFA				
Predictor	B	SE B	t-value	p-value
Constant	-0.1059	0.2122	-0.4993	0.6211
Age	0.0011	0.0064	0.1754	0.8619
WASI	0.0018	0.0015	1.1876	0.2440
d'				
Predictor	B	SE B	t-value	p-value
Constant	0.6185	1.6535	0.3740	0.7109
Age	-0.0426	0.0500	-0.8527	0.4003
WASI	0.0105	0.012	0.8764	0.3875
Criterion c				
Predictor	B	SE B	t-value	p-value
Constant	2.242	0.9694	2.3136	0.0275
Age	0.0135	0.0293	0.4607	0.6482
WASI	-0.0154	0.007	-2.2011	0.0353

Similarly, when I used SDT measures from the cheek as outcomes, and age and IQ as predictors, the model was statistically non-significant, $F(8, 56) = 1.629$, $p = 0.137$, Wilk's $\lambda = 0.658$. Regression coefficients, t-statistics and p-values are shown in Table 3.6.

Table 3.6. Multiple regression run for assessing influence of covariates for SDT analysis in the cheek condition. The table displays regression coefficients, SE of B, t-statistic and p-values.

pHit				
Predictor	<i>B</i>	<i>SE B</i>	<i>t-value</i>	<i>p-value</i>
Constant	1.073	0.514	2.087	0.045
Age	-0.011	0.0155	-0.733	0.469
WASI	0.002	0.0037	-0.555	0.583
pFA				
Predictor				
Constant	0.372	0.293	1.271	0.213
Age	-0.001	0.009	-0.212	0.833
WASI	-0.001	0.002	-0.612	0.545
<i>d'</i>				
Predictor				
Constant	2.01	1.291	1.55	0.130
Age	-0.023	0.039	-0.609	0.546
WASI	-0.002	0.0096	-0.223	0.824
Criterion c				
Predictor				
Constant	-0.990	1.173	-0.844	0.405
Age	0.032	0.035	0.909	0.370
WASI	0.006	0.008	0.77	0.44

All SDT parameters were entered into a two-way mixed model ANOVA to assess between group differences on SDT parameters on both hand and cheek, with factors *Group* (2 levels) and *Location* (2 levels) and SDT parameter as a dependent variable. No participant was excluded for this analysis. Means and standard error of mean for SDT parameters are shown in Table 3.4. First, there is no violation of sphericity since my Factors only have 2 levels, thus no correction is necessary and sphericity for all holds true. Sensitivity analysis was conducted using G*Power, to ascertain the necessary critical population effect size f (Cohen's f s 0.1, 0.25 and 0.4 are small, medium and large effects, respectively; see Faul, et al., 2007). The effect size is calculated based on α (the type I error rate), power ($1 - \beta$ error probability), sample size N , number of groups, and

number of measurements. For my data to achieve a power of 0.8 (80%), with $\alpha = 0.05$, $N = 34$, number of groups = 2 and number of measurements is = 2, the necessary effect size f needed is 0.29.

For pHit, Box's M test for the equality of covariance matrices was not significant (Box's M = 1.04, $p = 0.81$), indicating that the variance-covariance matrices are approximately equal. Similarly, Levene's test of equal error variances was not significant for either Hand location ($p = 0.08$) or Cheek location ($p = 0.4$). Descriptive statistics are shown in Table 3.4. The results of the two-way mixed model ANOVA showed there was a significant main effect of Location ($F(1, 32) = 12.59$, $p = 0.001$, $\eta_p^2 = 0.28$, Hand M = 0.476, SE = 0.041, Cheek M = 0.677, SE = 0.037, $f = 0.62$). This indicates that proportion of hits was significantly higher on the Cheek compared to the Hand, irrespective of diagnostic status. There was no significant Location X Group interaction ($F(1, 32) < 1$, $p = 0.75$, $\eta_p^2 = 0.003$), indicating that diagnostic status does not alter the pHit as a function of skin location. For the interaction, based on my data, the effect size was $f = 0.05$. The test of between-subjects effects showed no main effect of Group ($F(1, 32) = 1.54$, $p = 0.22$, $\eta_p^2 = 0.046$, $f = 0.22$) with control participants (M = 0.61, SE = 0.04) and patients with TS (M = 0.54, SE = 0.04) having approximately equal pHit.

For pFA, Box's M test was not significant (Box's M = 7.87, $p = 0.06$), indicating that the variance-covariance matrices are approximately equal. However, Levene's test was significant for both Hand pFA values ($p = 0.03$) and Cheek pFA ($p = 0.025$). This is not a great concern since Levene's test is not considered to be the most reliable. A good rule of thumb is that if the largest variance is not 1.5 times greater than the smallest, we are alright to continue. Here variance of CS = 0.063 and TS = 0.058 and the ratio of the two is 1.09:1. Results of the two-way mixed ANOVA showed a significant main effect of Location ($F(1, 32) = 10.56$, $p = 0.003$, $\eta_p^2 = 0.25$) indicating that across the entire sample, pFA was significantly higher on the Cheek (M = 0.199, SE = 0.20) than on the Hand (M = 0.12, SE = 0.015). The effect size for Location is $f = 0.58$. There was no Location X Group interaction ($F(1, 32) < 1$, $p = 0.61$, $\eta_p^2 = 0.008$ and $f = 0.09$). The test of between-subjects effects showed that there was a significant effect of Group ($F(1, 32) = 5.09$, $p = 0.031$, $\eta_p^2 = 0.14$). This means that irrespective of skin location, the CS group (M =

0.19, SE = 0.024) had greater proportion of false alarms than the TS group (M = 0.13, SE = 0.014). The effect size $f = 0.40$.

For d' , both the Box's M test was non-significant (Box's M = 0.792, $p = 0.864$), and Levene's test was non-significant for both Hand ($p = 0.613$) and Cheek ($p = 0.898$). The test of within-subjects effects did not show a main effect of Location $F(1, 32) = 1.53$, $p = 0.23$, $\eta_p^2 = 0.046$, $f = 0.21$, Hand M = 1.21, SE = 0.12, Cheek M = 1.43, SE = 0.09), nor a significant Location X Group interaction ($F(1, 32) < 1$, $p = 0.62$, $\eta_p^2 = 0.008$, $f = 0.09$). This indicates that d' did not change regarding skin location across the whole group and that change in d' was equivalent between the groups. Similarly, the test of between-subjects effects showed no effect of Group (CS M = 1.29, SE = 0.12, TS M = 1.34, SE = 0.10, $F(1, 32) < 1$, $p = 0.73$, $\eta_p^2 = 0.004$). The effect size for the main effect of Group was $f = 0.06$.

Finally, for Criterion c, the Box's M test was not significant (Box's M = 1.7, $p = 0.66$) while Levene's test was significant for Hand ($p = 0.045$) but not Cheek ($p = 0.99$). There was a significant main effect of Location ($F(1, 32) = 18.91$, $p < 0.001$, $\eta_p^2 = 0.37$, $f = 0.77$) with Hand (M = 0.67, SE = 0.07) showing much higher value of Criterion c than Cheek (M = 0.214, SE = 0.09). There was no significant Location X Group interaction ($F(1, 32) < 1$, $p = 0.91$, $\eta_p^2 < 0.001$, $f = 0.001$). And, the test of between-subjects effect showed a marginal main effect of Group ($F(1, 32) = 3.33$, $p = 0.077$, $\eta_p^2 = 0.09$). This indicates that ignoring skin location, the TS group had greater bias towards responding "no" (TS M = 0.55, SE = 0.08) compared to the CS group (CS M = 0.33, SE = 0.1). The effect size for the Group comparison was $f = 0.31$.

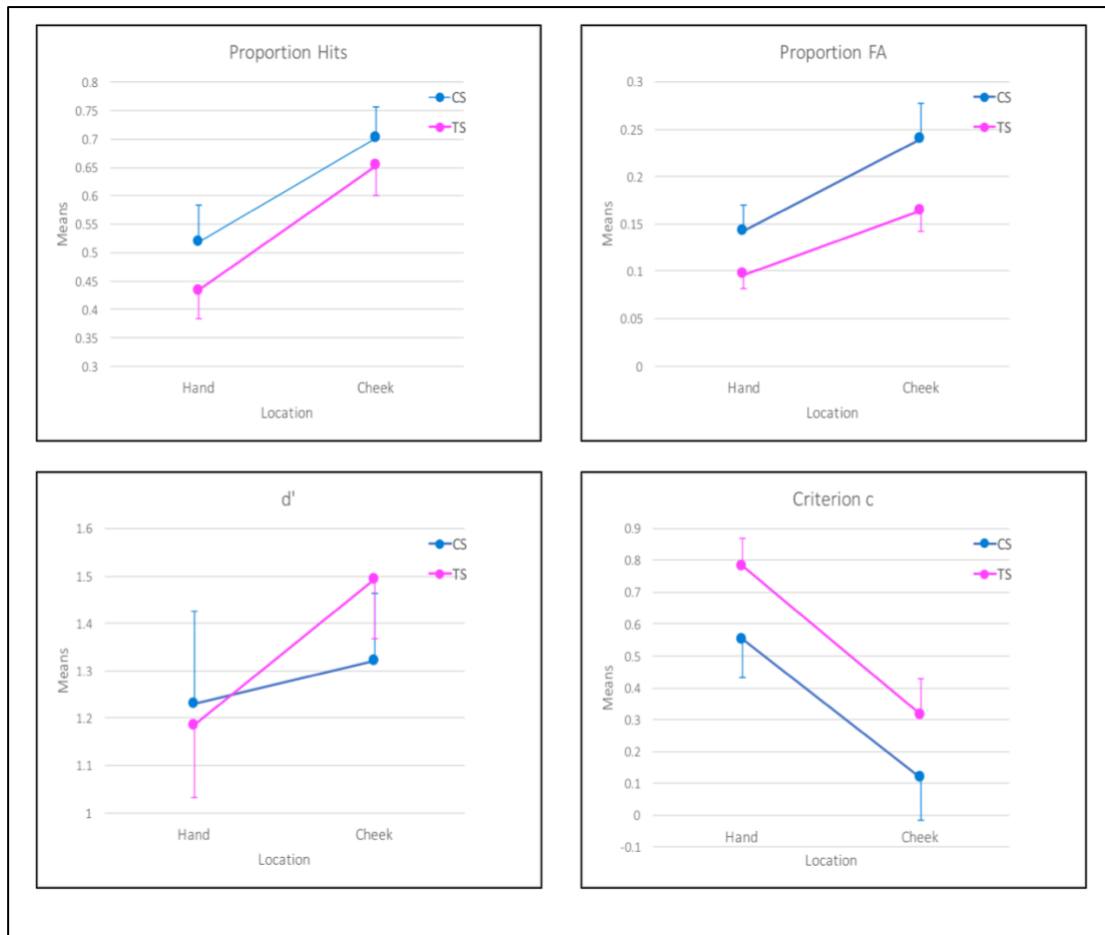


Figure 3.7. Signal detection analysis using mixed model ANOVA interaction plots. The error bars are standard error of the mean.

3.4.3 Correlation: PUTS with tactile thresholds

I also wanted to assess if there exists a relationship between PUTS scores, tactile thresholds, sensitivity and response bias. Here I used Pearson correlation coefficient. P-values are reported uncorrected for multiple comparison.

I found no significant relationship between thresholds and PUTS scores on the hand ($r = -0.27$, $p = 0.27$) or on the cheek ($r = -0.21$, $p = 0.49$, see Figure 3.8).

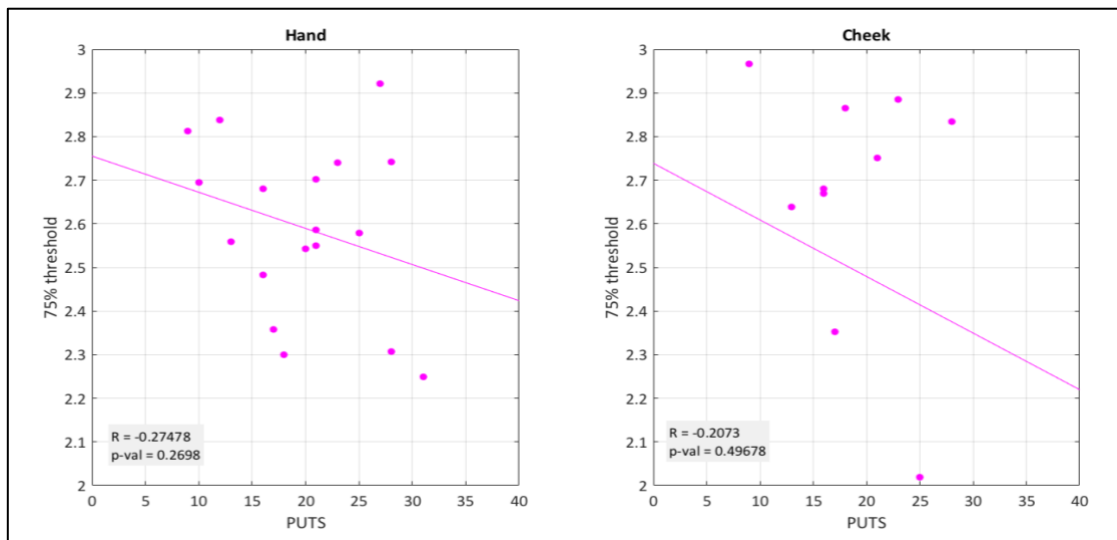


Figure 3.8. Correlation analysis between frequency of PSP (as measured by Premonitory Urge for Tics Scale) and 75% tactile force detection threshold on Hand (left) and Cheek (right). R : Pearson correlation coefficient.

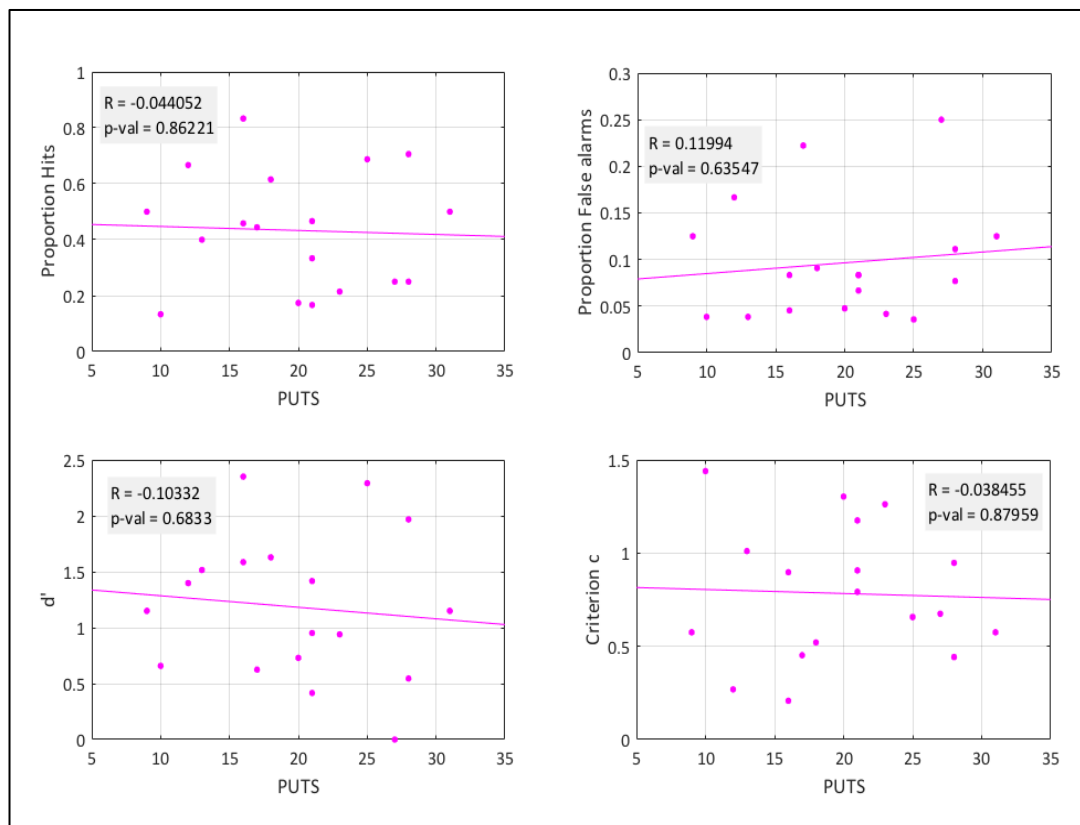


Figure 3.9. Correlation analysis between frequency of PSP (as measured by Premonitory Urge for Tics Scale) and SDT parameters in the **Hand** condition. R : Pearson correlation coefficient.

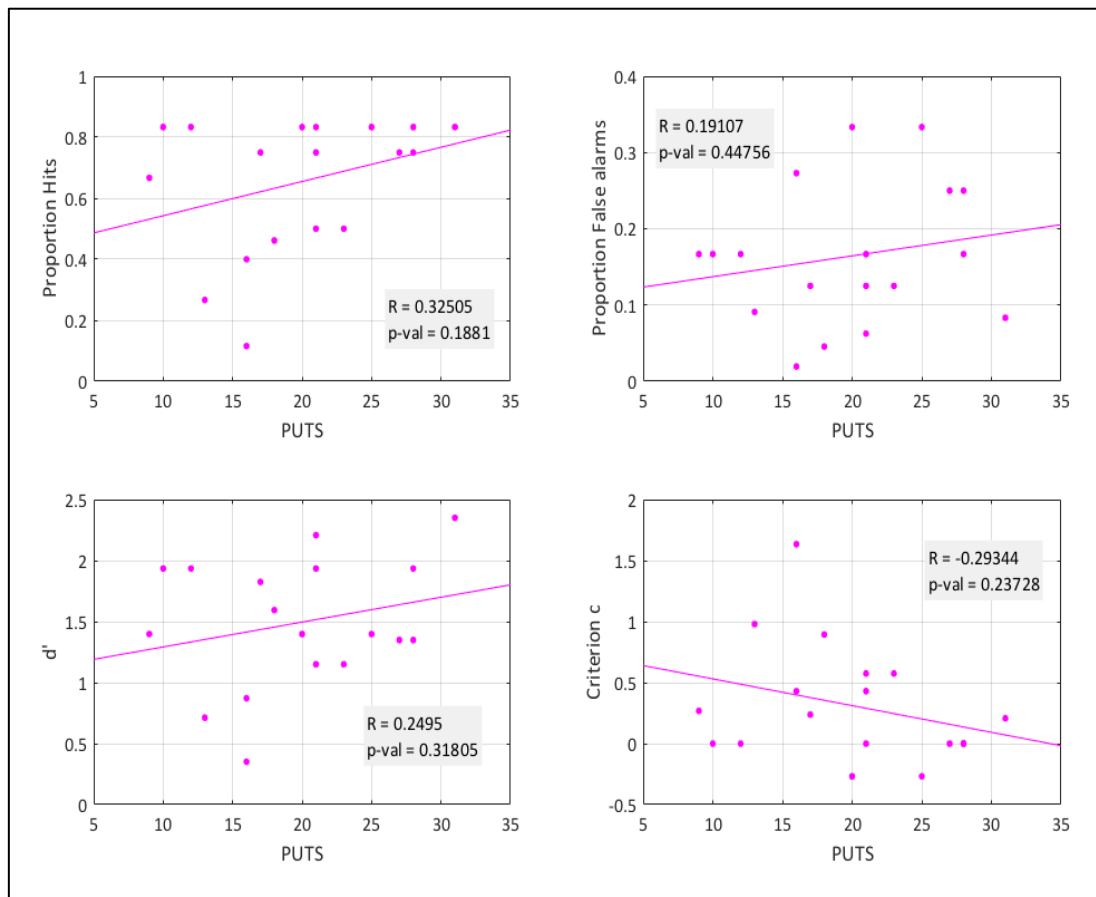


Figure 3.10. Correlation analysis between frequency of PSP (as measured by Premonitory Urge for Tics Scale) and SDT parameters in the **Cheek** condition. R: Pearson correlation coefficient.

For SDT parameters, I found no correlation between PUTS scores and any SDT parameter on the Hand (all $r < 0.2$, all $p > 0.6$) or Cheek (max $r = 0.33$, min $p = 0.19$). Correlation is displayed for Hand in Figure 3.9 and Cheek in Figure 3.10.

3.5 DISCUSSION

The aim of this study was to assess tactile force detection thresholds, sensitivity and response bias in a group of young patients with Tourette syndrome (TS) and, age and sex matched group of typically developing individuals. Few interesting results emerged from this study and each will be explained in detail and discussed.

3.5.1 Age or IQ does not affect tactile force detection or response tendency

Interestingly my results showed that age and IQ were not significant predictors of tactile force detection thresholds, sensitivity or response bias using multiple or multivariate regression analysis.

In TS, age related effects on tactile force detection thresholds have not been directly tested. My results suggest that tactile detection thresholds do not change as a function of age amongst young people in my sample, irrespective of diagnostic status. This possibly indicates that the function or number of mechanoreceptors in the palm or cheek does not differ between the youngest and oldest participants in this study.

3.5.2 Tourette syndrome is not associated with altered tactile force detection thresholds

I used sigmoidal psychometric function fitting on the data to determine tactile force detection thresholds. Detection of touch is known to be dependent upon the function of A β and CT low-threshold mechanoreceptors present in the glabrous and hairy skin (Abraira & Ginty, 2013; McGlone et al., 2014). In my study, I calculated the 75% touch threshold for both groups and both skin locations (Hand and Cheek). One tailed t-tests revealed that patients with TS do not present lower detection thresholds than matched control participants on either skin location. These results conform with previous studies in adults with TS (Belluscio, Jin, et al., 2011; Schunke et al., 2016) but are in contrast with the work by Puts and colleagues (Puts et al., 2015). Methodological differences between these studies and the current study render direct comparison difficult however. Puts and colleagues (2015) also tested children but used vibrotactile sensory tasks, which test discriminative touch thresholds. Such stimulation is known to activate A β afferents, but poorly excite the CT afferents (see Håkan Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). Thus, both tactile force and vibrotactile stimulation should excite similar but not completely the same LTMs. Furthermore, Puts, et al. (2015) stimulated the left index and middle fingers, whereas I stimulated the palm and the cheek on the dominant side. Interestingly, Puts and co-workers also measured the inhibitory neurotransmitter GABA from the right sensorimotor cortex in both

groups and was able to determine that GABA was significantly reduced in TS which also correlated inversely with motor tic severity. Moreover, whereas a significant correlation was observed in the control group between frequency discrimination thresholds and adaptation effects, and GABA concentration, such relationship was completely absent in the TS group. The authors postulated that GABAergic function might play an important role in sensory impairments observed in TS. Taken together, the results by Puts and colleagues (2015) is the first to date to show altered sensory detection thresholds in TS. It is possible that impaired vibrotactile performance in TS is related to cortical organization and suggests increased segregation between digits in the sensorimotor cortex. This hypothesis is explored in the next chapter of this thesis.

Of note, when using a similar paradigm as I used in this study, Belluscio and colleagues (2011) showed unaltered tactile force detection thresholds in TS, albeit in adults. The authors determined tactile thresholds by numbering the monofilaments and taking the average. In my analyses, however, I relied on the more robust force generated by the monofilaments as an indication of a threshold, as recently recommended (Bradman, et al. 2015). In my analyses I determined tactile force thresholds by fitting a sigmoidal function to the data, a method that is widely employed, with 500 repetitions to assure correct fitting. Also, I assessed thresholds from same two skin locations in all participants, one location as part of the glabrous skin and the other on hairy skin. In contrast, Belluscio et al. (2011) tested the lower leg and the site of most active tic and sensory urge. Therefore, due to differences in age, dissimilar definition of thresholds and different skin locations, comparing the two studies is difficult. Nonetheless, both yield similar results showing unaltered tactile force thresholds in TS.

In principle, sensory thresholds seem to be unaltered in adult patients while children demonstrate unaltered tactile force detection thresholds but inferior performance detecting vibrotactile discrimination stimuli.

3.5.3 *Sensory prediction is altered in TS*

I also analysed the data using signal detection theory (SDT). SDT assumes that there is no individual sensory threshold. Rather, observers are driven by internal response criterion, where the goal is to maximise the incentives but minimize the error associated with a decision; whether the signal or noise was present (Neil A. Macmillan & Creelman, 2005). This can be characterized by several measures such as d' (sensitivity) and Criterion c (response bias). Importantly within the framework of SDT, an observers' way of responding is dependent on the observers location of the criterion (Neil A. Macmillan & Creelman, 2005). To ascertain any group differences on these measures, I analysed the data using mixed model ANOVA. Two important findings are highlighted.

First, I found a significant Group effect on the proportion of false alarms (FAs). Specifically, the CS group had greater proportion of FAs than the TS group. Second, there was a marginal group effect on the Criterion c measure. Here the TS group had higher positive Criterion c than the CS group and was thus more inclined to respond 'no' when asked if the stimulus was present. No differences were found on the proportion of hits or sensitivity (d') measures. These results suggest that young patients with TS are more conservative responders and require the signal to be stronger before they indicate its presence. These results are perhaps not all too surprising since patients perceive sensory input as more intense and bothersome than what would normally occur. This might lead to a stricter response criterion.

Belluscio and colleagues (2011) suggest that the sensory system in TS is biased, possibly due to repeated exposure to motor and vocal tics, and sensory urges. With this in mind, my results fit well within the framework of predictive coding theories (Kok & de Lange, 2015; Seth, Suzuki, & Critchley, 2012; van Boxtel & Lu, 2013). Predictive coding states that models of the external sensory world are continuously generated by the brain, based on contextual information and from memory. In turn, these models are used to predict sensory inputs, since prediction is a fundamental feature of sensory processing (Kok & de Lange, 2015; Seth et al., 2012). Essentially, the experience of a sensory signal rests on the assumption that when a sensory input enters the brain, it is

processed by lower sensory areas and the information is forwarded to higher level cortical areas. Based on this feedforwarded input, a prediction is fed back by the higher-level area as its best prediction of the sensory data. This can essentially be thought of as a “prior experience” (Kok & de Lange, 2015). When the sensory signal does not “fit” within the pre-existing models of the sensory world, prediction error occurs (i.e., difference between expected and observed sensory information), which can essentially be thought of as the residual variance of the sensory signal (Kok & de Lange, 2015; van Boxtel & Lu, 2013). Prediction is an important aspect in the realm of predictive coding since prediction aids in suppression of expected sensory signals (Kok & de Lange, 2015). But how does this fit within TS?

van Boxtel and Lu (2013) argue that predictive coding can be used to explain perceptual deficits in patients with autism. Interestingly they suggest that very often the prediction does not match the input and hence expectations are violated. Moreover, the sensory processing at higher level cortical areas in autism are placid, resulting in less precise predictions and an increase in prediction errors. As a consequence of the ever-increasing prediction errors, their sensory system is overloaded with sensory stimulation (van Boxtel & Lu, 2013). In my view, the same principle applies to young people with TS. Numerous studies have suggested a faulty sensory processing in TS, and sensorimotor gating is an example of this. Several studies in TS have shown that patients display dysfunctional sensorimotor gating mechanisms, where patients are unable to predict a startle stimulus in the presence of a preceding weaker stimulus (Buse et al., 2016). This indicates that in TS sensory prediction might be abnormal.

The inability to adjust the senses (due to abnormal function of the sensorimotor gating mechanisms) coupled with repetitive motor outputs (tics) gives rise to noisy and distorted models of the sensory world, which affect the way patients process and respond to tactile stimulation, while not affecting sensitivity per se. This is exactly what I found in my study, where the sensitivity index d' was the same across the two groups, while patients with TS made far fewer false alarm responses and showed a tendency for a more strict response bias (i.e., more stringent internal response criterion). To put differently, I propose that the sensory information coming into the brain in patients is

unaffected. The difference lies in the brain's best guess of the cause and what consequence the sensory information holds, and it is this perception that changes what you consciously feel (Seth et al., 2012). This theory might also explain the self-perceived sensory hypersensitivity, since patients have learned not to trust their senses properly and possibly cannot update their sensory models. Indeed, a study using magnetoencephalography (MEG) on patients with autism and ADHD showed that patients display expectation abnormalities to an auditory oddball stimuli, resulting in the failure to properly contextualize sensory information (Gonzalez-Gadea et al., 2015).

Perhaps the greatest support for this theory comes from studies investigating the sense of volitional movements in TS. One study showed delayed experience of volition in adult patients (Moretto, Schwingenschuh, Katschnig, Bhatia, & Haggard, 2011). Moreover, delayed intention to a volitional movement is related to sensory urges in TS (Ganos, Asmuss, et al., 2015). Specifically, stronger PSP in patients delays the intention to move possibly due to several competing responses according to the author (Ganos, et al. 2015). Another study also showed that patients with TS have altered perception of agency (the feeling of control over self-produced actions; Delorme et al., 2016). Ganos and colleagues (2015) suggest that patients with TS have greater difficulty setting internal sensory thresholds because of abnormally noisy motor levels. This suggests that in TS, internal models are noisier than normal, and patients have greater difficulty separating noise from the signal, resulting in an unusually high internal criterion as I have shown here.

3.5.4 Limitations

A major caveat of this study is the necessary exclusion of participants from one condition due to floor effects. This occurred because in some cases the monofilaments were not sensitive enough to detect the true tactile threshold on the cheek. If I were to repeat or re-do this study I would develop new, thinner filaments capable of delivering lower forces, increase the number of trials and increase the number of test sites to get a broader perspective of tactile sensitivity in TS.

Another limitation is the lack of subjective measures of self-evaluated hypersensitivity in patients. Several quality questionnaires exist such as the Adult/Adolescent Sensory Profile (Dunn & Bennett, 2002) and the somatosensory amplification scale (Barsky et al., 1990). Unfortunately, I decided to send out these questionnaires in post after the testing session, with prepaid envelopes. Only 50% of the questionnaires were returned and some had several missing answers, rendering them useless. As a result, I cannot ascertain that my group of patients with TS perceive themselves as hypersensitive and, I cannot replicate previous findings in this type of patients (Belluscio, Jin, et al., 2011; Cohen & Leckman, 1992).

Lastly, it is important to discuss the use of the *method of limits* to substantiate a sensory threshold. Two sources of error are common using this method; *the error of habituation* and *the error of expectation* (F A A Kingdom & Prins, 2011). The error of habituation is one criticism where the participant becomes habituated to the stimuli and starts responding in the same way irrespective of stimulus level and their threshold (F A A Kingdom & Prins, 2011). Equally, the error of expectation is thought to arise when the participant anticipates that the stimulus might become more detectable or simply undetectable and make premature judgement. These two sources of error can be resolved by using a staircase procedure and average thresholds (F A A Kingdom & Prins, 2011). Indeed, this is exactly what I did in my method but this is dependent on if the participant made enough correct or incorrect responses (i.e. if he hopped up or went down a level). Also, I asked participants to close their eyes and they were not made aware that the stimulus would start at easy detection and become harder. Nonetheless, if I had to repeat this experiment I would opt for method of constant stimuli rather than the method of limits. Or perhaps another variant of the adaptive method, the psi method. The psi method is considered to be the most efficient of the adaptive methods, since the psi method efficiently and reliably estimates threshold and slope parameters of the psychometric function (F A A Kingdom & Prins, 2011; Kontsevich & Tyler, 1999).

3.6 SUMMARY, CONCLUSION AND CONTINUANCE

To recapitulate, patients with TS have unaltered tactile sensory detection as evident by the non-significant comparison of thresholds and sensitivity (d'). Interestingly, and in line with my hypothesis was that patients with TS show an altered way of responding to sensory input. These results are consistent with the interpretation by Belluscio and colleagues (2011) of their findings, saying that TS does not affect the perception of sensory input, but rather the feeling of sensory sensitivity must arise within the CNS. However, this has not been confirmed. In my view, self-perceived sensory sensitivity might best be explained in the realm of predictive coding theories due to prediction errors as the corollary of the inability to (1) adjust the senses properly, and (2) abnormally noisy internal models rendering response to sensory input difficult and setting an unusually high internal response criterion. How this occurs in TS has not been empirically tested but raises the question as to why patients perceive themselves to have heightened sensory sensitivity which is not necessarily captured by sensory testing. This forms the basis for the rest of this thesis, which explores the brain structure in young people with TS. In the next chapter I explore the possibility of cortical re-organisation, which might interfere with the ability of the brain to formulate the cause and consequence of what a sensory information holds. That is, it is possible that brain structure, especially within the sensorimotor cortex, in TS might be related to altered perception of sensory input, causing self-perceived sensory disturbances.

CHAPTER 4

Chapter Four – Sensorimotor cortical mapping in Tourette syndrome using neuronavigated transcranial magnetic stimulation

Sensorimotor representations are prone to being perturbed during sensory stimulation, motor learning and in hyperkinetic movement disorders such as TS. TS has also been associated with impaired operation of GABA (inhibitory) signalling and loss of important inhibitory interneurons in subcortical structures. Tales of self-reported somatosensory amplification and increased interoceptive awareness give rise to alteration in structural organisation of the sensorimotor cortex. Related hyperkinetic movement disorders suggest increased distance between or displacement of targeted muscle representations. In this chapter I present, for the first time in TS, a sensorimotor cortical mapping study using brain stimulation. Here I test the hypothesis that loss of separation and spatial specificity of sensorimotor representations might be attributed to the loss of GABA-mediated cortical inhibition, lack of neuroplasticity effects and/or repetitive sensory stimulation in TS. The hypothesis is tested by evaluating and comparing characteristics of sensorimotor maps, including location, distance between and variability of muscle representations on individual maps. Also, I investigate whether differences in the cortical representation of targeted muscles within the primary motor cortex are associated with somatosensory amplification and interoception. Importantly, this investigation shows the efficacy and feasibility of locating and outlining TMS-induced sensorimotor representations in young patients with TS.

Keywords: Transcranial magnetic stimulation, nTMS mapping, SICl, Interoceptive awareness, somatosensory amplification.

The study presented in this Chapter was introduced at the *10th European conference of the European Society for the study of Tourette syndrome* in Seville 2017.

4.1 INTRODUCTION

In the previous chapter I presented results on my tactile force detection measure ascribing self-perceived hypersensitivity to external stimuli to probable alterations in the CNS as previously suggested. Most prominent, I showed that patients with TS demonstrate altered way of responding to sensory stimulation, by setting an unusually high internal response criterion as shown by a (marginally) higher response bias and fewer false alarms. I explained my results using the framework of predictive coding, such that in TS there is greater prediction errors due to less precise predictions at higher cortical level. Consequently, the sensory system in TS gets overloaded with sensory stimulation possibly due to perturbed organisation of muscle representations in the sensorimotor cortex. As such, it is possible that altered perception of sensory input is related to the structural properties of the TS brain. The rest of this thesis investigates potential alteration in brain structure in patients, starting by employing a novel design of cortical mapping with TMS to assess the integrity of targeted muscle representations in the sensorimotor cortex, and also investigate the potential involvement of the inhibitory neurotransmitter GABA.

4.1.1 *Sensory inputs affect cortical organisation*

The sensorimotor (SM) cortex is organised topographically, where sensation and movement are anatomically separated yet functionally integrated. Evidence shows that SM cortical representations are dynamic and actively maintained and updated to reflect activity of afferent information.

Myriad of studies have shown that the brain actively adapts, and re-organisation occurs even during recovery from brain infarcts (see overview in Kalaska & Rizzolatti, 2013). Changes in cortical organisation can also be induced following repetitive sensory stimulation (Feldman & Brecht, 2005; Hamdy, Rothwell, et al., 1998; X. Wang et al.,

1995) or sensory de-afferentation when peripheral inputs are temporarily disrupted (Kolasinski et al., 2016; Ziemann, Corwell, & Cohen, 1998). Such changes have also been observed following motor learning (Nudo, Milliken, Jenkins, & Merzenich, 1996; van de Ruit & Grey, 2017).

In the context of TS, repetitive sensory stimulation might inflict changes in the cortical organisation due to the refinement of perception to sensory input. Indeed, one study in non-human primates showed that segregation of digit representations can be altered depending upon the temporal characteristics of the sensory stimuli (X. Wang et al., 1995). In humans, similar observations have been made using a combination of sensory de-afferentation (two digits were glued together) and functional neuroimaging (Kolasinski et al., 2016). Specifically, when the peripheral input is altered, changes become apparent in digit representations, promoting experience- or use-dependent cortical neuroplasticity (the process of brain adaptation, and the possibility of changing or forming new connections; Feldman & Brecht, 2005) in the SM cortex (Kolasinski et al., 2016). The most striking results of this study was the observation that this manipulation causes changes in segregation of adjacent digit representations only. What is more, when segregation of digit representations is reduced, participants performed better on a vibrotactile discrimination task, whereas performance deteriorated when segregation between digit representations increased (Kolasinski et al., 2016). The authors, presenting these results, postulated whether this could reflect some compensatory mechanisms, mediated by adopting the use of the free, non-manipulated fingers. With this in mind, it is interesting to mention again the results by Puts and co-workers (2015) who reported altered performance of young patients with TS on such vibrotactile tasks. The same study also established reduced concentration of GABA in the SM cortex. If comparable, then one might hypothesise that worse performance demonstrated by patients might be indicative of increased segregation and loss of spatial specificity of digit representations, possibly mediated by GABA. However, no study to date has systematically investigated this in TS.

4.1.2 *GABA maintains spatial specificity of cortical representations*

GABA, as mediator of neural communication, plays a pivotal role in neuroplasticity (Di Cristo, 2007). As such, Feldman and Brecht (2005) argue that neuroplasticity observed in cortical layers correlates significantly with the increase in the number and density of GABAergic synapses. Indeed, work by Donoghue and colleagues showed for example that bicuculline (a GABA_A antagonist) injected into the forearm muscle of a rat resulted in simultaneous contraction of both the lip and forearm muscles during stimulation, and posited that this must be dependent upon GABAergic inhibitory interneurons who would otherwise suppress this behaviour (Jacobs & Donoghue, 1991). Therefore, GABA and more specifically GABAergic inhibitory interneurons play an important role in both orchestrating the temporal activity of neuronal networks in the brain and controlling the spatial specificity of sensorimotor representations (Di Cristo, 2007; Feldman & Brecht, 2005; Griffen & Maffei, 2014).

Aberrant GABAergic mechanisms have consistently been demonstrated in TS (for an excellent review on the role of GABAergic interneurons in TS see Rapanelli, Frick, & Pittenger, 2017). These studies have both employed neuroimaging and brain stimulation paradigms. Using MR spectroscopy, several studies have demonstrated altered concentration of GABA specifically in sensory and motor areas of the brain (e.g., Draper et al., 2014; Puts et al., 2015). Similarly, post-mortem studies have reported reduced amount and altered distribution of GABAergic interneurons in the striatum in severe TS (Kalanithi et al., 2005; Kataoka et al., 2010). It is thus interesting to ponder if GABAergic interneurons could be missing at both cortical and subcortical level in TS.

Collectively, these studies give rise to the possibility that in TS, altered distribution and concentration of GABA and GABAergic mechanisms lead to loss of spatial specificity of SM cortical representations. In the context of the current thesis, the evidence seems to suggest that sensory adaptation might be impaired in TS, possibly as the consequence, cause or co-occurrence of GABAergic impairment.

4.1.3 *Short-interval intracortical inhibition (SICI)*

Cortical inhibitory mechanisms can be studied using TMS and parameters termed short-interval intracortical inhibition (SICI; see subsection 2.3.2 in Chapter 2). In general, SICI seems to be less effective in inducing cortical inhibition in TS compared to control groups (Ziemann et al., 1997) but often without reaching statistical significance (e.g., Moll et al., 2001; Orth, Amann, Robertson, & Rothwell, 2005; but see Orth, Münchau, & Rothwell, 2008). In children and adolescents specifically, there is limited evidence on the effectiveness of SICI inducing cortical inhibition. However, Moll and colleagues (2001) showed, in a subgroup analyses, that ADHD and ADHD+TS children had significantly reduced SICI in comparison to uncomplicated TS and control groups. These results have been confirmed in an ADHD sample only, where less SICI correlated with increasing ADHD severity (Gilbert, Isaacs, Augusta, MacNeil, & Mostofsky, 2011). Some evidence exists on the relationship between SICI and motor tic severity (Gilbert et al., 2004) but lacks supporting evidence.

In adults with TS, more available evidence suggests aberrant intracortical inhibition mechanisms (Martín-Rodríguez et al., 2015; Orth & Rothwell, 2009; Ziemann et al., 1997). In general, based on the studies mentioned above, it is apparent that reduced SICI in TS is most likely related to the co-occurrence of ADHD.

4.1.4 *Cortical organisation in hyperkinetic disorders*

As noted above, the exact nature of the relationship between brain structure and sensory phenomena in TS remains unknown. Few studies, in both TS and patients with focal hand dystonia (FHD), have observed abnormal function and structure of the SM cortex. FHD is a related hyperkinetic disorder with comparable underlying neuropathology and is characterised by dystonic postures of the hand and excessive muscle contraction. More importantly, patients with FHD experience sensory phenomena; all symptoms akin to the ones seen in TS patients (Berardelli et al., 1998).

For example, one study of TS patients showed abnormal functional activation of the SM cortex and SMA, characterised by enlargement of the response area, during a finger-to-thumb apposition (Biswal et al., 1998). In young patients with TS altered

physiological response was observed in the SM cortex, SMA, ACC and inferior frontal cortex during a cognitive control task. Additionally, the aberrant activation in the SM cortex was strongly related to tic severity (Jung, Jackson, Parkinson, & Jackson, 2013). Collectively, these studies suggest potential functional re-organisation. However, these studies did not investigate any potential shifts in cortical representations. The only study to date, to my knowledge, that demonstrates this showed a significant shift in the centroid of activated EEG channels during simple and complex hand movements (Stevens, Günther, Lutzenberger, Bartels, & Müller, 1996).

In FHD, one study investigated digit map plasticity in patients with writer's cramp (a task-specific focal dystonia of the hand) using fMRI (Nelson, Blake, & Chen, 2009). This study primarily showed that somatosensory maps of digit representations were characterised by reduced segregation and greater overlap between digits specifically involved in writing. However, studies employing fMRI are limited by poor spatial resolution, and more focal mapping techniques might be better suited to study the topography of the SM cortex. TMS is an example of this and was employed in a related study by Byrnes and colleagues (1998). In this study, the authors assessed the relative changes in muscle representations of the APB and FDI muscles of both the dominant and non-dominant sides using a TMS mapping protocol. The results showed a greater asymmetry of map positions (measured as the peak MEP amplitude) of the targeted muscles between hemispheres. Interestingly, these differences were largely mediated by the duration of the disorder, where patients with longer disease duration showed greater displacement of muscle representations involved in writing. This has more recently been extended upon, showing increased representation map sizes in patients with FHD, in addition to increased distances between the centre-of-gravity (COG) of representations, compared to healthy volunteers (Schabrun, Stinear, Byblow, & Ridding, 2009).

Taken together, two disorders characterised by abnormal motor outputs, sensory symptoms and altered sensory perception, both demonstrate a trend for altered muscle representations in the SM cortex. Empirical evidence seems to suggest that altered somatosensory and SM representations in patients with FHD specifically, might give rise to involuntary outputs (for review see Quartarone et al., 2014). Studying the

cortical organisation in these conditions can be of vital importance for therapeutic interventions. Also, reduced segregation of representations of muscles in these patients may affect the perception and interpretation of sensory inputs which occur before and during motor movements possibly mediated by dysfunctional sensory gating mechanisms (Buse et al., 2016; Murase et al., 2000).

4.1.5 *Summary, aim and hypotheses*

In this introductory text, I have presented the current knowledge of GABA-mediated cortical inhibition in TS and numerous instances for the re-arrangement of cortical representations which is possibly mediated by the loss or altered distribution of GABAergic interneurons. For the first time in TS, I present a nTMS study together with electromyography to assess muscle representation in young patients with TS and typically developing control participants. The primary objective of this study is to investigate if there are any fundamental changes in the organisation of the SM cortex regarding targeted muscle representations in young patients with TS and if these alterations can be related to GABA-mediated cortical inhibition. Primarily, nTMS-generated cortical maps are characterised by their location, distance between and variability of muscle representations. The secondary objective is to see if aberrant self-evaluated somatosensory sensitivity, amplification and interoceptive awareness can be established in my sample of patients, as previously described. Based on the evidence presented above, I hypothesise that loss of separation and spatial specificity of nTMS-induced muscle responses in TS can be related to altered GABA mechanisms and severity of sensory urges, sensory sensitivity and interoceptive awareness.

4.2 METHODOLOGY

4.2.1 *Participants*

Sixteen patients with TS (5 females, M: 20.4 ± 7.1 , range: 13.7 – 35.1) and 14 typically developing matched controls (CS; 4 females, M: 17.4 ± 4.0 , range: 12.2 – 24.8) took part in this study. Participants were excluded from participating if they were (1)

younger than 12 years of age, (2) had an IQ below 70 or (3) presented any contraindication to participating in a TMS experiment. One patient was administered the Tourette Syndrome Diagnostic Confidence Index (TS-DCI; Robertson et al., 1999) to ascertain the presence of TS and scored 74, above the reported average (Robertson et al., 1999). Another patient had a diagnosis of a chronic tic disorder (CTD). Note that TS and CTD are related disorder with similar pathologies and both show symptoms of sensory phenomena (Rozenman et al., 2015). Six patients were medicated at the time of testing, while none were seeking alternative therapeutic intervention. Three patients had either confirmed or suspected comorbidities (see Table 4.2 for patient specific characteristics). Participants were not asked to cease their medications prior to testing.

4.2.2 *Electromyography*

Electromyography (EMG) activity was recorded using pre-gelled Covidien Kendall Ag/AgCl disposable electrodes. The signal was amplified and bandpass filtered (10-2000 Hz, with 2000 Hz sampling rate) and digitalized using Brain Amp ExG and BrainVision Recorder (Brain Products GmbH). For TMS maps, MEPs were sampled from the FDI, deltoid (shoulder), lips (O. Oris), eyes (O. Oculi) and masseter muscles on the right side of the body (see Figure 4.1). The facial muscles were chosen based on the work of Saisanen and colleagues (2015) showing the feasibility of stimulating these facial muscles. Also, all muscles are known body areas associated with the occurrence of tics and PSP in TS (Ganos et al., 2012; Kwak et al., 2003; Schunke et al., 2016). During SICl, MEPs were collected from the FDI muscle only. Participants were kindly asked to maintain relaxed position of the hand, arm and face throughout the session. This is important to maintain low noise in the targeted muscles. Participants were told that TMS pulses triggered more laterally would invoke uncontrollable facial reflexes but were assured that this was normal. It was emphasised to all participants to express any feelings of discomfort and if they wanted to stop. Regular breaks were offered.

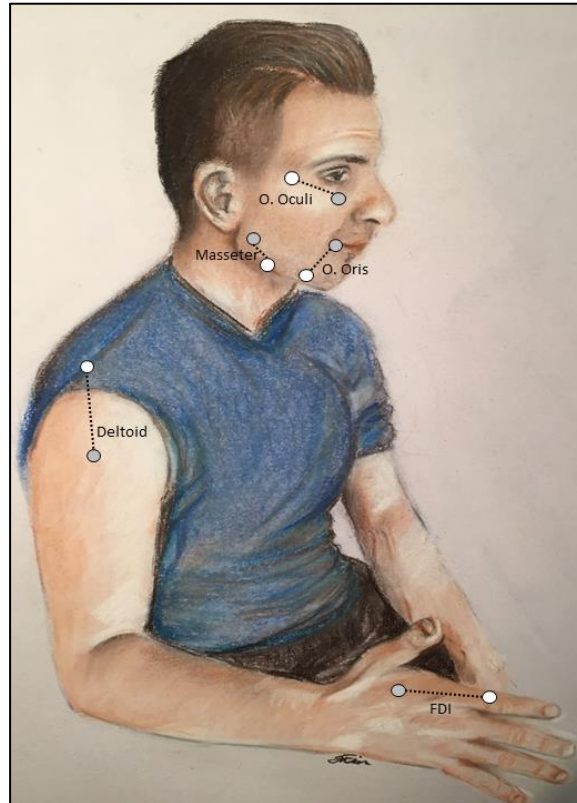


Figure 4.1. Electrode placement on hand, arm and facial muscles. The darker shade of grey indicates active electrodes and white shade indicates reference electrodes. All electrode pairings were at least 2 cm apart.

4.2.3 Cortical stimulation

Below is a brief description of how nTMS maps were created. More detailed information can be found in Appendix 2.

4.2.3.1 nTMS mapping

TMS pulses were generated using a paired Magstim bistim system (i.e., two separate units; Magstim, Whiteland, Dyfed, UK) using a figure-of-eight magnetic coil, with a 70-mm diameter of each winding. Resting motor threshold (rMT) was determined for all participants and was defined as the TMS stimulation intensity (as % of maximum stimulator output [MSO]) necessary to evoke a peak-to-peak MEP (ppMEP) amplitude between 50-100 μ V in > 5 out of 10 trials (Rossini, et al. 2009). TMS pulses were delivered at 200% of rMT, up to a maximum limit of 80% of the MSO from one unit of the Magstim system. During mapping, the coil was held with the handle

pointing posterior in a 45° angle, and the current flowing in a posterior-anterior direction. When applicable, individual anatomical MRI images were uploaded to a neuro-navigation system (Brainsight, Rogue Research Inc., Montreal, Quebec, Canada) to locate an approximate position of the left primary motor cortex (M1). In few instances, where no individual anatomical MRI image was available, a template constructed from a consenting individual anatomical image was used. 150 TMS pulses (with an ISI of 6 s) were delivered pseudorandomly within a 40 cm² virtual grid superimposed on the MRI scan in the neuronavigation software (BrainSight, Rogue Resolutions). The virtual grid encompassed the left precentral gyrus partially overlapping with the postcentral gyrus and premotor cortices (see Figure 10.1 in Appendix 2). Coordinates in 3D space of nTMS pulses were collected and stored within the neuronavigation software. For comfort and hearing protection all participants were asked to wear sound attenuating earplugs throughout the duration of the study.

4.2.3.2 Data analysis of nTMS maps

ppMEPs were time locked and extracted from each muscle EMG recording separately via a specific time frame, based upon the known latency for each muscle as specified by recent publications (Inoue, Tani, Taniguchi, & Yamamoto, 2003; Kallioniemi, Pitkänen, Säisänen, & Julkunen, 2015; Säisänen et al., 2015, see Table 10.1 in Appendix 2). Subsequently, MEPs were (1) synchronised to TMS scalp coordinates, (2) excluded if noise levels exceeded 50 µV or due to any obvious artefacts, (3) standardized using a z-transformation and (4) thresholded to $z \geq 1$ in all maps separately.

Data analysis workflow is depicted in Figure 4.2 (but see Appendix 2 for detailed description). Briefly, (A) TMS scalp coordinates are extracted from the neuronavigation software and are given with respect to location on the scalp. (B) Separate coordinate system for the coil (coil coordinates) are given as direction of cosines, where each direction x-coil, y-coil and z-coil represent the pitch, roll and yaw of each axis of the coil. (C) To ensure the correct location on the cortex, all scalp coordinates are transferred to cortex coordinates via a transformation matrix, where coil coordinates are used for trajectories onto the cortex. (D) The 2-dimensional SM maps are generated

by fitting a rectangular plane to the cloud of the 3-dimensional datapoints. (E) A bounding box was fitted to the plane coordinates, after finding the central point. The plane is then rotated to align with the respective X- and Y-axes via a rotation matrix through the angle θ (see Equation 10.2). And finally, (F) a full cortical surface maps are constructed of the targeted muscle representations. This last step is achieved using a triangular linear interpolation using the MATLAB toolbox 'Gridfit' (<http://uk.mathworks.com/matlabcentral/fileexchange/8998-surface-fitting-using-gridfit>). The final surface map is made up of 8100 pixels (a 90 x 90 map), where each pixel is appointed an approximated MEP (aMEP) based on the nearest MEP datapoint.

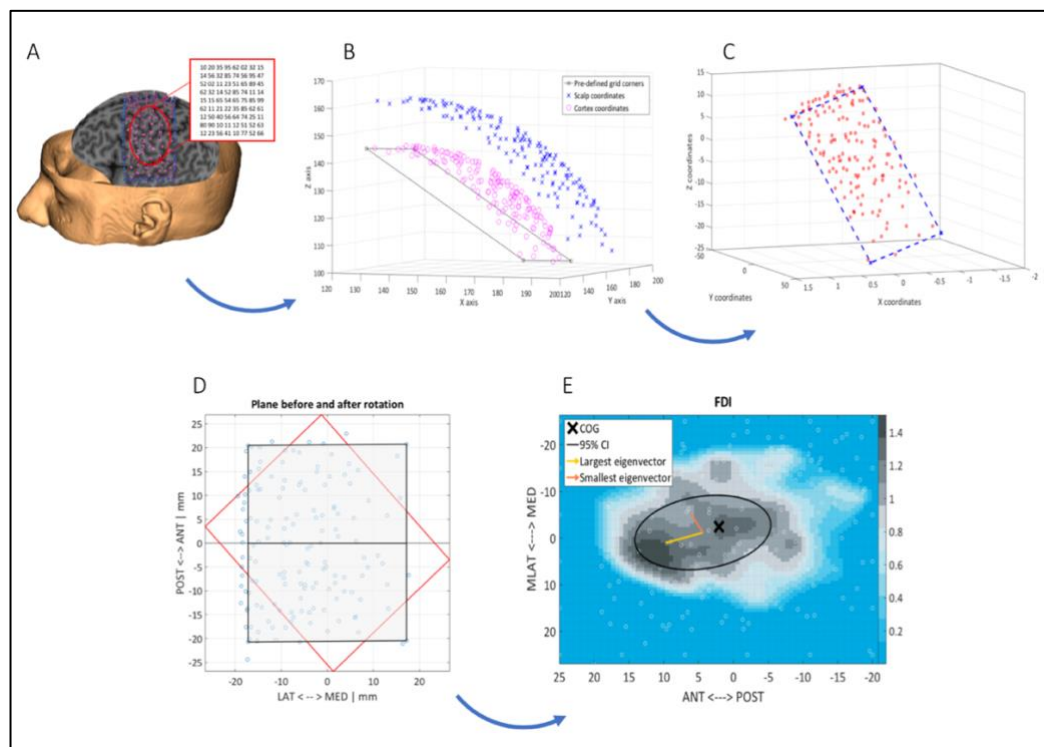


Figure 4.2. Data analysis workflow. A: TMS coordinates of TMS pulses are extracted from the neuronavigation system. B: The coordinates are transformed from scalp to cortex. C: A plane is fitted through the cloud of 3D data for transformation to 2D. D: The plane is rotated to align with the axes. E: A full cortical map is calculated for each muscle separately using triangular linear interpolation, generating approximate MEPs for each grid point (90x90). This map is then rotated for visual purposes so that the lateral-medial direction lies on the y-axis.

Three important map parameters were calculated for each map and subsequently compared between the two groups. First, *centre-of-gravity (COG)* for each muscle was

calculated in the same way as detailed in van de Ruit et al. (2015), where COG is the mean position in a map, based on weighted mean intensity of each pixel in a map (see Equation 10.3). COGs have been shown to yield more reliable estimates than peak activation (highest MEP amplitude; Weiss et al., 2013). Moreover, COG has been shown to have better between-session reliability as measured using intraclass correlation coefficient (Weiss et al., 2013). Also, COG has been shown to be stable irrespective of the ISI (van de Ruit, et al. 2015). Distances between COG of pair of muscle representations was determined using *Euclidean distances (EDs)* and calculated in 2D space using Equation 10.4 in Appendix 2. EDs can be indicative of spatial re-organisation (Elbert et al., 1994; Makin, Scholz, Henderson Slater, Johansen-Berg, & Tracey, 2015) and have shown good between-session reliability and less variability than equivalent distances derived from fMRI activation of several muscle representations (Weiss et al., 2013). Lastly, I calculated the variability of the data for each targeted muscle representation. The variability is derived from the eigenvalues of the covariance matrix, generated by fitting a 95% confidence interval ellipse to the peak activity. This results in an approximation of the *area* covered by the representation in a map and was calculated using Equation 10.5. The ellipse captures the variability of the aMEPs. For example, if there is great variability in the amplitudes, the ellipse will be larger. If, however, variability is low, and the peak aMEPs are confined to a small portion of the map, the ellipse becomes smaller. To assess the extent of each representation, the area within the ellipse was calculated (see Equation 10.5). This information can then be used to infer if muscle representations are generally more or less excitable when we move further away from the actual peak location with the TMS coil. Thus, if the hypothesis stands, the representations in the TS group will occupy a larger area (i.e., there will be a loss of spatial specificity).

4.2.3.3 *Short-interval cortical inhibition*

Cortical inhibition was assessed at rest. TMS pulses during this protocol were generated from both units of the Magstim system. Four subthreshold conditioning stimuli were delivered to the predefined motor hotspot at 60, 65, 70 and 75% of individual rMT. Also, a suprathreshold test stimulus, at 120% of individual rMT, was

delivered to the same location, through the same coil, 3 msec after the conditioning pulse. In total, the protocol consisted of 70 TMS pulse trials delivered to the participant's primary motor cortex, 30 of which were unconditioned (i.e., test stimulus alone) pulses and 40 pairings of conditioned-unconditioned pulses (10 at each conditioning intensity). The inter-trial interval was 6 s. A break was offered after every 20 pulses. The protocol used here has previously been established to invoke cortical inhibition in healthy participants (Dyke, Pépés et al., 2017). Raw MEPs were discarded if the preceding EMG activity exceeded 50 μ V or if the raw MEPs were < 50 μ V (under threshold determination criteria). Individual cortical inhibition was calculated for each participant by taking the median MEP amplitude for each conditioning intensity and divided by the median MEP amplitude of the 30 unconditioned trials. This results in a ratio value for each conditional pulse intensity. Between-group comparison in SICl was conducted using 2x4 repeated-measures ANOVA, entering the factors Conditional_intensity (4 levels) and Group (2 levels). Single value, indicating a level of inhibition for correlational analyses, was determined by taking the mean inhibition value of the four ratios. This value was chosen for two reasons: (1) Slope fitting of 4 values is not ideal and (2) the coefficient of determination (R^2) when a slope was fitted to the 4 values was deemed extremely poor (TS M R^2 : 0.61, range: 0.009 – 0.98; CS M R^2 : 0.66, range: 5.41-e5-0.99). This mean inhibition value was correlated with questionnaires and clinical measures.

4.2.4 *Measuring interoceptive awareness and somatosensory amplification*

To probe for differences in both self-evaluated interoceptive awareness and somatosensory amplification, all participants completed three sets of questionnaires (the AASP, the SAS and the MAIA, please refer to subsection 2.1.4 in Chapter 2 for details on each questionnaire) either immediately following or prior to the TMS session.

4.2.5 *Statistical analysis*

For continuous variables (age, IQ scores, rMT, the single dimension SAS questionnaire) any between-group differences were quantified using separate

independent sample t-tests, assuming equal variances unless stated otherwise. For categorical variables (i.e., gender and handedness), a Chi-square test was used.

Similarly, differences on map parameters between the two groups were assessed using independent sample t-tests, rather than multivariate analyses due to unforeseen errors (i.e., electrode malfunction) leading to missing data. Differences in means were calculated using a repeated sampling technique (i.e., permutation tests) with 10.000 permutations (without replacement; random allocation of data into groups, irrespective of group label) and assuming data was missing completely at random. The assumption of exchangeability was adhered to since group labels can be exchanged. The p-value was calculated as the percentage of simulations were the simulated t-statistic was more extreme than the observed t-statistic. A sampling distribution was constructed and the observed difference between the groups projected onto this distribution. To control for the error of multiple comparison, I applied the false discovery rate (FDR; Benjamini & Hochberg, 1995). Relationships between map parameters and PUTS scores was determined using Pearson correlation coefficient, corrected for multiple comparisons. I used multivariate analysis of covariance (one-way MANCOVA), controlling for the effects of age and IQ, to screen for any significant between-group differences on the multidimensional AASP and MAIA questionnaires.

4.3 RESULTS

Mapping of cortical representations using TMS was successfully accomplished in all participants without any adverse effects, except in one participant who complained of slight headache afterwards. However, this might also be attributed to the tightly fitting headband which holds the infra-red trackers to monitor head position. Out of all participants initially enrolled in the study (N = 30) only one had to be excluded completely due to head and coil tracking error. This participant was a 21-year-old male, part of the control group.

4.3.1 *Sample characteristics*

Age, IQ scores and rMT were tested for normality using the Shapiro-Wilks test. Age was not normally distributed ($W = 0.917$, $p < 0.05$), boxplots shown in Figure 4.3 reveal that one participant in the TS group (35-year-old male) was an outlier. This participant was not excluded to maintain statistical power. However, due to his mature age, his brain might show different cortical excitability. Consequently, results are interpreted accordingly. Age was not statistically different between the two groups ($t(27) = 1.66$, $p = 0.11$). WASI scores measuring IQ were normally distributed ($W = 0.936$, $p > 0.05$). Due to an oversight, WASI was not collected from one participant in the CS group. WASI scores were statistically different between the two groups ($t(26) = -2.31$, $p = 0.029$), while no participant scored below the exclusion criteria. rMT was also not normally distributed ($W = 0.896$, $p < 0.05$), while rMT was not significantly different between the two groups ($t(27) = 1.42$, $p = 0.17$). Finally, no difference in test pulse (the TMS pulse to stimulate the cortex and create SM maps) was observed, $t(27) = 0.45$, $p = 0.66$. For categorical variables, Chi-square tests showed that neither sex ($X^2 = 0.026$, $p > 0.05$) or handedness ($X^2 = 0.01$, $p > 0.05$) were different between groups (please see Table 4.1). All patients reported the presence of PSP (PUTS M: 22.9 ± 6.4).

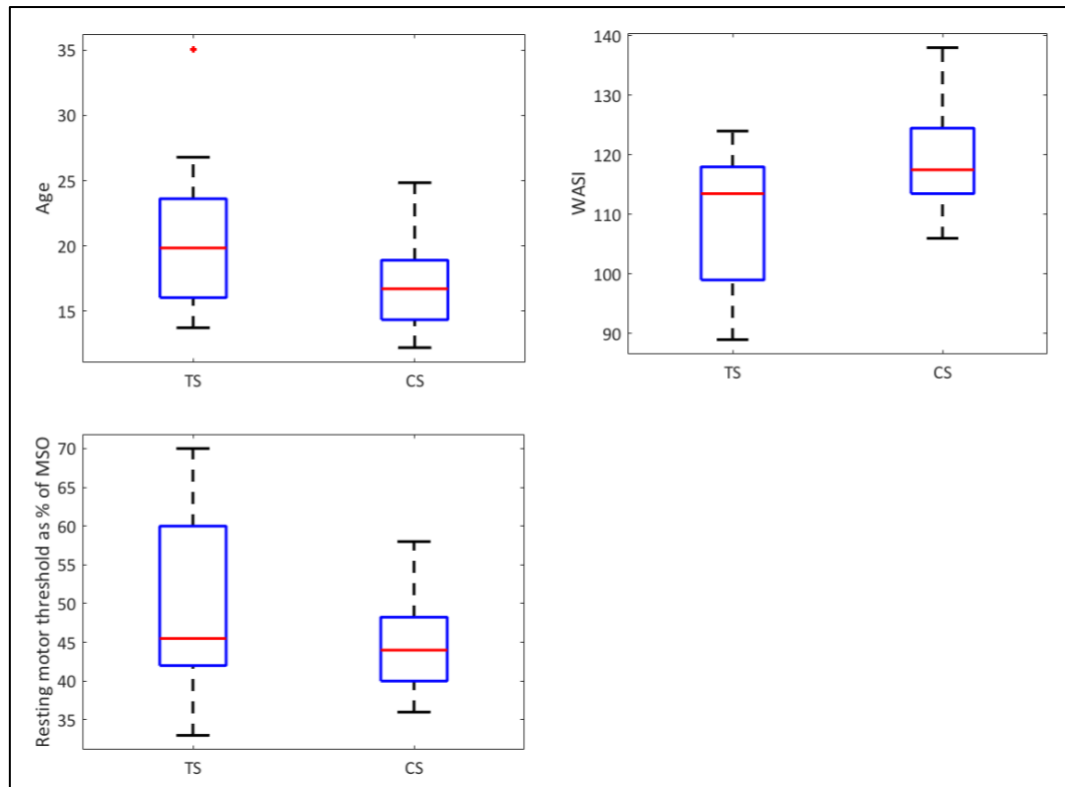


Figure 4.3. Group specific characteristics. Figure shows, top left: Age, top right: WASI scores and bottom left: rMT. Red line = median, box = 25th/75th percentiles, whiskers = to the most extreme data not considering outliers.

Table 4.1. Group specific characteristics. Table displays means (± 1 SD).

	Age	Sex (M:F)	WASI (IQ)	Handedness (R:L)	rMT	Test pulse
TS	20.4 (7.1)	11:5	109.5 (11.8)	15:1	49.3 (11.3)	78.6 (3.7)
CS	17.4 (4.0)	10:4	119.1 (9.3)	13:1	44.4 (6.0)	78.9 (2.6)
<i>p-value</i>	0.11	0.87	0.03	0.92	0.17	0.66

Table 4.2. Patient specific characteristics.

TS ID	Age	Sex	Handedness	WASI	PUTS	Yale Global Tic Severity scale (YGTSS)				Comorbidity	Medication	Other ^a
						Impairment	Motor	Vocal	Global			
TS001	18.7	M	R	120	27	25	14	11	50	None	None	None
TS002	17.4	F	R	118	26	10	17	7	34	None	None	None
TS003	15.5	M	R	113	14	5	8	5	18	None	None	None
TS004	16.6	M	R	118	21	10	8	18	36	OCD, ODD	None	None
TS005	20.0	M	R	103	10	5	8	5	18	None	None	None
TS006*	35.09	M	R	117	27	20	15	9	44	None	None	None
TS007	26.8	F	R	94	24	40	19	8	69	Possible OCD	Sertraline 100 mg, Detrinin, Folic acid	Past CBIT
TS008†	23.8	F	R	115	31	30	12	0	42	None	Clonidine 15 mg	None
TS009	13.7	M	R	92	23	10	10	14	34	None	None	None
TS010	14.8	M	R	124	18	0	10	0	10	None	None	None
TS011	23.4	F	R	89	13	10	11	10	27	None	Clonidine 2.5 mg	None
TS012	19.7	F	R	112	27	10	15	6	31	None	None	None
TS013	24.3	M	R	91	28	5	16	14	35	None	Aripiprazole 5mg, Antihistamines (hay fever)	Past CBT
TS014	19.9	M	R	121	27	5	12	5	22	None	None	None
TS015	22.3	M	L	114	28	5	14	12	31	ADD	Escitalopram 5mh Guanfacine 1mg, Sertraline 75 mg,	Past CBT
TS016	14.1	M	R	112	23	30	15	7	52	None	Lemeprazole (stomach acid tablets)	None
Average	20.4 (7.1)	-	-	109.56 (11.8)	22.94 (6.4)	13.75 (11.2)	12.8 (3.5)	8.2 (5.1)	34.56 (14.5)	-	-	-

Note: *Patient without formal diagnosis of TS; †Patient with Chronic tic disorder diagnosis. ^a Participants were asked if they had ever or currently seek alternative therapeutic interventions. CBIT: Comprehensive Behavioural Intervention of Tics. CBT: Cognitive-behavioural therapy.

4.3.2 Short interval intracortical inhibition (SICI)

Based on the exclusion criterion, 16% and 8% of MEPs were excluded from the TS and CS groups, respectively. For the 2 x 4 ANOVA with factors “Conditioning intensity” and “Group”, Mauchly’s test of sphericity showed a violation of the sphericity assumption ($W = 0.359$, $p < 0.001$) and thus a Greenhouse-Geisser correction was applied. There was a main effect of conditioning intensity ($F(1.78, 47.82) = 7.13$, $p = 0.003$, $\eta_p^2 = 0.21$ and observed power = 0.892) but no significant conditioning_intensity x Group interaction ($F(1.78, 47.82) = 0.34$, $p = 0.686$, partial $\eta^2 = 0.01$ and observed power = 0.1). *Post hoc* pairwise comparison of the significant main effect revealed a marginal significant difference in inhibitory effects of conditioning intensities at 60% and 65% ($p = 0.066$) and intensities at 60% and 75% ($p = 0.008$), Bonferroni corrected for multiple comparisons. The non-significant interaction effect indicates that there is no difference at any conditioning intensity eliciting inhibitory effects between the TS and CS groups (depicted in Figure 4.4|A). This figure shows that the line for the CS group is fairly linear whereas the TS group decreases more rapidly between 60% and 65% conditioning stimuli but then stabilises. This difference does not, however, reach statistical significance. Figure 4.4|A displays the mean inhibition value for each group which was correlated with PUTS scores. The correlation analysis revealed no significant relationship between mean inhibition and PUTS scores, $r = -0.24$, $p = 0.36$ (Figure 4.4|B).

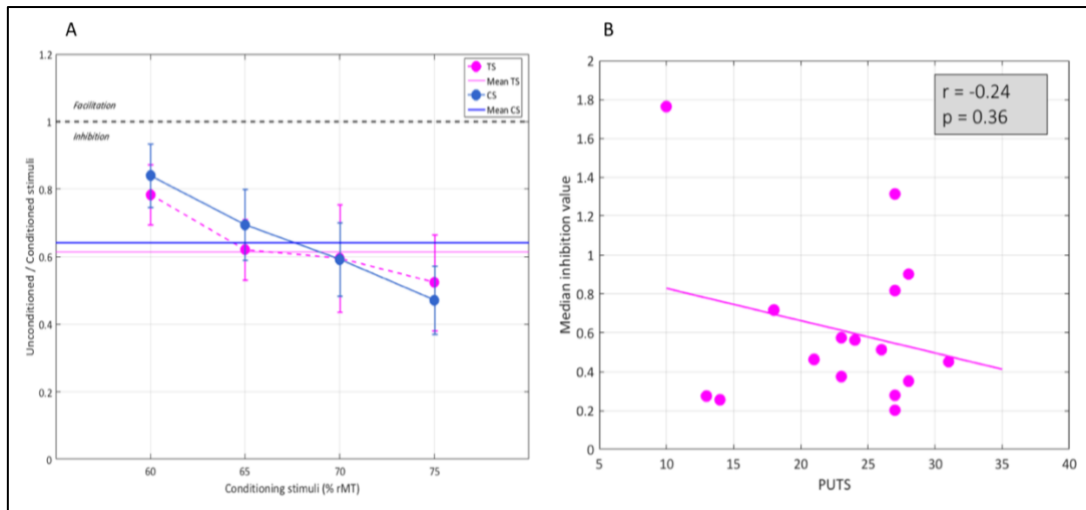


Figure 4.4. SICl results. **A:** Decrease in MEP amplitude as a result of conditioning intensity for both groups. Straight vertical lines are the group means of median inhibition, errorbars are SEM. Dotted line is the point of inhibition/facilitation. **B:** Correlation between PUTS scores and median inhibition in the TS group.

4.3.3 nTMS map parameters

From cortical maps, I calculated three map parameters: Location (COG), Euclidean distance (distance) between, and variability of SM representations (Area). Of note, quality of the data was assessed for each of the 5 EMG recordings (where each recording corresponds to one of the 5 targeted muscles), separately. In the TS group only, mapping of all targeted muscle representations was not achieved. Specifically, recordings from deltoid (6%), O. Oris (19%), masseter (19%) and O. Oculi (6%) had to be excluded. No recording was excluded from the FDI muscle. In most cases, the exclusion was due to electrode malfunction, inability to accurately locate the targeted muscle, or the inability of sticking an electrode on the face because of facial hair. No recording had to be excluded in the CS group. COG on the x (anterior-posterior) and y (lateral-medial) axes were analysed separately (see Table 4.3 and Table 4.4, respectively for descriptive statistics).

Table 4.3. Summary statistics table for anterior-posterior centre-of-gravity. Table displays mean (± 1 SD).

Muscle	TS	CS	p-FDR
FDI	-2.40 (3.40)	0.30 (2.94)	0.16
Deltoid	-4.37 ^a (3.91)	-3.71 (4.92)	0.87
O. Oris	6.95 ^b (4.47)	8.73 (3.76)	0.43
Masseter	6.69 ^b (4.64)	10.14 (5.51)	0.29
O. Oculi	4.86 ^c (4.29)	5.14 (5.04)	0.88

^amean based on N = 15, ^bmean based on N = 13, ^cmean based on N = 14.

Table 4.4. Summary statistics (mean ± 1 SD) table for lateral-medial centre-of-gravity.

Muscle	TS	CS	p-FDR
FDI	-6.55 (5.46)	-4.14 (3.14)	0.17
Deltoid	-9.22 (6.84)	-10.32 (2.75)	0.87
O. Oris	7.79 (5.82)	4.02 (4.0)	0.43
Masseter	9.23 (5.94)	8.9 (7.60)	0.27
O. Oculi	5.76 (6.59)	3.43 (8.94)	0.87

Permutation tests revealed that the FDI representation in the TS group was shifted significantly more medial compared to the CS group ($p = 0.03$, uncorrected) but this difference did not survive the FDR multiple comparison correction. No other shift in COG was observed in the TS group. The sampling distributions from the permutation tests are shown in Appendix 3.

Figure 4.5|left depicts group averages of each SM cortical representation with SEM in each direction. This figure shows that targeted muscle representations tested in this study correspond well to the known somatotopy of the SM cortex (Figure 4.5|right).

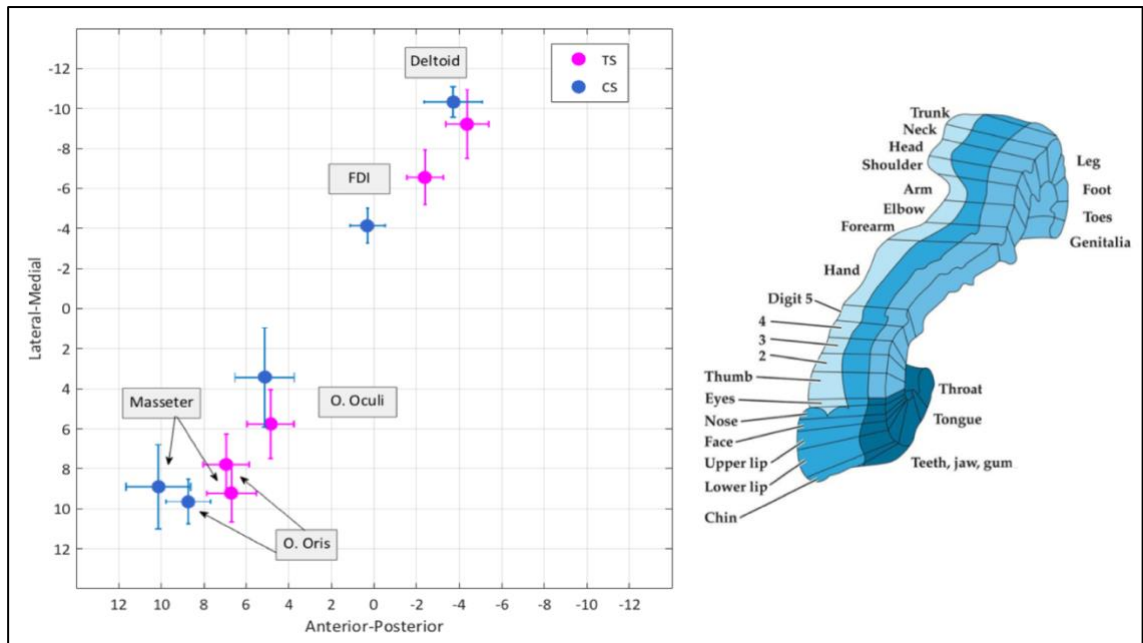


Figure 4.5. Location of targeted muscle representations during nTMS mapping. Left: x- and y-COG positions of each muscle representation. Right: A cartoon of the known somatotopy of the SM cortex (adapted from Levi, Wolfe, Kluender and Herz, 2005). Filled circles (blue and magenta) represent group averages and errorbars are SEM.

Distance between pairs of cortical representations was measured using the Euclidean distance (see Table 4.5 for group means). Permutation tests on each pair of muscle representations revealed no statistically difference in EDs between the two groups. The sampling distribution is depicted in Figure 11.3 in Appendix 3.

Table 4.5. Descriptive statistics for group-wise comparison of Euclidean distance between COGs (in mm). Table displays mean (± 1 SD).

Pair	TS	CS	p-FDR
<i>FDI - Deltoid</i>	9.48 (4.58)	7.92 (2.37)	0.69
<i>FDI – O. Oris</i>	19.05 (9.99)	17.01 (5.77)	0.69
<i>FDI – Masseter</i>	20.07 (10.00)	15.32 (7.38)	0.67
<i>FDI – O. Oculi</i>	16.59 (8.93)	12.12 (4.97)	0.67
<i>Deltoid – O. Oris</i>	23.06 (12.76)	24.35 (4.25)	0.69
<i>Deltoid – Masseter</i>	24.18 (12.83)	22.54 (6.53)	0.69
<i>Deltoid – O. Oculi</i>	21.00 (11.64)	17.58 (7.12)	0.69
<i>O. Oculi – Masseter</i>	3.19 (2.43)	5.13 (4.99)	0.69
<i>O. Oris – O. Oculi</i>	7.75 (6.96)	9.09 (8.14)	0.69
<i>Masseter – O. Oculi</i>	6.59 (6.20)	8.31 (4.28)	0.69

Lastly, I assessed the variability of each muscle representation by calculating the total area within a fitted 95% CI ellipse around the peak activity of each targeted muscle representation. Using permutation tests on each muscle representation separately, I found a significant difference in the FDI representation ($t(27) = 0.817$, $p\text{-FDR} = 0.032$, see Table 4.6 for means and SDs). No other area of muscle representation measured differed between the two groups, even at a more lenient uncorrected p-threshold. Sampling distributions are depicted in Figure 11.4 in Appendix 3. Figure 4.7 collectively demonstrates the results from all map comparisons.

Table 4.6. Summary statistics (Means $\pm$ 1 SD) for area within 95 CI ellipse for each cortical representation.

Muscle	TS	CS	p-FDR
FDI	228.82 (122.8)	349.49 (94.96)	0.032
Deltoid	183.48 (123.27)	151.56 (71.49)	0.72
O. Oris	221.29 (179.23)	311.67 (210.68)	0.72
Masseter	208.78 (145.61)	373.9 (242.18)	0.27
O. Oculi	337.59 (275.59)	405.32 (277.24)	0.72

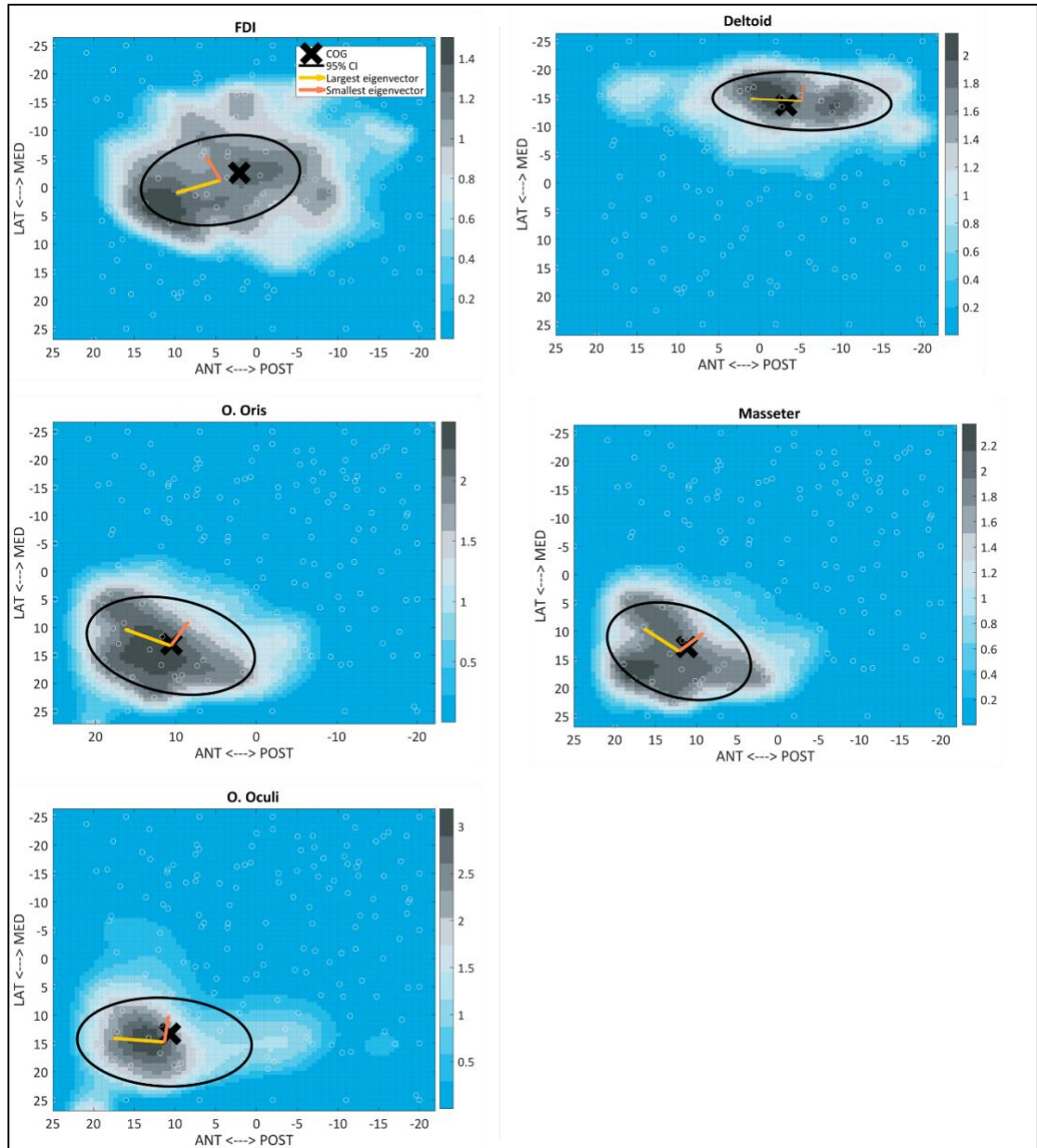


Figure 4.6. Example of sensorimotor maps for a representative participant in the TS group. The images depict a 2D contour plot with the transformed coordinate system on the x- and y-axes, and normalised MEP amplitude on the z-axis. Colorbar shows intensity of z-transformed MEPs. In each map, the blue colour represents MEPs falling below the z-score threshold criteria and represents no MEPs, while white-light grey-dark grey colours represent increasing amplitude of MEPs. COG is represented by a black X. Yellow and orange arrows represent the eigenvectors of the covariance matrix of the data, whereas the length of the arrows corresponds to the eigenvalues. Open circles: TMS pulse coordinates. The x-axis represents the anterior-posterior position and the y-axis the lateral-medial direction.

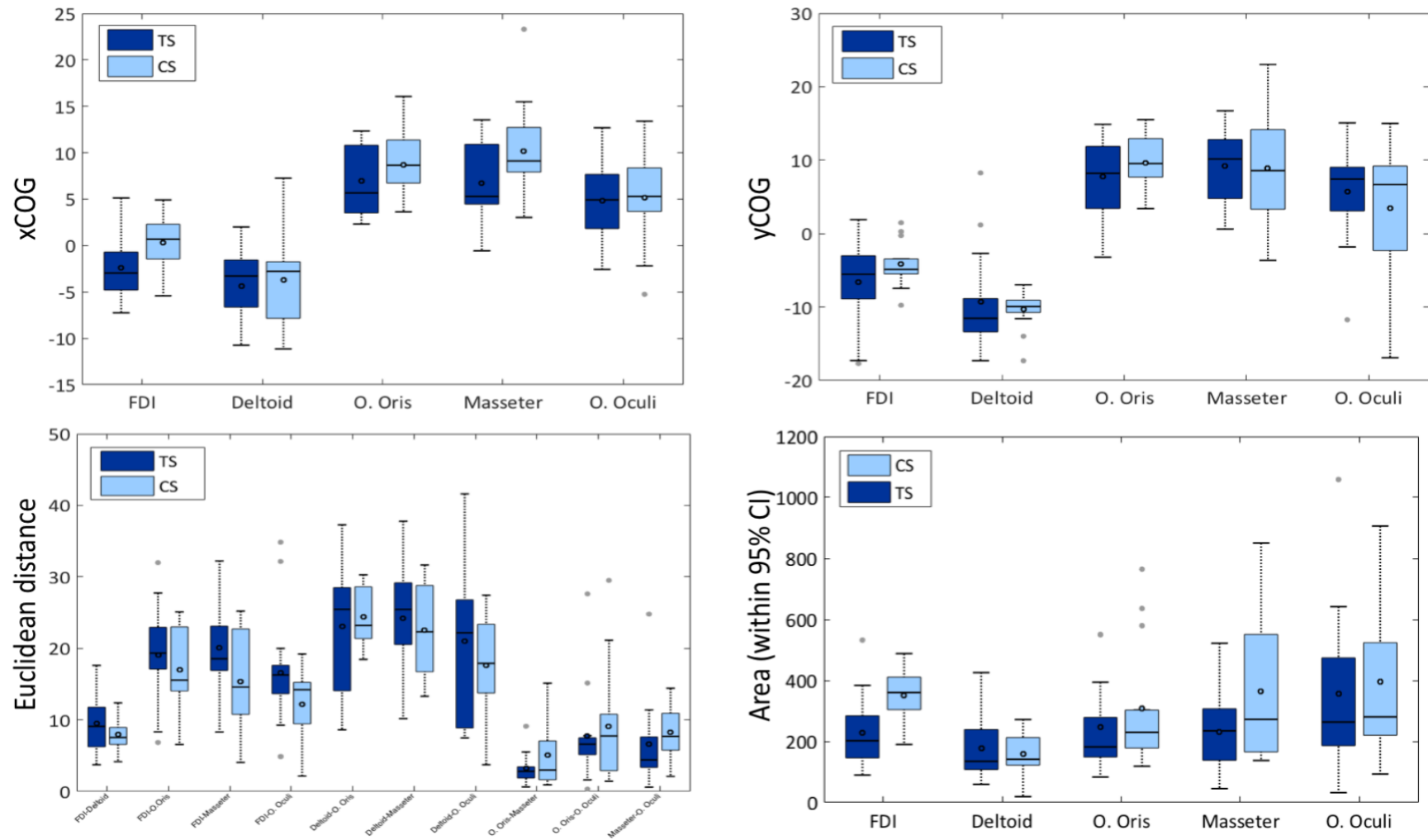


Figure 4.7. Group data on different map parameters. Top left: xCOG, top right: yCOG, bottom left: Euclidean distances, bottom right: Area.

4.3.4 Level of sensory sensitivity and interoceptive awareness

One participant returned incomplete AASP questionnaire and had to be excluded from the respective analysis. For the AASP, Box's M test of equality of covariance matrices was not significant ($M = 12.6$, $p = 0.42$) and Levene's test of equality of error variances was also non-significant for all variables (all $p > 0.05$). The overall model was not significant, $F(4, 20) = \text{Wilk's } \lambda = 0.90$, $p = 0.72$, $\eta_p^2 = 0.1$ and observed power = 0.15. Thus, no post-hoc tests were conducted. Means and the standard error for all measures is depicted in Figure 4.8|A. The SAS scale was compared between the two groups using an independent (two-way) samples t-test. Results showed no significant difference between the two groups, $t(27) = 1.1$, $p = 0.26$ (see Figure 4.8|B). Finally, interoceptive awareness was assessed in participants using the MAIA questionnaire. One participant had to be excluded due to incomplete questionnaire. Box's M test was not significant ($M = 61.42$, $p = 0.31$) and Levene's test of equality of error variances indicated equality of error variances (all $p > 0.05$). The overall model was not-significant, $F(4, 17) = \text{Wilk's } \lambda = 0.82$, $p = 0.87$ (see Figure 4.8|C). Thus, no post-hoc tests were conducted.

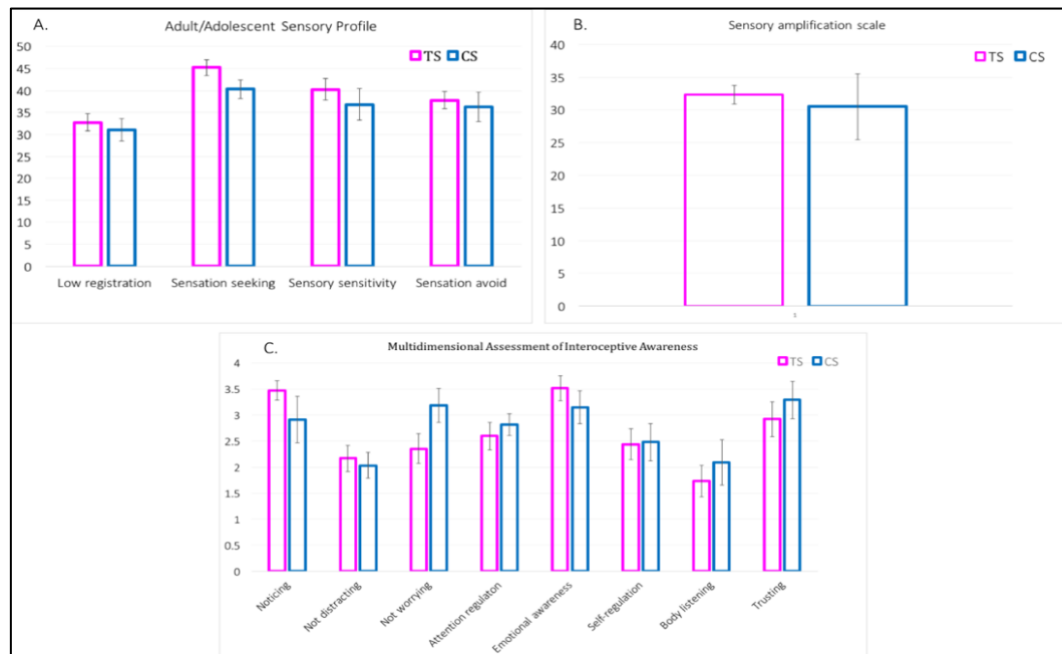


Figure 4.8. Results of the questionnaires. **A:** Adult/Adolescent Sensory Profile, **B:** Sensory amplification scale, **C:** Multidimensional assessment of interoceptive awareness. Errorbars are SEM.

4.3.5 Correlation: map parameters and PUTS scores

In the TS group alone, I assessed the relationship between PUTS scores and map parameters (COG, distance and area). P-values were corrected for multiple comparisons using FDR corrections. PUTS scores showed no significant relationship with any COG variable (all $p\text{-FDR} > 0.05$, see Figure 4.9|AB). Three significant, inverse correlations are observed between PUTS scores and EDs (see Figure 4.9|C): FDI-O. Oris ($r = -0.658$, $p\text{-FDR} = 0.05$), FDI-Masseter ($r = -0.758$, $p\text{-FDR} = 0.03$), and FDI-O. Oculi ($r = -0.625$, $p\text{-FDR} = 0.05$). This indicates that patients with greater separation between muscle representations reported less severe or fewer sensory urges. Finally, I found a significant correlation between PUTS scores and total area of the FDI and two facial representations. Specifically, size of the FDI representation was positively correlated with PUTS scores ($r = 0.58$, $p\text{-FDR} = 0.03$), such that larger FDI area is related to greater urges in patients. Conversely, smaller representation of both the masseter ($r = -0.75$, $p\text{-FDR} = 0.01$) and O. Oculi ($r = -0.66$, $p\text{-FDR} = 0.02$) was inversely related to PUTS scores, such that increased size of these representations was related to less severe or fewer sensory urges (see Figure 4.9|D).

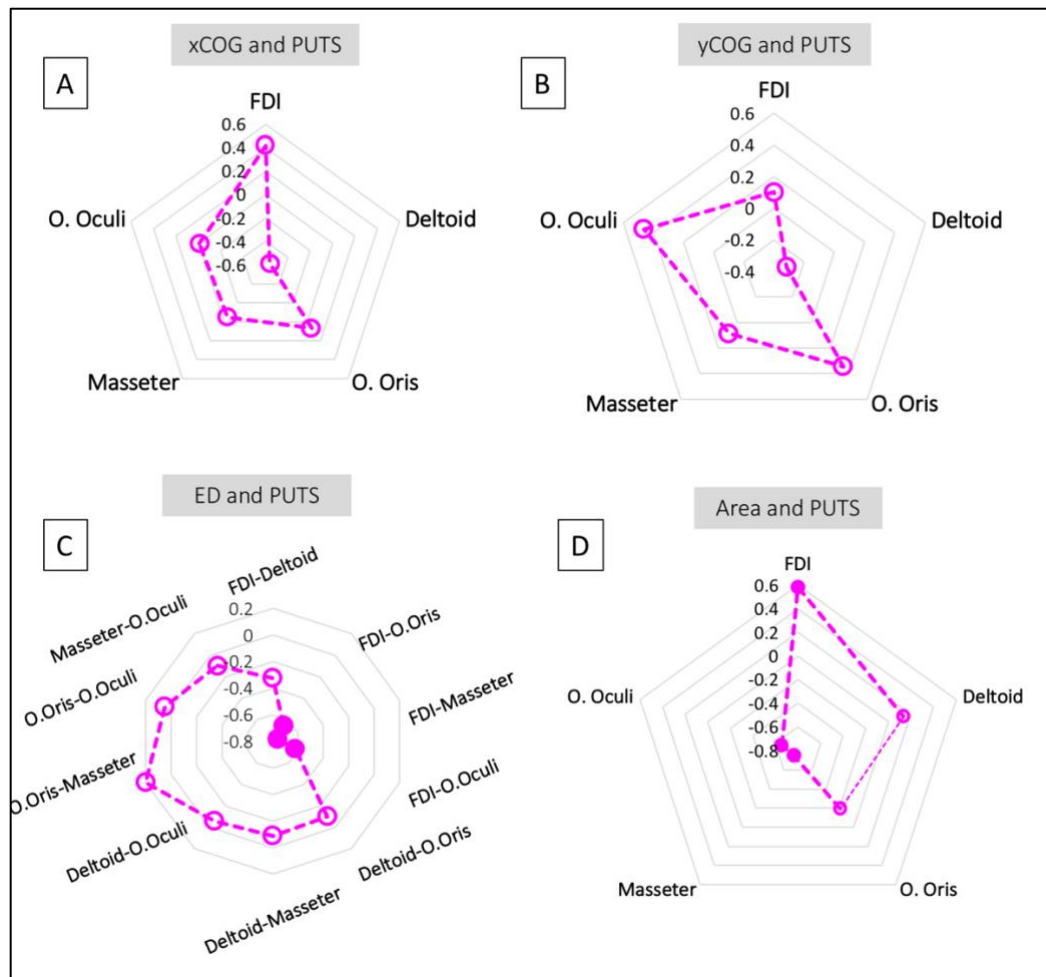


Figure 4.9. Spider plots of correlation analyses between map parameters and clinically measured sensory urges in the TS group. **A,B:** Correlation between COG and PUTS scores. **C:** Correlation between EDs and PUTS scores. **D:** Correlation between area of representations and PUTS scores. Note: Filled circles indicate a significant correlation after FDR correction at $p\text{-FDR} < 0.05$.

4.3.6 Is SICl of the FDI related to mapped FDI area?

One of the primary aims of this study was to investigate if GABA-mediated inhibition can be related to the specificity of muscle representations. Since SICl was measured from the FDI muscle, I ran linear regression analyses to see if amount of cortical inhibition can be used to predict the total area of the FDI representation, adjusted for the effects of age (prior age, IQ and the SICl test pulse were entered into a regression as predictors with FDI area as a dependent variable, and only age was found to be a significant predictor). We can assume greater area of the FDI representation is associated with less cortical inhibition. Thus, I entered “FDI” as a dependent variable, and “SICl” (median inhibition value) as a predictor, separately for groups.

Unstandardized and standardized regression coefficients, standard error, t-values and p-values are shown in Table 4.7. For all regression models, collinearity statistics (*Tolerance* < 10 and *VIF* $\cong$ 1) and DW tests were normal.

The overall TS model was not significant ($F(1, 15) = 0.008$, $p = 0.93$), and explained about 0.1% of the total variance ($R^2 = 0.001$, Adj. $R^2 = -0.07$). The Cook's distance measure flagged one participant in the TS group as being overly influential (Cook's $d = 2.6$). This participant indeed showed *facilitation* rather than inhibition (median inhibition value = 1.77). Even when this participant was excluded the TS model remained non-significant ($p = 0.101$). For the CS group, the overall model was highly significant ($F(1, 12) = 13.14$, $p = 0.004$) and explained 54% of the variance ($R^2 = 0.54$, Adj. $R^2 = 0.50$). Thus, SICl is a highly significant predictor of FDI area in the CS group but not the TS group after controlling for the effects of age.

Table 4.7. Regression analysis for SICl as a predictor of FDI area for each group.

Model		B	SE B	Beta	t-value	p-value
TS	<i>Constant</i>	-3.52	47.39	-	-0.07	0.94
	SICl	5.73	64.31	0.02	0.09	0.93
CS	<i>Constant</i>	-97.85	31.91	-	-3.10	0.01
	SICl	152.71	42.13	0.74	3.63	0.004

To test if the two regression slopes are different, I assessed the null hypothesis of $H_0 = B_{TS} = B_{CS}$, where B is the regression slope for *FDI*. I first entered the dummy coded variable "TS" (where TS is coded = 1 and CS = 0), SICl and TS x SICl product TS_SICl. This comparison of regression slopes between groups was marginally significant ($t(27) = -1.81$, $p = 0.08$), while the overall model was not significant ($F(3, 28) = 2.11$, $p = 0.12$), indicating that the regression slopes of the two groups are somewhat different. Unstandardized and standardized regression coefficients, standard error, t-values and p-values are shown in Table 4.8. Results are also depicted in Figure 4.10. Importantly, these results are not mediated by the test pulse since test pulse and area of FDI are not correlated.

Table 4.8. Regression analysis comparing regression slopes of FDI area as a predictor of rMT in both groups.

Model	B	SE B	Beta	t-value	p-value
Constant ^a	-97.85	45.98	-	-2.13	0.04
TS ^b	94.33	60.91	0.51	1.55	0.13
SICI ^c	152.71	60.71	0.68	2.52	0.02
TS_SICI ^d	-146.98	81.39	-0.69	-1.81	0.08

Note: This model is run without the extreme outlier. ^a Intercept for CS group (omitted group). ^b Intercept TS – Intercept CS. ^c Slope for CS group. ^d Slope TS – slope CS (i.e., $B_{TS} - B_{CS}$).

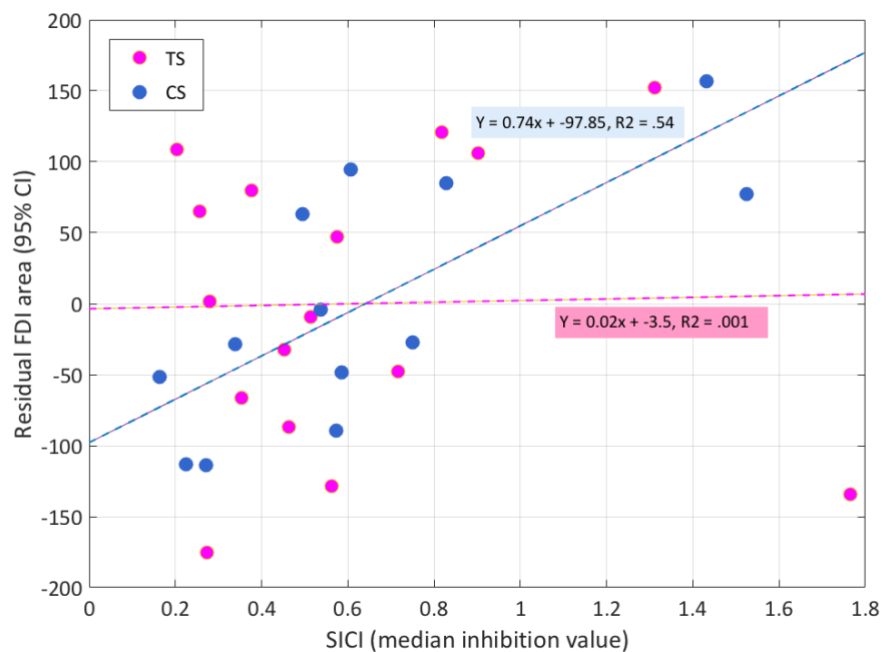


Figure 4.10. Linear regression analysis of the adjusted for age FDI area. Comparison of the groups with adjusted for age FDI area as a dependent variable and SICI as a predictor Eq: $Y = bx + a$. Dotted lines are least-squares fits.

4.3.7 Can SICI predict the distance between the FDI and other muscle representations?

As above, I assessed if SICI can explain distances between FDI and other targeted representations. I ran two separate multivariate multiple linear regression analyses inputting “SICI” as a predictor and the FDI-Deltoid, FDI-O. Oris, FDI-Masseter and FDI-O. Oculi distances as dependent variables. Prior, I determined that Age was not an

influential variable and thus was not controlled for. There was a trend for the TS model to be significant, $F(4, 9) = 3.45$, $p = 0.086$, Wilk's $\lambda = 0.303$. The overall CS model was not significant, $F(4, 8) = 1.44$, $p = 0.306$, Wilk's $\lambda = 0.581$. Regression statistics are shown in Table 11.1 and Table 11.2 in Appendix 3.

4.4 DISCUSSION

The primary objective of this study was twofold: (1) to investigate any fundamental alterations in targeted muscle representations, of the cerebral cortex known to be common areas of both tics and sensory urges in patients with TS, and (2) to relate any possible differences in map parameters to GABA-mediated inhibition. By completing this study, I hoped to gain a deeper understanding of the (commonly) self-reported sensory amplification in patients and the occurrence of altered perception of sensory input. The most significant finding of this study is the observed relationship between size of muscle representations in the hand and face, and the frequency or severity of PSP in patients. Also important was the observation that SICl measured from the FDI muscle is a highly significant predictor of size of the FDI area after age adjustment, while this relationship is completely absent in patients.

This is the first time a study has investigated the relationship between PSP measured using a standard clinical questionnaire (the PUTS) and cortical excitability using TMS in young patients with TS. I have here shown the efficacy and feasibility of locating and outlining nTMS-induced SM cortical representations of five targeted muscles using a rapid acquisition method. Figure 4.6 depicts maps from a representative participant. Such maps were consistently produced and visualised for all participants and were found to be of good quality. The protocol was also well tolerated, with no reporting of adverse effects in most participants, even at higher stimulation intensities. Overall, rapid acquisition of SM cortical maps could be an asset for clinical purposes. Below I will discuss my results in more detail.

4.4.1 *Cortical inhibition results and discussion*

Overall, the SICI protocol was successful in inducing cortical inhibition in most participants. My analysis showed a significant effect of conditioning intensity, but no significant interaction. Therefore, based on this data, I cannot confidently conclude aberrant GABA_A synaptic activity in TS. Inspection of the graph shown in Figure 4.4|A shows that the errorbars for the groups are quite large, and it is thus unlikely to find a significant difference between the groups. A potential remedy is to increase the number of trials for each condition and the unconditioned pulse. However, this could increase the length of the study session and potentially not be tolerated well by younger participants or TS patients who already spend considerable energy inhibiting their tics.

It is important to note that four participants (2 in each group) showed facilitation as opposed to inhibition (i.e., median inhibition value > 1), but interestingly the test pulse for all participants was in the normal range. Also, rMT was assessed twice and the coil was constantly monitored to ensure correct placement and that its orientation did not deviate more than 3-5° from its accurate position. Therefore, it is unlikely that any methodological errors can explain these results. The most probable explanation for the lack of a statistical effect can be sought to the work of Walther and colleagues (2009). In this study, the authors systematically investigated cortical inhibition in normally developing children, adolescents and adults. The study reported observing higher rMT and reduced SICI effects in children and adolescents in comparison to adults (Walther et al., 2009). The authors postulated whether the GABAergic system might not be fully matured in young people, explaining the lack of inhibitory effects. My sample consisted mostly of adolescents and young adults, and thus it may be possible that not all participants have fully matured GABAergic system.

Of note, it was recently established that spTMS can induce cumulative changes in cortical excitability when delivered at fixed ISIs such as I did in my mapping paradigm (Pellicciari, Miniussi, Ferrari, Koch, & Bortoletto, 2016). Since SICI was collected immediately following the mapping paradigm it is possible that this might have affected my SICI measures slightly. However, it is unlikely that this had any significant effects of

my results because (1) patients with TS do not normally demonstrate altered cortical excitability since rMTs are consistently found to be comparable between groups (e.g., Moll et al., 2001; Moll, Heinrich, Trott, Wirth, & Rothenberger, 2000; Orth et al., 2005, 2008) and (2) all participants experienced identical study session and so any effects of the preceding mapping session should be equal for all participants.

Overall, my results add to the ever confusing and inconsistent observations using SICl in TS. Primarily, SICl has been shown to be most effective of inducing cortical inhibition in adult patients, where TS shows less effective cortical inhibition but often not reaching conventional statistical thresholds (Orth, et al. 2005; Orth, et al. 2008). Ziemann, et al. (1997) were one of the first to report aberrant SICl in TS, showing higher mean MEP amplitude in patients (albeit across a range of ISIs). Importantly, they found no significant effect of the presence of sensory urges (Ziemann, et al. 1997). Similarly, Orth and colleagues (2005) observed difference in 3 out of 4 conditioning intensities between groups where patients demonstrated significantly reduced inhibition compared to controls. Most recently, these results were replicated in a group of adult patients with severe TS, although only using one conditioning intensity (Martin-Rodriguez, et al. 2015). In children and adolescents, however, the results remain somewhat inconsistent but suggest that differences in cortical inhibition is strongly mediated by the presence of ADHD comorbidity (Moll, et al. 2001; Gilbert, et al. 2011). These results highlight the importance of considering comorbidities during data interpretation in samples of TS patients.

4.4.2 *nTMS maps results and discussion*

A priori, I expected to observe some evidence of cortical ‘remapping’ in patients. Although the evidence is scarce in TS, studies on patients with FHD show consistent results on displaced cortical representations. Also, my hypothesis was supported by recent results suggesting that patients with TS might display reduced segregation of cortical representations, especially digits, which results in altered perception of discriminative touch (Kolasinski et al., 2016; Puts et al., 2015). In general, I found very

limited evidence of any altered spatial organisation in TS. Below I summarise these results.

COG measures the mean location in a map of a targeted muscle, based on the weighted mean intensity of each pixel in a map. I found no evidence of any significant displacement of cortical muscle representations in the TS group. Viewing Figure 4.5|A, the FDI muscle is slightly shifted medial and posterior in patients and is much closer to the deltoid representation than in the CS group. Also, the O. Oculi is shifted more lateral in patients and the O. Oris is more posterior and medial, while the masseter representation is more posterior in the TS group. However, none of these differences reached conventional statistical thresholds signifying differences between the two groups, and in most cases the SEM indicates that this could just be normal variation between participants. In addition, EDs between COGs measured in 2D were comparable between the two groups indicating no cortical re-organization in patients. Finally, I also calculated the approximated area covered by the representation within a 95% CI ellipse which was fitted around the peak activity. This gives an indication of the spatial specificity of the targeted muscle representation. Interestingly, the FDI muscle was significantly different between the two groups, where the area in the TS group was smaller, indicating less variability of this muscle.

In general, my results do not conform with previous work in patients with hyperkinetic disorders such as FHD (Byrnes et al., 1998; Elbert et al., 1994; Nelson et al., 2009; Schabrun et al., 2009). For example, COG is consistently shown to be displaced in hand muscles critically involved in writing or other tasks where hand is commonly used (Byrnes et al., 1998; Schabrun et al., 2009). Moreover, the literature in these types of patients is also consistent in showing reduced distances between COGs measured using ED (Elbert et al., 1998; Nelson et al., 2009; Schabrun et al., 2009). Also, studies measuring the volume of the hand muscle representations show higher volume in patients compared to controls (Schabrun et al., 2009). One study, for example, showed reduced distances between digits in patients with FHD which were specifically shifted more medially as measured using local maxima of activation in an fMRI design, so that for example digit 1 occupied similar area in patients as digit 2 in controls. Consequently, the shift in digit location decreased the distance between the first and

subsequent digits (Nelson et al., 2009). Also, in musician's dystonia and employing magnetic source imaging (MSI; which creates functional maps of brain activity by combining MEG and MRI), Elbert and colleagues (1998) demonstrated greater 'fusion' of digits in patients compared to controls. It is believed that such altered muscle representation at cortical level is related to a substantial loss of somatosensory neurons at subcortical level, specifically in the basal ganglia and cerebellar relay nuclei of the thalamus (Lenz et al., 1999; Vitek et al., 1999).

An unanswered question and a suggestion for future studies would be to study the existence of asymmetry of cortical muscle representations between hemispheres. For example, in healthy subjects there is a somatotopic arrangement of muscles responsible for swallowing, and there is an apparent asymmetry of these representations between the two hemispheres (Hamdy et al., 1996). In stroke patients, considerable rearrangement of representations occurs during recovery, and representations in the undamaged hemisphere are significantly enhanced (e.g., Hamdy, Aziz, et al., 1998). It is possible that patients with TS would display altered asymmetry of the location or specificity of hand, arm or facial muscles across hemispheres. Indeed, in FHD there is greater asymmetry of hand muscles between the two hemispheres whereas healthy subjects show remarkable degree of symmetry of the same muscles (Byrnes et al., 1998), while young patients with TS demonstrate significantly reduced asymmetry of the thalamic grey matter volume (Lee et al., 2006). The evidence is however limited (see e.g., Williams et al., 2013). It would also be important to measure the validity and reliability of nTMS maps, in a similar way as I have done in this study, over few days or even weeks.

It is important to keep in mind the current issue of interpreting changes in TMS-generated cortical maps. Especially, observed changes in map parameters do not necessarily reflect cortical re-organisation, but rather might be indicative of increased cortical excitability (Siebner & Rothwell, 2003). This limitation is primarily due to the TMS coil, since this method is much less focal than intracranial stimulation. Consequently, TMS-generated maps are the result of both the measured corticospinal map and the relative distance between the coil and corticospinal neurons (Siebner & Rothwell, 2003). Some have noted that the use of 'map area' might be unreliable, since

this is used sometimes as the total area activated by the TMS stimulation (e.g., see Byrnes et al., 1998). Therefore, I thresholded all maps to $z \geq 1$, thus eliminating any potential false positive MEP activation in the pixels in the maps and fitted a 95% CI ellipse around the peak activity. Consequently, my muscle area parameter is highly probable to be the true area measured.

4.4.3 *Muscle representations, GABA and sensory urges*

Viewing the data, it became apparent to me that there was a great variation in map parameters, especially within the TS group. To test if any of this variation can be explained by sensory urges, I conducted a correlation analyses between map parameters and PUTS scores. In particular, distances between hand and facial muscles decreased in patients who reported more frequent or severe sensory urges. Moreover, I found a positive relationship between the FDI area and PUTS scores. Larger area of the FDI was related to more frequent or severe PSP, while the opposite is observed in two out of three facial representations such that larger areas of the eyes and jaw representations is related to less frequent or severe PSP.

To my knowledge, only one study has observed and reported a relationship between neuroplasticity and sensory urges in TS. Brandt, et al. (2014) employed a combination of a plasticity-inducing peripheral, afferent stimulation and TMS, and reported that stronger long-term depression-like plasticity was related to less severe or fewer sensory urges as measured using the PUTS scale. Such neuroplastic changes in the brain are thought to be a GABA-dependent phenomenon (Bütefisch et al., 2000; Feldman & Brecht, 2005). As such, GABA mechanisms in TS might induce maladaptive neuroplasticity in patients. Indeed, several studies have confirmed that the TS brain might be resistant to changes in MEP amplitude following neuroplasticity-inducing stimulation protocols (Brandt et al., 2014; Martín-Rodríguez et al., 2015; Suppa et al., 2011). According to one author, this inability to induce neuroplastic changes in TS might be due to dysfunctional M1 intracortical neurons (Suppa et al., 2011). My results support this conclusion for the most part as discussed below.

The primary aim in this study was to investigate if GABA-mediated cortical inhibition could potentially explain any loss of spatial specificity of cortical muscle representations. My results showed that SICl significantly predicts the area of the FDI representation in CS, explaining more than 50% of the total variance, while such relationship was completely absent in the TS group. This, coupled with the observed correlation between FDI area and PUTS scores, suggests that the size of the cortical FDI representation potentially contributes to the maintenance of the frequency or severity of sensory urges in patients with TS. The reason for this remains somewhat elusive. However, several studies show that cortical re-organisation occurs during alteration of sensory input (Kolasinski et al., 2016). As such, the brain actively adapts to its environment and the sensory input we experience maintains the spatial specificity of motor representations (X. Wang et al., 1995). Moreover, loss of peripheral input (such as in the case of limb amputation) results in extensive cortical neuroplasticity of the SM cortex, characterised by migration of intact body parts towards the missing limb area (Makin et al., 2015). Motor training can also cause an acute significant shift in representations. One study showed that fine motor skill training of the fingers and wrist significantly enhances motor maps for the respective muscles (Nudo et al., 1996).

Taken together, I found very limited evidence of any spatial displacement of targeted muscle representations in patients with TS using nTMS-generated cortical SM maps. Therefore, I cannot concretely conclude that sensory urges or altered perception of sensory stimuli in TS induces experience dependent cortical neuroplasticity. I did, however, observe significantly reduced size of the FDI area in patients. Size of the FDI could be explained using SICl in the CS group but not in the TS group. The significant relationship between EDs and areas with PSP is worth further investigation.

4.4.4 Failure to replicate: No self-rated somatosensory sensitivity increases in TS

In my sample of participants, I also found no differences in self-evaluated sensory sensitivity or somatosensory amplification between the TS and CS groups. Inspecting Figure 4.8|A showing results of the quadrants in the AASP it is apparent that, on average, groups scored according to the norm and are thus “Similar to most people”

(C. Brown et al., 2001). Also, inspecting Figure 4.8|C showing results from the MAIA questionnaire, it is clear that, on average, the groups scored comparable to studies using the MAIA in an adolescent sample (T. A. Brown et al., 2017). Furthermore, no statistical difference was found on the SAS.

These results are in contrast to previous work, showing higher self-evaluated somatosensory sensitivity in both very young (Jewers et al., 2013; Ludlow & Wilkins, 2016) and adult patients (Belluscio, Jin, et al., 2011). Ludlow and Wilkins (2016) found sensory behaviours to differ between children with TS and ASD, and normally developing individuals, but not between the two patient groups. This is in contrast to my results. This could be explained by the age of my sample. In my study the age range was wide and much older than in Ludow and Wilkins' sample. Unfortunately, my sample is too small to make any significant sub-group analyses, and this would lack statistical power.

In regard to the measure of interoceptive awareness, only one study to date has measured this in TS, showing decreased awareness of interoceptive awareness (i.e., visceral sensations) in patients (Ganos, Garrido, et al., 2015). In this study, the authors also reported that interoceptive awareness had a strong relationship with PUTS scores, where stronger urges are associated with greater interoceptive awareness. This is perhaps not surprising since a recent study showed that a factor analysis of the PUTS might tap into the domain of interoception (Brandt, Beck, Sajin, Anders, et al., 2016).

4.4.5 Limitations

In my opinion, there are two potential methodological limitations to the study presented in this chapter. First, is the limited availability of structural brain scans for participants in this study. Originally, obtaining a structural brain scan was an inclusion criterion; however, recruitment of participants and specifically patients with TS was slow and this criterion was relaxed. This has two important implications: (1) I was unable to confidently view individual topology and precisely locate the SM strip as individual anatomy can be quite variable, and (2) I was unable to use skull-to-cortex distance as a covariate of no interest. This is especially important since this skull-to-

cortex distance has been shown to directly influence the magnitude of cortical stimulation using TMS (Stokes et al., 2007).

The second methodological limitation is that I defined the stimulation intensity for the mapping procedure based on individual rMT from the FDI muscle. Consequently, I did not tailor the stimulation intensity for each muscle separately and this might cause an issue when calculating the area occupied by the muscle representation in a map. As noted previously, facial muscles have much higher rMT and lower MEP amplitudes and representative map of these muscles might not be feasible at the stimulation intensity used. However, during pilot testing I observed that facial MEPs could be elicited at about 80% of MSO and the decision was made to use this as an upper limit. Overall, facial maps were successful in most participants.

Another potential source of variability is the wide age-range of my patient population, and specifically the inclusion of a significantly older participant. Primarily I wanted to focus on younger patient (as I do in other experimental chapters in this thesis) since older participants might have already adopted significant compensatory mechanisms to gain control over their tics. However, due to relatively small sample size, I decided to include all participants recruited and rather interpret my results accordingly. It is also possible that my results are limited by the muscles tested. All studies in FHD target the representations specifically involved in the disorder (i.e., hands in writer's cramp). Tics in TS vary considerably between patients and even vary frequently from time to time for a given patient (Jankovic, 2001). Some studies (e.g., Ulf Ziemann et al., 1997) measured the effect of distal tics on their results and found a trend for less cortical inhibition in patient subgroup with distal tics. Even though I measured the presence and location of current tics in patients I did not incorporate this into my design or statistical analyses. Nonetheless, the targeted muscle groups in this study were specifically chosen as these are frequent areas of tics and sensory urges.

4.4.6 Conclusion

In conclusion, the use of a rapid nTMS mapping protocol, targeting five muscle representations including the hand, arm and facial muscles proved successful. I was

unable to provide any conclusive evidence of any displacement of muscle representations in patients but observed important relationships between the spatial specificity of the hand muscle, sensory urges and GABA-mediated cortical inhibition, which highlights the clinical importance of this study. Studies investigating neuroplasticity in TS suggest that patients are resistant to neuroplasticity effects and this might explain my lack of significant between-group comparisons. This study suggests a closer look at GABAergic mechanisms in TS, which play an important role in maintaining spatial specificity of cortical representations and neuroplasticity.

Importantly, some have suggested that altered muscle representations at cortical level is related to the function and integrity of subcortical structures, specifically the basal ganglia and thalamus, which project to the SM cortex (Lenz et al., 1999; Vitek et al., 1999). Therefore, in the next chapter of this thesis, I systematically investigate the cortical and sub-cortical connectivity of WM fibre tracts, which could complement the results of the current study.

CHAPTER 5

Chapter Five – Alteration in the microstructure of white matter in children and adolescent with Tourette syndrome measured using tract-based spatial statistics and probabilistic tractography

Adults with TS have consistently been shown to demonstrate altered WM microstructure in key areas of the brain, while evidence on children and adolescents is limited. Few studies have also investigated WM connectivity in young patients with TS, while the ones who have are limited by small sample sizes. The aim of this study presented in this chapter was to assess WM abnormalities in a large sample of young patients with TS in comparison to a sample of matched typically developing control individuals (CS) using diffusion MRI. The study included 35 patients with TS (3 females; mean age: 14.0 ± 3.3) and 35 CS (3 females; mean age: 13.9 ± 3.3). Diffusion MRI data was analysed using tract-based spatial statistics (TBSS) and probabilistic tractography. Patients with TS demonstrated both marked and widespread decreases in axial diffusivity (AD) together with altered WM connectivity. Moreover, I showed that tic severity and the frequency of PSP were associated with increased connectivity of primary motor cortex (M1) and the caudate nuclei, and increased information transfer between M1 and the insula, respectively. This is to our knowledge the first study to employ both TBSS and probabilistic tractography in a sample of young patients with TS. Our results contribute to the limited existing literature demonstrating altered connectivity in TS and confirm previous results suggesting in particular, that altered insular function contributes to increased frequency in premonitory sensory phenomena.

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5.1 INTRODUCTION

In the previous chapter I presented my results on sensorimotor cortical mapping using nTMS and a non-grid based, rapid acquisition method. In general, I found little evidence supporting my hypothesis of the loss of spatial specificity of targeted muscle representations or altered GABA-mediated inhibition in patients with TS. However, I showed that the FDI representation is significantly smaller in patients and that this is significantly related to the severity or frequency of PSP reported by patients (see Figure 4.9 in chapter 4). Also, I showed that the area of the FDI was significantly predicted SICI (a measure of GABA-mediated inhibition), insofar as greater cortical inhibition measured from the FDI muscle, results in smaller measured area of the FDI muscle in the CS group, but this relationship is completely absent in the TS group. In the current chapter, I present a study investigating the white matter (WM) microstructure and WM connectivity of key areas of the brain, thought to be involved in the pathophysiology of TS (Albin & Mink, 2006; Leckman et al., 2010). Primarily, we can consider this as an extension to the previous chapter, such that if altered cortical representation are observed in TS (as with the FDI muscle) perhaps this could be mediated by the considerable plastic potential of subcortical structures, which is then mirrored in the cortex (e.g., Donoghue, 1995). In the study by Kolasinski and colleagues (2016), who showed that sensory de-afferentation resulted in considerable acute neuroplastic changes, the authors posited if this occurs due to re-organisation of lower level nuclei of the ascending somatosensory pathway (Kolasinski et al., 2016). As such,

we could theorise that patients might indeed demonstrate alteration in WM connectivity which results in atypical sensory processing. Thomalla and colleagues (2009), using probabilistic tractography and identifying anatomical connectivity of areas showing reduced WM diffusion in TS, found that this area of reduced diffusion was connected to cerebello-thalamo-cortical pathways of the somatosensory system. However, these probabilistic tractography maps were almost identical between the groups (Thomalla et al., 2009). Nonetheless, the study by Thomalla, et al. was conducted in adult patients with no reported comorbidities, and hence studies of a more representative sample of TS patients could yield different results.

The human brain is a complex and multi-faceted structure. In general terms, the brain is compartmentalised into grey matter (GM), white matter (WM) and cerebral-spinal fluid (CSF). In general, throughout our lifespan our brain undergoes constant changes at both microscopic and macroscopic levels (Gogtay et al., 2004; Kochunov et al., 2009). In several hyperkinetic movement disorders whose aetiology involve the basal ganglia (BG) nuclei and have a high rate of co-occurring neuropsychiatric disorders, have often been shown to exhibit alterations in brain white (WM) and grey (GM) matter (Hayhow et al., 2013). As detailed in Chapter 1, TS is a hyperkinetic movement disorder and is widely characterised as a fronto-striatal disorder and the syndrome aetiology is thought to involve widespread alterations in the functional and structural integrity of the brain. Importantly, several studies employing diffusion tensor imaging (DTI; see subsection 2.4.1 in Chapter 2 on detailed description of DTI) adhere to these models of TS aetiology, showing altered properties of WM microstructure in patients with TS in key areas of the brain (Govindan et al., 2010; S. R. Jackson, Parkinson, Jung, et al., 2011; Makki et al., 2008). However, majority of DTI studies include adult patients with TS, while few have investigated WM microstructure in children or adolescent patients. Therefore, there is great need to ascertain WM alterations in young patients. This is particularly important as one study showed clear differences in structural integrity between adult and young patients with TS (Plessen et al., 2004). These studies have demonstrated abnormal diffusivity in subcortical structures (Govindan et al., 2010; Makki et al., 2008; Saporta et al., 2010) and corticocortical association and fronto-striatal pathways, and insular cortices (Govindan

et al., 2010). One recent study in very young patients demonstrated a widespread increase in axial diffusivity (Y. Liu et al., 2013) with another study showing a negative relationship between mean diffusivity and tic severity (Govindan et al., 2010). Similarly, altered water diffusion in the corpus callosum has been reported in several studies (S. R. Jackson, Parkinson, Jung, et al., 2011; Plessen et al., 2006; Wolff et al., 2016), although one study found no differences across groups (Jeppesen et al., 2014). Collectively, these results are consistent with the hypothesis of altered structural integrity of CSTC circuitry in TS, and potentially reduced functionality of information transfer across hemispheres that may contribute to symptoms through reduced inhibition of cortical activity (Boroojerdi, Topper, Foltys, & Meincke, 1999; Orth & Rothwell, 2009). Unfortunately, there is little consensus across all these studies since patient characteristics vary widely, e.g., comorbidities and medication status, rendering comparison difficult.

Using DTI data, one can also employ a particular method termed tractography, where a model of known WM pathways is constructed *in vivo*. Using this technique, two studies in young TS patients have demonstrated increased thickness and density of these fibre bundles in the prefrontal WM tracts (D. Xu et al., 2007) and decreased probability of connections between the left hemisphere caudate and prefrontal cortex (Makki, Govindan, Wilson, Behen, & Chugani, 2009). With DTI tractography a connectivity matrix can be constructed if the study includes several regions of interests (ROIs) and tracks these fibre tracts connecting ROIs. This way, we can obtain estimates of brain network properties by applying graph theoretical analysis to the resulting matrices. Of note, such structural connectivity can only occur between anatomically connected brain areas and cannot be confused with functional connectivity, which can be observed between two, anatomically unconnected, regions (Rubinov & Sporns, 2010).

Graph theory is a nascent way of exploring both functional and structural integrity of the brain (Bullmore & Sporns, 2009). Graph theory gives rise to the possibility of characterising brain network topology, by using and calculating several graph metrics, which can describe network integration, segregation, connectedness and resilience (Rubinov & Sporns, 2010). In graph theory, networks are characterised by vertices

(nodes) and edges (links) indicating a connection between a pair of nodes (Bullmore & Sporns, 2009). Importantly, links can differ based on their weight and directionality, and can for example be binarised and as such simply indicate the presence or absence of a connection (Rubinov & Sporns, 2010).

To date, two resting-state fMRI studies have applied graph theory in the study of TS. Worbe et al. (2012) reported extensive alterations in CSTC networks in patients. These alterations were primarily a complete absence of hub-like nodes, an increase in short-range connections, and the overall increase in the number of connections. Furthermore, key nodes within networks that were assessed in that study correlated both with tic severity and complexity. Also, Tinaz and colleagues (2015) showed that patients demonstrate decreased connectivity in the parietal, limbic and, motor cortex regions, and increased connectivity of the thalamus and dorsal anterior insula in the right hemisphere.

Interestingly, only one study has explored the structural integrity of the brain using WM tractography and graph theory in young patients with TS (Wen, Liu, Rekik, Wang, Zhang, et al., 2017). Also, no other study has attempted to characterise the association between structural integrity of WM and measures of PSP in patients with TS. Only has this association been assessed using functional MRI. For example, Bohlhalter and colleagues (2006) associated several areas of the brain including the insular cortex with urges experienced immediately prior to tics, suggesting a specific urge-tic network.

In summary, both structural and functional studies in TS suggest impaired connectivity and abnormal water diffusion of key areas of the CSTC circuits in patients with TS. In this study, I employed DTI to assess WM microstructure in a large sample of children and adolescents with TS, and a matched group of typically developing controls using tract-based spatial statistics and probabilistic tractography (see subsection 2.4.1 in Chapter 2 on detailed description of these two techniques). As such, I tested two hypotheses in this study: (1) I want to establish that young patients with TS demonstrate altered water diffusion in key white matter pathways, and (2) to test the hypothesis of altered structural connectivity between cortical and subcortical regions of the brain, possibly characterised by loss of hub-like nodes in a network, greater number of connections and increased number of short range connections (Worbe et

al., 2012). Finally, I wanted to ascertain that network attributes in patients with TS can be explained by using measures of tic severity and PSP.

5.2 METHODOLOGY

5.2.1 *Participant characteristics*

The study was carried out in 35 children and adolescents (3 females, mean age: 14.0 ± 3.3 , age range: 8.6 – 21.8) diagnosed with TS according to DSM-IV (APA, 2000) and 35 typically developing controls (CS; 3 females, mean age: 13.9 ± 3.3 , age range: 8.5 – 21.2). Patient specific characteristics is shown in Table 5.1. In this sample, eight patients were medicated at the time of scanning. Nine out of the 28 included patients had no comorbidities, six had comorbid ADHD, two had OCD and eight had combined ADHD, OCD and/or ASD. Screening for one participant was lost. All patients reported the presence of PSP, and IQ was not statistically significant between the two groups in my final sample (TS mean: 110.1 ± 14.6 , CS mean: 119.9 ± 12.1 , $p > 0.05$).

Table 5.1. Patient specific characteristics. Clinical measures are demonstrated as score/maximum score.

Yale Global Tic Severity Scale (YGTSS)									
TS ID	Sex	Age (years)	Motor tic	Vocal tic	Impairment	YGSS	PUTS	Comorbidity	Medication
TS01	M	19.3	18	9	5	32	18	None	None
TS02	M	17.0	12	11	0	23	10	None	None
TS03	M	20.1	21	16	30	67	22	OCD, ADHD, possible ASD	None
TS04	M	15.4	3	0	0	3	14	None	None
TS05	M	15.0	13	15	5	32	18	OCD, ADHD	Sertraline and Melatonin
TS06	M	15.6	13	11	10	34	27	None	Clonidine
TS07	M	11	12	9	5	26	23	ADHD	None
TS08	M	15.1	21	17	25	63	28	OCD, ADHD	Melatonin
TS09	M	14.5	7	4	0	11	14	ADHD	None
TS10	M	15.6	10	11	10	31	21	ADHD	None
TS11	M	16.2	12	8	10	30	17	OCD	Aripiprazole 5mg
TS12	F	12.6	14	8	20	45	20	OCD	Melatonin
TS13	F	21.8	17	10	5	32	20	ASD	Citalopram 40 mg
TS14	M	12.8	15	10	5	30	23	None	None
TS15	M	10.1	12	8	5	25	17	None	None

Note: The table continues on next page.

Patient specific characteristics continued

TS ID	Sex	Age (years)	Motor tic	Vocal tic	Impairment	YGSS	PUTS	Comorbidity	Medication
TS16	M	15	12	14	5	31	21	ADHD, ASD	None
TS17	F	18.7	12	15	5	32	21	ADHD, ASD, possible OCD	None
TS18	M	14.5	13	0	10	23	33	ADHD	Clonidine 50 mcgs, Aripiprazole 5 mgs
TS19	M	8.6	10	3	10	23	18	None	None
TS20	M	15.3	10	13	10	33	30	Mild OCD, ADHD	None
TS21	M	10.5	16	14	10	40	20	Mild OCD, ADHD	None
TS22	M	14.1	10	9	5	24	18	ADHD	None
TS23	M	18.9	22	22	22	64	17	None	None
TS24	M	10.3	13	7	5	25	15	None	None
TS25	M	12.2	3	3	0	6	10	ADHD	None
TS26	M	16.4	23	15	40	78	23	Unknown	Aripiprazole 10 mg, Sertraline 100mg and Clonidine 200 mg
TS27	M	8.7	13	11	5	29	21	ADHD	None
TS28	M	12.4	15	15	30	60	32	Mild OCD, ADHD	None
<i>N = 28</i>		<i>14.5 ± 3.4</i>	<i>13.2 ± 4.7</i>	<i>10.3 ± 5.2</i>	<i>10.4 ± 10.2</i>	<i>33 ± 15.3</i>	<i>20.4 ± 5.8</i>	-	-

5.2.2 *MRI parameters*

Brain imaging data from all participants was acquired using a Philips 3T Achieva MRI scanner (Best, The Netherlands) equipped with a 32-channel SENSE head-coil at the Sir Peter Mansfield Imaging Centre (SPMIC), University of Nottingham. Participants were placed supine and head first into the scanner. Head motion was minimized by inserting foam pads between the participants' head and the head coil. Participants also wore headphones for hearing protection that provided additional control over head motion. Participants were instructed to lie as still as possible during and in between scans. Diffusion images were collected using an Echo-Planar Imaging sequence with 48 slices with 2mm slice thickness and no inter-slice gap, TR/TE = 7655/55ms, voxel size = 1x1x2 mm³, FOV = 224x224, matrix = 112x112, 32 gradient directions and a diffusion weighting (b-value) = 1000 s/mm². Normally, the b-value is selected within the range of 800 – 1200 s/mm² which is considered ideal from healthy adult brains. Based on this information, a value of 1000 s/mm² was selected as it is within this ideal range. Of note, there is a risk of no diffusion recording if the diffusion weighting value is below 800 s/mm², whereas any value above the upper range risks that no signal will be recorded. Therefore, the selected b-value is considered a good middle ground between diffusion and signal. The first volume in the sequence for each subject has no diffusion weighting (b = 0) and is used to align the brain to the diffusion-weighted data during analysis. In addition, I acquired high-resolution T1-weighted anatomical images using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR/TE = 8.41ms/40ms, FOV = 256x256, matrix = 256x224, flip angle = 8°, 180 contiguous axial slices with 1mm³ isotropic resolution.

5.2.3 *MRI image processing and quality assessment*

All DTI data was pre-processed using FSL's (v. 5.0.8) FDT toolkit (Behrens, Woolrich, et al., 2003; S. M. Smith et al., 2004). Diffusion-weighted images were corrected for subject motion and Eddy currents using affine registration to the non-diffusion weighted images (B0 volume). Next, the brain was extracted from the skull and excess air removed using the Brain Extraction Tool (BET) with a fractional intensity threshold

of 0.3. Diffusion tensors were fitted to each voxel of the brain using DTIFIT within FSL. For each participant, I quantified head motion. Visual inspection was conducted for all data after every processing step to ensure data quality and to screen for any obvious MR scanning artefacts. Head motion parameters were calculated to provide a quantitative measure of movement inside the scanner. These were derived from the three translation (x , y , z in mm) and three rotation (α , β , γ , in radians) parameters. Rotational parameters were converted from radians. Participants were excluded if any obvious distortions or artefacts were present during visual inspection or if any of the rotation or translation parameters exceeded 1.5 mm/degree. Post pre-processing showed that 7 patients with TS and 5 control subjects had to be excluded due to excessive head motion during the DTI scan as measured using rotation and translation parameters. The final sample therefore consisted of 28 patients with TS (3 females, mean age: 14.5 ± 3.8 , age range: 8.6 – 21.8) and 30 control subjects (2 females, mean age: 14.1 ± 2.9 , age range: 9.6 – 21.2).

5.3 TRACT-BASED SPATIAL STATISTICS (TBSS)

Diffusion maps were entered into a voxelwise statistical analysis using Tract-based spatial statistics (TBSS; S. M. Smith et al., 2006) to quantify differences in WM microstructure between patients and controls.

5.3.1 TBSS: Data and statistical analysis

The white matter skeleton used for the TBSS analysis is demonstrated in Figure 5.1|C, and was created from the mean FA image (Figure 5.1|B), to represent the centre of all tracts, with an intensity threshold of 0.2 (i.e., to exclude grey matter and CSF). Each subject's aligned FA image is then subsequently projected onto this skeleton. Between-group comparison on FA maps was accomplished using this skeleton. The original non-linear registration of FA images is then used on other diffusion scalars (i.e., MD, AD, and RD images), creating WM skeletons for each scalar (e.g., AD specific skeleton).

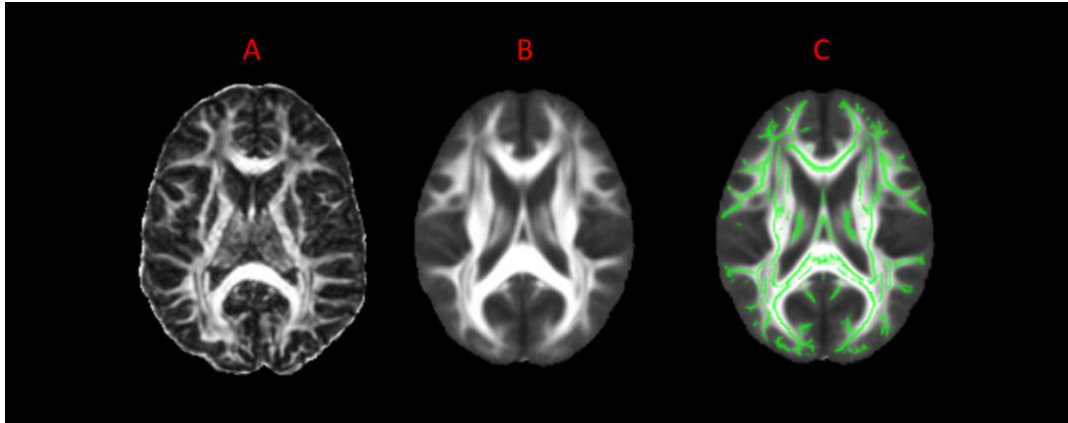


Figure 5.1. TBSS processing. **A:** Raw FA diffusion map from one subject. **B:** Mean FA map. All individual FA maps are registered to each other to determine the study specific target (the most representative subject) and then aligned to this specific target and subsequently transformed into MNI space. **C:** Mean WM skeleton used on the analysis. Based on the mean FA map generated in the previous step, WM tracts are thinned to create a WM skeleton. Subsequently, TBSS measures key parameters (e.g., FA or AD) at each WM voxel independently using the WM skeleton.

When assessing differences in water diffusivity, age and IQ were de-meaned and entered as variables of no interest to remove any confounding differences between the two groups (TS vs. CS). Diffusion maps were entered into voxelwise cross-subject statistics in FSL with 5000 permutations using the inbuilt function ‘randomise’ (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). For all analyses, multiple voxel-wise comparison was controlled using family-wise error correction with a threshold set at $p < 0.05$ and cluster size of ≥ 20 voxels. Therefore, all TFCE (threshold-free cluster enhancement) value images reported here were fully corrected for multiple comparisons. In addition, I ran correlation analyses in patients with TS only to assess whether any TBSS values correlated significantly with PSP (PUTS) and/or tic severity scores. Clinical scores and patient diffusion maps were entered in to a linear regression model in FSL with age and IQ as nuisance variables. Tracts were identified using the JHU White-Matter Tractography and JHU ICBM-DTI-81 White-Matter Label atlases embedded within the FSL package.

5.3.2 TBSS: Results and discussion

Results of the comparison between the group of patients with TS and matched control subjects demonstrated that there were widespread decreases in AD values in the TS group bilaterally (one large cluster of 32,988 voxels). Relevant data are presented in Figure 5.2. Four peak coordinates were identified being the right anterior thalamic radiation (ATR; MNI coordinates: X: 23 Y: -40 Z: 28, $t(56) = 2.99$, $p < 0.05$), the splenium of the corpus callosum (MNI coordinates: X: -11 Y: -35 Z: 24, $t(56) = 3.00$, $p < 0.05$), the genu of the corpus callosum (MNI coordinates: X: -11 Y: 20 Z: 20, $t(56) = 2.56$, $p < 0.05$) and the left forceps minor (MNI coordinates: X: -12 Y: 36 Z: 4, $t(56) = 2.70$, $p < 0.05$). I did not find any significant increases of AD in patients compared to controls. Furthermore, there were no differences between the two groups for FA or RD at $p < 0.05$. Finally, I found no effect of medication since a separate TBSS analysis, excluding patients on medication, yielded the same results demonstrating widespread decrease in AD in TS, but unaffected FA and RD.

These results of a substantial and widespread *decrease* in AD of several WM tracts is in contrast to a recently published study by Liu and colleagues (Y. Liu et al., 2013), who showed regional *increases* of AD. This discrepancy could be explained by differences in the age of participants. In the present study, the sample consisted largely of adolescents, whereas participants in Liu, et al.'s study were all very young children, with very short disease duration. Importantly, age has previously been shown to be a significant factor in diffusion MR studies (Asato, Terwilliger, Woo, & Luna, 2010). Specifically, we tend to see a significant linear decline in AD with age in healthy participants in almost all parts of the brain (Kumar, Nguyen, Macey, Woo, & Harper, 2012). Therefore, the two studies indicate that whereas axial diffusivity is enhanced in very young patients this reverses by early adolescence, in comparison with healthy control subjects. It is difficult to interpret these findings as TS is not known to affect WM directly. However, I theorise that these differences seen in patients with TS are due to increased freedom of cross-fibre diffusion as the patient grows older, affecting AD (A. L. Alexander et al., 2007; Song et al., 2002). Therefore, the apparent discrepancy of our results and the ones by Liu et al.'s could also indicate a more rapid decline of AD values in patients with TS by increased branching of WM tracts. At present this is a

postulation at best and a longitudinal study would clarify this. It is important to reiterate that our results cannot be attributed to differences in age of participants since age was used as variable of no interest.

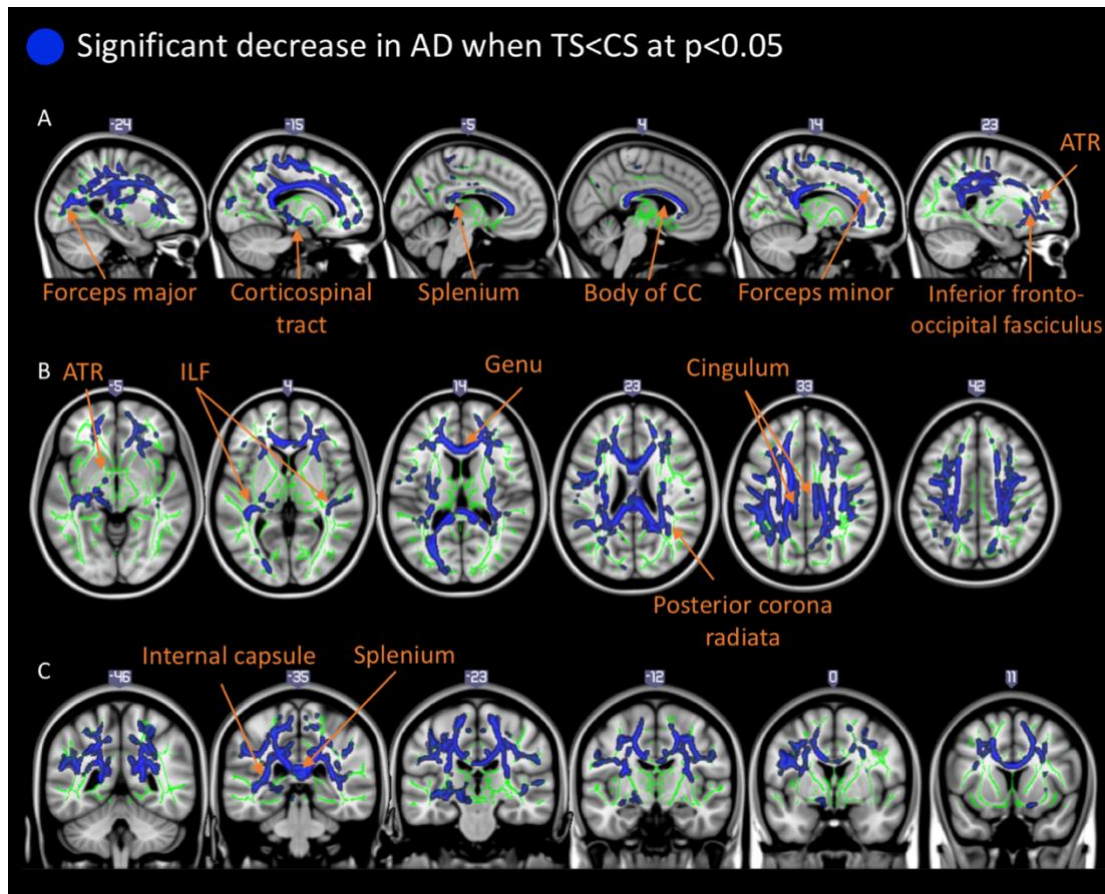


Figure 5.2. Illustrates key tracts exhibiting significant decreases in axial diffusivity (AD) ($p < 0.05$ corrected for multiple comparison). Differences are projected onto the mean white matter skeleton (green) and the MNI 152 template. Top panel, A: sagittal images showing significant tracts. Coordinate numbers are X coordinates in MNI space. Middle panel, B: axial images showing significant tracts. Coordinate numbers displayed are Z coordinates in MNI space. Bottom panel, C: images showing significant tracts. Coordinate numbers are Y coordinates in MNI space. Abbreviations, ATR = anterior thalamic radiation. CC = corpus callosum. ILF = inferior longitudinal fasciculus.

Our sample of patients with TS also presented with several comorbid disorders such as ADHD and OCD (see Table 5.1). Interestingly, our TBSS results do conform to diffusion studies in patients with OCD but not ADHD. Young patients with ADHD are thought present *increased* AD in several fronto-striatal, prefrontal and occipital WM pathways in comparison with control subjects (Silk, Vance, Rinehart, Bradshaw, & Cunningham,

2009; Tamm, Barnea-Goraly, & Reiss, 2012). However, AD seems to be significantly enhanced (there was no effect of any other diffusion scalar) in healthy controls in comparison with young OCD patients in both the genu and splenium of the CC (Silk, Chen, Seal, & Vance, 2013). These results indicate that whereas AD seems to be enhanced in ADHD patients, AD seems to be diminished in TS and OCD patients. Unfortunately, I was unable to carry out any sub-group analyses due to lack of power. Plessen and colleagues (2006) showed however that there is a significant reduction of WM connectivity in the CC in patients with TS, and these results remained the same during a subgroup analyses (TS+ADHD, TS+OCD).

I was unable to find any significant associations between clinical measures (i.e., PUTS or tic severity scores) and measures of WM diffusion. This is in line with recent study by Jeppesen and colleagues (2014). By contrast, other studies have reported significant correlations. For example, Liu, et al. (2013) showed that WM microstructure in the right ATR pathway and right cingulum were positively correlated with tic severity. Likewise, in a similar sample as to the current study presented here, WM water diffusion in the CC and forceps minor positively predicted tic severity (S. R. Jackson, Parkinson, Jung, et al., 2011). These results were interpreted by Jackson and colleagues to indicate that having TS might induce a compensatory functional reorganization. Regression analyses in the current study suggest that syndrome related decreases in AD are not associated with tic severity or frequency of PSP. Rather, structural differences in the brain can only be attributed to having TS.

5.4 PROBABILISTIC TRACTOGRAPHY

In addition to the TBSS analysis, I also analysed the data using probabilistic tractography to track WM fibers between several ROIs chosen *a priori* based on the TS literature and known TS pathology (Albin & Mink, 2006; Tremblay et al., 2015; Worbe et al., 2012)

5.4.1 *Tractography: Data and statistical analysis*

Region specific probabilistic streamline tractography was accomplished using the open-source diffusion MRI toolkit Camino (Cook et al., 2006). Using Bayesian techniques, the probability distribution function can be estimated on the principal fibre direction at each voxel in the brain and distribution of connectivity values between seeds (ROIs) and all other points are generated by repeatedly sampling the connected pathways (Friman, Farnebäck, & Westin, 2006).

The 12 ROIs were selected since the aim was to assess connectivity between cortical, subcortical and insular GM structures, and picked from widely used templates available from the literature. Specifically, I used sensorimotor ROIs specified in the human motor area template (HMAT; Mayka, Corcos, Leurgans, & Vaillancourt, 2006), including the primary motor and sensory cortices (M1 and S1), SMA and pre-SMA, and the dorsal premotor cortex. Next, subcortical structures were selected based on the basal ganglia human area template (BGHAT; Prodoehl, Yu, Little, Abraham, & Vaillancourt, 2008), including the caudate, putamen, globus pallidus and thalamus, in addition to adding the nucleus accumbens (part of the ventral striatum). Finally, I also chose to include the anterior and posterior portions of the insular cortex, extracted from the comprehensive parcellation analysis done by Kelly et al. (2012) whose analysis was based on over 1000 MR scans derived from the 1000 Functional Connectomes Project. The insula has been strongly implicated in PSP in TS (Draper et al., 2015; S. R. Jackson, Parkinson, Kim, et al., 2011; Tinaz et al., 2015), while the insular cortex is thought to play a primary role in coding the emotional significance of somatosensory signals (Jackson, Parkinson, Kim, et al., 2011).

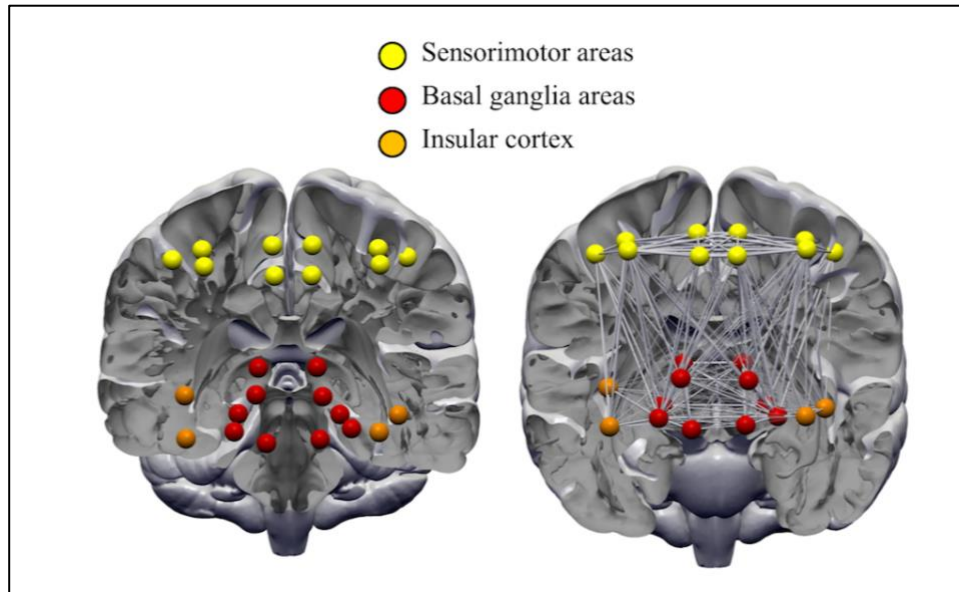


Figure 5.3. ROIs used in the probabilistic tractography analysis. ROIs were presented as nodes in a graph theoretical analysis. Yellow: Sensorimotor areas, Red: Basal ganglia/subcortical structures, Orange: Anterior and posterior insular cortex.

Registration of ROIs from MNI space to individual DTI native space was accomplished in three steps: 1) Individual anatomical images were co-registered to the B0 image using linear transformation (FLIRT), 2) the transformed T1-weighted images were next transferred to a standard template [ICBM152 Montreal Neurological Institute (MNI)] space using linear and non-linear transformation (FLIRT and FNIRT), and 3) the resulting transformation matrix was applied inversely to bring each ROI into DTI native space (i.e., each ROI had a voxel dimension of $1 \times 1 \times 2 \text{ mm}^3$). Distinct labelling of the ROIs was preserved using nearest neighbour interpolation. Finally, individual ROIs were combined into a single mask.

The first step in assessing WM connectivity I took the transformed, co-registered, T1-weighted images and segmented into GM, WM and CSF using the FAST segmentation tool in FSL (Zhang, Brady, & Smith, 2001). Whole-brain probabilistic streamline tractography was accomplished using the 'track' command within Camino. Segmented WM served as a starting seed for fibre tracking in a whole-brain technique termed 'exhaustive search method' (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Gong et al., 2009; Mori & Van Zijl, 2002). Individual FA maps were entered to restrict the tracking procedure to voxels with $FA \geq 0.2$ to exclude tracts entering GM or CSF.

Tracking was initiated from the centre of each WM voxel with a step size of 0.5 mm. Tracking continued until a voxel was entered which fell below the termination criteria or when local streamline curvature exceeded 60 degrees. Next, connectivity matrices were generated by recording how many streamlines connect each pair of ROI targets. Mean tract statistics from DTI scalars were extracted from each connected ROI pair. As a result, an undirected weighted structural brain network for each participant was represented by a symmetric 24 x 24 matrix. Finally, since raw streamline connectivity matrices might be influenced by brain volume I calculated the individual total intracranial volume (TIV).

Finally, I applied graph theoretical analysis to quantify any differences in connectivity across the 24 ROIs (using the 24 x 24 matrices). As noted above, a graph is represented by V number of nodes connected by E edges or links (Bullmore & Sporns, 2009). An important step in graph theory analysis is assessing networks at different thresholds (i.e., filter out weak and non-significant links which may have been spuriously produced; Rubinov and Sporns, 2010). However, few guidelines exist on the choice of these thresholds. Therefore, in this study networks were constructed based on a proportional thresholding (commonly used in patients vs controls studies) method such that any connection (i.e., link) value above an arbitrary percent threshold (i.e., 0.15 or 15%) were included as a connection, while other connections falling below this threshold were excluded. To be specific, this thresholding method excludes the weakest connections and maintains the strongest (e.g., 15%) connections. Subsequently, surviving connections (after thresholding) are binarized and entered into the analysis, such that 1 indicates a presence of a connection and 0 (zero) otherwise. Binarisation thus discards the weight of a connection which renders the networks simpler to characterize (Rubinov & Sporns, 2010). Based on this information I analysed the data across a variety of thresholds, ranging from 0.15 – 0.40 in steps of 0.01, equaling to 26 thresholds. Proportional thresholding ensures network compatibility across groups by keeping the number of nodes and edges the same and improves network measure stability (Garrison, Scheinost, Finn, Shen, & Todd, 2015). Eight graph metrics: global efficiency; small-worldness; assortativity; density; degree; betweenness centrality; shortest path length; and local efficiency, were calculated and are detailed

in Table 5.2 (I refer the reader to the article by Rubinov & Sporns, 2010 to see how these are calculated).

It is possible that with 24 ROIs my networks could lack small-world properties, which is an essential factor in graph theory. According to the seminal work done by Watts and Strogatz (1998) and further iterated by others (e.g., Humphries, Gurney, & Prescott, 2006) small worldness can be confirmed in networks using real and random network clustering coefficient and characteristic path length. Therefore, to examine the small worldness of our networks I calculated the normalised clustering coefficient (γ) and normalised path length (λ). These two metrics are calculated using null-networks. In particular, I generated 500 null-networks, with the same number of nodes and edges, and degree distribution as the real networks for each subject (Maslov & Sneppen, 2002), then $\gamma = \text{Cluster_coef}_{\text{REAL}}/\text{Cluster_coef}_{\text{RAND}}$ and $\lambda = \text{Path_length}_{\text{REAL}}/\text{Path_length}_{\text{RAND}}$. To determine the small-worldness of my networks I calculated the small-world coefficient σ as $\sigma = \gamma/\lambda$. If $\sigma > 1$, a network can be considered to be small-world.

Finally, I defined ‘hubs’ using the following criteria: betweenness centrality and degree were normalised across nodes (z-score) and thresholded at $z \geq 2$. Hubs are thought to promote integration between different parts of functional networks.

For statistical analysis I assessed the graph metrics across groups using a general linear model with group as a between subject factor and age, IQ and TIV as nuisance covariates. I then used a multiple linear regression to assess any association between graph metrics and clinical measures in patients only. Statistical differences in graph metrics were assessed using 1000 permutation tests. Statistical difference was first explored at a more lenient $p < 0.001$ uncorrected. p -values were also corrected for multiple comparison using false discovery rate (FDR; Benjamini & Hochberg, 1995) at $p\text{-FDR} < 0.05$. Graph metrics and statistical analysis was accomplished using the Graphvar interface for the Brain Connectivity Toolbox (Kruschwitz, List, Waller, Rubinov, & Walter, 2015; Rubinov & Sporns, 2010).

Table 5.2. Graph metrics used in the study.

Graph metric	Explanation
Assortativity	A correlation coefficient between degrees of all nodes between pair of nodes. When assortativity is positive it indicates that nodes tend to connect to other nodes with same or similar degree.
Betweenness centrality	High values indicate that nodes participate in a greater number of shortest paths.
Characteristic path length (local)	An average shortest path length of a node to the rest of the network.
Clustering coefficient	The fraction of a nodes neighbours, which are also neighbours of each other. This is zero if nodes are isolated or only connect with one other node.
Degree	Total number of links connected to a node.
Density	A fraction of present connections to all possible connections in a network.
Network global efficiency	Average inverse shortest path length in the network.
Network local efficiency	This is calculated as global efficiency on node neighbourhoods.
Small-worldness	Measures the extent of how tightly clustered the network is.

5.4.2 Tractography: Results and discussion

Analysis of tractography data was carried out using AD maps for each subject. This was preferred over using the more conventional FA maps since our TBSS result showed significant group differences on AD maps. Therefore, for each pair of ROIs I extracted the mean AD value of WM tract that connects the two.

Network density was not significantly different across groups at any threshold (Figure 5.4A; $t(56) = 0.61 - 0.68$, $p > 0.05$). This indicates that the any observed differences between groups in graph metrics cannot be attributed to differences in network density (as depicted in Figure 5.4|A. No other global metric (i.e., small-worldness, γ , λ , global efficiency, and assortativity) showed any significant difference

across groups (Figure 5.4|B-F; all $p > 0.05$). By contrast, I found significantly enhanced betweenness centrality with respect to the left putamen of the TS patients at several thresholds (thresholds: 25-24%, 22-19%, CS grand mean: 39.6, TS grand mean: 46.65, $t(56) = -1.69 - -2.17$, $p < 0.001$ uncorrected). The difference in betweenness centrality became non-significant after stringent multiple comparison correction, and results are interpreted with this in mind. The characteristic path length was also significantly higher in patients across several thresholds for the right accumbens (thresholds: 28%-20%, CS grand mean: 4.30, TS grand mean: 4.62, $t(56) = -1.37 - -1.89$, $p < 0.001$ uncorrected). No threshold survived our stringent multiple comparison correction. No other graph metric showed any significant between group differences. Additionally, we calculated hubs from metrics betweenness centrality and degree. Nodes satisfying the condition of having z-scores ≥ 2 across both metrics were considered as hubs. As can be seen in Figure 5.5, both groups had two nodes showing hub-like characteristics, the right putamen and left SMA.

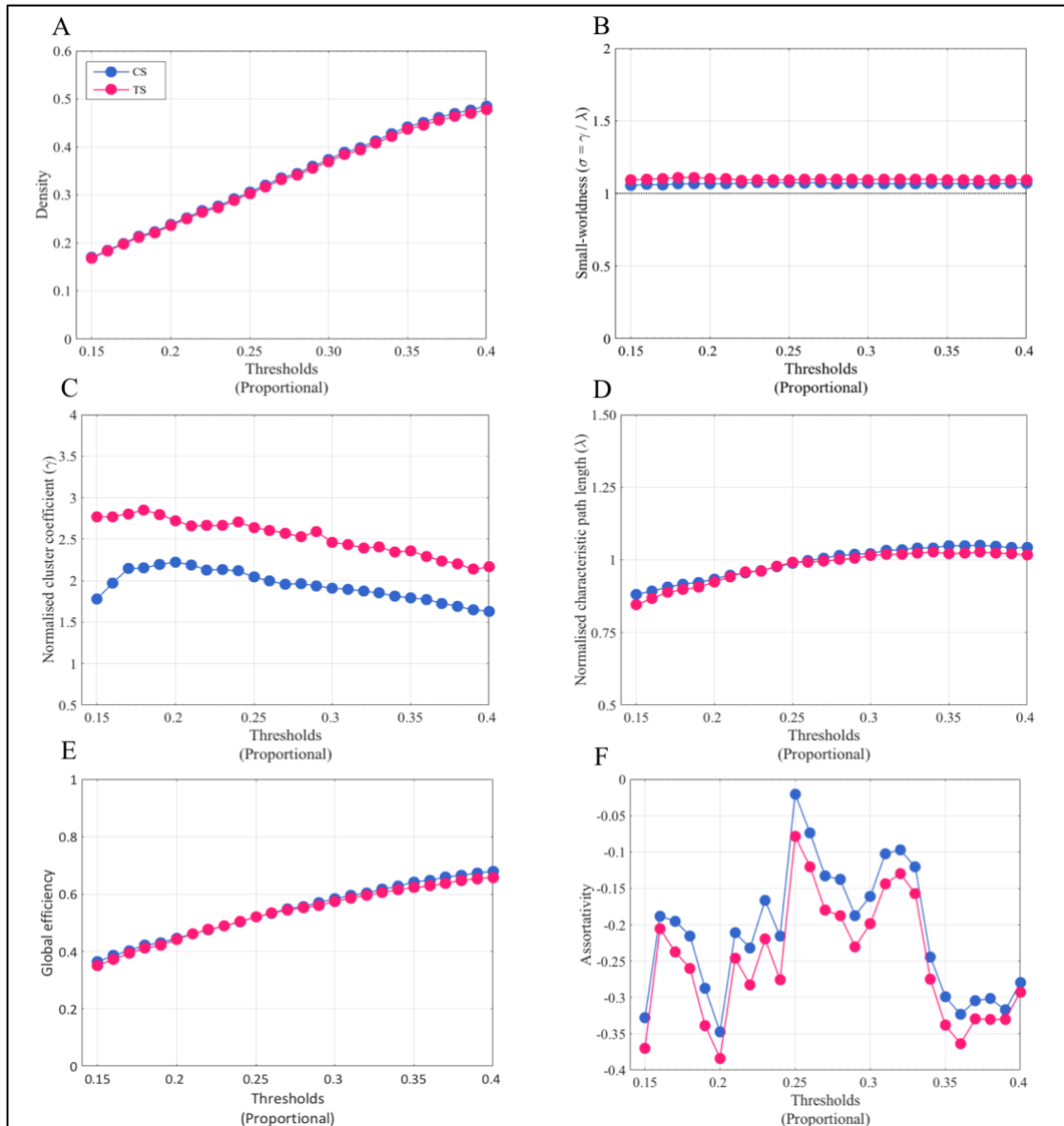


Figure 5.4. Comparison of global metrics between groups. Global metrics: A) density, B) small-worldness, C) global efficiency and D) assortativity, were compared across the two groups. None of the global metrics were significantly different across groups (all $p > 0.05$).

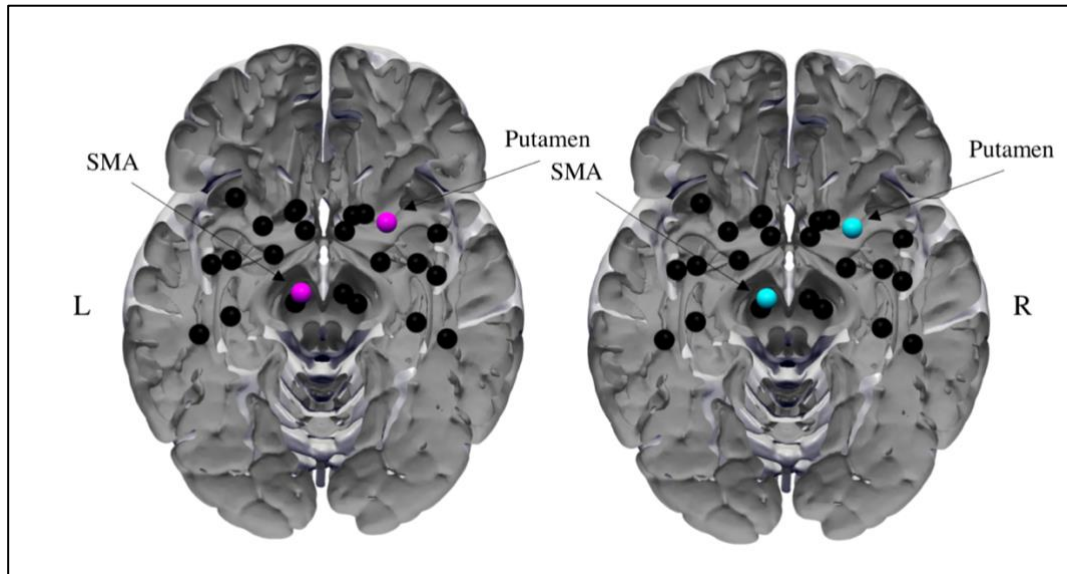


Figure 5.5. Hubs. Nodes with hub-like characteristics were constructed from betweenness centrality and degree metrics. Nodes with z-score ≥ 2 across both metrics were considered to show hub-like characteristics. Two nodes, left SMA and right Putamen showed such characteristics in both groups (Left: TS group, Right: CS group).

I used multiple linear regression analysis to investigate any association between the different graph metrics (adjusted for the effects of age, IQ and TIV) and tic severity (YGTSS) or PSP (PUTS) in TS patients. PUTS scores showed a significant association with local efficiency on three nodes (ROIs). First, the left caudate was negatively associated with PUTS scores (thresholds: 27%-24%, 22-20%, $\beta = -0.55 - -0.57$, $t(22) = -2.66 - -2.94$, $p < 0.001$). Second, there was also a significant positive association with PUTS scores for the right posterior insula in four threshold (thresholds: 21-18%, $\beta = 0.55$, $t(22) = 2.79$, $p < 0.001$). Third, there was a positive association with PUTS scores for the left anterior insula (thresholds: 16-15%, $\beta = 0.60$, $t(22) = 3.14 - 3.25$, $p < 0.001$). All thresholds survived correction for multiple comparisons. The relationship between PUTS scores and the residual local efficiency is depicted in Figure 5.6. Tic severity scores and measures of betweenness centrality showed a significant positive association on three nodes. The left thalamus (thresholds: 28%-15%, $\beta = 6.66 - 17.35$, $t(22) = 1.82 - 3.79$, $p < 0.001$) with two thresholds surviving FDR correction; the right M1 (thresholds: 40-38%, 35-33% and 29-15%, $\beta = 7.59 - 16.27$, $t(22) = 1.51 - 3.49$, $p < 0.001$), with one threshold surviving FDR correction; and the right dorsal premotor cortex (thresholds: 40-33%, 20% and 18-15%, $\beta = 7.97 - 16.42$, $t(22) = 1.44 - 3.45$, $p < 0.001$) with no

threshold surviving a multiple comparison correction. No association was found between clinical measures and any global metric (all $p > 0.001$).

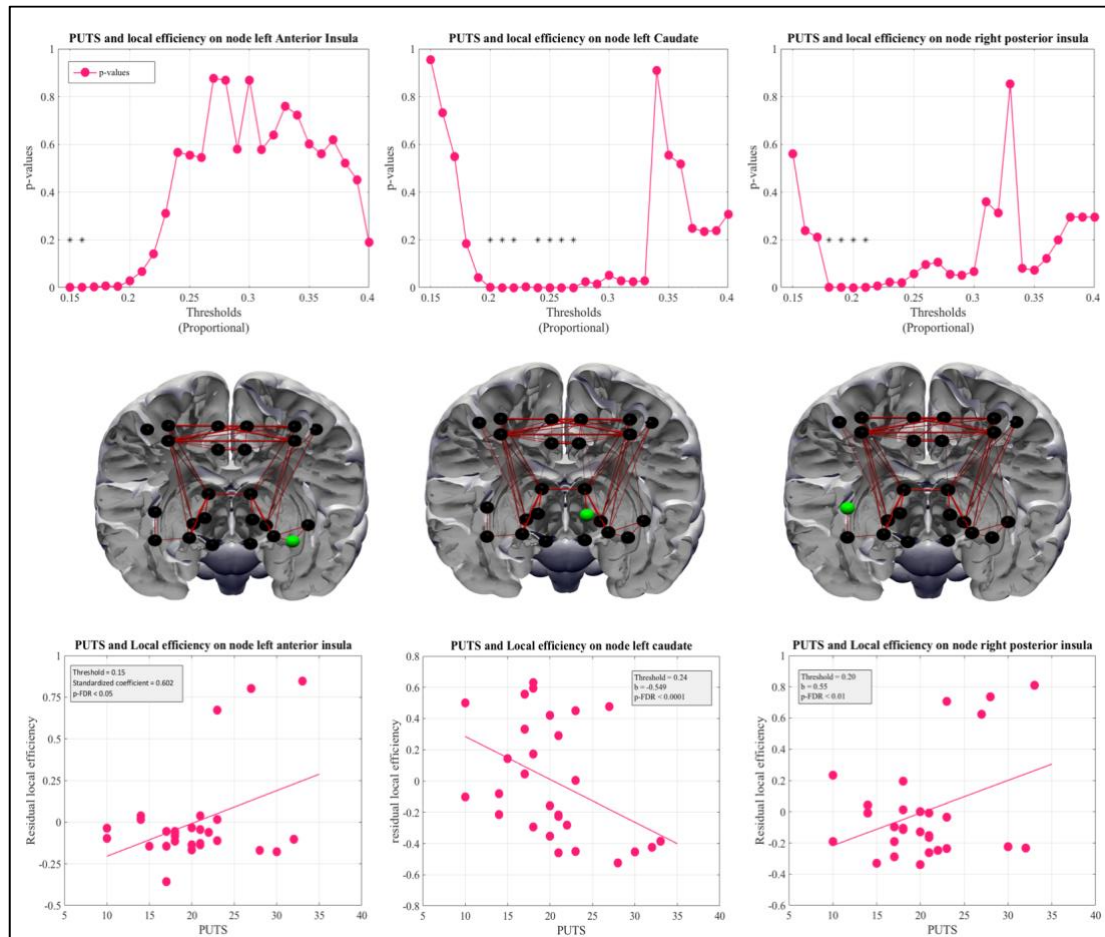


Figure 5.6. Local metrics showing association with PUTS scores. Local efficiency of three nodes showed a significant association with PUTS scores. Column A shows results from the left anterior insula; Column B shows results from the left caudate; Column C shows results from the posterior insula. Top row: p-values across thresholds. Middle row; nodes are coded in green. Bottom row: regression plots showing relationship between local efficiency and PUTS scores. * p -FDR<0.05.

The tractography and graph theory results showed that patients displayed increased number of connections amongst the *a priori* defined ROIs, but also less functionally integrated networks as measured using the characteristic path length metric. However, most of my results did not survive a stringent multiple comparison correction, possibly due to lack of power, and interpretation of these effects is made with caution.

Previously, Worbe and colleagues (2012) reported a complete lack of functional hubs, more functionally integrated networks and increased number of connections, in a sample of adult patients with TS. In my sample, I found no hub-related differences between the two groups. Hubs are considered as important nodes in a network, with a maximum number of connections, they also facilitate integration between parts of a network (Rubinov & Sporns, 2010). In my data, I identified two nodes (left SMA and right putamen) classified as hubs in both groups. Interestingly, this was also demonstrated in a recent paper where both patients and control subjects had highly similar hub distribution (Wen, Liu, Reik, Wang, Zhang, et al., 2017). Similarly, in adults, both the left SMA and right putamen have been shown to display increased betweenness centrality in patients (Tinaz et al., 2015). This betweenness centrality measure is often used alone or in combination with other metrics as an indication of a node hub-ness. Collectively, these results indicate that amongst both children and adults, these two nodes might play a significant role in pathology of TS.

To ascertain any relationship between clinical variables and graph metrics I ran a multiple regression analysis on my sample of patients. Most notably, I observed a positive linear association between the frequency of PSP in patients and the efficacy of information transfer in the right posterior insula and left anterior insula as well as a negative relationship with information transfer in the left caudate after correcting for age, IQ and TIV. Thus, PUTS scores explain a significant amount of variance in local efficiency after the variance associated with these other variables has been controlled for. The insular cortex has been associated with interoception and activate significantly in fMRI studies during somatosensory stimulation and suppression of bodily urges (Berman, Horovitz, Morel, & Hallett, 2012; S. R. Jackson, Parkinson, Pears, & Nam, 2011). More specifically, the right posterior insula has been shown to be specific for action and perception while the left anterior insula is important for cognition and emotion (Kelly, et al. 2012). The left anterior insula was also a key part in the model proposed by Jackson and colleagues (2011) as this was proposed to code for the sensations which are associated with the urge-to-act. The results I have presented here support this notion. These results are also in accord with previous studies demonstrating that functional connectivity of the right dorsal anterior insula has a

significant relationship with urge frequency and tic severity in adult patients with TS (Tinaz et al., 2015). Similarly, in children it has been shown that grey matter thickness of the left insula is negatively associated with PUTS scores (Draper et al., 2015).

I also noted that tic severity was significantly associated with betweenness centrality on two nodes; a positive correlation with the left thalamus and right M1, indicating that as tic severity increases in patients these two nodes participate in a greater number of shorter paths within the network and might act as aberrant hub-like nodes.

5.5 OVERALL DISCUSSION AND IMPLICATION

In general, this chapter has explored the WM microstructure and connectivity in young people with TS. By utilizing diffusion MR imaging and applying TBSS and probabilistic tractography, I wanted to investigate if young people with TS display altered water diffusion and WM connectivity of key WM tracts connecting several GM ROIs. The TBSS method was used as a general, whole-brain investigation to see if patients display altered water diffusion in accordance with recently published results in non-adult sample of patients (S. R. Jackson, Parkinson, Jung, et al., 2011; Y. Liu et al., 2013). The TBSS results were then used as a guidance for further investigation using tractography to characterize the connectivity between SM, subcortical and insular ROIs. In particular, I wanted to investigate the relationship between connectivity of the insular cortices and clinical measure of sensory urges. To my knowledge, no study has ever emphasized this relationship. Most important, my results showed: (1) widespread decrease in axial diffusivity in patients, (2) a trend for enhanced centrality (a node that is essential in efficient communication between other nodes in the graph) of the left putamen in patients, (3) similar hub distribution between the two groups, and (4) the importance of the insular cortex in maintaining effective communication in a network and the relationship between efficiency of the network and clinically measured sensory urges reported by patients. Interestingly, the relationship between local efficiency graph metric in the insular ROIs and PUTS scores was not reproduced using tic severity scores. This indicates that this relationship of increased local efficiency in patients can

only be related to increased frequency or severity of sensory urges in patients but not tic severity.

The insular results are particularly interesting due to the significant role played by the insular cortex in the embodied self, including body representation and interoception, and the processing of pleasant and unpleasant somatosensory stimuli (Craig, 2003; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Olausson et al., 2002; Seth, 2013). Most recently, neural response of the anterior left and posterior right insular cortex was shown to be significantly associated with a stimulus preceding cue indicating the probability of stimulus type (i.e., painful or non-painful [expectation]) and when mismatch occurred between the expectation and the stimuli (in predictive coding terms labelled prediction error) (Geuter, Boll, Eippert, & Büchel, 2017).

As mentioned above, investigating WM follows logically from my previous chapter, where the organization of SM cortical maps was studied using TMS, since cortical re-organisation might be induced by aberrant thalamocortical connections within the internal capsule (a WM pathway connecting the thalamus to the cerebral cortex, and with descending fibers from the fronto-parietal cortex to subcortical nuclei; Noback, Strominger, Demarest, & Ruggiero, 2005). In general, my comparison of WM connectivity across several ROIs including connections between bilateral thalamus and sensorimotor cortex conforms well and provide further support for my results I presented in Chapter 4, showing limited cortical re-organisation of several sensorimotor cortical representations.

5.5.1 Clinical implication

Although not the main focus of this study, it is interesting to consider how my results could be implemented into clinical practice. For example, my results of increased information transfer (i.e. efficiency of certain areas of the insula) contributing to increased frequency of PSP suggests hyper-connectivity of the insula to the rest of the nodes in a network. It is yet to be explored whether this increased connectivity can be reversed with behavioural therapy. One previous study showed that comprehensive behavioural intervention for tics (or CBIT) resulted in decreased task-related activation

of the putamen in patients with TS (Deckersbach et al., 2014). By contrast, typically developing individuals demonstrated increased activity in the same region. The authors interpreted this finding as to indicate that CBIT might reduce hyper-elevated activity of the putamen and improve inappropriate activation of the putamen. The efficacy of other non-pharmacological remedies such as high aerobic exercise has been shown to reduce the frequency of tics, outlasting the duration of the exercise (Nixon, Glazebrook, Hollis, & Jackson, 2014). No study has investigated the effect of behaviour therapy on white matter connectivity. Nonetheless, the evidence exists that greater habitual behaviour in patients with TS is related to stronger white matter connectivity within the cortico-striatal network. I therefore urge future studies to look at the effect of behavioural therapy or exercise on the integrity of white matter pathways.

5.6 CONCLUSION

In this study, I have demonstrated, for the first time in a young sample of patients with TS, clear atypical WM microstructure and evidence for altered structural connectivity using diffusion MRI in comparison to matched typically developing control subjects. These results add to the existing literature of altered connectivity of the insula which might play a role in the frequency of PSP experienced by patients, and lend further support to my theory of increased prediction error in TS as the main culprit of the emergence in the self-perceived sensory hypersensitivity. Finally, I showed that, in contrast to very young patients, axial diffusivity decreases exponentially during adolescence.

CHAPTER 6

Chapter Six – Longitudinal assessment of grey matter volume and clinical outcome in Tourette syndrome using Voxel Based Morphometry and pattern recognition

By contrast to the last chapter where I investigated WM microstructure, in this chapter I present a study which investigates grey matter volume measured at two timepoints separated by one year. Developmental studies, focusing on the maturation of the brain have shown exponential decrease in the volume of grey matter during adolescence, specifically in frontal and parietal cortices. Past studies in TS have shown converging evidence for altered grey matter volume in patients. This longitudinal, prospective study includes the use of both univariate and multivariate statistical approaches. Structural MRI scans from 17 patients with TS and 17 of their peers were used in this study. By contrast to controls, patients with TS demonstrated an *increase* in grey matter volume between the two timepoints, specifically in frontal, cingulate and insular cortices. Multivariate, pattern recognition approach confirmed these results but was unable to correctly categorise an individual brain according to diagnostic status. The results of this study suggest a compensatory adaptation of the brain rather than a developmental delay.

Keywords: *Structural MRI, Grey matter, Voxel based morphometry, Multivariate pattern recognition, Multiple-kernel learning.*

In the last chapter, Chapter 5, I explored the WM microstructure and connectivity in a large group of patients with TS and matched group of typically developing individuals. My results primarily showed that the insular cortex might play a putative role in the frequency and severity of PSP in patients. It is well possible that changes in white matter are paralleled by similar perturbations in grey matter (GM). Therefore, in this chapter I am going to continue my investigation of the structural integrity of the brain in patients, and present for the first time a prospective, longitudinal investigation of the volume of grey matter (GM) with measurements acquired twice. This study also investigates (1) the relationship between PSP and change in GM volume in patients and (2) if change in GM volume can be used to predict the diagnostic label of all participants.

6.1 INTRODUCTION

Structural MRI (sMRI) are detailed anatomical images of the brain. sMRI images can be used to investigate either whole brain or region-specific volume, density or magnitude, non-invasively. Aberrant GM volume has previously been reported in TS (e.g., Greene et al., 2017). Furthermore, GM development and decline has been studied extensively in typically developing children and adolescents (Giorgio et al., 2010; Gogtay et al., 2004; Kochunov et al., 2011; Paus, 2005), which is discussed below.

6.1.1 *TS-related changes in grey matter*

GM alterations in patients with TS has been reported, where most studies seem to suggest diminished GM volume or thickness of fronto-striatal areas (Kassubek et al., 2006; Peterson et al., 2003; Singer et al., 1993) and parietal lobe (Sowell et al., 2008). By contrast, some studies have reported null-results, indicating that perhaps TS does not affect GM volume or thickness (Roessner et al., 2009; L. Wang et al., 2007; Williams et al., 2013). I have previously mentioned the reduced volume of the striatum in adults with TS (Peterson et al., 1993, 1992). However, a recent, multi-centre study, and one of the largest to date with brain scans from over 200 children and adolescents aged between 7-17 years failed to show any differences of striatal nuclei, while reporting *enhanced* GM volume in two clusters in the TS group, overlapping the pulvinar nucleus

of the left thalamus and bilateral hypothalamus which extended into the ventral midbrain (Greene et al., 2017). Greene, et al. (2017) posited if the GM volume enhancement in the left thalamus might relate either to multisensory integration or the mechanistic link between sensory input and movement related areas. This comes from the knowledge that the pulvinar nucleus of the thalamus projects to the entire parietal association cortex and it thus plays an important part in the detection and interpretation of the perceptual experience of the world (Noback et al., 2005a). It is therefore possible that TS-related symptoms could be related to thalamic perturbations. In very young patients, Liu and co-workers (2013) reported increased GM and paralleled decreased WM volume in the motor-sensory gyrus in patients, possibly implicating this area in the regulation of tics in TS. In general, this conclusion is not surprising since movement disorders have for long been implicated to affect sensorimotor integration (Abbruzzese & Berardelli, 2003; Hallett, 1995; Patel et al., 2014), and is consistent with studies done in TS (S. R. Jackson et al., 2013).

Based on this information, three prime questions remain: (1) Which, if any, areas of cortical GM can be considered as a potential biomarker for syndrome progression or prognosis, (2) what role does change in GM volume play in the presence, absence or persistence of sensory phenomena in TS and (3) can alterations in GM volume/thickness in TS be attributed to adaptation mechanisms or ‘developmental delay’. These questions are difficult to answer, specifically since the latter question largely depends on longitudinal studies. The former could be answered using a nascent methods of pattern recognition algorithms (i.e., machine learning). Both techniques have limited occurrence in the TS literature.

6.1.2 Longitudinal assessment of grey matter in TS

Most studies to date are cross-sectional, demonstrating TS-related GM hyper- or atrophy at a single timepoint. Consequently, these results are often biased by the large between-individual variation reported in brain shape and volume in typically developing individuals (Paus, 2005). Based on a single MRI scan, limited inference can be made, as well as accurate localization of group differences. Thus, recording numerous MRI scans over a period of year or years brings about the possibility to track

disease progression. Longitudinal studies are informative, since key individual changes can be measured and quantified. However, these are also met with several challenges such as participant drop-out, complicated statistical analysis and determining the direction of causality (Caruana, Roman, Hernández-Sánchez, & Solli, 2015). Longitudinal assessment of GM and WM development in neurologically healthy children and adolescents show consistent results with systematic decrease of GM volume in frontal and parietal areas starting at ~11-12th year of life, whereas GM in temporal lobe seems to reduce more slowly and less progressively (Giorgio et al., 2010; Paus et al., 1999). Parallel increases in WM density are observed primarily in the corticospinal and frontotemporal pathways (Giorgio et al., 2010; Paus et al., 1999).

Unfortunately, longitudinal sMRI studies in the realm of TS are limited and to my knowledge only two studies have been published to date including imaging analyses (Bloch, Leckman, Zhu, & Peterson, 2005; Debes et al., 2015). Bloch and colleagues (2005) set out to evaluate the relationship between volume of the caudate in childhood and severity of tic symptoms and/or comorbid OCB's in early adulthood. sMRI data and clinical assessment was collected from 43 children prior to the age of 14 years. Follow up clinical assessment was conducted, on average, 7.5 years later. All participants were still under the age of 16 years. First, all participants demonstrated significant reduction in tic severity at follow up compared with baseline. In contrast, OCBs had significantly enhanced at follow up. More importantly, the authors reported that caudal volume at baseline inversely predict both severity of tics and OCBs at follow up. To put differently, greater caudal volume in childhood is related to decreased severity of tics but increased severity of OCBs with time in patients with TS. Interestingly, Bloch and colleagues (2005) reported no relationship between caudal volume at the time of scan and symptom severity of tics or OCBs. This study is important for two reasons. First, results are in good agreement with the notion that while tic severity tends to diminish in late adolescence and/or early adulthood, OCBs tend to increase in severity (Leckman, 2002). Second, this study shows the necessity for longitudinal sMRI studies in patients with TS to ascertain symptom related effects of the brain. Even though caudal volume does not have the ability alone to predict the clinical course of TS, the authors point out that the power of sMRI to detect this association (but not clinical characteristics)

could eventually translate in to clinical practice. Nonetheless, the study by Bloch and co-workers is limited by the absence of a control group. A control group is necessary to determine the progression of caudal volume in typically developing individuals of same age and sex. Also, caudal volume was also not measured at follow up. This is an important limitation since change in caudal volume could have been a better predictor of disease progression.

Debes and colleagues (2015) also ran a longitudinal neuroimaging study to assess simultaneous progression of tic symptoms and structural alterations in patients with TS in comparison to a group of healthy volunteers. This study assessed both macroscopic and microscopic changes in the brain using GM volume and WM diffusion. The mean age of patients at baseline was 14 years and on average 4.4 years elapsed between timepoints. The authors reported that there was a significant decrease in tic severity at follow-up (YGTSS scores: 19.4 at baseline, 12.6 at follow up). The control group was of comparable age. However, the study is limited by a shorter time elapsing between measurements on average for the control group (3.8 years) and the patient group had a much higher ratio of males. Assessment of regional GM volume showed significantly decreased volume of the left putamen in controls, which was not apparent in the TS group. Furthermore, TS sub-group analysis containing patients with persisting tics and patients in remission of tics showed no significant group effects. The authors also measured WM diffusion and reported a substantial decrease in parallel (axial diffusivity) WM water diffusion in the caudate, thalamus and frontal lobe in the right hemisphere with age in the TS group but contrasting increase in controls. Greater decline of diffusion in those areas was associated with greater persistence of tics. It is perhaps most interesting that these results could be an indication of disease-related compensatory adaptation, which is not necessarily related to the severity of symptoms specifically since it appears that patients do not follow the normal tissue related development (Paus, 2005).

Most striking perhaps, and most relevant to this thesis, is that neither of these two studies explored the relationship between sensory phenomena and TS-related hypertrophy- or atrophy in GM volume.

6.1.3 *Grey matter and sensory phenomena*

Limited number of studies have assessed the relationship between sensory phenomena and brain structure, especially in TS. One study by Draper and colleagues (2015), including 29 young patients with TS, demonstrated significant, inverse correlation between PSP (measured with the PUTS scale) and GM thickness in the sensorimotor cortices and the left insular cortex (Draper et al., 2015). To put differently, greater severity or frequency of PSP is associated with thinner GM cortex in these areas. In adults, Draganski, et al. (2010) reported a significant, positive correlation between GM volume of the left primary somatosensory cortex (S1) and PSP severity. As such, greater volume of the left S1 is associated with more severe or frequent PSP. These results are completely opposite to the work by Draper and colleagues and suggests that the relationship between the neuropathology of persistent and severe TS (in adults) sensory aspects of the disorder are completely different to younger patients.

In patients with OCD, one multi-centre study, investigated the relationship between brain structure and sensory phenomena (Subirà et al., 2015). Specifically, the authors contrasted images from patients reporting the presence of sensory phenomena against patients with OCD who did not and healthy volunteers. Interestingly, results showed that OCD with sensory phenomena was associated with increased GM volume in the sensorimotor cortex bilaterally in comparison to patients without sensory phenomena. Furthermore, in comparison to controls, patients with sensory phenomena showed significant volume increases in bilateral sensorimotor cortex, left posterior putamen, pallidum and thalamus, while no structural differences were observed between patients without sensory phenomena and controls (Subirà et al., 2015). These results indicate that the presence and the experience of sensory phenomena alone can significantly alter GM volume.

6.1.4 *Multivariate pattern recognition to identify TS-specific neuroimaging biomarkers*

One of the largest, and most widely cited study on brain structure in TS to date showed reduced volume of the caudate nucleus in children and adults (Peterson et al.,

2003). The authors postulated that GM hypertrophy of this area could be a good biomarker for TS. However, no relationship between symptom severity and regional volumes was reported in the study (Peterson et al., 2003). Others have, however, disagreed with this conclusion stating that the caudate cannot be “a prime target for adaptive changes in response to the presence of tics” (Eichele & Plessen, 2013, pp. 36) since this reduction was apparent in both older and younger patients. The majority of studies to date, which explore the structural integrity of patients with TS have relied on univariate methods to localize TS-related hypertrophy- or atrophy in cortical GM. However, in the last decade multivariate techniques, relying on machine learning algorithms, have increased in popularity (please refer to Chapter 2 subsection 2.4.4 for a comprehensive introduction to machine learning). Machine learning, in the realm of TS, could be of vital importance since high quality and reliable diagnostic, disease and treatment prognosis tools are lacking. To date, five studies have been published in TS implementing machine learning algorithms (see Table 6.1 for an overview). All studies mentioned have been able to produce highly significant prediction accuracies when discriminating between participants with and without TS using PR. These 5 studies have employed a variety of neuroscience techniques such as rs-fMRI, DTI and sMRI. Three studies used rs-fMRI connectivity as measures (Greene et al., 2016; Liao et al., 2017; Wen et al., 2018). These three studies indicate that rs-fMRI can be used to reliably classify an individual as having TS. Two further studies (Wen, Liu, Rekik, Wang, Chen, et al., 2017; Wen, Liu, Rekik, Wang, Zhang, et al., 2017) assessed the ability of machine learning on spatial discrimination in patients with TS and controls using sMRI and diffusion MRI (DTI). Both produced excellent discriminative accuracy. Using sMRI, Wen, Liu, Rekik, Wang, Chen, et al., (2017b) identified GM volume of several brain areas as the most discriminative regions separating the two groups such as the pallidum, S1, inferior temporal gyrus and putamen, all key areas in the pathology of TS.

However, despite the novelty of and the clinical importance of these studies, none explored the neural substrates of PSP in patients with TS. Furthermore, only one of these studies mentioned above (Wen, Liu, Rekik, Wang, Chen, et al., 2017) investigated the discriminability of GM volume to accurately predict diagnostic status. Other studies,

all looked at either functional (rs-fMRI) or structural (DTI) connectivity, which is, as mentioned above, subjected to spurious correlations and prone to false negatives.

Importantly, no study to date has investigated the long-term changes in GM volume in patients with TS using machine learning algorithms and an investigation of the long-term impact of having TS is warranted.

6.1.1 Summary, aim and hypotheses

In summary, only two longitudinal, brain imaging studies have been published to date. One showed that the caudate could play a significant role in syndrome prognosis (Bloch et al., 2005) while the other suggests that the volume of the left putamen and more rapid decline of parallel diffusivity of frontal and subcortical areas might be indicators of syndrome persistence (Debes et al., 2015). In this chapter I will explore the anatomical changes in patients with TS using GM volume measured at two timepoints spaced approximately one year apart. Specifically, I attempt to locate and identify TS-related atrophy and potential neuroimaging biomarkers employing machine learning algorithms using longitudinal structural MRI data. Given the strong empirical evidence, I hypothesise to observe significant GM volume reduction in patients, specifically in the sensorimotor cortices, striatum and frontal areas between timepoints. Also, I expect to observe a significant association between PUTS scores and GM volume in the insula and sensorimotor cortices. Finally, I also expect the machine learning algorithms to be able to discriminate between the two groups based on the change in GM volume.

Table 6.1. Literature overview of studies to date employing machine learning algorithms to study function and structure of the brain in TS patients.

Author	Year	Age group	N	Imaging modality	Classifier	Prediction accuracy	Main results
Greene, et al.	2016	Children/adolescents	84 (42 TS)	rs-fMRI	SVM	74%	• The combination of somatomotor and control (frontoparietal, cingulo-opercular, salience, dorsal attention and ventral attention) systems provided the greatest prediction of group allocation. • Pattern recognition was not able to reliably predict tic severity based on functional connectivity scores
Wen, et al.	2017	Children/adolescents	66 (29 TS)	rs-fMRI	SVM	89%	• Similarity network fusion algorithm (combining thresholded networks) was able to significantly and accurately predict an individual brain as TS or not. • Superior frontal gyrus, rolandic operculum, Heschl's gyrus, inferior frontal gyrus, putamen, caudate nucleus and postcentral gyrus (amongst others) were the regions that most discriminated between the two groups.
Liao, et al.	2017	Children/adolescents	56 (24 TS)	rs-fMRI and DTI	SVM	93%	• This study used voxel-mirrored homotopic connectivity (WMHC) and observed significant group differences in several connections (e.g., bilateral ventral striatum, M1 and S1 and ACC as most discriminative regions). • Using results from the univariate approach, the PR method correctly labelled brains according to diagnostic status with high accuracy.
Wen, et al.	2017b	Children/adolescents	92 (44 TS)	sMRI & DTI (TBSS)	MKL	94%	• Using MKL, accuracy of classification was 94.2%, when combining features from white matter diffusion and grey matter volume • For grey matter, most discriminative regions classifying according to diagnostic status were: R supramarginal gyrus, R pallidum, R postcentral gyrus, L inferior temporal gyrus and L putamen.
Wen, et al.	2017	Children/adolescents	85 (44 TS)	DTI (Tractography)	MKL	86%	• This study shows that combining network parameters (from graph theory) can more comprehensively contribute to accurate diagnosis of TS as opposed to rely on a single dimensional feature
Abbreviations. rs-fMRI: Resting-state functional MRI, DTI: diffusion tensor imaging, sMRI: structural MRI, SVM: Support vector machine, MKL: Multiple-kernel learning.							

6.2 METHODOLOGY

6.2.1 *Participants*

sMRI images from 37 patients were available from Timepoint 1 (mean age: 13.39 ± 3.25 , range: 8.6 – 21.8, 3 females). Twenty-nine patients returned for their second scan approximately a year later (please refer to Figure 6.1 for study timeline). The sMRI images were acquired in a one-hour scan session along with diffusion MRI, functional task-based MRI and resting state MRI. The sMRI image was acquired first in the scan sequence. Based on initial screening of the TS sMRI images, 12 patients had to be excluded based on obvious image distortions and artefacts due to motion (both visually and using the novel retrospective quality assurance framework within the Computational Anatomy Toolbox (CAT12; <http://www.neuro.uni-jena.de/cat/>) running on Matlab which was then subsequently used for analysing the sMRI data. CAT12 reports on several parameters such as noise, inhomogeneities and image resolution.

As a result, 17 patients with TS had high-quality sMRI scans and were included in the study (see Table 6.2 for patient specific characteristics). Three patients had confirmed clinical diagnosis of OCD comorbidity and one patient had suspected Asperger's. At Timepoint 2 one other patient had received a confirmed diagnosis of comorbid OCD. Furthermore, all participants were also screened for symptoms of ADHD, OCB and ASD using the Conners-3, CY-BOCS and SCQ, respectively, by a trained research nurse. By definition, two patients had possible OCB at T1 and T2, while one patient had developed more severe OCB at T2. Five patients had possible ADHD at T1, while three patients had developed more severe ADHD symptoms at T2. Finally, one patient had suspected ASD at Timepoint 1 and another at Timepoint 2.

Nine patients were medicated at Timepoint 1 (Citalopram, Sertraline and Haloperidol, Sertraline and Melatonin, Clonidine, Melatonin, Aripiprazole, Citalopram, Clonidine, and Aripiprazole and Clonidine). At Timepoint 2, three patients had stopped their medication use. Next, 17 control subjects (CS) matched for age and sex with high quality sMRI images (screening was done in the same way as for the patient's sMRI

images) for two consecutive years were included and served as a control group (CS; mean age at Timepoint 1: 14.8 ± 3.2 , range: 9.6 – 21.2, 2 females).

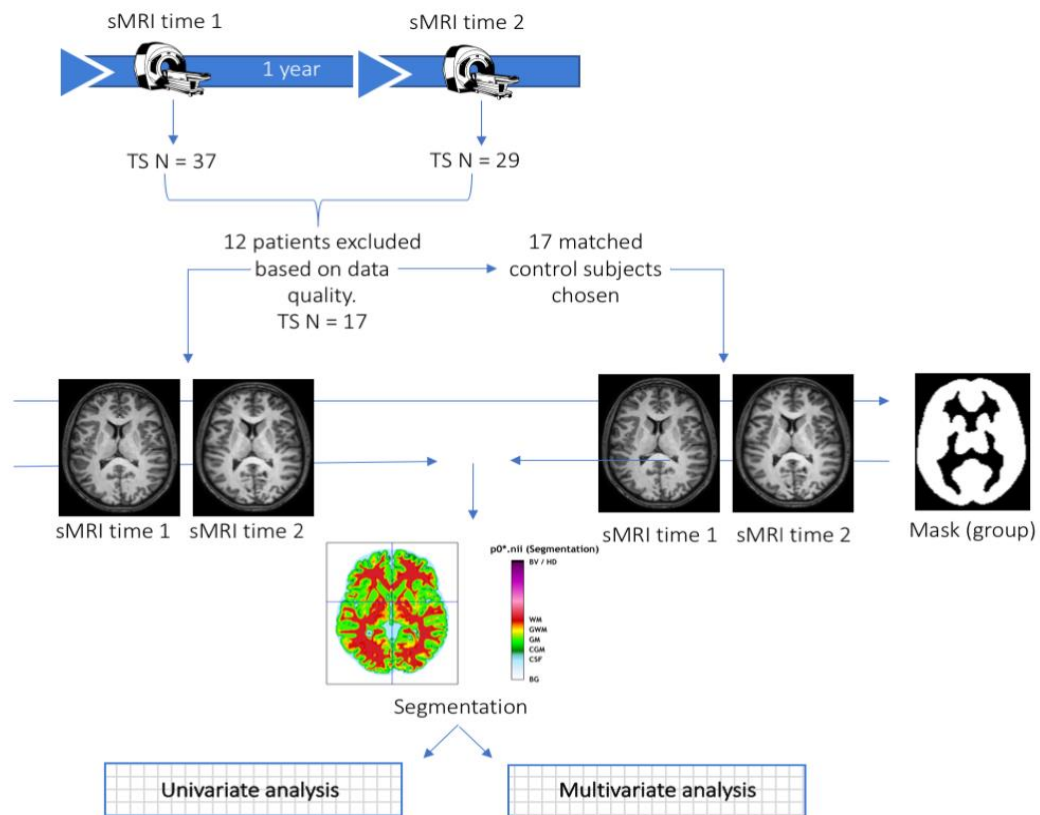


Figure 6.1. Study timeline. 37 patients had structural MR images done at timepoint 1. Twenty-nine patients returned for their appointment at timepoint 2. Based on initial screening, 12 patients had to be excluded. Seventeen healthy controls matched for age and sex were chosen to act as a control group. The sMRI images from both timepoints were preprocessed using the ‘Longitudinal segment’ module as part of CAT12 toolbox (Schrouff et al., 2013). A group mask was also created. The sMRI images were segmented into GM, WM and CSF. Univariate and multivariate analyses were done to assess any TS-related GM change across time.

6.2.1 MR image acquisition

Whole-brain, high-resolution, T1-weighted structural MRI (sMRI) brain images were acquired for each participant on a 3T Philips Achieva MRI scanner using a 32-channel SENSE head-coil and a MPRAGE sequence (180 contiguous axial slices, 8.6 ms repetition time (TR), 4.0 ms echo time (TE), 256 x 224 mm matrix size, 256 x 256 FOV and 1mm^3 isotropic voxel resolution). Prior to acquiring the sMRI scan, participants were asked to

lie as still as possible. Foam padding was added for extra stability, while all participants also wore noise-cancelling headphones.

6.2.1 *Structural MR data analysis*

Post-processing of all sMRI images was accomplished using SPM12 and the proposed pipeline of the 'Longitudinal Segment' module within the CAT12 toolbox. First, structural brain images (in Nifti format) were re-oriented to set the origin lying on the AC-PC line using an automated registration. Successful reorientation was assessed using the 'Display' function in SPM12. Next, all images were re-aligned and a mean image is calculated for each subject. This mean image is then used as a reference image in subsequent realignment. All images are then corrected for signal inhomogeneities with regard to the reference mean image, and segmented into tissue classes: GM, WM and CSF. The normalisation parameters (derived from the mean bias-corrected image) are then applied to the segmented individual timepoints, and resampled to a 1.5 mm standard template (Ashburner, 2007), freely available within the CAT12 toolbox. Finally, I smoothed the segmented GM images using an 8-mm isotropic Gaussian kernel and calculated the total intracranial volume (TIV) and used as a covariate to control for differences in brain volume.

Table 6.2. Patient specific characteristics. Note: T1 = Timepoint 1, T2 = Timepoint 2.

TS ID	Age T1	Age T2	Sex	PUTS T1	PUTS T2	Co- morbidities T1	Co- morbidities T2	Medication T1	Medication T2
TS001	19.3	20.3	M	17	25	None	None	None	None
TS002	17.0	18.0	M	10	9	None	None	None	None
TS003	19.1	20.1	M	16	22	Possible ADHD	Possible OCB, ADHD	Citalopram	None
TS004	15.4	16.6	M	14	18	None	None	Sertraline Haloperidol	None
TS005	14.1	15.1	M	21	18	Possible ADHD	OCD, possible ADHD	Sertraline, Melatonin	None
TS006	15.6	16.8	M	27	16	None	None	Clonidine	None
TS007	15.2	16.2	M	28	19	OCD, possible ADHD and ASD	OCD, possible ADHD	Melatonin	None
TS008	12.1	13.5	M	12	9	None	None	None	None
TS009	13.6	14.6	M	21	21	OCD	OCD	None	None
TS010	16.3	17.2	M	17	20	OCD	OCD	Aripiprazole (5 mg)	Aripiprazole
TS011	21.8	22.8	F	20	33	Possible Asperger's	Possible Asperger's	Citalopram (40 mg)	Citalopram (40 mg)
TS012	13	14.0	M	25	28	Possible OCB and ADHD	Possible OCB, ADHD, ASD	Clonidine	Clonidine
TS013	12.4	13.5	M	31	30	None	Possible ADHD	Aripiprazole, Clonidine	Aripiprazole, Clonidine, Melatonin
TS014	8.6	9.6	M	18	27	None	Possible ADHD	None	None
TS015	9.5	10.5	M	16	20	None	None	None	None
TS016	13.2	14.0	M	18	22	Possible ADHD	Possible ADHD	None	None
TS017	12.2	13.2	M	9	10	Possible ADHD	Possible ADHD	None	None

6.2.2 Statistical analysis

I decided that the simplest way to quantify differences in GM volume was to create difference images for each subject by calculating Timepoint 2 minus Timepoint1 (i.e., Δ in GM volume). Thus, any voxel with a positive value is indicative of increase in GM volume and any voxel with a negative value indicates a decrease in GM volume. Prior I thresholded all images to voxels where GM volume was $> 20\%$. Based on these segmented, normalised difference images I created a group mask (for both groups and TS group only) and this mask was entered as an exclusive mask to include only voxels with sufficient tissue class proportions in all subsequent analyses.

6.2.2.1 Univariate approach

Smoothed difference images were entered into a GLM in SPM12 to assess any group-related differences in GM volume in time. Age at timepoint 1, average TIV $((\text{Timepoint 1} + \text{Timepoint 2})/2)$ and Time (number of days between scans) were de-meaned and entered as variables of no interest. This was done for the following reasons: (1) Age is an important variable in the study of children and adolescents on account that cortical thickness decreases in the typical brain through adolescence (Giorgio et al., 2010), (2) GM volume is influenced by TIV and in the analysis I found that TIV was significantly different between the two groups (see Results section), and finally, (3) Time is entered since time between scans varied between participants and could this have a significant effect (although t-tests show that Time was not significantly different across the two groups, $t(32) = 0.26$, $p\text{-value} = 0.79$), indicating that elapsed time between first scan and second scan was comparable between the two groups.

The resulting statistical parametric maps (t-maps) were thresholded at peak t-value ≥ 3.4 (with 29 degrees of freedom, this t-value roughly corresponds to $p < 0.001$) and corrected for multiple comparison at *voxel-level* with $p\text{-FDR} < 0.05$, and cluster extent at ≥ 50 voxels. If no voxels survived my stringent multiple comparison correction threshold I reverted back to uncorrected $p\text{-value} < 0.001$. Statistical parametric maps were visualized, labelled and corrected for multiple comparison using xjView (<http://www.alivelearn.net/xjview>).

6.2.2.2 *Multivariate approach*

In the context of neuroimaging, conventional univariate statistical methods are performed at each individual voxel in the brain. Multivariate methods, however, consider data from ‘all features’ (i.e., brain regions). Fundamentally, PR techniques are used to detect and learn a classifier by correctly classifying a training dataset to correctly label a dataset deprived of any labels.

Multivariate pattern recognition analyses were completed using Pattern Recognition Toolbox for Neuroimaging (PRoNTo v. 2.0; Schrouff et al., 2013), a user-friendly toolbox running on MATLAB and serves as an interface for LibSVM toolbox. With this method, I asked several questions such as whether a PR technique can discriminate between the two groups based on diagnostic status, which brain regions can lead to best discrimination and whether PR techniques can predict clinical scores (YGTSS and PUTS) based on change in GM volume. To achieve this, I entered the GM difference maps for each subject into the PRoNTo software. Importantly, I entered a group mask which was created using the SPM masking toolbox (Ridgway et al., 2009). SimpleMKL was used as the classification machine, and the procedure here was done according to the example provided in the PRoNTo manual. The machine is implemented in the toolbox and is used here to determine specific regional contribution of brain areas that might have the greatest prediction power to correctly classify a brain. As such, multiple kernels are built based on regions found within the AAL atlas (<http://www.gin.cnrs.fr/AAL-217>). The leave-one-subject-out cross-validation (LOOCV) scheme was used to evaluate performance of the classifier (i.e., one subject is removed while a classifier is trained on the remaining dataset, and then tries to predict correct group label of the removed subject). Statistical significance was estimated using a permutation testing with $N = 1000$ permutations and a p -value < 0.05 .

Finally, to determine if change in GM volume in patients could be used to predict tic severity and urge frequency and severity, I ran a kernel ridge regression (KRR) analysis. KRR is the non-linear form of a regression and prevents overfitting of the data with regularisation, and employs a squared-error loss function (Vu et al., 2015). Here,

one can then assess the correlation between the true and the predicted clinical scores. As before, the LOOVC scheme was used, with the same number of permutations.

6.3 RESULTS

6.3.1 *Data quality*

Quality of the data was assessed using the ‘sample homogeneity’ module within CAT12 toolbox. This quality assessment evaluates correlation between participant sMRI images and displays any potential outliers (data with bad quality). High correlation indicates data homogeneity. Overall the data provided high overall quality with all correlations > 0.82 and mean of 0.855.

6.3.2 *Sample characteristics*

Sample characteristics (age and time between scans) were assessed between groups using two-tailed two-sample t-tests assuming equal variances (see Table 6.3). Age was not significantly different at either Timepoint ($t(32) = -0.22$ and -0.19 , p -value = 0.822 and 0.848). Time in days between scans was not significantly different between the two groups ($t(32) = 0.26$, $p = 0.79$). A two-way repeated measures ANOVA, to assess TIV at both Timepoints, with Time as a within-subject factor and Group as a between-subject factor, showed no main effect of Time ($F(1,32) = 1.308$, p -value = 0.261, partial $\eta^2 = 0.039$ or Time x Group interaction ($F(1,32) = 0.158$, p -value = 0.694, partial $\eta^2 = 0.005$). The test of between-subjects effects showed, however, a significant main effect of Group ($F(1,32) = 5.819$, p -value = 0.022, partial $\eta^2 = 0.154$), indicating that when holding Time constant, TIV is significantly different between the two groups. Differences in TIV has been reported before in boys with TS (Hong et al., 2002) but not in adults (Draganski et al., 2010).

Table 6.3. Sample characteristics. Data is shown as mean (± 1 SD).

Measure	TS		CS	
	<i>T1</i>	<i>T2</i>	<i>T1</i>	<i>T2</i>
Age	14.6 (3.4)	15.7 (3.4)	14.8 (3.2)	15.9 (3.2)
TIV	1590.8 (81.1)	1593.2 (140.1)	1684.0 (141.1)	1690.2 (140.1)
Time [†]	-	370.9 (30.4)	-	367.2 (48.4)

[†]Time as measured in days between timepoints. Abbreviations: T1: Timepoint 1, T2: Timepoint 2, TIV: Total intracranial volume.

6.3.3 Progression of PSP in patients

Frequency of PSP was assessed at both timepoints. In this chapter, my main aim is to attribute change in the frequency of PSP with change in GM volume in patients with TS. Then, I would be able to draw conclusion indicating which and to what extent change in GM volume can be attributed to change in the frequency of PSP.

A two-tailed, paired-samples t-test showed that frequency of PSP did not change significantly between the two timepoints (see Figure 6.2), even though, on average, this frequency increased at follow up (mean Timepoint 1 = 18.8 ± 6.21 , range: 9 – 31; mean Timepoint 2 = 20.41 ± 6.98 , range: 9 – 33, $t(16) = -1.07$, $p = 0.299$). I ran the same analysis on the tic severity measure (YGSS) and found that there was a non-significant trend for a decrease in severity between T1 and T2 (mean T1: 38.29 ± 21.9 , range: 9-31, mean T2: 31.94 ± 6.98 , range = 9-33, $t(16) = 1.63$, $p = 0.061$).

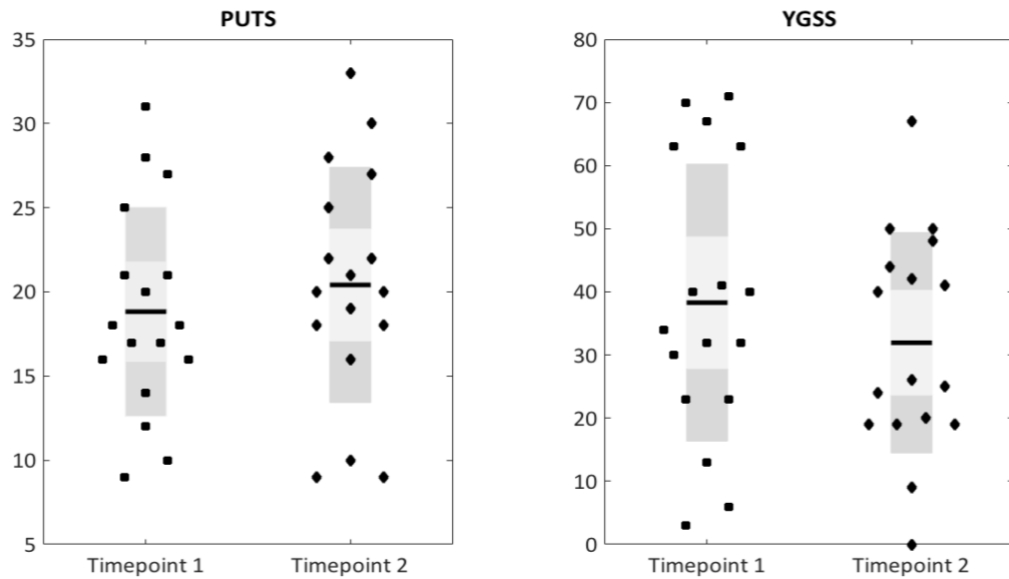


Figure 6.2. Progression of PUTS and YGSS scores between the two timepoints. Light grey box = standard deviation, dark grey box = 95% standard error of the mean, black line = mean.

6.3.4 Between group comparison on change in GM volume

My univariate, voxel-wise exploratory comparison of change in GM volume in time using the T2-T1 difference images resulted in six clusters showing significantly enhanced GM volume in patients with TS (TS>CS [1 -1 contrast]), reaching statistical significance at uncorrected voxelwise threshold of $p < 0.001$ (see Figure 6.3 and Table 6.4), but not surviving a stringent multiple comparison correction (FDR). Clusters were labelled according to AAL atlas (<http://www.gin.cnrs.fr/en/tools/aal-aal2/>). Primarily, these clusters were located in the frontal cortex, insular cortex, parietal lobe and cerebellum.

Table 6.4. Results on the comparison in change in GM volume between TS and CS. Table shows results for the TS > CS and CS > TS results. Each cluster is labelled in the AAL column, coordinates in MNI space are reported in the MNI column, number of voxels for each cluster, peak t and the hemisphere are also shown.

Contrast	MNI			# voxels	Peak t	Hemisphere	AAL
	x	y	z				
TS > CS	37.5	36	-21	144	4.81	R	IFG
	-36	13.5	-9	194	4.49	L	Insular cortex
	-43.5	-7.5	-10.5	61	4.23	L	STG
	-24	25.5	36	68	4.05	L	MFG
	-7.5	-9	36	58	4.05	L	Mid cingulum
	22.5	9	46.5	66	4.57	R	SFG
CS > TS	-25.5	-48	-30	314	4.64	L	Anterior cerebellum

Abbreviations: IFG (inferior frontal gyrus); STG (superior temporal gyrus); MFG (middle frontal gyrus); SFG (superior frontal gyrus). The cluster for the anterior cerebellar lobe was found to lie in area IV.

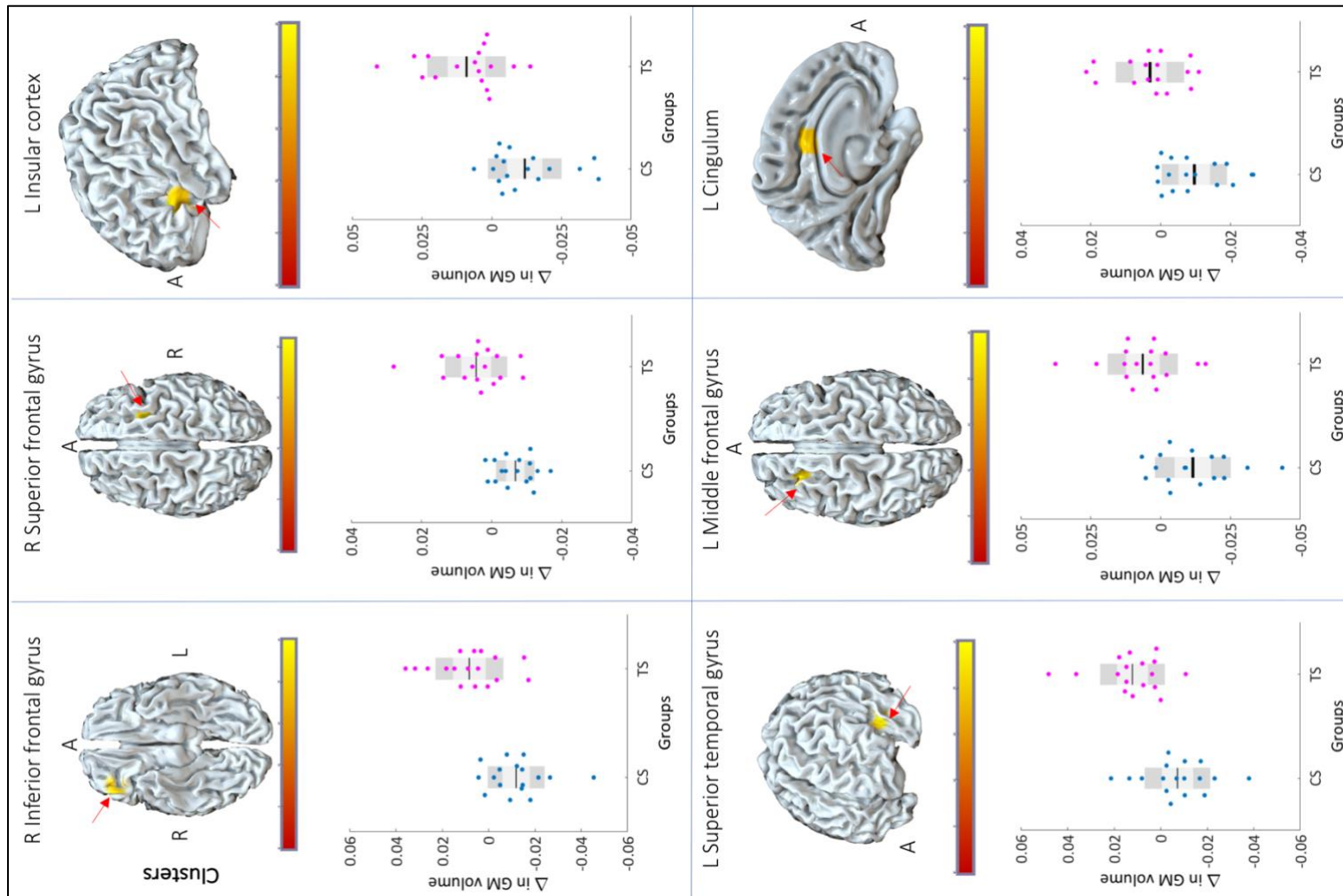


Figure 6.3. Regions showing increased grey matter volume in patients with TS. The first and third panels depict t-maps projected onto a template brain showing brain areas significantly difference across groups at uncorrected $p < 0.001$. The second and fourth panels depict individual change in GM volume (based on T2-T1 difference maps) per group (magenta: TS, blue: CS). Light grey box = standard deviation, dark grey box = 95% standard error of the mean, black line = mean, CS = control subjects, TS = Tourette syndrome. Colorbar shows the t-value.

The increase of GM volume in these 6 clusters in patients with TS, was paralleled by a significant decrease in the anterior left cerebellar lobe, at an uncorrected $p < 0.001$, but not surviving an FDR correction (see Figure 6.4 and Table 6.4).

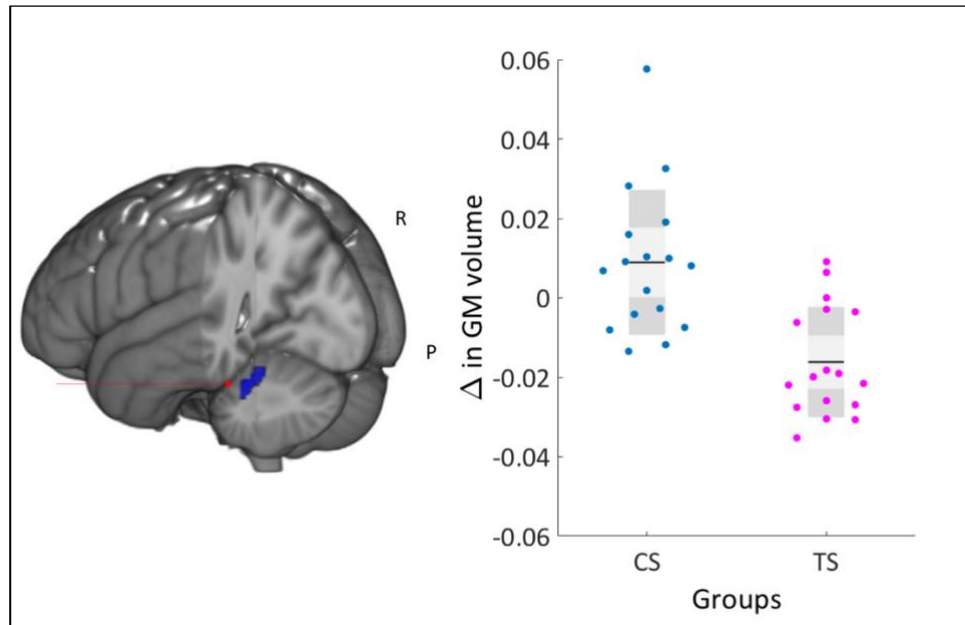


Figure 6.4. A region of the left anterior cerebellar lobe showing significant group difference. Left: A t-map projected onto a template brain showing area of significantly decreased GM volume in TS patients (based on T2-T1 difference maps). Right: Individual change in GM volume in the region (magenta: TS, blue: CS).

To determine the influence of my covariates (TIV, Age and Time between scans) in my univariate analysis, I ran a multiple linear regression on each cluster separately. First, I extracted the raw values for each participant using REX toolbox. I then entered Group (dummy coded as 1s and 2s), de-meaned Age, TIV and Time as predictors. Cluster was entered as a dependent variable. Results are shown in Table 6.5. In all models, Cook's d was < 1 indicating no overly influential on the model's ability to predict all cases. Similarly, collinearity statistics were always in the normal range ($Tolerance < 10$ and $VIF \cong 1$). None of the predictors are significant except for *Group*, for all clusters evaluated: R IFG ($F(4, 29) = 6.02$, $p = 0.001$, DW-test = 2.22), R SFG ($F(4, 29) = 6.27$, $p = 0.001$, DW = 2.39), L Insular cortex ($F(4, 29) = 5.54$, $p = 0.002$, DW = 2.26), L STG ($F(4, 29) = 5.32$, $p = 0.002$, DW = 2.0), L MFG ($F(4, 29) = 4.65$, $p = 0.005$, DW = 2.4), L Cingulum ($F(4, 29) = 4.70$, $p = 0.005$, DW 1.85), L cerebellum ($F(4, 29) = 5.15$, $p = 0.003$, DW 2.22).

Table 6.5. Multiple linear regression on significant between-group clusters on change in GM volume with covariates as predictors.

Cluster	Predictors	B	SE	Beta	<i>t</i>	<i>p</i>
R IFG	Constant	-0.032	0.007	-	-4.48	< 0.001
	Group	0.02	0.005	0.61	4.46	< 0.001
	Age	-9.46E-5	0.001	-0.02	-0.013	0.90
	TIV	-4.30E-5	0.000	-0.29	-1.91	0.07
	Time	4.42E-6	0.000	0.01	0.07	0.94
R SFG	Constant	-0.02	0.004	-	-4.61	< 0.001
	Group	0.01	0.002	0.62	4.54	< 0.001
	Age	-0.001	0.00	-0.25	-1.72	0.09
	TIV	-2.0E-5	0.00	-0.25	-1.65	0.11
	Time	3.39E-5	0.00	0.15	1.02	0.31
L Insula	Constant	-0.03	0.007	-	-4.40	< 0.001
	Group	0.02	0.005	0.62	4.44	< 0.001
	Age	-0.00	0.001	-0.11	-0.70	0.49
	TIV	-2.65E-5	0.000	-0.18	-1.13	0.27
	Time	8.48E-5	0.000	0.20	1.34	0.19
L STG	Constant	-0.03	0.007	-	-3.59	0.001
	Group	0.02	0.005	0.58	4.13	< 0.001
	Age	-0.001	0.001	-0.21	-1.36	0.18
	TIV	-8.0E-6	0.000	-0.05	-0.34	0.73
	Time	0.000	0.000	0.25	1.65	0.11
L MFG	Constant	-0.03	0.007	-	-4.15	< 0.001
	Group	0.02	0.004	0.58	3.99	< 0.001
	Age	0.00	0.001	0.10	0.63	0.53
	TIV	-1.8E-5	0.000	-0.13	-0.81	0.43
	Time	6.95E-5	0.000	0.18	1.15	0.26
L Cingulum	Constant	-0.02	0.005	-	-4.35	< 0.001
	Group	0.01	0.003	0.57	3.91	0.001
	Age	0.000	0.001	0.09	0.55	0.58
	TIV	-1.56E-5	0.000	-0.16	-0.96	0.34
	Time	6.33E-5	0.000	0.22	1.45	0.16
L Cerebellum (area 6)	Constant	0.03	0.009	-	3.78	0.001
	Group	-0.03	0.006	-0.63	-4.40	< 0.001
	Age	0.000	0.001	-0.07	-0.43	0.67
	TIV	1.86E-5	0.000	0.10	0.66	0.52
	Time	-5.14E-5	0.000	-0.100	-0.67	0.51

Abbreviations: IFG = Inferior frontal gyrus, SFG = superior frontal gyrus, STG = superior temporal gyrus, MFG = medial frontal gyrus.

Figure 6.5 also gives better picture of the change in GM volume as a function of age for both groups. The figure demonstrates a trend for both groups to show a decrease in GM volume in frontal, insular and cingulum cortices with age at T1. In all clusters, however, there is a progressive increase in GM in patients while we observe a parallel decrease in the CS group.

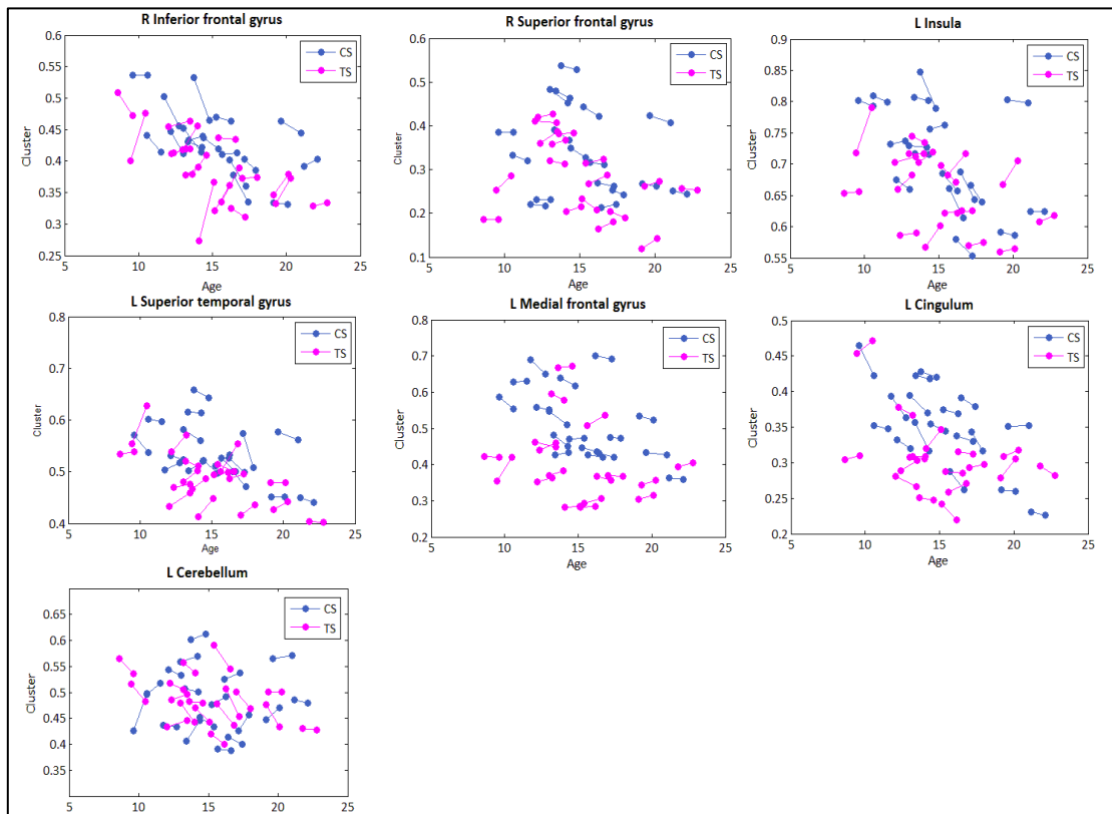


Figure 6.5. Change in GM volume as function of age in the TS and CS groups. Each participant is plotted twice in either blue (CS) or magenta (TS) circles connected with a line to represent the increase/decrease in GM volume after 1 year. Note: Cluster values are uncorrected for TIV.

6.3.5 ROI correlation analysis with clinical measures

To determine if any of the differences in GM volume could be attributed to clinical measures (urge and tic severity), I ran a correlation analysis using the Pearson correlation coefficient (Pearson's r). To avoid spurious and potential false positive correlations, I based my analysis on the significant between-group comparison contrast results using the corrected GM difference values (i.e., corrected for Age, TIV and Time). As such, the resulting residuals, per cluster, are values that cannot be accounted for by

these three predictors. I assessed the correlation in change in GM volume with clinical measures measured at T1, T2 and the change in tic or urge severity scores (T2-T1). Correlation coefficients are reported uncorrected for multiple comparison unless otherwise stated.

Overall, I found no significant correlations between residualised change in GM volume in patients and PUTS scores at T1 (max $r = 0.22$, $p = 0.4$), T2 (max $r = 0.36$, $p = 0.15$ or the change in PUTS scores (max $r = 0.35$, $p = 0.17$; See Table 6.6).

Table 6.6. Correlation between change in GM and PUTS scores.

<i>Cluster</i>	PUTS T1		PUTS T2		Change in PUTS	
	<i>Pearson R</i>	<i>p-value</i>	<i>Pearson R</i>	<i>p-value</i>	<i>Pearson R</i>	<i>p-value</i>
R IFG	0.22	0.40	-0.07	0.78	-0.31	0.23
R SFG	-0.01	0.96	0.29	0.25	0.35	0.17
L Insula	-0.16	0.54	-0.04	0.86	0.11	0.67
L STG	-0.05	0.85	-0.14	0.59	-0.11	0.66
L MFG	0.19	0.45	0.36	0.15	0.22	0.40
L Cingulum	-0.12	0.63	0.02	0.95	0.15	0.58
L cerebellum	0.18	0.50	0.22	0.39	0.08	0.77

Again, using the Yale tic severity scores, I found no significant correlation with residualised change in GM volume in patients. The R IFG did, however, show significant correlation with the change in YGSS but this became non-significant when corrected for multiple comparison (see Table 6.7).

Table 6.7. Correlation between change in GM and tic severity.

Cluster	YGSS T1		YGSS T2		Change in YGSS	
	Pearson <i>R</i>	<i>p</i> -value	Pearson <i>R</i>	<i>p</i> -value	Pearson <i>R</i>	<i>p</i> -value
R IFG	0.46	0.06	0.09	0.73	-0.54	0.026
R SFG	0.11	0.67	0.20	0.45	0.06	0.82
L Insula	0.19	0.47	0.12	0.64	-0.12	0.64
L STG	0.33	0.19	0.23	0.38	-0.21	0.43
L MFG	0.44	0.08	0.28	0.27	-0.29	0.26
L Cingulum	0.27	0.30	0.37	0.16	0.03	0.90
L cerebellum	-0.16	0.54	-0.29	0.26	-0.09	0.73

Next, I correlated the residualised change in GM volume with the Yale motor tic scores (see Table Table 6.8). There was a significant positive correlation between Yale motor T1 and R IFG ($r = 0.62$, $p = 0.009$), Yale motor T1 and L STG ($r = 0.50$, $p = 0.04$), Yale motor T1 and L MFG ($r = 0.56$, $p = 0.02$), and change in motor tic scores and R IFG ($r = 0.57$, $p = 0.017$). When corrected for multiple comparison using FDR correction none of the above-mentioned relationships survived at $p\text{-FDR} < 0.05$.

Table 6.8. Correlation between change in GM volume and motor tic scores.

Cluster	Yale motor T1		Yale motor T2		Change in motor tic scores	
	Pearson <i>R</i>	<i>p</i> -value	Pearson <i>R</i>	<i>p</i> -value	Pearson <i>R</i>	<i>p</i> -value
R IFG	0.62	0.009	0.21	0.43	0.57	0.017
R SFG	0.24	0.36	0.19	0.44	0.08	0.75
L Insula	0.36	0.16	-0.18	0.48	0.26	0.31
L STG	0.50	0.04	0.31	0.23	0.31	0.23
L MFG	0.56	0.02	0.40	0.11	0.27	0.29
L Cingulum	0.44	0.08	0.30	0.24	0.25	0.39
L cerebellum	-0.16	0.55	-0.25	0.32	0.09	0.74

Finally, I assessed the relationship between Yale phonic tic scores at T1, T2 and change in phonic tic scores and the residualised change in GM volume. There was a significant positive correlation between the Yale phonic T1 and R IFG ($r = 0.59$, $p = 0.01$) and change in phonic tic scores and R IFG ($r = -0.53$, $p = 0.03$). Again, however, these became non-significant following a multiple comparison correction at $p\text{-FDR} < 0.05$ (see Table 6.9).

Table 6.9. Correlation between change in GM volume and vocal tics scores.

<i>Cluster</i>	Yale vocal T1		Yale vocal T2		Change in vocal tic scores	
	<i>Pearson R</i>	<i>p-value</i>	<i>Pearson R</i>	<i>p-value</i>	<i>Pearson R</i>	<i>p-value</i>
R IFG	0.59	0.01	0.13	0.61	-0.53	0.03
R SFG	0.07	0.80	0.04	0.89	-0.04	0.87
L Insula	0.28	0.28	0.11	0.67	-0.21	0.43
L STG	0.48	0.05	0.22	0.39	-0.34	0.19
L MFG	0.48	0.05	0.30	0.25	-0.26	0.35
L Cingulum	0.31	0.22	0.19	0.45	-0.17	0.51
L cerebellum	-0.24	0.35	-0.35	0.16	-0.05	0.84

6.3.6 Multivariate pattern recognition

Using pattern recognition (PR) techniques and multiple-kernel learning (MKL) I attempted to classify individual subject's brain image according to diagnostic status using the GM volume difference maps (i.e., T2-T1). The results showed that based on change in GM volume, the PR technique was unsuccessful in accurately classifying individual brain according to diagnostic status (total accuracy = 56%, specificity = 65%, sensitivity = 47%, $p = 0.25$, 0.14 and 0.59, respectively, see Figure 6.6 depicting the results).

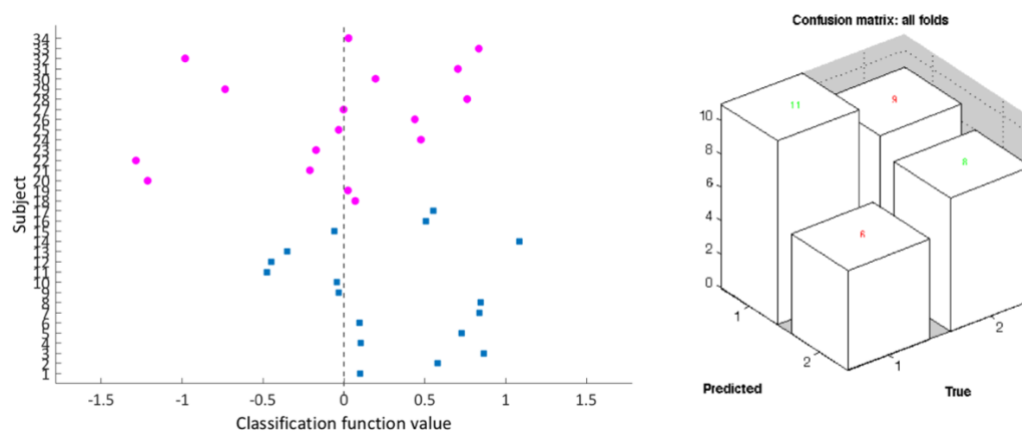


Figure 6.6. Results of the pattern recognition analysis. Left: The prediction plot for classification. The dotted line represents the decision threshold. When a classifier is well defined it will produce very different function values for samples of different classes. Function values are plotted for each fold (here for each subject). Right: The confusion matrix showing counts of predicted class labels and displays the predicted class against the true class.

The classifier weight map is an important aspect of PR. This map illustrates areas of the brain which contribute to the ability of the machine to classify a brain correctly. Even though the classification accuracy was not significant, the classifier weight map highlighted four areas: the left middle frontal gyrus (19.6%), right postcentral gyrus (18.6%), left insular cortex (15.7%) and left Cerebellum 6 (14.3%), which together contributed to over 50% of the decision function. It is imperative to emphasise that classifier weight maps should not be interpreted as statistical tests. Rather, these maps only provide a weight specifying to what extent a brain area can discriminate between the groups (Schrouff et al., 2013). Interestingly, areas highlighted by the multivariate analysis overlap well with the results from the univariate analysis (Figure 6.7), but provide a clearer picture of potential neuroimaging biomarkers and TS-related GM atrophy.

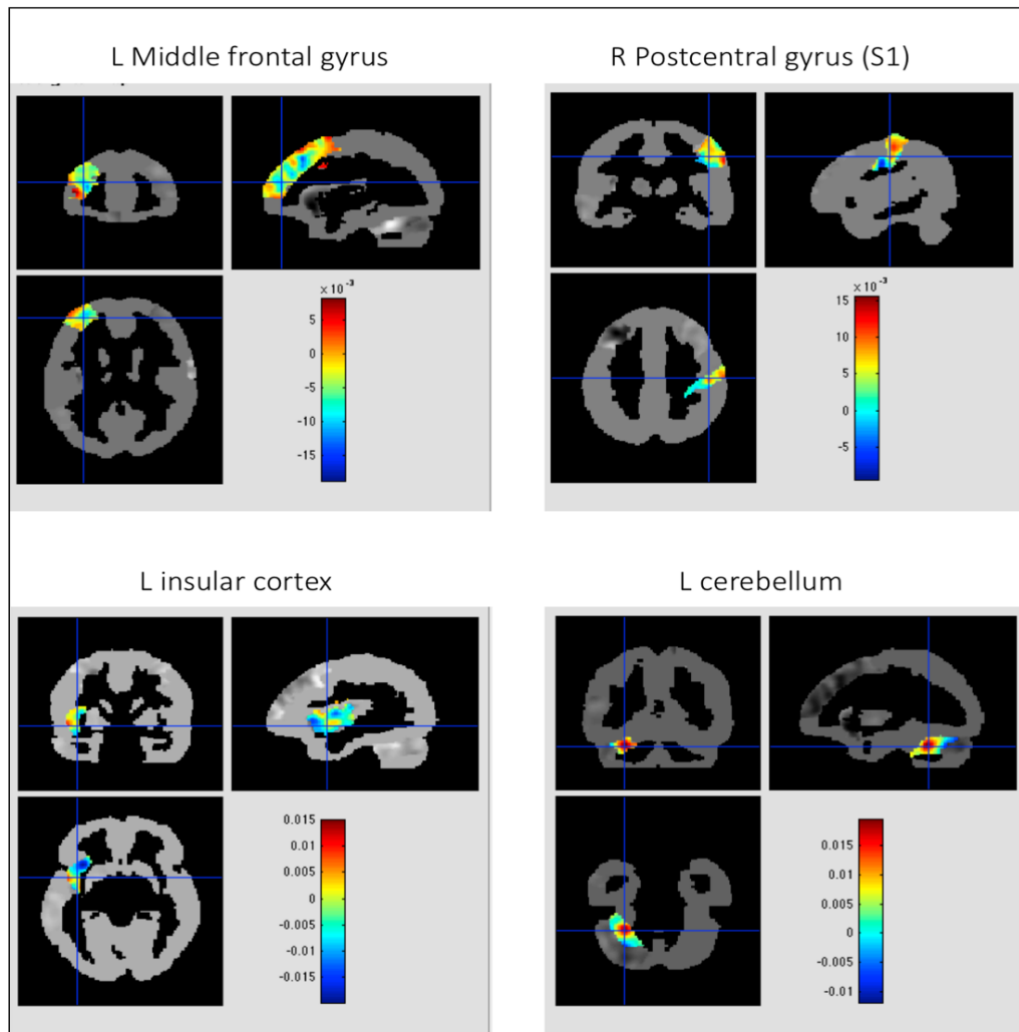


Figure 6.7. Brain areas showing the highest classification accuracy, predicting individual subject's group label. The colorbar represents the relative importance of the voxel in the decision function.

6.3.7 Multivariate regression analysis

Using KRR, I assessed if changes in GM volume (entering difference maps) can significantly predict the clinical course of PSP and tic severity. As such, changes in PUTS and YGSS scores, and scores at T2 were entered with the difference maps into the PR algorithm and the correlation between true and predicted clinical scores were examined. Results are depicted in Figure 6.8.

This analysis demonstrated that change in PUTS scores could not be significantly predicted by change in GM volume ($r = -0.15$, $p = 0.46$, $R^2 = 0.02$, normalised mean

square error (nMSE) = 1.94). Change in GM volume could also not significantly predict PUTS scores at T2 ($r = 0.07$, $p = 0.24$, $R^2 = 0.01$, nMSE = 2.38). When using change in GM volume, there was a near significant correlation with change in Yale severity (YGSS) scores ($r = 0.25$, $p = 0.097$, $R^2 = 0.06$, nMSE = 3.49). Finally, change in GM volume could not significantly predict tic severity scores at T2 ($r = -0.43$, $p = 0.78$, $R^2 = 0.19$, nMSE = 6.13). These results are in line with my univariate results showing no relationship between the significant between-group clusters and clinical measures.

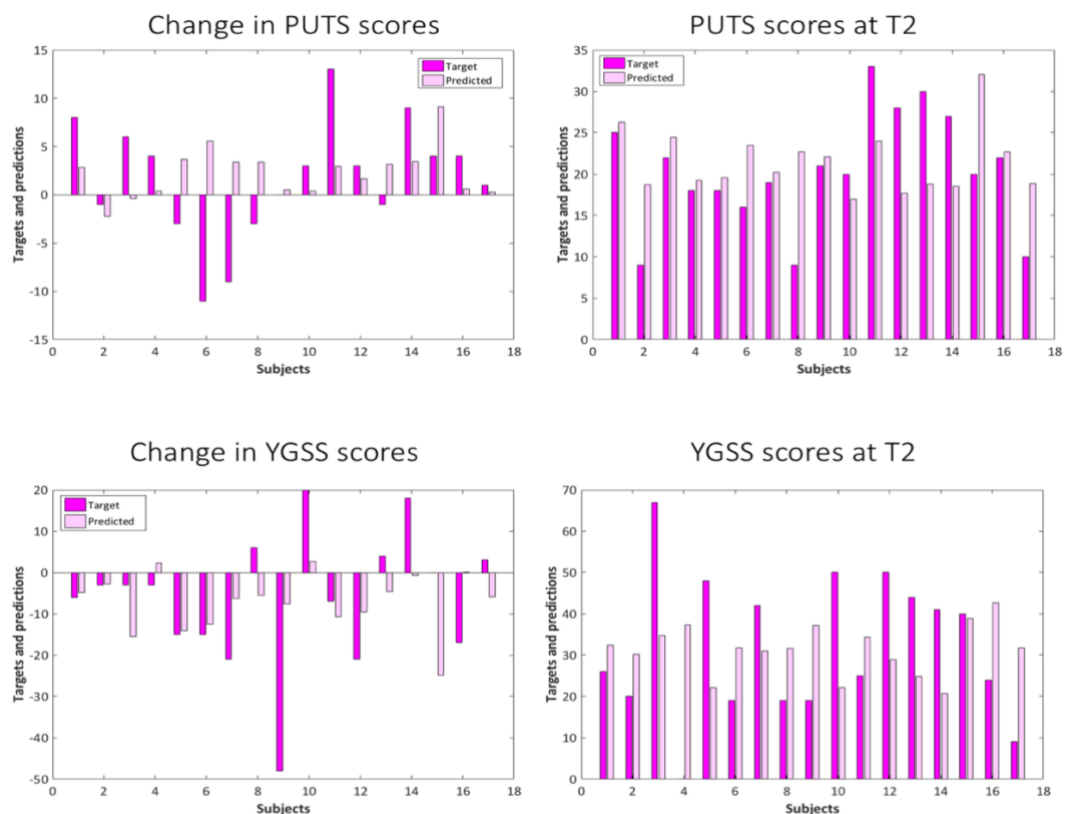


Figure 6.8. Kernel ridge regression (multivariate prediction) of clinical measures in patients with TS based on change in GM volume. Top left: Change in PUTS scores. Top right: PUTS scores at T2. Bottom left: Change in tic severity scores. Bottom right: YGSS scores at T2.

6.4 DISCUSSION

In this study, I presented for the first time in young patients with TS, a longitudinal, prospective brain imaging study, investigating the long-term effects of having TS on GM volume, in comparison to a group of typically developing individuals. I also explored the relationship between change in GM volume and clinical measures such as tic severity

and PSP severity and frequency. I employed both a mass-univariate, explorative and multivariate pattern recognition (machine learning) methods. The main results of this study were: (1) Frequency and severity of PSP increased between timepoints, non-significantly while there was a trend for a significant decrease in tic severity, (2) the univariate approach showed that patients with TS show region specific hypertrophy in GM volume, specifically in the frontal and limbic areas, while significant atrophy was apparent in the left cerebellum, (3) correlation analysis signified that these GM changes are non-specific to sensory urges or tic severity, finally (4) the PR method performed at approximately guess rate, but showed that the most discriminant regions corresponded well to results from the univariate analysis. Below I will discuss these results in detail and wonder if these GM changes can be attributed to a 'developmental delay' or compensatory adaptation mechanisms.

6.4.1 Progression of symptom severity

In my sample, 10 patients reported more or stronger PSP at Timepoint 2 compared to Timepoint 1 (see Figure 6.2) while 7 patients reported a decrease in their PSP between Timepoints. Conversely, 5 patients reported increased tic severity at T2, while symptom severity seems to decrease in majority of patients. This is in line with the work of Bloch and colleagues (2005) and Debes and colleagues (2015). Both noted a significant decrease in tic severity at follow-up compared to baseline. Interestingly, in both studies, much longer time had elapsed between measurements (7.7 and 4.4 years, respectively) than in the current study, where measurements were taken approximately 1 year apart. This corresponds well with the widely known fact that tic severity decreases as the patient grows older, but this is the first time a study has empirically shown that severity and frequency of PSP increase (about 1.6 points) between measurements. In a large prospective study of 1032 patients in Germany found an increase in the prevalence of PSP with age, as well as the ability to inhibit tics (Sambrani, Jakubovski, & Müller-Vahl, 2016). Further longitudinal studies with more timepoints are needed to further investigate this and perhaps use more comprehensive measurements of sensory phenomena in TS than the PUTS scale.

6.4.2 *Greater change in GM volume in TS*

In this study, patients with TS demonstrated hypertrophy of GM volume in several areas of the brain encompassing the frontal, temporal and limbic lobes and GM atrophy in the cerebellum in comparison to a group of matched, typically developing individuals. This subsection starts by comparing the current study with the two previous longitudinal studies in TS. Then I review the results from the univariate and multivariate analyses focusing on (1) frontal and temporal areas, (2) limbic areas, and (3) the cerebellum.

6.4.2.1 *Frontal and temporal lobe*

Patients with TS showed a significant hypertrophy of right IFG and SFG, and left STG and MFG. The left MFG was also highlighted by the multivariate PR analysis as an area that contributed highly to the decision function whether a brain belonged to the TS or CS groups.

Several studies have reported altered brain structure in patients with TS. Muellner and colleagues (2015) used a novel design of measuring cortical sulci depth, length, folding and thickness in adult patients with TS. Results from this study showed a substantially shallower sulci formation and reduced GM in several areas of the brain in TS, including the pre- and postcentral cortices. Reductions in GM were also noted in the inferior and superior frontal sulci (Muellner et al., 2015). In adults, Worbe and colleagues (2010) also reported reduced cortical thickness of motor and premotor cortices. Moreover, the extent and distribution of the thinning differed between patients with simple and complex tics (Worbe, Gerardin, et al., 2010). In very young patients, Liu et al. (2013) showed altered brain volume in patients in several areas such as the left STG. Finally, in one study with a large cohort of participants demonstrated larger prefrontal volumes in children with TS and a parallel smaller premotor and orbitofrontal volumes in boys with TS (Peterson, Staib, et al., 2001). In the same study, the dorsal prefrontal volume appeared larger in childhood which then decreased linearly with age (Peterson, Staib, et al., 2001). Furthermore, worst ever tic severity was inversely related to the volume of the orbitofrontal region. These results are in contrast

to what I have presented here, where I found an enhanced volume of the right IFG after 1 year. Investigating Figure 6.3 more closely one can see this area corresponds well with the OFC.

The superior, middle and inferior frontal gyri are separated by the superior and inferior frontal sulci. The right IFG has been shown to play a significant role in motor control and is part of the neural network thought to be involved in response inhibition (Aron, Robbins, & Poldrack, 2004). Importantly, this network is considered to be right lateralised and encompasses, in addition to the IFG, the SMA and preSMA, M1, STN and the striatum. It has been suggested that dysfunction of the IFG results in motor impulsivity (Aron et al., 2004).

The right SFG (more specifically in my study the enhancement can be specifically localised to the dorsomedial prefrontal cortex [dmPFC]) has been shown to be important for behavioural inhibition, specifically when needed to suppress temporally inappropriate response (de Wit, 2006; Narayanan & Laubach, 2006). In TS, volume of the SFG has been associated with symptoms of OCB (Worbe, Gerardin, et al. 2010). Several participants in my study had a confirmed diagnosis of OCD or suspected/probable OCB's and this could explain my observation of enhanced GM volume in the STG. The MFG has been suggested to play a role in cognitive control (Wig, Schlaggar, & Petersen, 2011). In the realm of TS, the left MFG was shown to activate in a patient performing unsuppressed phonic tics and in a control subject who mimicked the same behaviour (Gates et al., 2004). Lastly, the STG, has been implicated in the associative circuit, which is thought to be critical for the 'selection of action' (G. E. Alexander et al., 1986; Tremblay et al., 2015). This area is involved in the 'associative' circuit and might be more related to the complexity of tics, or comorbid ADHD (Tremblay et al., 2015).

Of the three frontal regions that showed significantly enhanced volume in TS, the IFG has been widely reported in the literature and the orbitofrontal region has been consistently implicated in the pathology of TS (Peterson, Staib, et al., 2001; Weeks, Turjanski, & Brooks, 1996). In a recent fMRI study in uncomplicated adult patients, the left IFG demonstrated increased regional homogeneity during tic inhibition in comparison to a 'free-to-tic' condition (Ganos, Kahl, et al., 2014), suggesting that the

left IFG might be important for inhibiting the unwanted behavioural response (i.e., the tic). Similarly, reduced GM volume of the right IFG was reported in a similar sample of patients (Ganos, Kühn, et al., 2014). Interestingly, one recent study involving a large cohort of young patients with TS observed a reduced volume of WM in the orbitofrontal cortex (Greene et al., 2017). In comparison to results of the current study (increased GM volume), the results by Greene, et al. showing decreased WM volume of the OFC is in direct contrast to the normal developmental trajectories seen in typically developing individuals (Paus, 2005). This might indicate some sort of adaptive mechanisms where WM is reduced in TS and consequently GM volume appears greater in TS compared to control. In support, Marsh, et al. (2009) postulated whether patients with TS display inappropriate increase in GM volume and if this might be associated with a reduction in tic severity. The results I have presented here might support this theory since I find: (1) a significantly enhanced GM volume of the right IFG between timepoints and (2) a trend for an inverse association between this enhancement and change in tic severity scores (see Table 6.7). To put differently, when tic severity scores decrease with time we observe a non-significant trend of increased GM volume of the right IFG. And so, GM volume enhancement of those areas could be the result of the constant attempt to gain control of their tics through tic suppression. Suggesting that the observed enhancement of GM in frontal areas is indicative of compensatory mechanisms. Obviously, these are simply hypotheses and a more comprehensive and detailed longitudinal study with more timepoints will shed light on this.

6.4.2.2 Insula and cingulate

In addition to enhanced GM volume of frontal and temporal areas, there was also increased GM volume in the left insula and cingulum. The left insula was also highlighted by the multivariate analysis, contributing strongly to the decision function.

These results correspond well to findings presented in the previous chapter showing the importance of the insular cortex in maintaining effective communication in a network and the relationship between efficiency of the network and clinically measured PSP reported by patients. In the present study, however, neither area was related to either clinical measure used in this study. Closer inspection of Figure 6.3.

shows that the cluster of significantly enhanced GM in TS is located in the mid-cingulum.

Two studies have previously demonstrated a significant association between GM volume or thickness and the frequency and severity of PSP in patients. First, Draganski, et al. (2010) reported that PUTS scores were positively correlated with GM volume and thickness in the left somatosensory and dorsal premotor cortex, and the right prefrontal cortex in adult patients. The authors postulated whether this might indicate ongoing neural plasticity of those areas. Second, Draper and colleagues (2015) reported a negative correlation between right insula and SM cortex thickness and PUTS scores in children and adolescents. Furthermore, the authors also showed reduced GM thickness of the SM cortex, insula and cingulate cortices in patients with TS compared to a group of matched control participants. The authors suggest that these areas might be responsible for the uncomfortable sensations which are reported by patients to accompany the urge to tic, which is also in line with results of other studies (e.g., Bohlhalter et al., 2006). As such, enhanced GM volume in patients might be driven by both abnormal intake of sensory information and enhanced processing of bodily states (Craig, 2002; Critchley et al., 2004; S. R. Jackson, Parkinson, Kim, et al., 2011).

Altered processing of sensory information, both externally and internally, might also drive changes in GM volume in the cingulum. The cingulum has been associated with the weighting of the importance of incoming external stimulation and formulating the appropriate emotional response (Devinsky, Morrell, & Vogt, 1995; Weeks et al., 1996). Weeks (1996) argued that the cingulum might be an area of interest in the pathology of TS. Interest in the cingulate cortex comes mainly from studies showing that electrical stimulation of the cingulate cortex can produce stereotyped involuntary movements and the movement was a reaction to a sensory feeling (Weeks et al., 1996). Furthermore, aberrant activity of the anterior and posterior cingulate regions produces tic-like movements and hyperactivity like state in non-human primates (Worbe et al., 2013).

6.4.2.3 *Cerebellum*

Lastly, I found a significantly decreased GM volume of area 6 of the cerebellar lobe in patients between timepoints. The cerebellum plays a significant role in motor control but was also recently shown to have a significant role in the acquisition of visuomotor learning during an adaptation task (Galea, Vazquez, Pasricha, Orban De Xivry, & Celnik, 2011). Some have also suggested that hyperkinetic movement disorders are not only affected by the cortico-striatal circuits but also cortico-cerebellar circuits (Hayhow et al., 2013; Patel et al., 2014). The cortico-cerebellar circuits involve the frontal cortex, pontine nuclei in the brainstem, the cerebellar cortex and associated nuclei, the ventrolateral thalamic nucleus and the motor cortex (Ramnani, 2006).

As noted in Chapter 1, several studies have implicated the cerebellar cortex in the pathology of TS. Volumetric, ligand tracing and functional imaging studies have demonstrated this. It is perhaps of most interest to note the work of Lerner and others (2007), who observed significant activations of the cerebellum (primarily area 6), insula, thalamus and putamen during tic release. Suggesting that metabolic demand of these areas is associated with tics and in the elimination of the PSP. Two studies on TS patients have focused on the volumetric properties of the cerebellum. In an early study of 19 boys with TS (mean age 9.8) showed no volumetric differences of the cerebellar GM volume in either right or left hemisphere (Hong et al., 2002). In a more comprehensive study, focusing solely on the cerebellum, including 278 participants, of which 139 had TS (98 were younger than 13 years of age), showed specific GM reductions in several sections of the cerebellum in patients, including area 6 bilaterally (Tobe et al., 2010). This study also reported a trend for this reduction to be more pronounced in children, albeit not reaching the traditional statistical threshold. The authors also noted that greater reduction of area 6 of the cerebellar lobe was associated with greater tic severity, specifically vocal tics (Tobe et al., 2010). My results only support these previous results of the cerebellar volume in TS since I was not able to relate the volumetric reduction over time in TS with any clinical measure (tic severity or severity and frequency of PSP).

6.4.3 *Machine learning results*

In addition to analysing change in GM volume using a univariate approach, the data was also subjected to a PR method, where a group label of one participant during each fold is obscured and the machine makes a best guess if the brain belongs to the TS or CS groups after training on the remaining dataset. The MKL machine was able to predict change in GM volume with maximum accuracy of 56%, near guess rate. In spite of the inability of the machine of correctly classifying a brain belonging to either group, four GM areas contributed to ~50% of the decision function. This means that not all areas are predictive of diagnostic status, rather the left MFG, left insula, left cerebellum and right postcentral gyrus (S1) are those areas that the PR method recognised as being mostly different between the two groups. These areas are in good agreement to what has previously been reported by studies employing machine learning algorithms in TS (see Table 6.1 for an overview of all studies to date).

These areas, specifically the MFG, insula and cerebellum, overlap with the univariate results, while the right precentral gyrus is concordant with several previous volumetric studies in TS (Sowell et al., 2008). Cortical thinning has previously been reported in children with TS, where tic severity was also found to be inversely related to cortical thinning of the S1 (Fahim et al., 2010; Sowell et al., 2008). The inability of the PR method to correctly classify individual brain according to diagnostic status and only achieving a slightly-above guess-rate accuracy of 56% is in contrast to the previously published results using machine learning algorithms. Specifically, past studies have demonstrated 74% or higher classification accuracy. In 42 young children with TS, and resting-state functional connectivity is used as features, the machine achieved an accuracy of 74% (Greene et al., 2016). Resting-state functional connectivity is subjected to noisy and spurious connections, which could be attributed to subtle micro head movements (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), and thus there is a high possibility of false positive connections. The authors did however correct for these micromovements using 'scrubbing' measures which should give adequate control over such artefacts (Greene et al., 2016). More recently, Wen and colleagues (2017) used the combination of sMRI and DTI to predict group labels in 85 very young participants (44 of which had TS). The machine gained a classification accuracy of 94%. These two

studies suggest that the inability of the PR method in this study to significantly classify changes of GM correctly might be due to the lack of statistical power which can be attributed to the limited sample size of 17 subjects in each group.

In addition to attempting to correctly predict group label, I also tested the ability of the machine to correctly predict the progression of tic severity and the severity and frequency of PSP in patients only. Overall, the method was unable to predict symptom progression based on the change in GM volume. This is in line with the work of Greene and colleagues (2016) who used support vector regression to predict clinical tic severity. In line with their interpretation, change in GM volume might not possess the necessary information to capture the disease progression with respect to severity and frequency of tics or PSP.

6.4.4 Does TS follow the normal developmental trajectory?

As mentioned previously, my results could indicate either that patients with TS demonstrate developmental delay or altered GM volume due to compensatory adaptation mechanisms. According to the seminal work done by Giedd and colleagues (1999), there are quadratic effects of age observed in frontal, parietal and temporal GM volume. In the frontal and parietal cortices, peak GM volume is achieved at the age of 11 in girls and 12 in boys (Giedd et al., 1999). Decrease in cortical GM during adolescence is thought to occur due to the elimination of redundant synapses excessively produced during development, in a process termed ‘synaptic pruning’ (Huttenlocher, 1984). Gogtay, et al. (2004) also observed that cortical thickness decreases with age in a back-to-front fashion. As such, the sensorimotor areas lose GM first whereas the dorsolateral prefrontal cortex and the posterior part of the STG appear to lose GM last. Another explanation for reduced GM volume has been offered (see Paus, 2005). It is possible that reduced GM in frontal areas is the result of increased myelinated WM (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Indeed, WM density of several WM tracts such as the internal capsule increase between ages 4-17 years (Paus et al., 1999).

Interestingly, my results show that with age there is an abnormal increase of those two areas in the TS group whereas I observed the to-be expected loss of GM volume in the CS group. Some have suggested that differences in cortical volume between these two groups is indicative of a developmental delay in patients with TS (Sowell et al., 2008). However, a more likely explanation is that differences in GM or WM volume is the result of compensatory adaption mechanisms. In support, volumetric differences are also observed in adults with TS, specifically in prefrontal and parietal cortices (Ganos, Kühn, et al., 2014; Worbe, Gerardin, et al., 2010). Furthermore, there seems to be limited reduction of GM volume in the temporal lobe (Giedd et al., 1999) and increased GM volume in the STG as we have reported here cannot be explained with the argument of developmental delay, but rather that this might be the result of some adaptation in patients. It is however difficult to make such claims based on differences in GM volume alone. GM volume most likely represents the combination of total thickness and surface area, while differences in volume can reflect one or the other (Mechelli et al., 2005). Also, most MRI sequences are not delicate enough to catch subtle changes in neurobiological processes such as myelination or synaptic pruning and more high-resolution anatomical imaging is warranted.

The theory of a developmental delay in TS comes from two resting-state functional connectivity studies (Church et al., 2009; Worbe et al., 2012). Both studies demonstrate characteristically ‘immature’ connectivity of several areas in the CSTC circuits (Worbe et al., 2012), and fronto-parietal and cingulo-opercular networks (Church et al., 2009). However, this was recently cast into doubt by Greene and colleagues (2016). The authors showed that support vector regression accurately predicts connectivity maturity according to age and this was not different between patients and controls. This suggest, at least with functional connectivity, that patients with TS do not demonstrate immature development of connectivity but rather that alteration in connectivity is a sign of compensatory adaption mechanisms. In this longitudinal study the evidence seems to suggest the latter, since I did not observe any significant relationship between the change in GM volume and age in either group. It is important to note, however, that more comprehensive analyses are needed to confirm these findings and especially including measures of WM density in addition to GM. Finally,

both studies by Worbe, et al. and Church, et al. do not correct for small micro-movements as noted above (Power et al., 2012) and therefore spurious functional connections cannot be excluded.

Lastly, great support has been given to the compensatory adaptation theory by Jackson and colleagues using white matter diffusion and cognitive control tasks, suggesting that increased control over tics is related to compensatory neural re-organisation of particular WM tracts (S. R. Jackson, Parkinson, Jung, et al., 2011). First, on cognitive control tasks young people with TS demonstrate superior performance in comparison to their peers (G. M. Jackson, Mueller, Hambleton, & Hollis, 2007; S. R. Jackson, Parkinson, Jung, et al., 2011; Jung et al., 2013; Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006). Second, the TS group shows reduced WM structural integrity (as measured by fractional anisotropy [FA; see Chapters 2 and 5 for more comprehensive explanation on FA]) of the forceps minor (a WM fibre bundle projecting to the prefrontal cortex), which correlated inversely with performance on the cognitive control task (S. R. Jackson, Parkinson, Jung, et al., 2011). Also, greater WM structural integrity was associated with greater tic severity scores. As such, those subjects who had the least amount of FA in the prefrontal cortex (greatest difference between groups) had the least severe tics (Jackson et al. 2011). This is further supported by the reduced WM volume in the OFC in TS (Greene et al., 2017) and supports the argument by some stating that reduced structural connectivity of the frontal regions occurs to gain control over tics (G. M. Jackson, Draper, Dyke, Pépés, & Jackson, 2015; S. R. Jackson, Parkinson, Jung, et al., 2011).

6.4.5 *Limitations*

My study is rather limited by the sample size, with only a total of 34 participant, it is possible that my non-significant machine learning results are simply due to the lack of statistical power. Moreover, my sMRI scans are acquired using a MRI scanner with a field strength of 3T, whereas 7T scanner has superior signal-to-noise ratio, which has been shown to be important when using machine learning algorithms by increasing accuracy of classification (Iwabuchi, Liddle, & Palaniyappan, 2013).

CHAPTER 7

Chapter Seven – General discussion and thesis conclusion

In this thesis I have primarily focused on the sensory aspects of TS, both exteroceptive and interoceptive. Although TS is generally regarded as a disorder of the motor system, sensory information and integration play a major role in symptom formation and maintenance and are now considered core phenomena of TS (Rajagopal et al., 2013; Ruhrman et al., 2017; Weisman et al., 2018). There were two primary aims of this thesis: (1) to investigate if and why patients with TS report heightened perception of external (exteroceptive) sensory input and (2) to investigate more closely the neural correlates of PSP (interoceptive) in young patients, with a specific focus on brain structure. Collectively, my results have provided evidence in support of previous studies such as un-altered tactile thresholds, aberrant white matter (WM) connectivity and grey matter (GM) volume. Also, results here lend support to some theories that the insular cortex might be the epicentre of the generation and maintenance of PSP (S. R. Jackson, Parkinson, Kim, et al., 2011). By contrast, studies in this thesis have also brought about new evidence such as the suggestion of altered prediction of the consequences of external sensory stimuli and increased prediction errors, a trend toward a different sensorimotor cortex muscle representations, and reduced WM connectivity of key areas of the fronto-striatal limbic circuit.

Below I will provide a brief discussion of my results collectively, which is organized according to three major discussion points which demonstrate similarities between my results and the knowledge of TS pathology, and what is currently known about sensory processing disorders (SPD).

7.1 UNALTERED SENSORY DETECTION IN TS

Evidence suggests that both young (Ludlow & Wilkins, 2016) and adult (e.g., Belluscio, Jin, Watters, Lee, & Hallett, 2011) patients report feeling hypersensitive to external stimuli across all sensory modalities. Yet, no study to date had empirically tested affective touch thresholds in young people with TS. Based on their results, Belluscio and others (2011) determined that these subjective feelings had nothing to do with altered detection of sensory stimuli since their sample of patients demonstrated comparable detection thresholds to their peers. Rather, they argued that the perception of hypersensitivity must involve central processing networks. This motivated the first two studies presented in this thesis.

In Chapter 3 I studied the affective touch thresholds in young patients with TS, using a tactile force-detection paradigm. By applying Von Frey monofilaments to two skin locations (the palm of the hand and the cheek) I was able to identify the 75% touch detection threshold for both groups. Additionally, I analysed the data using signal detection theory, calculating the proportion of hits (pHit), proportion of false alarms (pFA), sensitivity (d') and response bias (c). In line with previous results, I could not find evidence for lowered tactile sensory thresholds in the TS group. It was, however, clear that the TS group demonstrated lower pFA (fewer false alarms) and marginally (non-statistically) higher response bias (c ; indicating greater bias toward responding “no” when asked if a touch had occurred or not). Based on these results, I make the conclusion that in TS sensory prediction is altered and that the sensory system might be biased, conforming with the conclusion of Belluscio and others. However, Belluscio, et al. (2011) gave no biological explanation for their hypothesis nor tested it empirically. In my view, my results could well be explained within the framework of predictive coding (Kok & de Lange, 2015).

Predictive coding assumes that sensory models are based on contextual information and the sensory world, and these models are used to predict the sensory input and its consequences. When the sensory input does not “fit” within the pre-existing models, prediction error occurs. Predictive coding has previously been used to explain perceptual deficits in patients with autism (see van Boxtel & Lu, 2013) and the

same principle can be applied to TS. That is, patients are unable to update their sensory models accordingly, and consequently find certain sounds, smells and touches uncomfortable and extremely irritating. This then possibly manifests as PSP and is inappropriately linked with tics. The principle of predictive coding is to reduce the discrepancy between the predicted and the actual consequences of the sensory input (Friston, 2014). This can be achieved, for example, by updating the perceptual expectations or through active inference (Friston, 2014). Accordingly, patients with TS might be unable to update their models to concur with the sensory world. This is supported by one study showing patients having reduced sense of agency, which relies heavily upon sensory-motor integration (Delorme et al., 2016). This evidence provides good support for my notion that patients with TS are unable to update their sensory models, have difficulty with sensory-motor integration, and therefore have increased prediction errors.

There is however another possibility as to why patients with TS demonstrate heightened sensory sensitivity. With respect to the sensory symptoms, it is likely that patients with TS are showing signs of co-occurring sensory disorders collectively termed sensory processing disorders (SPD) (Ruhrman et al., 2017; Weisman et al., 2018).

Altered response to sensory stimulation is prevalent amongst typically developing school-aged children (Ahn, Miller, Milberger, & McIntosh, 2004). Moreover, it is also common to observe sensory abnormalities such as hypo- and hyper-responsiveness to sensory stimulation in many neurodevelopmental disorders (Ahn et al., 2004). SPD is an umbrella term for three distinct disorders: sensory modulation disorder (SMD), sensory discrimination disorder (SDD) and sensory-based motor disorder (SBMD) (L. J. Miller & Lane, 2000). SMD, which is defined as those individuals who show exaggerated or inappropriate response to sensory input (Bar-Shalita, Vatine, & Parush, 2008), can be further categorized as sensory over-responsivity, sensory under-responsivity and sensory seeking/craving. Furthermore, SBMD can include postural disorders and dyspraxia (L. J. Miller & Lane, 2000).

SPD and TS share many similarities such as being much more common in boys, co-occur with ADHD and autism and be accompanied by anxiety, while both disorders share strikingly similar pathologies (Albin & Mink, 2006; Koziol, Budding, & Chidekel,

2011; Leckman, 2002; Owen et al., 2013). In general, it is believed that the occurrence of SPD is due to immaturity of sensory processing mechanisms and the deficit in sensory information processing is the result of excessive CNS arousal (as seen in Bar-Shalita, Vatine, Parush, Deutsch, & Seltzer, 2012), similar to what has been described in TS (Belluscio, Jin, et al., 2011; Stern, Blair, & Peterson, 2008). Few studies have investigated directly the prevalence of SMD in patients with TS. One recent study, however, did. Weisman and colleagues (2018) studied 92 patients with TS or CTD aged 7-14 years of age and employed a range of sensory testing for example using Von Frey monofilaments to test affective touch thresholds and the short sensory profile. Based on the sensory profile questionnaire, the authors determined that 47% of TS patients had definite or suspected SMD. Several interesting results emerged: Individuals with and without SMD did not differ in regard to PSP or tic severity (as measured with YGTSS). Patients with TS+SMD did however show significantly higher total OCD score and poorer quality of life. Also, there was no correlation between sensory thresholds (Von Frey) and scores of the sensory profile questionnaire. Unfortunately, the authors made no comparison of sensory thresholds between subgroups (i.e., TS+SMD vs TS only), and I urge future studies to look at this. Nonetheless, this study shows clearly that there is a high prevalence of SMD amongst patients with TS and this study further corroborates my results from Chapter 3, showing no relationship between sensory thresholds and PUTS scores. This is perhaps not surprising since the PUTS does not question patients about sensitivity to external sensory input (Brandt, Beck, Sajin, Anders, et al., 2016; Woods et al., 2005).

7.2 THE PATHOPHYSIOLOGY OF TS SUGGESTS SIMILARITIES TO DISORDERS OF IMPAIRED SENSORY INTEGRATION

In Chapter 4, the aim was to investigate why patients might perceive and perhaps show abnormal perception of external sensory input (e.g., Puts et al., 2015), by employing a novel brain mapping method using TMS. There were several other motives for this study. The study was motivated by the notion that patients with TS demonstrate marked reduction or altered distribution of GABAergic inhibitory interneurons in the

striatum (Kalanithi et al., 2005), and we hypothesized that these interneurons might also be missing at cortical level and could play a role in maintaining the spatial segregation of cortical representations. Also, similar conditions to TS such as focal hand dystonia (FHD), who demonstrate abnormal posture of limbs and experience sensory symptoms, have been shown to demonstrate altered arrangement of cortical sensorimotor representations compared to neurologically healthy individuals (Elbert et al., 1998; Hallett, 1995; Patel et al., 2014).

The nuclei of the thalamus project to the somatotopically organized S1, where segregation of specialized areas must be maintained to prevent cross-over of signals (Gardner, 2010). In the event of a tactile touch, some receptors in the skin are highly activated, while others are less activated and this is governed by GABAergic interneurons (Gardner, 2010). The role of these interneurons is to suppress weakly stimulated neurons, and enhance and refine the signal coming from those LTM's that are more strongly activated (Gardner, 2010). Based on this information, it is conceivable that the segregation of muscle representations on the cortex is different in TS giving rise to altered perception of touch.

The study presented in Chapter 4 also used specific TMS parameter settings, making it possible to investigate cortical inhibition (SICI) which is mediated by GABAergic interneurons (Di Lazzaro & Ziemann, 2013). The final motivation was the observation of the results by Kolasinski and colleagues (2016) that sensory deafferentation results in altered detection of discrimination of vibrotactile stimuli and that young patients with TS demonstrate reduced adaptation on similar tasks (Puts et al., 2015). Results from the study in Chapter 4 showed that a large part of the SM cortex responsible for a small muscle in the hand (the FDI) was significantly reduced in the TS group, and the size of this muscle was positively associated with the frequency and severity of PSP (see Figure 4.9 in Chapter 4). This indicates that those patients who are most dissimilar to their peers (smaller FDI area) have the least severe PSP. This study also showed that there was a relationship between the size of the FDI representation and cortical inhibition in the CS group, while this relationship was completely absent in the TS group. It is therefore conceivable that GABAergic interneurons govern the structural properties of muscle representations, which is then mirrored by the

inhibitory tone of the motor cortex, and this is aberrant in TS. However, I was not able to demonstrate any group differences in cortical inhibition, and therefore it is possible that disorganization of cortical representations in TS is the result of reduced subcortical interneurons and/or repetitive sensory stimulation during critical maturation periods (Quartarone et al., 2014; Ravinder et al., 2016). This is also consistent with what I note in Chapter 1 - that patients with TS show faulty sensorimotor gating mechanisms (e.g., Buse, Beste, Herrmann, & Roessner, 2016), leading to the inability of filtering sensory input. Animal studies show that when they are exposed to excessive sensory stimulation during early childhood, they start to show severe behavioural changes such as hyper activity and enhanced potential for drug rewards (Ravinder et al., 2016). Moreover, these changes are associated with an alteration in glutamatergic (excitatory) neurotransmission in the NAcc and amygdala (Ravinder et al., 2016).

Interestingly, in Chapter 5 I found increased WM connectedness of the right NAcc (at uncorrected statistical thresholds) in the TS group, indicating that the average number of minimum connections needed to connect from the NAcc to other nodes is possibly greater in patients. The NAcc plays a critical role in goal-directed behaviour and reward (or reinforcement) (Haber & Knutson, 2010). Also, the NAcc receives major glutamatergic input from the frontal cortex and thalamus, and receives input as well from the insular cortex (Haber & Knutson, 2010). Taken together, an overloaded sensory system during a critical period of maturation in TS might inflict both cortical re-arrangement explaining perceived sensory hypersensitivity and increased connectedness of key WM tracts leading to aberrant formation of habits. Indeed, the NAcc is vital to the habit-learning system (Graybiel, 2008) and patients with TS have been shown to demonstrate greater habit formation, favouring habitual and outcome insensitive choices (Delorme et al., 2015). The ventral (limbic) striatum which includes the NAcc has also been shown to play an important role in sensorimotor gating (McCairn & Isoda, 2013), while both GABAergic and cholinergic interneuron ablation of the dorsolateral or dorsomedial striatum (sensorimotor and associative territories) do not produce deficits in sensorimotor gating (M. Xu et al., 2015; M. Xu, Li, & Pittenger, 2016). In the study in Chapter 5 I was however not able to demonstrate any association between the connectedness of the NAcc and measures of PSP and as such I was not

able to confirm a relationship between the severity and frequency of PSP and connectivity of the NAcc.

The study presented in Chapter 5 investigated WM microstructure and connectivity in young people with TS. Primarily, TBSS results showed marked and widespread reduction in axial (parallel) diffusivity. Closer inspection of the data revealed four specific WM tracts that showed the greatest difference between the groups: the anterior thalamic radiation (ATR), forceps minor, and the genu and splenium of the corpus callosum. The ATR is a projection tract connecting the PFC and OFC with the dorsomedial and anterior thalamus and other limbic structures (Mori et al., 2002). The forceps minor is a WM pathway connecting the lateral and medial areas of the PFC and has previously been shown to demonstrate reduced FA in TS (S. R. Jackson, Parkinson, Jung, et al., 2011). The genu is the most anterior part of the corpus callosum and connects the bilateral frontal and anterior cingulate cortices, while its projections form the forceps minor (Witelson, 1989). By contrast, the splenium is the most posterior part of the corpus callosum and homologous areas of the parietal cortex (including the S1) are connected via the postero-superior region of the splenium (Huang et al., 2005). Based on this, it is clear that the TS group shows prominent decrease in WM water diffusion in key sensory-motor related tracts.

These results are in accord with what is observed in patients diagnosed with SPD. Owen and colleagues (2013) employed identical methods to mine in a sample of 16 boys aged 8-11 years with SPD. Interestingly, the study showed specific increase in radial (perpendicular) diffusivity in the splenium, ATR and forceps minor (Owen et al., 2013), results which were further corroborated in a larger sample (Chang et al., 2016). Owen et al. comment that based on their results, patients with SPD demonstrate marked alteration in several WM tracts which are key to higher-order processing and multimodal sensory integration. This further underlines the importance to consider the possibility that patients with TS might present similar pathology to SPD.

In Chapter 6 I also showed that there is a specific reduction of GM volume in only one cluster in TS, localized in area 6 of the cerebellum (see Figure 6.4 in Chapter 6). As noted previously, area 6 specifically has been implicated in the generation of tics (Lerner et al., 2007). Interestingly, the cerebellum has also been implicated in the

pathology of SPD, where reciprocal connections between cerebellum and cortex might play an important role in hypo- or hypersensitivity and the amplified response to sensory input (Koziol et al., 2011; Ramnani, 2006). The role of the cerebellum (and specifically area 5 and 6) has been highlighted by a meta-analysis where these areas activate significantly during sensorimotor tasks (Stoodley & Schmahmann, 2009) and by studies of children with agenesis of the cerebellum. These children exhibit atypical behavioural and emotional responses to external sensory input, a characteristic feature of SPD (Koziol et al., 2011). The cerebellum also has a primary role in motor learning (Galea et al., 2011) and constructs internal models (estimation of the consequences of a desired action without performing it), which are refined and adjusted when specific behaviour is repeated (Wolpert & Ghahramani, 2000). Reduced GM volume in the cerebellum might therefore be related to the difficulty in TS to construct precise internal models since they have difficulty relying on sensory feedback. This fits well with my results from Chapter 3, where the TS group showed greater response bias than the CS group, indicating that the internal models are noisier and thus patients have greater difficulty separating the noise from the signal resulting in higher internal criterion.

When interpreting the results from Chapter 6 on reduced GM cerebellar volume it is important to consider what I am actually measuring from sMRI images when segmenting the brain into GM and WM. This segmentation procedure is based on signal intensities as noted before, and the GM is thought to be composed of neural cell bodies, axons, dendrites, glia and blood vessels (Paus, 2005). It is now widely believed that GM volume decreases through adolescence possibly due to elimination of redundant synapses [synaptic pruning] (Giedd et al., 1999). By contrast, studies report increased WM volume possibly as the result of increased myelination of the useful, non-eliminated connections (Lebel et al., 2008). As such, decreased GM might be the consequence of increased myelination, and voxels of the brain that were previously classified as having signal intensities reminiscent of GM would now be classified as WM because of more myelin and thus changed signal intensity (Paus, 2005). This leads to the suggestion that in area 6 of the cerebellum, patients with TS have increased WM connections. It is obvious that I could have tested this in the study presented in Chapter

5 (using DTI) but unfortunately the field of view used when planning the MRI scans was smaller than the brain and the cerebellum was sacrificed.

7.3 MAJOR ROLE OF THE INSULAR CORTEX IN PSP IN TS

The most prominent result emerging from the two neuroimaging studies presented in Chapters 5 and 6 implicate areas of the limbic circuit and the insular cortex, where TS patients demonstrate an increase in GM volume in a longitudinal study and an association between the importance of the insular node in maintaining efficient information transfer and PSP.

In the study presented in Chapter 5 I showed a strong positive association between local efficiency of the left anterior and right posterior insula with PUTS scores. This indicates that greater information is exchanged between neighbouring nodes when the frequency and severity of PSP in TS increases when these two insular nodes are removed from the network. These results could indicate that these two nodes might be some sort of mediators, maintaining homeostasis and control of sensory urges in TS, but when fault occurs patients experience greater, more severe and bothersome sensory urges than otherwise. However, neither of the insular nodes were flagged as hubs.

The insular cortex is located deep within the Sylvian fissure and is both inter- and intra-connected. Of interest are connections with limbic and associative cortices, where the insula also receives afferent projections from the thalamus and sensory areas, and sends efferent projections to the premotor cortex and ventral (limbic) striatum (Nieuwenhuys, 2012).

The dichotomization of the insular cortex in anterior and posterior portions is well supported, and its involvement in sensorimotor function is substantial (Nieuwenhuys, 2012). Two resting-state fMRI studies have also established functional connectivity between the anterior and posterior insula with the anterior and mid-cingulate, and the posterior insula with primary and secondary somatosensory cortices (Deen, Pitskel, & Pelphrey, 2011; Taylor, Seminowicz, & Davis, 2009). In behaviour, the insula is

particularly involved in the generation of the sense of agency (Farrer et al., 2003) and in the perception of body ownership, supported by empirical and lesion studies showing activation and disruption, respectively, of the insula during body ownership tasks (Baier & Karnath, 2008; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). The role of the insula in detection of innocuous cutaneous stimuli is well established (Schneider, Friedman, & Mishkin, 1993; Wei & Bao, 2013). Moreover, during cutaneous touch, the posterior insula shows a functionally active brain network along with the superior parietal lobule, superior temporal gyrus and inferior parietal cortex (Wei & Bao, 2013). This has important implications for the interpretation of results from Chapter 3, where I showed altered response bias in TS, and Chapters 5 and 6 which showed alteration in both WM and GM in the insula in TS. For example, and as noted before, I explained my results from Chapter 3 using predictive coding, suggesting increased prediction error in TS which explains the subjectively perceived sensory amplification.

One recent study by Geuter and co-workers (2017) employed a somatosensory stimulation paradigm, where painful or non-painful heat stimulation was preceded by a cue, indicating the probability of the stimuli being either painful or not. The study is conducted on the premise that the insula (a pain processing region) will show increased prediction error-related activity when stimulation is more painful than expected. This study primarily showed that the combination of expectation and prediction error can explain neurophysiological responses (skin conductance and pupil dilation) to painful and non-painful stimuli. Moreover, neural response measured of the anterior insula using fMRI strongly supports the predictive coding model, stating that the physiological responses are the weighted sum of the prediction and prediction error (Geuter et al., 2017). Also, activity of the posterior insula indicated that this part is the coding station for the stimulus intensity, while the anterior insula is responsible for signalling the summation of expectation and the prediction error when the stimuli is unexpected. This study clearly shows that the insula plays an important role in the expectation and processing of exteroceptive stimuli. Others have also argued for the anterior insula to be a key structure in generating, comparing and updating interoceptive predictions (Seth, 2013), where interoceptive, exteroceptive and motivational signals possibly converge (Seth & Critchley, 2013).

The study presented in Chapter 5 therefore lends support to conclusion of previous studies, demonstrating altered functional connectivity (Tinaz et al., 2015) and structural thickness (Draper et al., 2015) of both anterior and posterior portions of the insular cortex. Consequently, there is strong empirical evidence to suggest that the insula (in TS) processes both internal and external sensory information differently and contribute to the amplified response to sensory input and to the generation of PSP. This notion is in line with the work of Jackson and colleagues (2011) who provided convincing evidence that the insula plays a major role in sensorimotor prediction. The insula then generates greater prediction error which is not dealt with properly by higher-order processing. This might be due to reduced neural activity of higher cortical areas, specifically the anterior cingulate, prefrontal and sensorimotor cortices and cerebellum, which play a particular role in the integration of somatosensory stimuli (Swerdlow et al., 2016). Because of altered processing capabilities of the insula and dormant higher-order cortical areas, the sensory system becomes easily overloaded, as proposed by Buse and colleagues (2016). In their study, Buse and others showed reduced fMRI BOLD response in TS during a PPI paradigm of several higher-order cortical areas such as the MFG, S1, superior parietal and cingulate cortices and the caudate. Several of these areas, notably the MFG, S1 and cingulate overlap with results I presented in Chapter 6, showing aberrant and unusual increase of GM volume in the TS group.

It is important to note that the change in GM volume in TS patients as presented in Chapter 6 did not correlate with change in PUTS scores, and this can be explained by the lack of questions in the PUTS asking about sensorimotor gating or sensitivity to exteroceptive stimuli. This further supports my argument that the change in GM volume of these areas might be an adaptive reaction to repetitive bombardment of sensory input.

7.4 FUTURE WORK & THESIS LIMITATIONS

It is now clear that patients with TS demonstrate several disturbances of the sensory system, which are inherently interoceptive (e.g., the bodily urge to act) and

exteroceptive (somatosensory amplification). As such, this has led some to postulate that abnormal somatic sensory sensitivity might contribute to the re-occurrence of PSP (S. R. Jackson, Parkinson, Kim, et al., 2011; Weisman et al., 2018). Consequently, and given the notion that TS is also characterized by recurrent motor outputs, patients demonstrate impaired sensory-motor integration (i.e., the ability to employ sensory information to accurately guide motor planning and execution) (Avanzino, Tinazzi, Ionta, & Fiorio, 2015). Studies exploring sensory-motor integration and exteroceptive awareness in TS are lacking and only one study, to my knowledge, has investigated the sense of agency in TS (Delorme et al., 2016). This study included 37 adult (>18 years of age) patients and thus no study has investigated this phenomenon in children and adolescents with TS. Also, studying proprioception in TS is warranted, although two studies to my knowledge have investigated postural control, with both studies suggesting reduced postural control stabilities in patients (Lemay et al., 2007; W. Y. Liu et al., 2015).

If patients with TS are demonstrating signs of SPD/SMD, it is imperative, in my opinion, to investigate this more closely. For example, the pathophysiology of TS and SPD/SMD share many similarities, involving several CSTC circuits, and connectivity of the cerebellum (Koziol et al., 2011). It would be interesting to see if patients with TS demonstrate signs of sensory craving or sensory seeking, or sensory avoidance. With regard to SPD, children with sensory seeking tendencies are observed to constantly touch everything, from objects to people, perhaps due to the fact that these children do not experience enough sensations and feel the need to actively seek out sensory stimulation as a compensation (Koziol et al., 2011). In Chapter 4 I employed the Adult/Adolescent Sensory Profile (which is most often used to diagnose children or adolescents with SPD) and although I did not observe any statistically significant differences, I noticed that one quadrant termed 'sensation seeking' is where patients with TS score marginally higher compared to their peers.

In this thesis I have attempted to answer all questions originally proposed but some limitations are obvious. I have detailed some of these in individual chapters, but some limitations are general to all studies. In my opinion this thesis is limited by the lack of a record of patients' onset of tic symptoms. Patients with greater symptom duration

might present altered brain states and this could be a confounding factor which was not controlled for. Also, I did not properly record medication or alternative medication use (over the counter medication not specified by patients or parents) or if patients were seeking alternative therapies such as CBT, HRT (habit-reversal therapy) or CBIT (comprehensive behavioural intervention for tics). Most studies are also limited by small sample sizes, rendering sub-group comparisons impossible. For example, TS is a very heterogeneous disorder (as introduced in Chapter 1) and investigating differences between patients with 'pure' TS and TS with ADHD or OCD is important, especially since sensory phenomena is a prominent feature of OCD (Ferrão et al., 2012; Subirà et al., 2015).

7.5 CONCLUSION

TS is a complex and heterogeneous disorder and based on the literature, knowledge about TS is significantly behind other hypo- or hyperkinetic movement disorders. However, we have begun to see a pattern recognizing TS as an exciting avenue of research and more research labs are becoming dedicated to identifying the neural correlates of TS to aid in therapy. Relatively little is known about the sensory aspects of TS and in this thesis, I have tried to highlight the lack of knowledge or consensus in the literature and attempted to fill in some gaps. In Chapter 3 I was able to confirm unaltered affective touch thresholds in TS but also made a suggestion and explanation to why patients subjectively perceive themselves as being hypersensitive to external input. Findings from Chapter 4 suggest that the sensory aspects of TS can possibly be explained by altered organization of the sensorimotor cortex and reduced function of GABAergic interneurons. Chapters 5 and 6 further advanced the knowledge of WM and GM structure in TS, and also provide new evidence of altered structural connectivity of the insular cortex in patients which is related to the severity and frequency of PSP. Also, Chapter 6 highlights the need for further and more comprehensive longitudinal studies to investigate brain structure in TS to elucidate how and why some patients find remission in their symptoms in young adulthood, while we see an increase in the severity of symptoms in others. Finally, in Chapter 7 I attempted to combine the known

pathology of TS and my results to make a strong argument for the hypotheses that patients with TS demonstrate classical signs of sensory processing disorders. In the end, I also highlighted the need to further study sensory-motor integration in children and adolescents with TS.

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APPENDIX 1

Appendix 1 – Details of Psychometric function fitting and signal detection theory

In this appendix I will further explain the use of psychometric function fitting to determine individual sensory thresholds and how we can measure sensitivity and response bias in observers using signal detection theory (SDT). Both methods are used in Chapter 3.

9.1 PSYCHOMETRIC FUNCTION FITTING

The approach to fitting a psychometric function (PF) to data from a psychometric study is explained, but I recommend several resources for further and more comprehensive understanding (Klein, 2001; Myung, 2003; Prins, 2012; Treutwein & Strasburger, 1999; Wichmann & Hill, 2001a, 2001b).

Performance on a task and sensory thresholds can be quantified using a PF fitting procedure. Simply, the PF can assess the relationship between a behavioural measure (e.g., proportion correct $P(c)$ responses in a Yes-No experiment) and the magnitude of a sensory stimulus (e.g., the force generated by a tactile monofilament). In its simplest form, the PF starts at the value of zero and monotonically increases to ~100% correct and is described by a sigmoidal curve. A sensory threshold is then defined as a point on the function (e.g., 50% correct [chance], or 75% correct points). According to Wichmann and Hill (2001a) three steps are necessary to accurately fit a PF: (1) choose a model with appropriate parameters to minimise error, (2) estimate errors of parameters, and (3) calculate and assess the goodness-of-fit between the model and the data. The PF can be modelled using the following formula:

$$\psi(x; \alpha, \beta, \gamma, \lambda) = \gamma + (1 - \gamma - \lambda)F(x; \alpha, \beta)$$

Equation 9.1. Psychometric function formula.

Where ψ is the function of choice (e.g., logistic, Weibull, etc.) and x represents the stimulus intensity. Most important here are parameters α and β . α is the threshold and determines the positioning of the curve on the abscissa. In a logistic function, α represents the $P(c)$, lying halfway between the lower and upper asymptote (e.g., the 75% line). Parameter β determines the slope of the curve and gives an indication of the rate of change in stimulus detection as a function of stimulus intensity. Importantly, these parameters need to be estimated since we never truly know their true value (Wichmann & Hill, 2001a). One way of estimating these parameters is to use the maximum-likelihood estimation (MLE; Myung, 2003), resulting in the approximation of the parameters, threshold $\hat{\alpha}$ and slope $\hat{\beta}$. The other two parameters γ and λ do not represent the participant's sensory mechanism, rather these are fixed values based on the experimental design (Prins, 2012; Treutwein & Strasburger, 1999). γ defines the lower asymptote of the PF and pertains to the guess rate. As a consequence, it describes the participant's performance during low intensity stimuli (Klein, 2001). Most commonly this value is fixed to a $1/a$ where 'a' is the number of alternatives in the design (Wichmann & Hill, 2001a). Finally, λ is the lapse rate, and represents the distance between upper asymptote and a perfect performance. On every trial, there is the possibility that a participant failed to attend to the stimuli. Thus, the best performance a participant can achieve is $100 - \lambda\%$ correct. Some suggest simply to fix this value to 0.01 (Prins, 2012; Wichmann & Hill, 2001a). Since we are only able to estimate α and β it is good practice to use bootstrap analysis to estimate the error of the fitting. In the study, I presented in Chapter 3, I used bootstrap analysis with $N_{bootstrap} = 500$ iterations to estimate the error of the two outcomes from a randomly generated hypothetical data simulated by the real data. Finally, it is good practice when modeling any sort of data to calculate error terms to assess the goodness-of-fit, to ascertain that the function fits well to the real data (Wichmann & Hill, 2001a). Several metrics can be calculated to measure goodness-of-fit of PF fitting. One which I used in the study presented in Chapter 3 is *deviance*, which is a log-likelihood ratio (Wichmann & Hill,

2001a). If deviance is 0 no residual error has occurred, where larger values indicate greater residual error.

9.2 SIGNAL DETECTION THEORY

The concept of signal detection theory (SDT), as a branch of psychophysics, was first conceived by Swets and Green in 1964, to counter the error in classical psychophysics methods due to response biases (Swets, 1964). That is, the proportion correct of indicating the presence of a stimulus is a problematic measure when one considers the possibility of changes in or when influencing response bias (Neil A. Macmillan & Creelman, 2005; Swets, 1964). Primarily, Swets and Green argued that methods using proportion correct are unable to discriminate between real sensitivity and response bias in participants. This distinction has served as a major contribution to experimental psychology and remains still a relatively influential paradigm shift, largely still in its original form (Stanislaw & Todorov, 1999).

According to SDT, the observer's (or participant's) task during a psychophysics experiment is to detect a weak signal and is required to determine whether some sensory event is due to the true signal or the noise (Swets, 1961, 1964). Therefore, SDT focuses both on measuring an observer's sensitivity to detect a stimulus as well as the decision-making process. Within the classical framework, SDT states that noise is always present but is coupled with the signal on some trials (signal+noise). Importantly, the theory states that there is no absolute threshold as Fechner had argued. Rather, the observer's detection of a stimulus relies on a combination of factors such as the intensity of the stimulus, background noise, the observer's physical condition (e.g., arousal, vigilance and attitude) and the observer's level of motivation (Neil A. Macmillan & Creelman, 2005; Swets, 1961, 1964). Consequently, the concept of an absolute threshold is arbitrary. For example, a radar observer might better detect an unexpected signal at the start of her shift than at the end of it, possibly due to fatigue, decrease in vigilance and possibly motivation since at home a warm, freshly prepared dinner awaits.

In research, SDT holds the assumption that an observer responds to maximise the incentive, but minimise the error associated with a decision; whether the signal+noise or noise only was present (Neil A. Macmillan & Creelman, 1990). During a SDT experiment, one of four outcomes are possible after a single trial, and these are summarised in Table 9.1. To use my previous example, I run a Yes-No, 1AFC experiment with 100 trials. On 50 trials, I present a touch stimulus on the hand, but for the remaining 50 trials I perform no touch. When a touch stimulus is presented, and the observer responds “Yes, I felt a touch” we label this as a *hit*, but a *miss* if the observer says “No, I did not feel the touch”. When no touch trial is performed, and the observer responds “Yes” this is called a *false alarm* (FA), but a “No” response is coded as a *correct rejection* (CR). Here *hit* and *FAs* are of most interest.

Table 9.1. A 2x2 contingency table of possible outcomes in a single trial.

		Stimulus type	
		Signal + noise	Noise
Response	“Yes”	Hit	False alarm
	“No”	Miss	Correct rejection

The decision to respond to a stimulus varies between observers, and some observers can be categorised as liberal responders if they say “yes” very frequently (also during no stimulus trials). Another observer might be categorised as a conservative responder and this observer only says “yes” when they are absolutely sure they felt the touch. The response criteria in an observer can also be manipulated using incentives such as payoffs.

The perception of the stimulus by the observer is conveniently summarised in probability distribution (Figure 9.1 depicts an example of probability distributions for one participant). The probability distribution depicts the likelihood of the observer perceiving a stimulus as *noise* or *signal+noise* (Stanislaw & Todorov, 1999).

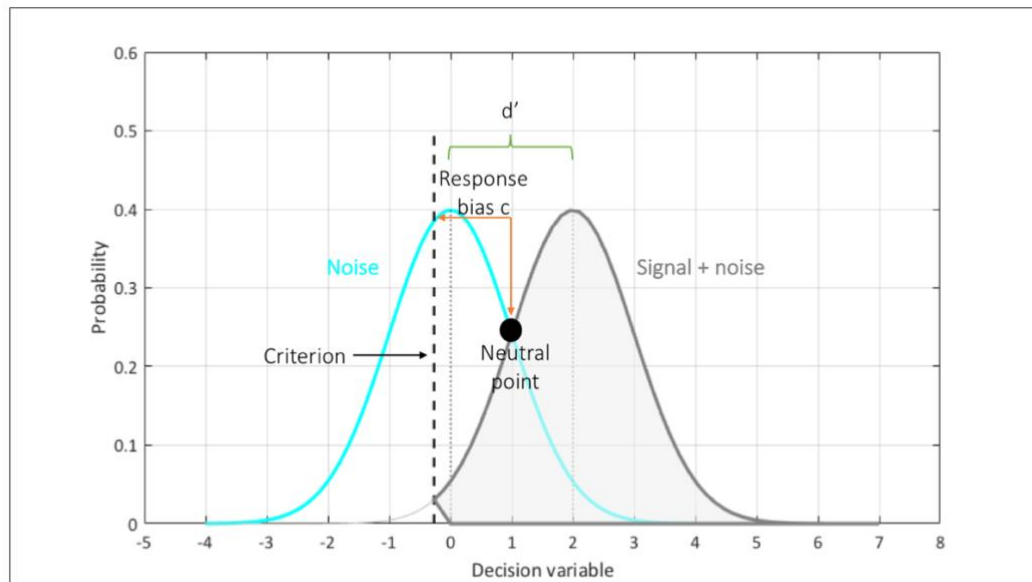


Figure 9.1. Probability distribution in a SDT experiment. Figure is adapted from Stanislaw and Todorov (1999).

The probability distribution depicts several important variables calculated using SDT and is characterised by two normal distributions, one representing *noise* and the other *signal+noise*. An observer's responses are modelled by two distinct parameters, the sensitivity and response bias (Neil A. Macmillan & Creelman, 2005). In a Yes-No experiment, an observer bases his/hers response on the value that a decision variable achieved during each stimulus presentation. If, during a given trial, the decision variable is sufficiently high, the observer responds *yes* but *no* otherwise (Neil A. Macmillan & Creelman, 2005). This value, that the response depends on is called the *criterion*.

Sensitivity is denoted by d' and measures the observer's ability to discriminate between the signal+noise and the noise in standard deviation units. Consequently, this is the heart of SDT, the ability to distinguish between the signal and the noise (Stanislaw & Todorov, 1999; Swets, 1964). d' is calculated using the following formula according to Stanislaw and Todorov (1999):

$$d' = \phi^{-1}(pHit) - \phi^{-1}(pFA)$$

Equation 9.2. Equation for d' (dee-prime).

That is, first we convert hits and FAs into probabilities by dividing number of hits and FAs by the total number of signal+noise trials and noise trials, respectively. Next, these are converted into z-scores using ϕ^{-1} (inverse phi), since ϕ^{-1} converts probabilities into z-scores. If $d' = 0$ the observer is unable to distinguish between the signal+noise and noise, increasing value of d' indicates greater ability to distinguish between signal+noise and noise alone, indicating greater sensitivity. In some cases, d' can be infinite, indicating that a participant has 100% hits and 0% FAs. This indicates a ceiling effect and can be misleading. Macmillan and Creelman (2005) offer a solution to this problem. If a proportion is 0 then $1/(2N)$ and if proportion is 1 then $1-1/(2N)$, where N is the total number of trials on which the proportion is based (i.e., either total signal+noise trials or noise trials).

Response bias on the other hand measures the observer's criteria to report the presence or the absence of the signal+noise. To put differently, we can quantify the tendency to respond *yes* or *no*, as determined by the location of the criterion (Stanislaw & Todorov, 1999). This could often be interesting when assessing differences between two groups in the way they respond to potential harmful stimuli. For example, one study demonstrated that individuals with high anxiety sensitivity (i.e., the tendency to interpret arousal sensations as having harmful consequences) adopted a more conservative response criterion (stricter criterion for the presence of the stimuli; Pollock, Carter, Amir, & Marks, 2006).

Macmillan and Creelman (2005) discuss three types of metrics to measure response bias in observers, c , c' and *likelihood ratio* (β). Response bias c assumes that an observer responds *yes* when the decision variable exceeds their individual criterion, but *no* when it does not (Neil A. Macmillan & Creelman, 1990; Stanislaw & Todorov, 1999). Stanislaw and Todorov (1999) argue in passing in favour of using response bias c , rather than c' or the likelihood ratio, mainly since c is directly based on the decision variable, whereas the likelihood ratio is, as the name implies, based on a likelihood. Furthermore, others

argue that c is preferable since changes in sensitivity (d') affects the likelihood ratio and c' , but c remains unaffected (Neil A. Macmillan, 1993; McNicol, 1972). The response bias c metric is determined by the distance between the criterion and the neutral point (i.e., zero-point bias) of the probability distribution and is given in standard deviation units. The neutral point lies at the intersection of the signal+noise and noise distributions. Response bias c can be calculated using the following formula according to Stanislaw and Todorov (1999):

$$c = -\frac{\phi^{-1}(pHit) + \phi^{-1}(pFA)}{2}$$

Equation 9.3. Equation calculating response bias (c).

If an observer's criterion lies at the neutral point, c becomes 0, and the observer prefers neither response and is said to be *bias free*. If the observer's criterion lies to the left of the neutral point (a negative value of c) the observer is said to be biased towards responding "yes" and can be considered a liberal responder. If, however, the criterion lies to the right of the neutral point the observer has a bias towards responding "no" and can be considered a conservative responder (Neil A. Macmillan, 1993; Stanislaw & Todorov, 1999).

APPENDIX 2

Appendix 2 for Chapter 4 – Creating nTMS maps

This appendix describes the nTMS mapping procedure in greater detail. This appendix is organised to describe (1) the procedure of how maps are acquired and (2) how maps are constructed offline and how map parameters are calculated.

10.1 PROCEDURE

TMS pulses were generated using a paired Magstim bistim system (i.e., two separate units; Magstim, Whiteland, Dyfed, UK) using a figure-of-eight magnetic coil. This type of coil has been shown to be superior in the mapping of the SM cortex in comparison to other coil types and provides better focality (e.g., Brasil-Neto, et al. 1992). Similar coils have also been used in other nTMS mapping studies (van de Ruit, et al. 2015; Tsao, et al. 2008). The upper limit of the pulses delivered of the stimulator were determined during the pilot stages since this intensity was acceptable in eliciting motor responses from facial muscles without causing significant discomfort. Importantly, a recent study showed that increasing TMS intensity during mapping only affects map area, but not COG or boundaries of a fitted ellipse around the peak activity (van de Ruit, et al. 2016). Therefore, during statistical analyses I did not find it necessary to control for pulse intensity.

The coil was held with the handle pointing posteriorly in a 45° angle, and the current flowing in a posterior-anterior direction. Some have suggested orienting the coil at 0° (Saisanen, et al. 2015) or 120° (Guggisberg, et al. 2001) to elicit MEPs of the facial muscles. Nonetheless, difference between 0° or 45° is minimal and has little impact on areas where MEPs are induced during nTMS mapping (Saisanen, et al. 2015). A 0°

orientation might induce stronger MEPs, but this has little effect on the location of representations on the cortex (Saisanen, et al. 2015). Consequently, the coil was constantly kept at 45° during the mapping procedure.

When applicable, individual anatomical MRI images were uploaded to a neuro-navigation system (Brainsight, Rogue Research Inc., Montreal, Quebec, Canada) to locate an approximate position of the left primary motor cortex (M1). In few instances, where no individual anatomical MRI image was available, a template constructed from a consenting individual anatomical image was used. Based on the location of the motor hotspot and visualising the individual MRI image I superimposed a 40 cm² virtual grid encompassing the left precentral gyrus, partially overlapping with the postcentral gyrus and premotor cortices since this was shown to elicit MEPs in lower facial areas (Saisanen, et al. 2015; see Figure 10.1 for demonstration of grid placement). Subsequently, 150 TMS pulses were delivered within the boundaries of the virtual grid using the pseudorandom walk method (van de Ruit, et al. 2015) with an inter-stimulus-interval (ISI) of 6 s.

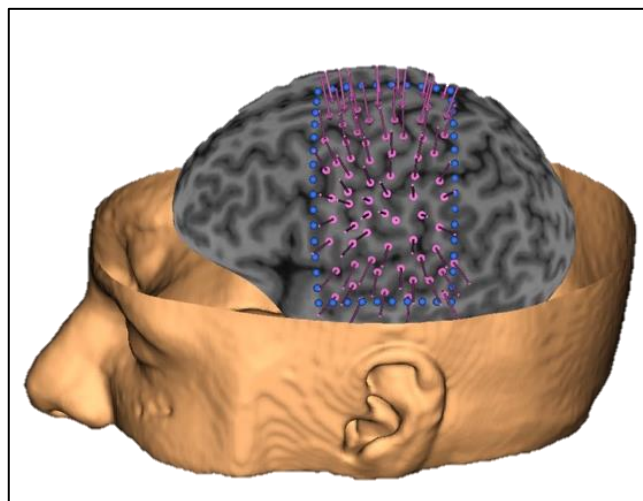
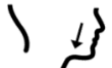


Figure 10.1. Example of a superimposed virtual grid used for motor mapping, with TMS pulses sampled within the grid at random.

10.2 DATA ANALYSIS

Peak-to-peak MEP amplitudes were time locked and extracted from each muscle EMG recording separately via a specific latency window, based upon the known latency for each muscle as specified by recent publications (Kallionemi, et al. 2015; Inoue, et al. 2003; Saisenen, et al. 2015, see Table 10.1). Then, MEPs were synchronised with TMS scalp coordinates offline. MEPs were excluded if the preceding EMG recording (about 50ms prior to stimulation) exceeded 50 μ V. I also excluded any trials where MEPs were distorted by artefacts. Analysis of MEPs and SM maps was done using custom written scripts in Matlab. All MEP data was standardised using a z-transformation since random MEP samples from the scalp were not normally distributed (Shapiro-Wilk test confirmed this with $p < 0.05$). Subsequently, to restrict the analysis and exclude any spurious MEPs unlikely to be related to a muscle contraction which would skew the maps, I thresholded all z-scores ≥ 1 .

Table 10.1. Peak-to-peak MEP latency and range for targeted muscles in msec.

Muscle	Latency start and range	Reference
	20 – 40 msec	Kallionemi, et al. 2015
	10 - 30 msec	Inoue, et al. 2003
	12 – 35 msec	Sasainen, et al. 2015
	12 – 35 msec	Sasainen, et al. 2015
	12 – 35 msec	Sasainen, et al. 2015

Data analysis workflow is depicted in Figure 2.2 and explained briefly in Chapter 4. Below I will explain in greater detail how the cortex coordinates are transformed from 3-D to 2-D using plane fitting and calculation of the map parameters.

The data was transformed from 3-D to 2-D by fitting a rectangular plane to the cloud of the transformed 3-D datapoints. First, cortex coordinates are normalised by taking the mean of each vector (i.e., $x \leftarrow X_i - \bar{X}$, $y \leftarrow Y_i - \bar{Y}$, $z \leftarrow Z_i - \bar{Z}$). Next a fitting function is used where X coordinates are dependent on the Y and Z coordinates (in this instance we are interested in coordinates Y [anterior-posterior] and Z [superior-inferior]) such that $(f(y, z), y, z)$ (Eberly, 2017). A combination of parameters A, B, and C are computed, by solving Equation 10.1 leading to a minimum error between $\hat{x}$ and x , to be used for the plane fitting function.

$$[A, B, C] = \begin{bmatrix} \Sigma y^2 i & \Sigma y \cdot zi & \Sigma yi \\ \Sigma y \cdot zi & \Sigma z^2 i & \Sigma z \\ \Sigma y & \Sigma z & 1 \end{bmatrix} \setminus \begin{bmatrix} \Sigma y \cdot xi \\ \Sigma z \cdot xi \\ \Sigma x \end{bmatrix}$$

Equation 10.1. Three parameter (A, B, C) solution for plane fitting.

Finally, the cortex coordinates are converted to plane coordinates using the change of basis. This transformation method changes one coordinate system to another, perpendicular to the predefined plane, and is a key step in mapping the original x, y, z coordinates to the plane. The plane is then rotated using a standard rotation matrix through the angle θ :

$$R = \begin{bmatrix} \cosine \theta & -sine \theta \\ sine \theta & cosine \theta \end{bmatrix}$$

Equation 10.2. Rotation matrix through the angle θ

Subsequently, I calculated three map parameters for each participant. The COG was calculated for each axis of a map:

$$xCOG = \frac{\Sigma(Xi \times aMEP)}{\Sigma(aMEP)}, yCOG = \frac{\Sigma(Yi \times aMEP)}{\Sigma(aMEP)}$$

Equation 10.3. Centre-of-gravity.

Where xCOG is the COG on the anterior-posterior axis and yCOG the COG on the lateral-medial axis, and $\Sigma(\text{aMEP})$ is the sum of all approximated MEPs in a map (sum of the weighted amplitudes of all pixels).

I also calculated the EDs between each pair of muscle representation using the COG values:

$$Distance = \sqrt{(xCOG_n - xCOG_m)^2 + (yCOG_n - yCOG_m)^2}$$

Equation 10.4. Euclidean distance equation.

where $xCOG_{n,m}$ is the COG on X-axis for muscles n, m , and $yCOG_{n,m}$ are the COG on the Y-axis for muscles n,m . This results in 10 EDs for each participant.

And finally, I calculated the variability of the data for each muscle, represented by the eigenvalues of the covariance matrix, generated by fitting a 95% confidence interval ellipse to the peak activity. This Area metric was defined using the following formula:

$$Area = \pi \times (\sqrt{2.4477 \times EV1}) \times (\sqrt{2.4477 \times EV2})$$

Equation 10.5. Map area is calculated by using the inverse of the chi-square cumulative distribution of the 95% confidence interval (2.4477) and the major and minor axes of the 95% confidence interval ellipse (EV1 and EV2, respectively).

Where EV1 (major axis) and EV2 (minor axis) are the first and second eigenvalues of the covariance matrix derived from the aMEPs in each map

APPENDIX 3

Appendix 3 for Chapter 4 – supplementary nTMS map results

Differences in COG was measured using a repeated sampling technique (permutation tests), and for every dependent variable the distribution of the random allocation of group labels was recorded and plotted. Figures found below depict this distribution and provide an indication of the mean and observed differences between the two groups.

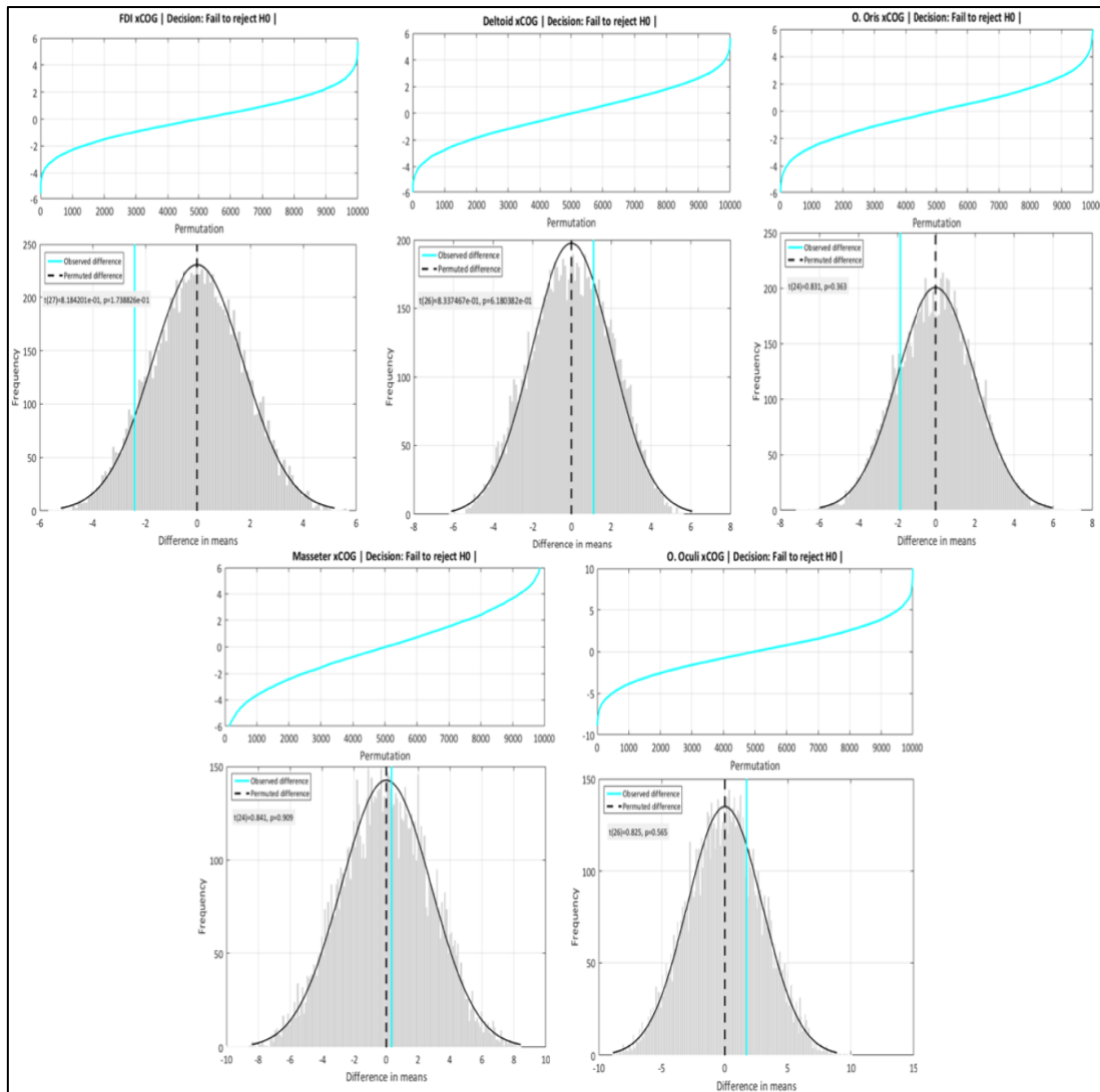


Figure 11.1. Group comparison on the anterior-posterior COG. Each figure represents one muscle. The cyan vertical line is the observed difference between the groups, while dotted vertical line is the permuted difference (centers around zero). *t*-tests are performed to assess statistical difference of whether the permuted difference is proportionally equal to the observed difference.

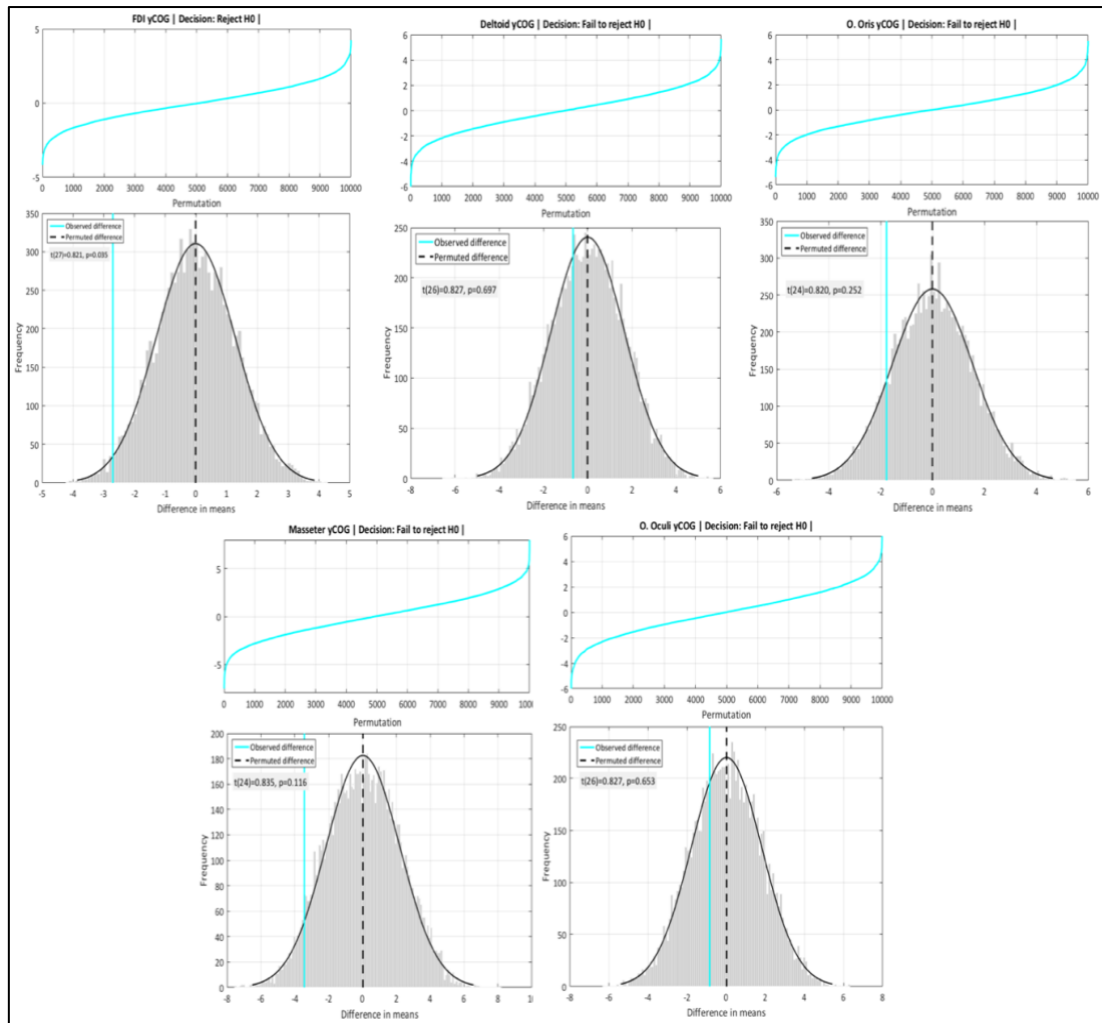


Figure 11.2. Group comparison on the lateral-medial COG. Each figure represents one muscle. The cyan vertical line is the observed difference between the groups, while dotted vertical line is the permuted difference (centers around zero). t-tests are performed to assess statistical difference of whether the permuted difference is proportionally equal to the observed difference.

Similarly, same technique was applied to the ED data and this is depicted in Figure 11.3. The figure demonstrates little evidence for any differences between the two groups with regard to EDs between pairs of muscle representations calculated as the distance between COGs.

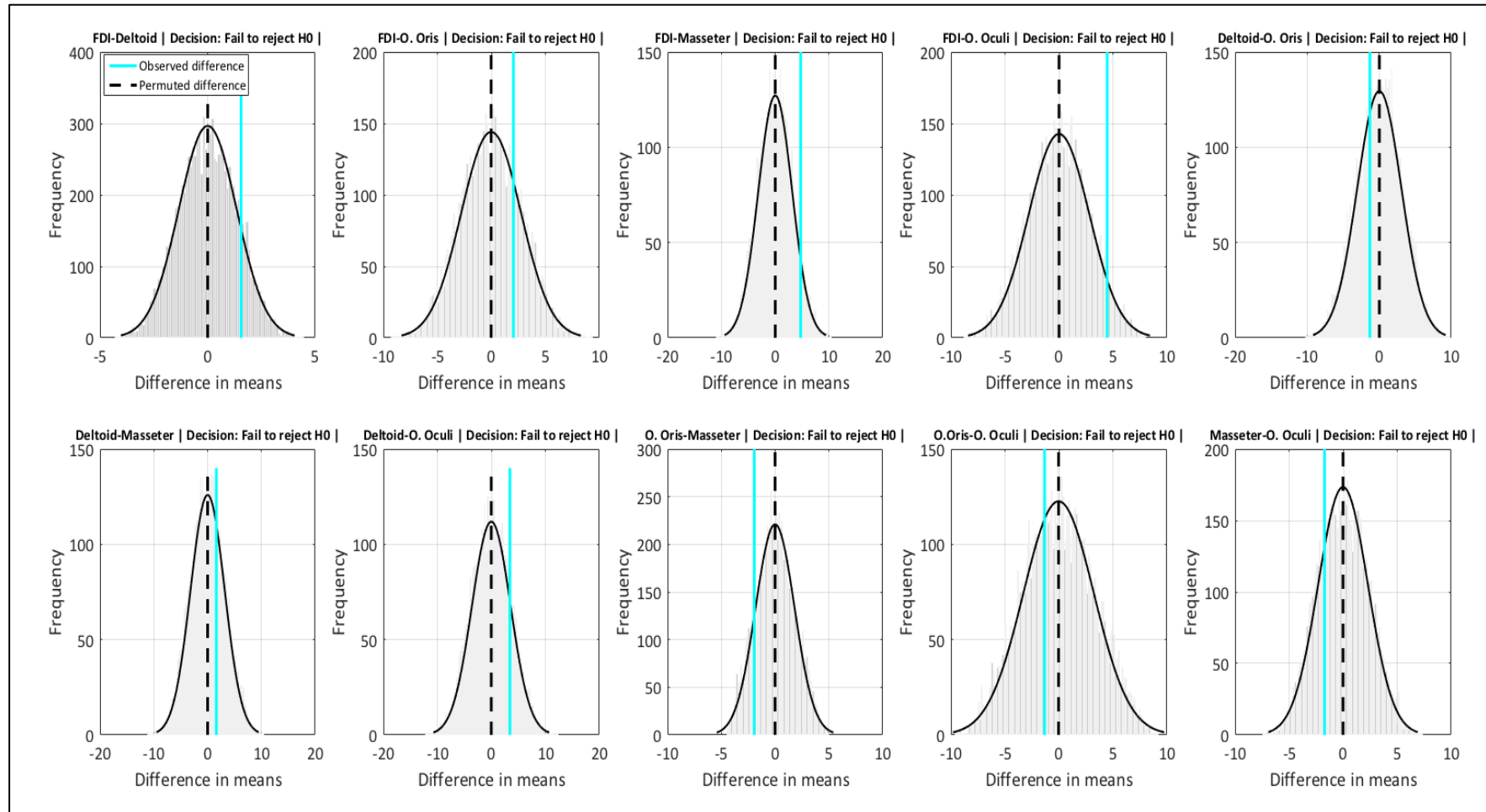


Figure 11.3. Euclidean distances group comparison. Each figure represents one muscle pairing. The cyan vertical line is the observed difference between the groups, while dotted vertical line is the permuted difference (centers around zero). t-tests are performed to assess statistical difference of whether the permuted difference is proportionally equal to the observed difference.

Finally, Figure 11.4 demonstrates the sampling distribution for all muscle areas calculated from the fitted 95% CI ellipse. The figure shows significant differences between the two groups with regard to the FDI area, corrected for multiple comparison.

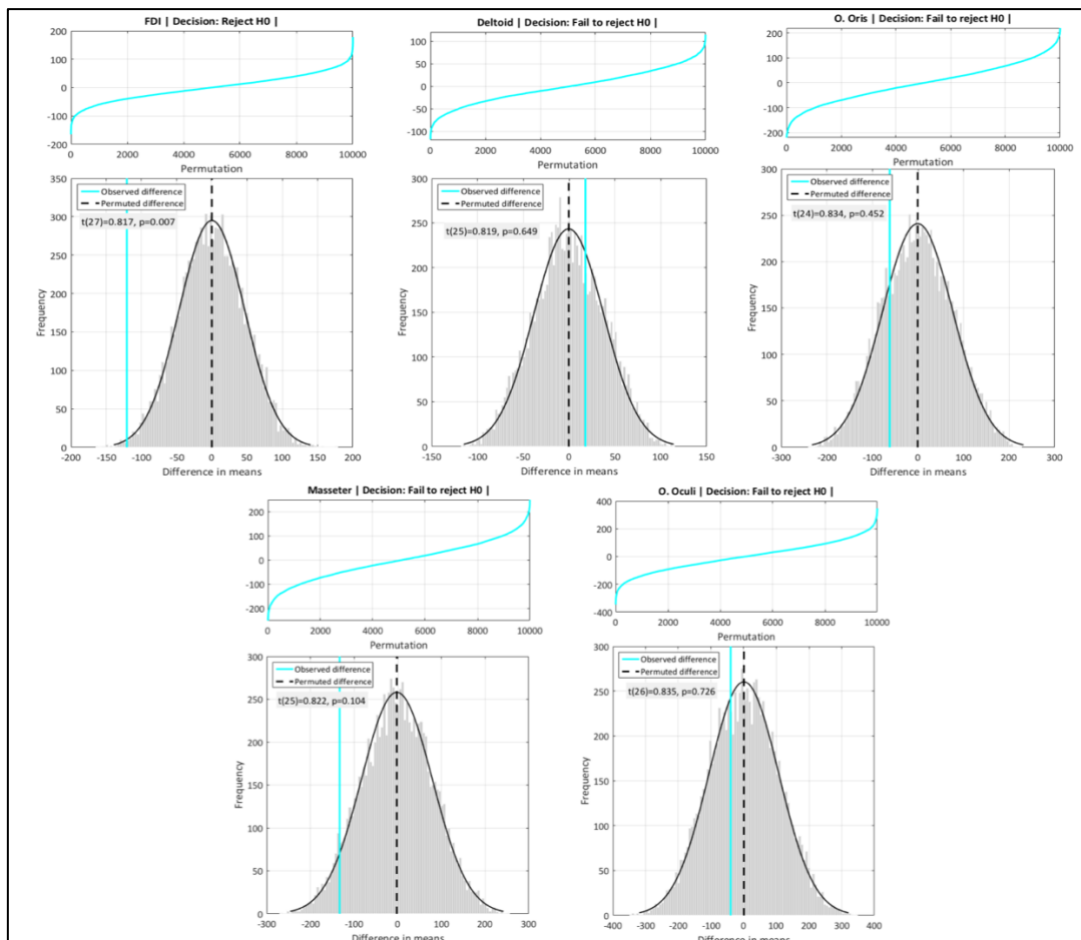


Figure 11.4. Group comparison of muscle area. Each figure represents one muscle pairing. The cyan vertical line is the observed difference between the groups, while dotted vertical line is the permuted difference (centers around zero).

Overall, I found no evidence for SICI being able to predict EDs between the FDI and other muscle representation in either the TS or CS groups.

Table 11.1. Multivariate regression analysis with median inhibition value (SICI) as a predictor and EDs between FDI and other representations as dependent variables for the TS group.

FDI – Deltoid distance						
Predictor	<i>B</i>	<i>SE B</i>	<i>t-value</i>	<i>p-value</i>	<i>R</i> ²	<i>Adj. R</i> ²
Constant	5.30	3.51	1.51	0.17	0.15	0.05
SICI	8.78	7.10	1.24	0.25		
FDI – O. Oris distance						
Constant	24.87	4.72	5.28	< 0.001	0.15	0.06
SICI	-12.10	9.53	-1.26	0.24		
FDI – Masseter distance						
Constant	21.99	4.92	4.70	< 0.001	0.03	-0.08
SICI	-5.03	9.94	-0.51	0.63		
FDI – O. Oculi distance						
Constant	18.40	6.65	2.77	0.02	0.02	-0.08
SICI	-6.40	13.44	-0.48	0.65		

Table 11.2. Multivariate regression analysis with median inhibition value (SICI) as a predictor and EDs between FDI and other representations as dependent variables for the CS group.

FDI – Deltoid distance						
Predictor	<i>B</i>	<i>SE B</i>	<i>t-value</i>	<i>p-value</i>	<i>R</i> ²	<i>Adj. R</i> ²
Constant	6.31	1.59	5.45	< 0.001	0.19	0.12
SICI	2.51	1.53	1.64	0.13		
FDI – O. Oris distance						
Constant	22.68	2.41	9.41	<0.001	0.41	0.36
SICI	-8.84	3.18	-2.78	0.018		
FDI – Masseter distance						
Constant	20.44	3.59	5.70	< 0.001	0.21	0.13
SICI	-7.97	4.73	-1.68	0.12		
FDI – O. Oculi distance						
Constant	14.15	2.61	5.42	< 0.001	0.07	-0.01
SICI	-3.17	3.44	-0.92	0.38		