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"Tics as event files – perception-action binding in Gilles de la Tourette syndrome"

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Zusammenfassung

Kapitel I der vorliegenden Arbeit beschreibt das “Gilles de la Tourette Syndrom”, welches heute als neuropsychiatrische Entwicklungsstörung kategorisiert wird, die durch mehrere motorische und mindestens einen phonetischen Tic gekennzeichnet ist. Tics werden häufig intuitiv als Folge fehlender top-down Inhibition wahrgenommen, allerdings konnte in Studien nie eindeutig ein Inhibitionsdefizit bei Tourette Patienten gezeigt werden. Eine Reihe von Studien konnte sogar eine verbesserte Inhibitionsfähigkeit bei Tourette Patienten im Vergleich zu gesunden Kontrollprobanden feststellen. Allerdings tendieren Tourette Patienten dazu, Bewegungen Anderer zu imitieren, insbesondere wenn diese Bewegungen Teil des Tic-Repertoires des betreffenden Patienten sind. Tics sind ansteckend und können suggeriert oder extern ausgelöst werden. Darüber hinaus, gehen die meisten Tics mit einem unkontrollierbaren Drang einher den Tic auszuführen. Dieser Drang wird zunehmend stärker, wenn ein Tic unterdrückt wird. Neben anderen Hinweisen deuten diese Befunde darauf hin, dass Tics nicht primär das Resultat einer fehlenden top-down Kontrolle sind, sondern wahrscheinlich motorische Ereignisse darstellen, die einfacher ausgelöst werden können als andere, vergleichbare Bewegungen. Diese Annahme kann in die „Ideomotor Theorie“ eingebettet werden, welche annimmt, dass das antizipieren des (sensorischen) Effektes einer Bewegung automatisch zu der Tendenz führt, diese Bewegung auszuführen. Darauf aufbauend postuliert die „Theorie der Ereigniskodierung“, dass einzelne Komponenten einer Aktion, wie beispielsweise sensorische und motorische Komponenten, in teilweise überlappenden Kodes in einem gemeinsamen „Ereignisordner“ gespeichert werden. Wird eine der Komponenten aktiviert, so wandert die Aktivierung automatisch in die damit verbundenen anderen Komponenten des Ereignisordners. Tics könnten nun als Ereignisordner betrachtet werden, deren einzelne Komponenten übermäßig stark miteinander verbunden sind.

Diese Arbeit widmet sich der Frage, ob es Hinweise darauf gibt, dass Tics als übermäßig stark gebundene Ereignisordner betrachtet werden können. In den Studien 1 und 2 (Kapitel II) wurde anhand einer adaptierten Version des “Modified Rush Video Protocol” – eines Videoprotokolls zur Erfassung der Symptomschwere bei Tourette Patienten – gezeigt dass die Tic-frequenz steigt wenn die Aufmerksamkeit auf eigene Tics gesteigert wird. In Studie 3 (Kapitel II) wurde die Aufmerksamkeit mittels eines Verhaltensparadigmas gezielt über verschiedene Stufen variiert. Die Ergebnisse zeigen, dass die Tic-frequenz insgesamt im Vergleich zu einer „Ruhe Baseline“ (auf einem Stuhl sitzen) sinkt, wenn Tourette Patienten sich auf eine motorische Aufgabe konzentrieren. Innerhalb der motorischen Aufgabe war die Tic-frequenz allerdings am höchsten, wenn der Aufmerksamkeitsfokus auf eigene Tics

gelenkt wurde. Diese Ergebnisse lassen sich im Sinne der Theorie der Ereigniskodierung dahingehend interpretieren dass bereits ein erhöhter Aufmerksamkeitsfokus auf Tic-Bewegungen die Tendenz schafft diese Bewegungen auszuführen.

Für Studie 4 (Kapitel III) wurde das „Imitations-Inhibitions-Paradigma“ angepasst, um Bewegungsinterferenzen von Tic-Bewegungen zu untersuchen. Die Studie zeigte, dass faziale Bewegungen, die sich im Tic-Repertoire eines Tourette Patienten befanden, anders als Bewegungen die sich *nicht* im Tic-Repertoire befanden, keinem Interferenzeffekt (Verlangsamung der Reaktionszeit) durch inkompatible visuelle Bewegungsstimuli unterlagen. Die Befunde zeigen, dass ein Tic-Ereignis, wenn es einmal ausgelöst worden ist, nicht durch inkompatible visuelle Informationen gestört wird. Dies unterstützt die Annahme, dass die einzelnen Komponenten von Tic-Ereignissen möglicherweise sehr stark miteinander verbunden und daher weniger störungsanfällig sind.

Es wird angenommen, dass das Erstellen von Ereignisordnern auf Lernmechanismen basiert, die auf der Basis neuronaler Plastizität möglich sind. Während bestimmte motorische Fertigkeiten, wie beispielsweise Tennis spielen, in großen Anteilen explizit gelernt werden, geschieht das Lernen von Tics vermutlich hauptsächlich implizit. Studie 5 (Kapitel IV) beleuchtet Lernen und Konsolidierung expliziter und impliziter motorischer Lernaufgaben, sowie deren neuronale Grundlagen – synaptische Plastizität, oder genauer „Langzeitpotenzierung“ – mit Hilfe von „Transkranieller Magnetstimulation“. Langzeitpotenzierung im primären motorischen Cortex wurde anhand einer erregenden Version des „paired associative stimulation“ Paradigmas simuliert. Sofort nach der Induktion der synaptischen Plastizität, sowie neun Monate später, wurde explizites Lernen anhand des „rotary pursuit task” und implizites Lernen anhand des „serial reaction time task“ gemessen. Weniger stark betroffene Tourette Patienten zeigten paradoxe Effekte der synaptischen Plastizität als Reaktion auf die Transkranielle Magnetstimulation (Langzeitdepressionsähnliche Effekte), während stärker betroffene Patienten, wie auch gesunde Kontrollprobanden, mit Langzeitpotenzierungsähnlicher Plastizität reagierten. Langzeitpotenzierungsähnliche Effekte korrelierten über alle Probanden hinweg mit besseren Leistungen im impliziten motorischen Lernen direkt nach der Induktion der synaptischen Plastizität. Darüber hinaus korrelierte die Konsolidierung des expliziten motorischen Lernens in der Kontrollgruppe positiv mit Langzeitpotenzierungsähnlichen Effekten, in der Patientengruppe jedoch negativ. Basierend auf den Befunden einer Umkehrung der synaptischen Plastizität in weniger stark betroffenen Tourette Patienten, sowie deren Zusammenhang mit reduziertem impliziten Lernen und einer besseren

Langzeitkonsolidierung expliziter Lerninhalte im Vergleich zu stärker betroffenen Patienten, lässt sich ein Kompensationsmechanismus vermuten.

Kapitel V beschäftigt sich abschließend mit der übergreifenden Diskussion der Befunde, deren Integration in das Modell der Ereigniskodierung, sowie der Möglichkeit der Widerlegung des Konzeptes von Tics als übermäßig stark gebundenen Ereignisordnern. Zudem widmet es sich der Frage nach künftiger Forschung, sowie der Konsequenzen der hier dargestellten Befunde für mögliche künftige Verhaltenstherapien des Tourette Syndroms.

Abstract

Chapter I comprises a detailed description of the "Gilles de la Tourette syndrome", a neuropsychiatric, childhood-onset disorder, characterised by the presence of both motor and phonic tics. Although tics intuitively appear like excess movements that arise due to a failure in inhibiting context-inappropriate motor output, inhibition difficulties have never been unambiguously shown in patients with Tourette's syndrome. A line of studies even showed increased cognitive top-down control in Tourette patients, compared to healthy controls. However, patients tend to imitate movements in others, primarily if they are part of the patients' own tic repertoire. Tics are suggestible, contagious, and can be cued. Moreover, most tics are associated with an uncontrollable urge to execute the tic, which increases if the tic is suppressed. Amongst other evidence, these findings suggest that tics may not primarily occur due to decreased top-down inhibition but may be triggered more easily than other, comparable, movements. The findings described above fit well with the "ideomotor theory", which proposes that anticipating action effects, automatically leads to a tendency to execute the action. Based on the ideomotor theory, the "theory of event coding" provides an information-processing framework that could accommodate tics in a new manner. The theory assumes that individual features of an event, such as motor and perception features of an action are bound into a common event file. Activating one component of the event file automatically activates the other components of the same event file. Tics might be viewed as event files that are characterised by hyper-binding. Re-defining tics as abnormally strongly bound event files might alter the way tics are perceived, investigated, and treated.

This thesis addresses the question of whether tics can be viewed as excessively bound event-files. In study 1 and 2, presented in chapter II, the "Modified Rush Video Protocol", a video protocol that is frequently used to assess symptom severity in Tourette patients, was adapted to show that tic frequency increases when patients pay increased attention to their own tics, as compared to an "idle state" baseline. In study 3 (chapter II), attention was varied more systematically, using a behavioural paradigm. The results suggest that tic frequency decreases overall compared to the baseline, when patients focus their attention on a motor task. However, within the motor task, tic frequency was significantly higher when patients focused their attention on their tics as compared to focusing attention on finger movements or stimuli on a computer screen. This is in line with the theory of event coding, suggesting that thinking about a tic and its sensory effects may be enough to trigger its execution.

Study 4 (chapter III) used an adapted version of the "imitation-inhibition paradigm" in order to investigate interference in tic imitation. The results showed that facial tic-like movements,

compared to non-tic movements, are not influenced by incompatible visual movement information in Tourette patients, indicating that, once triggered, tic-event files are not influenced by competing visual information. This suggests that tics are so strongly bound that activation within the event file might spread quickly, irrespective of competing input.

Establishing motor event files is based on learning mechanisms, which are assumed to rely on synaptic plasticity on the neural level. While some motor skills, such as playing tennis, are usually acquired largely through explicit motor learning, tics are thought to possess large implicit motor learning components. Study 5, presented in chapter IV, investigated short-term and long-term explicit and implicit motor learning as a proxy to tic movement acquisition and the underlying neural mechanisms of motor learning, i.e. synaptic plasticity, using transcranial magnetic stimulation. The study employed an excitatory version of the "paired associative stimulation paradigm", which can be used to induce long-term potentiation-like effects in the primary motor cortex. Explicit motor learning was assessed using the rotary pursuit task, while implicit motor learning was assessed using the serial reaction time task. Both were measured immediately after inducing synaptic plasticity as well as nine months later. The results obtained in study 5 showed that healthy participants responded with the expected long-term potentiation-like plasticity, whereas the majority of GTS patients responded with long-term depression-like plasticity to the paired associative stimulation. Long-term potentiation-like responses correlated with superior short-term acquisition of implicit motor sequences across all participants. Moreover, long-term potentiation-like responses correlated positively with long-term consolidation of explicit motor learning skills in healthy participants but negatively in Tourette patients. Based on the finding that long-term depression-like responses in Tourette patients were associated with milder symptoms, reduced learning of implicit motor sequences, and superior long-term consolidation of explicit motor skills, a compensatory mechanism might be assumed.

Chapter V summarizes, integrates, and discusses all results on the basis of the theory of event coding, suggesting that it might be helpful for future research to conceptualize tics as event files that are characterized by hyper-binding and that synaptic plasticity might modulate binding of event-files. The chapter also provides an outlook into future research that will be needed to further corroborate the hypothesis that tics can be viewed as event files, it discusses how the hypothesis could be rejected and takes into account, which consequences the findings may have for future behavioural therapies for patients suffering from Tourette's syndrome.

Chapter I:

General Introduction

1.1 Gilles de la Tourette syndrome

Tics are a very common phenomenon in children (M. M. Robertson, 2008a) and can severely influence social interactions and daily functioning (Debes, Hjalgrim, & Skov, 2010), as well as subjective quality of life (Bernard et al., 2009), yet tics are still often not recognized as a neurological symptom (Mol Debes, Hjalgrim, & Skov, 2008). The French physician Jean-Marc Itard was the first person to describe Gilles de la Tourette syndrome (GTS) in 1825. He reported a single case of GTS in the Marquise de Dampierre (Teive, Chien, Munhoz, & Barbosa, 2008). However, the disorder was named after Georges Edouard Albert Brutus Gilles de la Tourette, who described nine patients suffering from what he called „maladie des tics", sixty years later (Gilles de la Tourette, 1885). Today, GTS is categorized as a childhood onset, neuropsychiatric disorder, that is characterized by multiple motor and phonic tics (DSM-5, 2013), and represents the upper end of the tic disorder spectrum.

According to the Diagnostic and Statistical Manual of Mental disorders, 5th edition (DSM-5), a diagnosis in the tic disorder spectrum can fall in one of the following categories: 1) *GTS* is characterized by i) multiple motor tics and phonic tics, ii) the tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset, iii) tic onset was before age 18, and iv) tics are not attributable to drugs (e.g. cocaine, amphetamines, methylphenidate, levodopa) or another medical condition (e.g. Huntington's disease, autism spectrum disorder, encephalitis); 2) *persistent (chronic) motor or vocal tic disorder*: the same criteria apply as in GTS, but tics are limited to either motor or vocal tics, and the patient has not been diagnosed with GTS; 3) *provisional tic disorder*: the same criteria apply as in chronic tic disorder but the symptoms have been present for less than 12 months (DSM-5, 2013). The other categories 4) *other specified tic disorder*, and 5) *unspecified tic disorder*, delineate tics that do not fall into the other categories but cause impairment, e.g. adult onset tics, or tics caused by drug intake (DSM-5, 2013).

Tics are suggestible (Jankovic, 1997) and contagious (Finis et al., 2012), and typically occur in bouts (DSM-5, 2013). They tend to wax and wane in frequency and intensity over the course of seconds, hours, days, and years. Moreover, the tic repertoire of a given patient typically changes over time.

1.1.2 Tics

Tics can be divided into motor, phonic (vocal), cognitive, and sensory tics (DSM-IV, 1993). Motor tics are sudden, repetitive, patterned movements, resembling voluntary movements or actions, but appear exaggerated and serve no apparent purpose. Phonic tics are sounds that are

produced by air movement through the vocal cords, nose, or mouth (Cath et al., 2011). The term "vocal" tic was replaced by the more precise term "phonic" tic, because the vocal chords do not necessarily have to be involved. Cognitive tics, or "impulsions", are repetitive thoughts, but, contrary to obsessions, they are not anxiety-driven. Instead, they typically constitute reactions to auditory, visual, tactile, or inner stimuli that trigger the urge to tic (Cath et al., 1992; A. K. Shapiro, Shapiro, Young, & Feinberg, 1988). Sensory tics are not tics in a strict sense. They are sensations that are associated with tics, and are currently assumed to grow increasingly unpleasant prior to a tic, until the tic is executed (see 1.3. for a detailed description of premonitory urges). Tics can be simple, for instance eye blinking, squinting, nasal flares, mouth twitches, throat clearing, single high pitched noises, barking or grunting; or complex, e.g. gestures, single words or sentences, squatting, jumping, repetitive touching or even rituals. Complex tics may appear intentional or compulsion-like, but are not intention-driven (Jankovic, 1997). Most tics occur in the face, head, shoulders, and neck (Jankovic, 1997).

Simple single tics are not easily distinguishable from single voluntary movements either phenomenologically (Paszek et al., 2010) or electrophysiologically (Flanagan, Jakobson, & Munhall, 1999). Electrophysiological data from a single patient showed that tics, like voluntary movements, involve an anticipatory tightening of the grip on an object, which the patient was holding, suggesting a voluntary component to tics, or at least awareness of a tic before it occurs (Flanagan et al., 1999). Moreover, a single eye-blinking tic does not look different from "normal" eye blinking. What sets blinking tics apart from physiological blinking is its repetitive and exaggerated nature (Paszek et al., 2010). More complex symptoms associated with GTS involve coprophenomena, i.e. copropraxia (automatic and involuntary execution of obscene gestures) and coprolalia (automatic and involuntary swearing); paliphenomena, i.e. palipraxia (automatic repetition of own actions) and palilalia / palilogia (automatic repetition of own syllables or words) (Munchau, 2011); and echophenomena, i.e. echopraxia (automatic imitation of others' actions) and echolalia (automatic imitation of others' syllables or words) (Ganos, Ogrzal, Schnitzler, & Munchau, 2012). All of these symptoms are currently classified as complex tics, although there is some debate as to whether these phenomena should fall into the same category as tics (Ganos, Ogrzal, et al., 2012). Echopraxia is a common phenomenon in GTS (Paszek et al., 2010), whereas coprophenomena, despite their public perception as the main phenomenon characterising GTS, only occur in 10-15% of all GTS patients (M. M. Robertson, 2011).

Tics have some similarities with other extra movements including myoclonus, chorea or

dystonia. However, two characteristics distinguish tics from other hyperkinetic movement disorders. First, most GTS patients experience tics as voluntary, intentional movements that are executed to transiently relieve an involuntary and uncontrollable urge to tic (Cavanna & Nani, 2013; Kompoliti & Goetz, 1998; Kwak, Dat Vuong, & Jankovic, 2003). Second, despite the increasing discomfort, tics can be suppressed to a certain degree for a few minutes up to a few hours (Jankovic, 1997), and patients often report suppressing their tics in public or "diverting" their most obvious tic, such as facial grimacing, to less obvious movements, for instance, leg or foot movements. Third, most tics are associated with premonitory sensations (see 1.1.3.). Interestingly, tics can occur during sleep, albeit less frequently than during the day. Sleep studies indicate, that overall movements in GTS patients are increased during sleep, suggesting hyper-arousal (Cohrs et al., 2001).

1.1.3 Premonitory urges

For a long time, tics were viewed as entirely automatic and uncontrollable motor phenomena. However, they appear to possess involuntary as well as voluntary action components (Cavanna & Nani, 2013). Not the execution of the tic is perceived as involuntary but the sensation associated with the tic, a premonitory sensation, or inner urge to move, which cannot be suppressed or controlled (Crossley, Seri, Stern, Robertson, & Cavanna, 2014; Kwak et al., 2003; Leckman, 2003; Reese et al., 2014). Approximately 80% of all GTS patients report to experience premonitory urges, especially adolescents and adults, making urges a prominent feature in the disorder (M. M. Robertson, 2011). It was thus later proposed to refer to tics as "intentional involuntary actions" (Jankovic, 1997; Lang, 1991); for review please see (Cavanna & Nani, 2013). In terms of sensory quality, premonitory urges have been likened to an itch (Lang, 1991), or the irresistible feeling that precedes sneezing. Some studies have used eye blink suppression in healthy controls as a control condition to create a strong urge to execute a blink (Berman, Horovitz, Morel, & Hallett, 2012; Mazzone et al., 2010).

Technically, premonitory phenomena may be divided into a) "sensory tics", i.e. "somatic sensations in the body, which lead the individual to perform voluntary movements to relieve the sensation", b) sensory phenomena / premonitory experiences, i.e. "uncomfortable, physical sensation in skin, muscles, joints or other parts of the body that may be accompanied by perceptual stimuli (visual, auditory, tactile)", c) urge, i.e. "a drive or impulse to perform repetitive behaviour in the absence of any obsession, worry, fear, or bodily sensation" and d) just-right experience, i.e. "a force, triggered by visual, auditory, or tactile perceptions, as well as a feeling of imperfection about actions and intentions, that leads to the individual

performing compulsive acts until the actions are felt by the individual to be complete" (Cavanna & Nani, 2013).

Just-right experiences are reminiscent of obsessions, apart from the lack of anxiety, which typically accompanies obsessions. However, the other three sub-divisions of premonitory sensations are debatable. They are partly overlapping and may have been introduced because they are subjective experiences and patients' descriptions tend to vary. Some patients are not even aware that they experience these phenomena, until asked about them in detail. Therefore, I will only refer to "premonitory urges" or simply "urges" in my thesis to capture the subjectively perceived urge to execute a tic.

It is yet unclear whether urges precede, occur at the same time, or follow the onset of tics ontogenetically. Self-reports of adult GTS patients suggest that they first became aware of urges around the age of 10, approximately 3 years after the average onset of tics. Although this may suggest that urges develop as a consequence of having tics, Robertson (2011) and Leckman and colleagues (1993) pointed out that this estimate may be due to difficulties of children at the age of 5-7 years to understand and describe the concept of urges (Leckman, Walker, & Cohen, 1993; M. M. Robertson, 2011). Moreover, it has been shown that awareness of premonitory sensations increases with age, not with tic duration, and may thus depend on cognitive development rather than time since tic onset (Banaschewski, Woerner, & Rothenberger, 2003). It is also still largely unclear why premonitory urges develop and what their neural underpinnings are (for more detail see paragraph 1.1.9.). However, it is clear that they significantly impair GTS patients' well-being. It has recently been shown that premonitory urges are positively associated with tic severity, comorbid symptoms of obsessive-compulsive disorder (OCD), anxiety; and negatively associated with perceived quality of life (Eddy & Cavanna, 2013).

1.1.4 Prevalence and course

GTS is a common disorder with a prevalence of approximately 0.3-1%, depending on the population investigated and the measures used (Centers for Disease & Prevention, 2009; M. M. Robertson, 2008a; Schlander, Schwarz, Rothenberger, & Roessner, 2011). The overall international lifetime prevalence of GTS has been estimated to be approximately 1% (M. M. Robertson, 2008a, 2011). That in children and adolescents aged 5-18 has been estimated to be approximately 0.4-3.8% (M. M. Robertson, 2008a). Epidemiological studies in the UK suggest prevalence rates in the range of 3.4-24.4% for all tic disorders (M. M. Robertson, 2008a). Estimations of prevalence rates may vary, due to changing definitions of GTS,

waxing and waning of tics, the ability to suppress tics, the decrease of tic severity over time in most affected individuals, and possibly the masking effects of co-morbidities (M. M. Robertson, 2008b).

GTS is 3–4 : 1 times more likely to occur in males than in females (Centers for Disease & Prevention, 2009; M. M. Robertson, 2008a). Data concerning the administrative 12 months prevalence in a sample of 2.2 million individuals in Germany found a prevalence of 0.8% for all tic disorders, indicating that they might generally be underdiagnosed and undertreated (Schlander et al., 2011). Most parents do not classify tics as a neurological symptom; hence, the average time until GTS is diagnosed (if at all) is at least 5 years (Mol Debes et al., 2008). Patients are typically relieved to receive a diagnosis because their tics are often misinterpreted as misbehaviour by their environment (Mol Debes et al., 2008). Prevalence rates are highest around the age of 10 and then decrease markedly after the age of 12 (M. M. Robertson, 2011; Schlander et al., 2011). This finding is probably due to the fact that most patients experience a peak in symptom severity around the of age 8-12 years, and seek medical advice as a result (Leckman et al., 1998). The first motor tics typically develop around the age of 5-7 years, phonic tics commonly follow several months to years later (M. M. Robertson, 2011).

The long-term prognosis for individuals with tic disorders is generally good. Clinical and epidemiological studies indicate that 59-85% of patients who are diagnosed with a tic disorder in childhood, are tic-free, or only have mild tics upon entering adulthood (Hassan & Cavanna, 2012; Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003). However, in the remaining 20%, the symptoms continue, may become even more pronounced after the age of 18 and then often have a debilitating effect on work and social life (Pappert et al., 2003). Good predictors for the long-term outcome in GTS patients are still lacking, mostly because GTS is a complex disorder, with a number of heterogeneous symptoms and comorbidities. It would require very large, longitudinal studies to determine developmental trajectories for relevant sub-groups. A recent review of the literature identified the following predictors for a poor long-term outcome in GTS: a higher tic severity in childhood, smaller caudate volume, poorer fine motor skills, and untreated comorbidities (Hassan & Cavanna, 2012).

1.1.5 Comorbidities

Approximately 90% of all GTS patients suffer from comorbidities, the most common of which are attention deficit hyperactivity disorder (ADHD; 60%) (M. M. Robertson, 2011) and OCD (41%) (Bloch et al., 2006). Anger control problems, learning disabilities, mood and anxiety disorders, oppositional defiant and conduct disorders, self-injurious behaviour, sleep

disorders, and autism have also been listed as comorbidities in GTS, but are much less common than ADHD and OCD (Ghosh et al., 2014; Khalifa & von Knorring, 2006). For instance, depression has an estimated lifetime risk of 10% in GTS (M. M. Robertson, 2006). However, the inferences that can be made from the existing data are limited, due to small sample sizes, inadequate statistical analyses, and cross-sectional data. In fact, different components of oppositional defiant disorder (ODD) have been recently associated with comorbid ADHD and OCD, rather than GTS (Roessner, Becker, Banaschewski, Freeman, et al., 2007; Thériault et al., in press). Not surprisingly, based on prevalence rates, male GTS patients are more often affected by ADHD, conduct and oppositional defiant disorders, anger control problems, and learning disabilities than female patients, whereas the latter are more often affected by OCD and self-injurious behaviour (M. M. Robertson, 2000).

While GTS and OCD appear to share some genetic components, ADHD and GTS co-occur but are not genetically correlated (Mathews & Grados, 2011). Longitudinal studies show that tic severity in childhood predicts tic severity in adulthood (Bloch et al., 2006), while childhood intelligence quotient predicts the persistence of OCD symptoms (Bloch et al., 2006). The association between tics, OCD symptoms and ADHD has been assessed in a longitudinal study in a sample of 776 individual, who were randomly selected in the US in 1975 (Peterson, Pine, Cohen, & Brook, 2001). The data show that tics in childhood predict an increase in OCD symptoms in early adulthood. Furthermore, OCD symptoms in childhood predict ADHD symptoms in adulthood, while ADHD symptoms in childhood predict OCD symptoms in adulthood (Peterson et al., 2001).

Mood disorders could, at least in a sub-group of GTS patients, be a consequence of the psychosocial pressure that is associated with having severe tics. In accordance with this assumption are longitudinal data showing that OCD symptoms and psychosocial stress predict future depressive symptoms in GTS patients (Lin et al., 2007). Patients with uncomplicated GTS have a better prognosis than patients with GTS and comorbid ADHD, or comorbid ADHD and OCD (Rizzo, Gulisano, Cali, & Curatolo, 2012). However, longitudinal studies in larger samples are needed to analyse associations between comorbidities in GTS more closely.

1.1.6 Genetic factors

GTS is a highly heritable disorder. First-degree family members of GTS patients have an estimated 5-100-fold increased risk to develop GTS (Pauls, Raymond, Stevenson, & Leckman, 1991; Scharf et al., 2013). An early twin study revealed concordance rates of 53-

56% for 46 monozygotic pairs and 8% for 13 dizygotic pairs for GTS, and 77-94% and 23% respectively, for tics. The study corroborates the assumption that the susceptibility to develop GTS might be largely genetically determined, but that the degree, to which symptoms develop, might be influenced by environmental factors (Hyde, Aaronson, Randolph, Rickler, & Weinberger, 1992; Price, Kidd, Cohen, Pauls, & Leckman, 1985). Environmental factors and gene x environment interactions might also explain why no single gene or genetic polymorphism has been identified yet to cause susceptibility to GTS, However, no study has specifically investigated gene x environment interactions in GTS yet.

In contrast to family studies, which look for rare alleles with a large disease-related effect, genome-wide association studies (GWAS) look for common variants, single-nucleotide polymorphisms that occur in many individuals, and only have a small effect concerning the investigated trait. This approach has become very popular because it works hand in hand with the common disease – common variant hypothesis (Reich & Lander, 2001). This hypothesis assumes that common disorders are caused by common alleles, alleles that many people carry. Only the accumulation of several of these common risk factors, each one benign as a single polymorphism, leads to a susceptibility to the disorder. The first GWAS investigating GTS was only published recently. The study included 1285 European GTS patients and, disappointingly, found no significant markers for GTS. The strongest signal was identified in rs7868992, which is located in a gene, involved in the expression of fibrillar collagen, primarily in cartilage, but also in the cerebellum (Scharf et al., 2013).

Rare variants associated with the risk to develop GTS have been found in genes associated with dendritic growth (Abelson et al., 2005; Kajiwara, Buxbaum, & Grice, 2009), histaminergic, and serotonergic pathways (Ercan-Sencicek et al., 2010; Fernandez et al., 2012; Moya et al., 2013). A large family study in 2040 individuals identified a region on Chromosome 2p to be significantly associated with GTS and chronic tic disorder (Tourette Syndrome Association International Consortium for Genetics, 2007). Surprisingly, none of the dopamine (DA) candidate genes that were targeted so far have shown a consistent association with GTS, although DA appears to play a pivotal role in GTS (Paschou, 2013).

Interestingly, GTS patients are more likely than the general population to have a first-degree family member with GTS, chronic tics, or early-onset OCD, irrespective of whether patients have OCD symptoms or not (D. Curtis, Robertson, & Gurling, 1992; Eapen, Pauls, & Robertson, 1993; Frankel et al., 1986; Kidd, Prusoff, & Cohen, 1980; McMahon et al., 1996; Pauls, Cohen, Heimbuch, Detlor, & Kidd, 1981; Price et al., 1985; M. M. Robertson & Gourdie, 1990; M. M. Robertson, Trimble, & Lees, 1988). Vice versa, OCD patients are more

likely than the general population to have a family history of tics. While OCD symptoms are more likely to occur in female relatives of patients with OCD or GTS, tics are more likely to occur in male relatives. Recent data suggest a heritability point estimate of 0.58 for GTS, and 0.37 for OCD. The genetic correlation between GTS and OCD was .41, confirming that there is some genetic overlap between the two disorders but that they might have distinct genetic architectures (number, frequency and distribution of genetic risk factors) (Davis et al., 2013). Rare alleles (frequency < 5%) explained 21% of the variance of GTS heritability but 0% in OCD heritability (Davis et al., 2013). Matters are additionally complicated by data indicating that GTS might be inherited bilineally (transmission by both parents) (Hanna, Janjua, Contant, & Jankovic, 1999). Bilineal transmission presupposes non-random mating behaviour in GTS patients and patients with OCD symptoms and adds to the complexity of genetic analyses. ADHD is also more common in family members of GTS patients, but is mostly accompanied by tics (O'Rourke, Scharf, Yu, & Pauls, 2009). No genetic correlations have been found between GTS and ADHD, but there is a genetic association between OCD and ADHD (Mathews & Grados, 2011).

In summary, transmission of GTS is probably multifactorial, polygenic, and bilineal, partly overlapping with OCD. Together with changing diagnostic criteria, similarities between GTS symptoms and OCD symptoms, and a pathophysiology that is only starting to be unravelled, it is not surprising that genetic risk factors, specific for GTS, could not yet be identified (Paschou, 2013).

1.1.7 Environmental factors

Numerous pre- and perinatal factors have been proposed to foster the development of GTS. However, with the exception of birth weight and maternal smoking, the associations between risk factors before, and during birth and tics are weak and inconsistent (Chao, Hu, & Pringsheim, 2014), even questionable (Taylor, Stern, Williams, Simmons, & Robertson, 2014).

Because GTS is more commonly found in men and because it peaks in puberty, it has been hypothesized to be connected to androgenic steroids (Conelea, Ramanujam, Walther, Freeman, & Garcia, 2014). Peterson and colleagues (1998) were able to show in a double-blind placebo-controlled crossover study that motor tic were transiently ameliorated by the intake of flutamide, a selective androgen receptor blocker (Peterson, Zhang, Anderson, & Leckman, 1998).

Also frequently reported is an association between stress and tic exacerbation, which has not been confirmed experimentally. In accordance with the hypothesis, patients report that tic exacerbation can be caused by strong emotional excitement, either positive (e.g. impending birthdays or a vacation trip) or negative (e.g. emotional trauma, social gatherings) (Silva, Munoz, Barickman, & Friedhoff, 1995). However, a small study in 8 children with GTS and anxiety disorder showed no relationship between physiological arousal (heart-rate) and tic frequency during stressful tasks (Conelea et al., 2014), and a study inducing stress experimentally in 10 adolescent GTS patients failed to record an increase in tic frequency, or severity, during stress. Tic suppression was less effective under stress though (Conelea, Woods, & Brandt, 2011). However, overall motor tics, phonic tics, depression, and anxiety in 60 children and adolescents with GTS were correlated with the number of minor negative life events (e.g. relations with family and peers, school achievements), whereas the severity of compulsions, aggression, and ADHD symptoms were correlated with the subjective evaluation of major negative life events (e.g. divorce of parents) (Steinberg, Shmuel-Baruch, Horesh, & Apter, 2013).

A longitudinal study by Lin et al. (2007) suggests that adolescent GTS patients experience overall higher stress levels than healthy controls, with higher stress levels predicting depressive symptoms two years later. Moreover, higher psychosocial stress levels and symptoms of depression significantly predicted higher severity of GTS-related symptoms two years later (Lin et al., 2007). A recent study reported that older GTS patients (age 40-60) experience elevated levels of social impairment even compared to younger GTS patients (Man et al., 2014). Research on the physiological stress response showed that, although GTS patients appear to have normal diurnal-dependent cortisol levels and a normal down-regulation of cortisol levels after a stress response, they had an enhanced reactivity of the hypothalamic-pituitary-adrenal axis during increased stress levels prior to and in response to a lumbar puncture compared to a control group (Chappell et al., 1994), corroborating the assumption that GTS patients may be more vulnerable to stress than healthy individuals. Unfortunately, in addition to being more susceptible to social stress, children with GTS typically experience more social and educational problems than healthy children because of their salient motor or phonic tics, especially coprolalia. As a result, children with tics are often victims of bullying and stigmatization, which can cause withdrawal, depression, and anxiety. Comorbidities can additionally aggravate these problems by causing objective (Debes et al., 2010) and subjective impairment, more than tics do (Bernard et al., 2009).

1.1.7.1 Consequences

Tics are partially suppressible for a few minutes up to a few hours (Jankovic, 1997), and patients frequently suppress their tics in public or "divert" their most obvious tics to less obvious movements, to avoid drawing attention in public. Although tic suppression requires attention, effortful control, and is accompanied by an increasing, uncomfortable urge to execute tics, the majority of patients frequently choose to suppress tics, due to the social friction they can cause. More than 68% of a large sample of 672 participants with a chronic tic disorder reported to have been treated differently because of their symptoms. Over 30% had been discriminated against rudely and 17% had even been asked to leave a public place (Conelea et al., 2013). Over 40% reported avoiding social events or group activities because of their tics. It is, thus, not surprising that tic frequency, the severity of premonitory urges, and comorbidities have been associated with psychosocial impairment and lower quality of life in GTS patients (Eddy & Cavanna, 2013).

Approximately 25-50% of patients between 40-60 years are single or divorced (Man et al., 2014). Out of 200 patients, 5.9% were not able to work or retired early, 2.2% reported their GTS symptoms were the determining factor (Dodel et al., 2010). Suicide attempts were recorded in 4.8% of a sample of 524 GTS patients. This group was characterized by higher symptom severity, a higher rate of comorbidities (especially depression, anxiety, and ADHD), as well as drug or alcohol abuse, unemployment, a forensic history, or a family history of suicide attempts (Gharatya et al., 2014). Much less attention has been paid to factors that naturally alleviate tics. Patients frequently report that their tics decrease when they focus on a task that can induce flow (Csikszentmihalyi & Rathunde, 1992), such as playing a musical instrument or exercising (Gilbert, 2006).

1.1.8 Dopamine

DA has received most attention in connection with GTS (Buse, Schoenefeld, Munchau, & Roessner, 2012). Before describing neurotransmitter-related hypotheses and findings in GTS, it should be pointed out, that the precise delineation of abnormalities in neurotransmitter transmission in humans is difficult. DA levels in humans can only be measured indirectly. Moreover, any differences in a neurotransmitter system that are associated with a disorder could be the cause of that disorder, or the consequence of the system adapting to the disorder, or another symptom based on a common cause. To complicate matters further, DA phasic and tonic levels, as well as receptor density, are regulated by complex feedback mechanisms. Therefore, most findings could be caused by a number of different factors. For instance,

phasic DA is released as the result of action potentials, whereas tonic DA refers to the relatively stable, extracellular DA concentration in the synaptic cleft. Tonic DA levels depend on how quickly DA diffuses, and how efficiently DA transporters channel DA from and to the synaptic cleft, based on the concentration of DA levels in the synaptic cleft, which is determined via stimulation of auto-receptors in the membrane of the neurons. The number of postsynaptic DA receptors can also be adapted based on available extracellular DA levels. Any of these mechanisms could be affected and / or compensated for in GTS patients, making neurotransmitter-related findings difficult to interpret (Grace, 1995). Moreover, given the wide array of symptoms and comorbidities associated with GTS, interactions between different neurotransmitter systems are likely, but even more difficult to investigate.

Neurotransmitter systems other than DA so far implicated in GTS include serotonin, noradrenaline, glutamate, Gamma-Aminobutyric acid (GABA), acetylcholine and opioids. However, DA has been the prime candidate neurotransmitter system investigated in GTS, mainly for two reasons. First, because GTS can be successfully treated with D2 DA receptor blockers (e.g. haloperidol) (Pringsheim, 2009; E. Shapiro et al., 1989; Weisman, Qureshi, Leckman, Scahill, & Bloch, 2013) and DA re-uptake inhibitors (e.g. tetrabenazine) (Porta et al., 2008), and second, because DA is highly active in the prefrontal cortex (PFC) and the striatum; both areas have been found most consistently to be structurally and functionally altered in GTS (please see paragraph 1.1.9). In addition to DA, serotonin is also highly active in the basal ganglia (BG) (Gurevich & Joyce, 1996) and has been associated with OCD. The assumed imbalance / hyperactivity of DA in GTS led to a number of hypotheses, including DA hyperinnervation, supersensitive DA receptors, pre-synaptic DA abnormalities, DA tonic-phasic dysfunction, or a combination of these factors (Buse et al., 2012; Leckman, Bloch, Smith, Larabi, & Hampson, 2010).

The hyperinnervation hypothesis proposes that GTS is based on an excessive number of presynaptic DA terminals, especially in the striatum. This hypothesis was investigated with a number of different approaches. Studies measuring binding in vesicular monoamine transporter type 2 found mixed results but the majority of studies showed no differences between GTS patients and healthy controls (Albin et al., 2009; Ben-Dor et al., 2007; Meyer et al., 1999). While a number of in vivo (Malison et al., 1995; Muller-Vahl, Berding, Brucke, et al., 2000) and post-mortem studies (Minzer, Lee, Hong, & Singer, 2004; Singer, Hahn, & Moran, 1991; Yoon, Gause, Leckman, & Singer, 2007) measuring DA transporter binding consistently found increased DA transporter binding in the striatum and frontal areas, single-photon emission computed tomography (SPECT) findings were inconclusive. An increase in

DA transporter density in the striatum was found in 35 GTS patients compared to healthy controls (Liu et al., 2010; Malison et al., 1995; Muller-Vahl, Berding, Brucke, et al., 2000), but could not be replicated in other samples of overall 40 GTS patients (Heinz et al., 1998; Hwang, Yao, Fu, & Yang, 2008; Stamenkovic et al., 2001). Most of the patients investigated in these studies received medication. SPECT studies in medication naïve GTS patients revealed an increase in DA transporter binding in 19 GTS patients (Cheon et al., 2004; Serra-Mestres et al., 2004), but no difference in another 14 patients (Wong et al., 2008). Interestingly though, this study found increased serotonin transporter binding in the caudate/putamen in GTS patients with and without comorbid OCD (Wong et al., 2008).

Supersensitivity of DA receptors refers to an increase in the number of postsynaptic DA receptors. This hypothesis was corroborated by two post-mortem studies showing an increased number of D2 receptors in the PFC of GTS patients (Minzer et al., 2004; Yoon et al., 2007). Positron emission tomography (PET) and SPECT studies found heightened D2 density in the caudate and left ventral striatum (Wolf et al., 1996; Wong et al., 2008), whereas a study investigating medication-naïve GTS patients found no difference between patients and healthy controls (Muller-Vahl, Berding, Kolbe, et al., 2000). In contrast, decreased D2 binding has been reported for a number of extrastriatal regions in 8 medication-naïve GTS patients (Steeves et al., 2010). Similarly, a recent PET study also indicated that the binding potential for D2 receptors in bilateral putamen was decreased in both GTS patients and, to a lesser degree, GTS patients with comorbid OCD. This indicates decreased striatal D2/3 receptor availability. A single dose of amphetamines increased symptom severity in uncomplicated GTS patients, but not in patients with comorbid OCD, and correlated with changes in binding potentials in the striatum (Denys et al., 2013). Overall, findings concerning hyperinnervation of the striatum and supersensitivity of DA receptors in GTS remain inconclusive. However, it should be pointed out that the brain is a homeostatic system and may adapt do dopaminergic medication over time (Grace, 1995). This, and the inclusion of patients with comorbidities in samples that are too small to control for the effect of comorbidities, make it difficult to draw firm conclusions from the studies described above.

The most popular model is based on tonic and phasic DA. Decreased tonic DA levels in GTS may lead to an increase in phasic DA release, either by decreased stimulation of pre-synaptic auto-receptors, signalling a deficit in DA, by decreased stimulation of postsynaptic receptors leading to a compensatory increase in the number of those receptors, or by increased activity of DA transporters, which would also account for decreased tonic extracellular levels of DA. The main support for this model stems from the fact that neuroleptics (D2 receptor blockers)

can be successfully used to treat tics (Pringsheim, 2009; Weisman et al., 2013). Further evidence has been provided by studies reporting tic onset or exacerbation as a result of cocaine abuse (Cardoso & Jankovic, 1993; S. Chouinard & Ford, 2000), or the development of tic-like movements in patients suffering from Parkinson's disease as a result of levodopa intake (Black et al., 2003). However, the aggravating effect of DA-agonists on tics has been challenged by studies showing that cocaine may, in some cases, lead to a decrease in tics (Linazasoro & Van Blercom, 2007) and levodopa may not change symptom severity in patients with GTS or chronic tic disorder (Black et al., 2003; Gordon et al., 2007); it may even lead to a decrease in symptom severity (Black & Mink, 2000). Hence, the relationship between stimulants and tics is still largely unclear. PET studies suggest though, that subcortical DA release appears to be higher in GTS patients compared to healthy controls in response to a stimulant, supporting the assumption of excessive phasic DA (Singer et al., 2002; Wong et al., 2008).

To summarize, although DA appears to play an important role in the pathophysiology of GTS, there is still a lot to be learned about which mechanisms are disrupted and how they interact with other neurotransmitter systems. Further insight may be gained by investigating more homogeneous GTS samples in terms of age, comorbidities and medication intake. A more detailed analysis of interactions between transmitter systems, especially DA and serotonin may be necessary to learn more about the development of GTS and its relationship to OCD.

1.1.9 Brain areas associated with tics and urges

Actions that are primarily externally triggered, have been associated with activation in parietal, frontal (premotor) and primary motor cortex (M1), while actions that are primarily internally initiated, have been related to activation in prefrontal cortex, the SMA, pre-SMA, BG and M1 (Haggard, 2008). Functional magnetic resonance imaging (fMRI) studies investigating brain activation preceding tics, found activation in the insula, the parietal and cingulate cortices, M1, somatosensory cortex and SMA, 2 seconds prior to tic onset (Bohlhalter et al., 2006; Neuner et al., 2014). One second prior to tic onset, the sensorimotor cortex, thalamus, anterior cingulate, putamen, insula, amygdala, and cerebellum were activated (Bohlhalter et al., 2006; Neuner et al., 2014). These results suggest that tics and associated premonitory urges are complex processes, possibly composed of externally, as well as internally generated action components, but also emotional processes. While activation in M1, the BG, the thalamus, and the cerebellum are likely tic related, activation in the SMA, somatosensory cortex and amygdala have been ascribed to premonitory urges and their

sensory and emotional components. Premonitory urges were further investigated by comparing tics to self-paced movements, replicating increased activation in somatosensory and posterior parietal cortex, putamen, amygdala and, additionally, hippocampus. Activity in these regions correlated positively with tic severity, whereas activation in caudate nucleus and anterior cingulate cortex correlated negatively with tic severity (Wang et al., 2011). A study comparing tics to voluntary movements showed that tics were mainly characterised by strong cross-correlations in SMA - M1 activation (Hampson, Tokoglu, King, Constable, & Leckman, 2009), lending further support to a model that assumes that urges are based on the activation of motor plans in the SMA, leading to an increased likelihood to execute the activated motor plan (please see section 1.1.11.).

Tic suppression typically leads to an increase in premonitory urges and engages wide networks including prefrontal cortex, which has been consistently associated with top-down control, as well as primary sensorimotor cortex (probably urge-related activation), temporal, parietal and cingulate regions, the BG and the thalamus (Peterson, Skudlarski, et al., 1998). Comparing the urge to blink in healthy controls and GTS patients, revealed increased activation in fronto-striatal areas in GTS patients, suggesting increased activation in the BG but also increased frontal top-down control (Mazzone et al., 2010). A recent study was able to extract an increase in regional homogeneity in the left inferior frontal gyrus, which specifically correlated with the ability to suppress tics inside and outside the scanner (Ganos, Kahl, et al., 2014). This region has also been associated with externally triggered inhibition (Swick, Ashley, & Turken, 2011).

Overall, it can be assumed, that activation in the SMA, somatosensory areas and the amygdala are mainly associated with premonitory urges and that activation in motor cortices and the BG are primarily involved in tic generation (Wang et al., 2011). Three studies have attempted alleviating tics, using low-frequency repetitive transcranial magnetic stimulation (rTMS). Stimulation of the SMA caused a significant reduction in tic severity (Kwon et al., 2011; Mantovani et al., 2007) but not stimulation of the pre-motor cortex or M1 (Munchau et al., 2002).

1.1.10 Pathophysiology

Parallels between tics and habits have been drawn, partly because the BG, the thalamus, and the frontal cortex are associated both with the formation of habits and with tics (Ganos, Roessner, & Munchau, 2012; Leckman et al., 2010), and partly because tics, like habits, are outcome-independent, stimulus driven actions that do not require specific attention.

Furthermore, both are repetitive actions but are also subject to change over time. The strongest evidence for the involvement of the thalamus and the BG in GTS pathophysiology currently stems from the successful treatment of tics with deep brain stimulation of the thalamus, and the internal segment of the globus pallidus (GPi). At least 63 very severely affected GTS patients experienced moderate to large improvements in symptom severity in response to deep brain stimulation (Muller-Vahl et al., 2011).

Structurally, the BG can be sub-divided into several nuclei, which play an important role in action selection, implementation of learned motor and cognitive sequences and performance monitoring in goal directed behaviour. The BG, consisting of the striatum (putamen & caudate), the subthalamic nucleus, the GPi, the globus pallidus externus (GPe), and the substantia nigra, receive input from motor, associative and limbic areas of the cortex. The output structures of the BG send inhibitory signals to motor parts of the thalamus, either directly via the GPi, or indirectly, via the GPe and the subthalamic nucleus. The thalamus then projects back to frontal cortical areas. This feedback loop has been termed the cortico-striato-thalamo-cortical (CSTC) loop. Because the information sent from different input areas of the cortex is processed in anatomically different regions within the BG, the CSTC loop has been functionally subdivided into motor, associative and limbic circuits (Alexander & DeLong, 1985).

The striatum is the only BG structure that contains a network of interconnected GABAergic neurons, the medium spiny neurons, connecting the neurons that project to other nuclei in the BG. These medium spiny neurons represent weak, inhibitory connections between projection neurons (Jaeger, Kita, & Wilson, 1994). However, approximately 25% of neurons within the striatum, consisting of one type of cholinergic interneuron and three different types of GABAergic, local interneurons, exert strong inhibitory control over projection neurons (English et al., 2012); for a review please see (Tepper, Tecuapetla, Koos, & Ibanez-Sandoval, 2010). Neurochemically, the striatum can be divided into two parts. The matrix consists of matrisomes, and receives its main input from sensorimotor areas. It is therefore part of the sensorimotor loop. The striosomes receive their input primarily from the orbitofrontal cortex, the anterior cingulum and the insula and are therefore part of the limbic-associative loop (Crittenden & Graybiel, 2011).

Neuroimaging studies suggest that structural abnormalities of the sensorimotor loop might be associated with the development of tics, while more complex behavioural disorders might be related to structural changes in the associative and limbic loops (Singer, 2005; Worbe et al., 2010). Moreover, imaging techniques showed an abnormally high connectivity within the

CSTC loops in GTS patients, suggesting delayed, or absent maturation of connectivity patterns in GTS. Changes in connectivity in the sensorimotor and associative loops were correlated with the occurrence of simple and complex tics, while changes in the limbic and associative loops were correlated with OCD symptoms (Worbe et al., 2012).

Post-mortem studies revealed a decreased number, as well as an abnormal distribution of cholinergic and GABAergic inhibitory interneurons in the sensorimotor and associative areas in the striatum in GTS patients compared to healthy controls (Kalanithi et al., 2005; Kataoka et al., 2010). Kalanithi and colleagues (2005) found an imbalance of parvabulmin positive, fast-spiking, GABAergic interneurons in the striatum and the globus pallidus. Moreover, the total number of neurons was increased in the GPi, while it was decreased in the GPe and the caudate nucleus, (Kalanithi et al., 2005). Kataorka and colleagues (2010) found a decrease in both parvabulmin positive interneurons and cholinergic interneurons in the caudate nucleus and the putamen of 5 GTS patients. Cholinergic interneurons were only decreased in the sensorimotor and associative regions of the striatum, pointing to a disrupted inhibitory-excitatory balance between sensorimotor, associative and limbic loops in GTS patients (Kataoka et al., 2010). The abnormal distribution could be caused by genetically determined, aberrant neuronal migration of interneurons from the precursor of the GP to the precursor of the striatum, the cortex and the hippocampus, during embryogenesis (Kalanithi et al., 2005).

Selectively inhibiting the same group of fast-spiking GABAergic interneurons in the sensorimotor part of the striatum of mice leads to abnormal, excessive movements, similar to tics (Gittis et al., 2011). Moreover, injection of the GABA-A antagonist bicuculline into the anterior or posterior striatum in rats, triggered somatotopically related tic-like movements in forelimbs or hindlimbs respectively (Bronfeld, Yael, Belelovsky, & Bar-Gad, 2013).

Bronfeld and colleagues (2011) conducted a spatio-temporal analysis of tic-related activity in cortical and subcortical, motor-related brain areas on the basis of single cell recordings in monkeys (Bronfeld, Belelovsky, & Bar-Gad, 2011) (see Figure 1). The recordings showed that activation in cortical motor areas both preceded and followed tic-like movements, whereas activation of the medium spiny neurons in the striatum mostly preceded the movement, as well as activation in cortical areas. Activation in the striatum was specific for the somatotopic area representing the body part, in which the tic was about to occur. The medium spiny neurons' firing pattern was characterised by an unusual lack of specificity. Additional tic-related activity was found in cholinergic interneurons, a class of neurons, which has been also associated with reward-related motor learning and receives input from dopaminergic neurons (Graybiel, Aosaki, Flaherty, & Kimura, 1994). The GPe showed large-

amplitude, diffuse tic-related activation following movement onset, whereas activation in the GPi was characterized by a significant decrease or even complete cessation of the firing rate, following movement onset (Bronfeld et al., 2011). Single cell recordings in the GPi of 8 GTS patients confirmed that approximately 50% of the investigated neurons exhibited tic-associated activity. However, in humans the firing rate increased (Zhuang et al., 2009).

Interestingly, a recent fMRI study indicates that activation in the CSTC loops, preceding tics in adult GTS patients, appears to set off in cortical areas and then spreads to subcortical areas (Neuner et al., 2014). These data are more congruent with a model, suggesting that certain states can trigger motor plans in the supplementary motor area (SMA), which might trigger the urge to tic (Maia & Frank, 2011), at least in adults with GTS. However, fMRI is not an optimal method to investigate time-sensitive activation patterns.

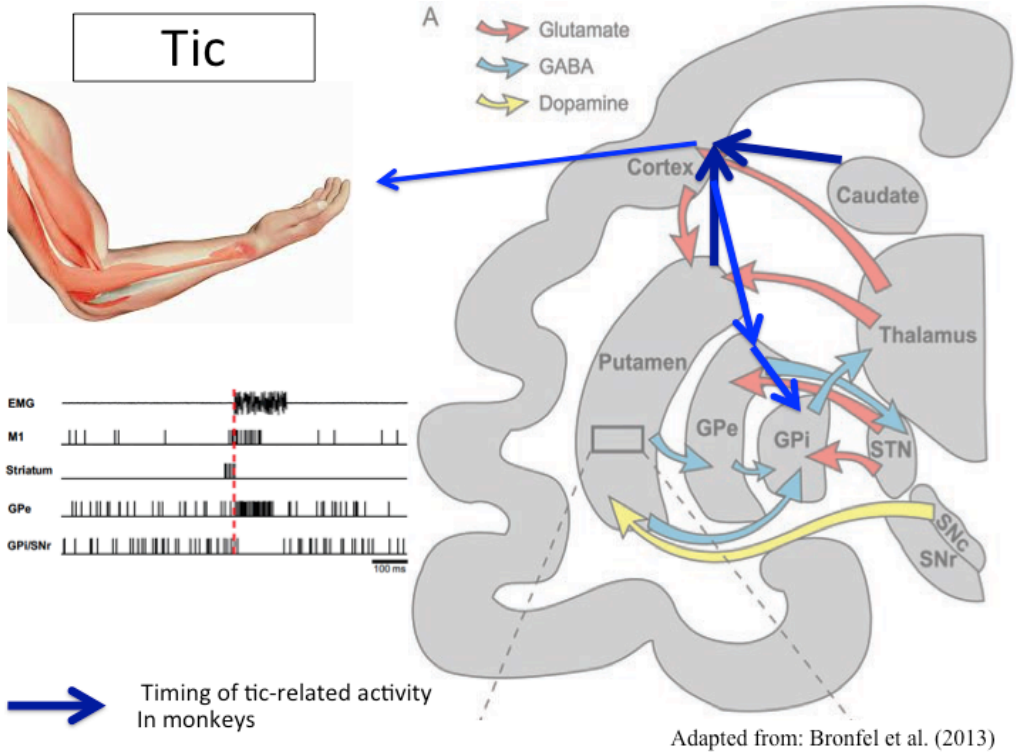


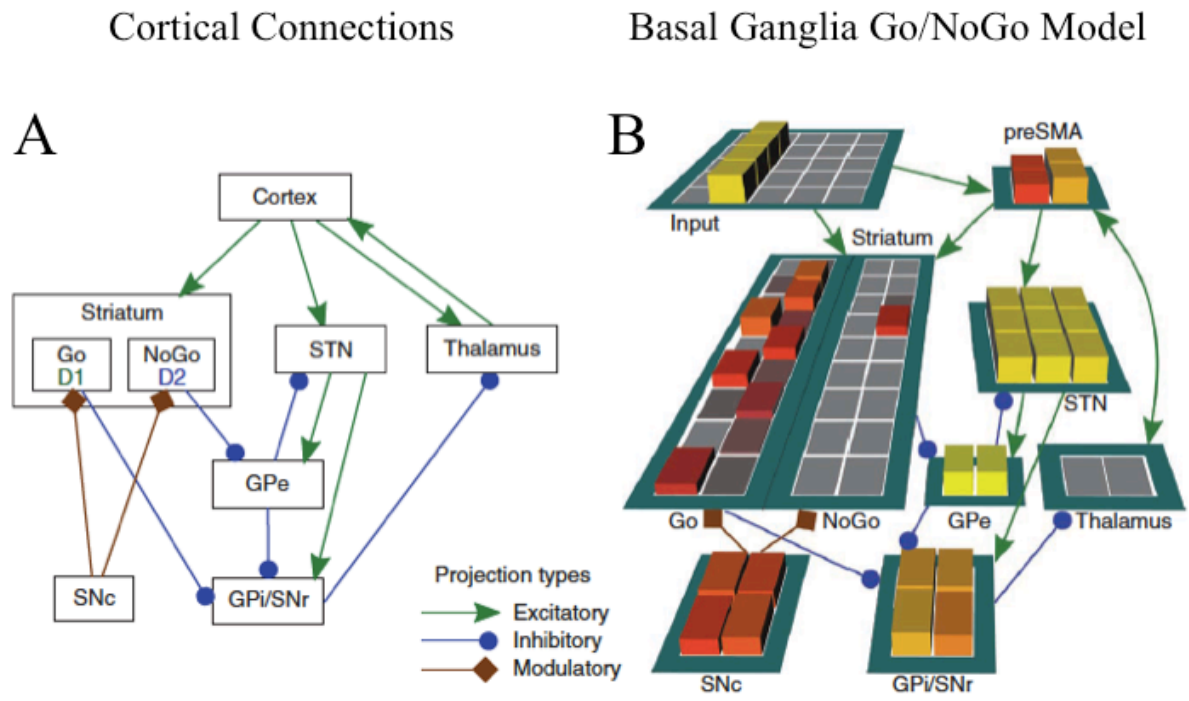
Figure 1: Tic-related Activation pattern. *Displayed are connection patterns in the cortico-striatal-thalamo-cortical (CSTC) loop. Blue arrows represent the timing of activation patterns associated with tics, measured by single cell recordings in monkeys. Activation in the medium spiny neurons in the striatum (caudate/putamen) precedes activation in M1 and muscle activity. M1 becomes active shortly before the muscle shows activation. Onset of muscle activation and activation of the GPe coincide; thereafter, the GPi changes its activity.*

1.1.11 Basal Ganglia Go/NoGo Model

Any given situation can be met with a set of different responses. If, for instance, a person enters a crowded room, he / she may instantly think of a variety of different alternatives to react. These may include looking for someone they know, trying to enter into a conversation with a group or someone who appears to be alone, or leaving the room. According to the basal ganglia Go/NoGo model (see Figure 2), current inputs or states (e.g. entering a familiar room, experiencing stress, the itch of a tag in clothing) will activate a selection of appropriate action plans in the SMA via cortico-cortical connections that have been coupled with the state before (by Hebbian learning). For instance, if someone typically reacts to social situations by leaving the room, this response would be currently prevalent because it is strongly linked to the situation by past learning mechanisms. The BG then „select" and gate one action that has the best reinforcement history, which is encoded by the Go and No-Go pathways (Frank, 2006). To come back to the example, leaving the room may offer relief from social anxiety and may therefore be experienced as rewarding.

Assuming an increased excitability of the Go-pathway relative to the No-Go pathway in GTS, Maia and Frank (2011) suggested that motor tics initially occur coincidentally together with certain states because the likelihood of a Go signal relative to a No-Go signal is overall higher. Based on the finding that stimulating the SMA creates urge-like sensations, it was assumed that urges are a reflection of the activation of motor plans (Fried et al., 1991). The SMA is a key cortical relay of the CSTC loop and would be activated by excessive BG activation. At the same time, cortico-cortical projections may pass on activation created by a state. A set of motor plans would be activated in the SMA every time a movement was coupled with a certain state. After a few pairings of state, SMA motor plan and BG gated action, the state would automatically cause the activation of a motor plan in the SMA by Hebbian learning mechanisms, thereby producing an urge to move (Maia & Frank, 2011).

For instance, if a stressful situation (e.g. a test in school) were initially coupled a few times with a certain motor tic, experiencing stress may already activate the motor plan for this tic. The activation of the motor plan may cause the urge to execute the movement. If the movement was strongly represented in the action repertoire, it might be easily triggered. Hence the experience of stress could easily trigger the urge to perform a tic and/ or the execution of the tic itself.



From: Maria & Frank (2011)

Figure 2: Basal Ganglia Go/NoGo Model. *Displayed are, on the left side a schematic illustration of cortico-striatal-thalamo-cortical (CSTC) connections and on the right side a computation model, simulating activation patterns within the CSTC loop.*

A: *Neurons of the striatal "Go" pathway project to and inhibit the globus pallidus internus (GPi)/the substantia nigra pars reticulate (SNr), which leads to reduced inhibition of the thalamus and thereby facilitates action execution. Neurons of the striatal "NoGo" pathway also project to the GPi, but indirectly via the globus pallidus externus (GPe). The GPe tonically inhibits the GPi hence, increased activation of the NoGo pathway leads to a reduction in thalamus activation and suppression of actions. Neurons from the cortex to the sunthalamic nucleus (STN) represent the "hyperdirect" pathway and are thought to modulate all actions to a degree.*

B: *The Go/NoGo model simulates input from current states, which is passed on to the (pre-) supplementary motor area (preSMA/SMA), where it activates a selection of different possible actions. The basal ganglia (BG) then "select" and facilitate the action with the best reinforcement history, represented by the activation in the Go and NoGo pathways, and suppresses all competing action plans.*

1.1.12 Cognitive control

Tics are often intuitively associated with failure of inhibition. However, studies show that young GTS patients exhibit increased top-down behavioural control over automatic motor response tendencies (G. M. Jackson, Mueller, Hambleton, & Hollis, 2007; Jung, Jackson, Parkinson, & Jackson, 2013; S. C. Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006). One study asked participants to switch between looking towards a visual target (pro-saccade) and looking away from a visual target (anti-saccade). Executing an anti-saccade requires high levels of cognitive control; switching between the two tasks is even more demanding and results in high error rates for anti-saccades (25-40%) in healthy controls (G. M. Jackson et al., 2007). GTS patients made significantly fewer errors but responded equally fast or even faster (depending on the timing of the cue) than healthy controls (G. M. Jackson et al., 2007; S. C. Mueller et al., 2006).

Enhanced cognitive control in GTS patients may be a result of permanently exerting inhibitory control over tics. GTS patients tend to suppress tics, especially in public, and may thus achieve training effects, and the associated structural changes of top-down inhibition (Jung et al., 2013; Muller-Vahl, Grosskreutz, et al., 2014). Further support for this assumption stems from a study conducted by Serrien et al. (2005), who found that tic suppression was associated with increased coherence in the alpha frequency band of the same prefrontal and sensorimotor networks that were associated with inhibition of voluntary movements in healthy participants (Serrien, Orth, Evans, Lees, & Brown, 2005).

1.1.13 Therapeutic interventions

Two things should be taken into consideration before treating GTS. First, subjective impairment does not depend on tic severity and should be assessed independently. Second, for many children and adolescents GTS does not interfere with daily life. In fact, the most important part of the treatment is psychoeducation of the patients and their families about the waxing and waning nature of tics, their natural course and their relationship with stress. Moreover, patients often suffer more from their comorbidities than their tics and these can often be treated successfully (Debes et al., 2010). Treatment is recommended predominantly when tics are so severe that they cause pain or injuries (Cath et al., 2011).

The most common pharmacological treatment of GTS is anti-dopaminergic medication (neuroleptics / antipsychotics) (Pringsheim, 2009; Weisman et al., 2013). GTS can also be treated with a variety of other drugs (e.g. alpha-2 agonists, tetrabenazine, clonazepam, naloxone), or in severe cases tetrahydrocannabinol (A. Curtis, Clarke, & Rickards, 2009;

Muller-Vahl & Grotenhermen, 2013) or even deep brain stimulation (Muller-Vahl et al., 2011). Some tics can be treated with botulinum toxin, temporarily weakening the muscle (Marras, Andrews, Sime, & Lang, 2001). However, some tics do not disappear but simply migrate to a different muscle.

There are also behavioural therapies for GTS, the most common one being the "habit reversal therapy" (HRT), alluding to similarities between tics and habits (Dutta & Cavanna, 2013). HRT teaches the patient to avoid tics by producing a response that is incompatible with the execution of the tic (Azrin & Nunn, 1973). A second approach is "exposure with response prevention", a classic behavioural approach (Hoogduin, Verdellen, & Cath, 1997). Exposure with response prevention instructs the patient to suppress tics as long as possible in order to habituate to the premonitory sensations. The concept was introduced in order to treat anxiety-related disorders because anxiety naturally subsides (Foa & Chambless, 1978). However, it has never been systematically shown that premonitory urges subside during tic suppression.

In light of those behavioural approaches, it has been suggested that the awareness of premonitory urges improves the ability to suppress tics in some patients (Leckman et al., 1993). Banaschewski et al (2003) investigated 254 children and adolescents aged 8-19 years. There was a significant increase in the number of children who reported premonitory sensations as well as an increasing ability to suppress tics with age. However, whereas 37% reported premonitory sensations 64% were able to suppress tics. Also, only 60% of children who gave unequivocal answers to both questions showed an overlap of premonitory sensations and the ability to suppress tics. Thus, the authors concluded that premonitory sensations are not a necessary prerequisite for tic suppression (Banaschewski et al., 2003). Moreover, it was shown in a sample of adults with uncomplicated GTS that there was no correlation between the ability to suppress tics and the extent of premonitory urges as measured by a questionnaire, further corroborating existing evidence that premonitory urges are not required to suppress tics (Ganos, Kahl, et al., 2012).

1.2 Theory of Event Coding

In this thesis, I would like to introduce the idea that tics may be considered event files, which are characterised by hyper-binding and thereby challenge the assumption that tics are the result of decreased inhibitory capacities in GTS patients. Any perception or action activates a network of brain areas, involved in processing the information received or required. The question is, how these distributed pieces of information can be flexibly bound into a coherent picture or event. The theory of event coding (TEC) (Hommel, Musseler, Aschersleben, &

Prinz, 2001) proposes that information about actions, objects, and events is stored in "files". Action files contain information about actions and the perceptions that are associated with them, i.e., whereas object files store information about objects and their specific features, such as chairs, bird, etc. Event files bind response-relevant features to stimulus-features. Hommel et al. (2001) proposed that individual components of an event, such as motor and perception components, may be represented in associated codes, that are stored in common event files (Hommel et al., 2001).

Event files can be created and investigated by simple reaction time (RT) tasks. Hommel (2004) showed that participants reacted faster and more accurately, either when a stimulus was repeated twice and required a response for the same hand, or when the stimulus and the hand switched compared to a switch either only in the response or only in the stimulus. According to Hommel, this indicates that costs in responses occur, if the current and the previous event file overlap partially. An imaging study confirmed that one paring of a stimulus (a picture of a house or a face) and a response (left-hand or right-hand mouse click) is already enough to create an event file that binds the stimulus and the response together. If one part of the event file is encountered again, the other part will be automatically retrieved. If a stimulus was repeated, i.e. a house or a face, but the required response changed, activation in the M1 that was associated with the previous response was suppressed. If a right-hand or left-hand response was repeated but the stimulus changed, activation of the competing stimulus region, i.e. the fusiform face area or the parahippocampal place area respectively decreased, suggesting automatic retrieval and inhibition of competing processes (Kuhn, Keizer, Colzato, Rombouts, & Hommel, 2011).

The TEC was based on the ideomotor theory, proposed by Carpenter (Carpenter, 1852) and adapted by James (James, 1950), which states that perceiving actions of others or imagining actions, evoke the tendency to perform this action, if the observer knows which perceptual effects the action produces. This has also been referred to as "ideomotor response activation"

Studies investigating the neural substrates of ideomotor response activation have found associated activation in the SMA and the hippocampal area; structures, that are typically associated with the storage of motor plans and declarative memory (Elsner & Hommel, 2001; Melcher, Weidema, Eenshuistra, Hommel, & Gruber, 2008). Based on these results, Melcher et al (2013) investigated the neural substrates of ideomotor learning (more specifically, the formation of action-effect associations), and found that it was associated with activation in areas comprising the hippocampus, the parahippocampal gyrus, the caudate nucleus and the angular gyrus (Melcher et al., 2013). While the structures located in the medial temporal lobe

have been typically associated with declarative memory, the basal ganglia are thought to be involved in habit learning (Knowlton, Mangels, & Squire, 1996; Packard & Knowlton, 2002), and tic formation (see paragraph 1.1.11.). The angular gyrus has been associated with sensory aspects in motor learning (Rosenthal, Roche-Kelly, Husain, & Kennard, 2009) and the monitoring of action consequences (Farrer et al., 2003).

Tics affect both action and perception and because their execution encompasses voluntary (most tics) as well as involuntary (urge to tic) components (Cavanna & Nani, 2013), they cannot be classified as a movement disorder in the classical sense like, for instance chorea or myoclonus. Flanagan et al. (1999) did not only show that grip force was adjusted in the anticipation of a tic in a single patient, but also, that tics can be cued. The patient in this study was asked to make a movement in one of two cued directions when given a "go" signal. The patient executed a tic more often in the cued direction during the waiting period between the cue and the "go" signal than in the other direction (Flanagan et al., 1999). Moreover, tics are suggestible (Jankovic, 1997) and contagious (Finis et al., 2012). All of these findings indicate that activating part of a tic-event file leads to the execution of a tic and may thus suggest hyper-binding of "tic event files". I will introduce new evidence that further supports an integration of tics into the TEC.

1.3 Questionnaires used to assess symptom severity

1.3.1 Yale Global Tic Severity Scale (YGTSS)

GTS symptom severity within the last week was assessed in all studies by a clinician, using the Yale Global Tic Severity Scale (YGTSS; (Leckman et al., 1989). The YGTSS includes a list of current symptoms, as well as number, frequency, intensity, complexity and interference with voluntary actions, which can be rated on an ordinal scale form 0-5 for motor and phonic tics. The overall tic severity (phonic & motor) score ranges from 0-50 and can be combined with an item ranking impairment by those symptoms from 0-50, so that the total score can range between 0-100. Of the existing GTS scales, the YGTSS appears to have the best psychometric properties. It covers a broad range of symptoms and it exhibits high internal consistency, stability and convergent as well as discriminant validity (Storch et al., 2005).

1.3.2 Modified Rush Video Protocol

It can also be useful to assess tic frequency immediately prior to a study because tics tend to wax and wane. The Modified Rush Video Protocol offers a standardized way of assessing tic frequency and intensity on a given day (Goetz, Pappert, Louis, Raman, & Leurgans, 1999).

Patients are seated on a chair and are then filmed for 1 minute alone in a room and for 1 minute with an experimenter present. In both conditions, once the whole body is filmed and once only the head and shoulders are filmed.

A slightly altered version of the Modified Rush Video Protocol was used in the studies presented here. First of all, a "tic suppression" condition was added, in order to assess how well patients are able to suppress their tics, taking into account their baseline tic severity. Second, patients were filmed for 2 minutes and the tic count was divided by two, in order to increase reliability of the tic count. This is especially important for patients who are only mildly affected. Tic suppression was filmed after the baseline conditions because it is yet unclear whether GTS patients experience "rebound effects" (a period of increased ticcing) after tic suppression (Verdellen, Hoogduin, & Keijsers, 2007).

1.3.3 Diagnostic Confidence Index (DCI)

The Diagnostic Confidence Index (DCI; (M. M. Robertson et al., 1999) is a questionnaire that assesses whether typical symptoms of GTS are present or were present in the past. This index can be used to establish the lifetime likelihood of having GTS. It is also suited to ensure that healthy controls have not had any symptoms in the past that are typically associated with GTS. However, psychometric properties have yet to be investigated. The score can range from 0 to 100 but different symptoms are weighed more heavily than others (e.g. coprolalia = 15 points, complex motor tics = 7 points), hence an ordinal scale will be assumed for testing.

1.3.4 Premonitory Urge for Tics Scale (PUTS)

Premonitory urges were measured using the validated German version of the "Premonitory Urge for Tics Scale" (PUTS; (Rössner, Müller-Vahl, & Neuner, 2010). This questionnaire was originally developed for children but has been validated in adult GTS patients and can range from 10-40 (Rössner et al., 2010; Woods, Piacentini, Himle, & Chang, 2005). Psychometric properties are good, but only in individuals above the age of 10 years (Reese et al., 2014; Woods et al., 2005).

1.3.5 The Attention Deficit Hyperactivity Disorder Self-Rating (ADHD-SR)

Current ADHD symptoms were assessed using the German ADHD self-rating scale (ADHD-SR; (Rosler et al., 2004), which ranges from 0 – 66 (cut-off varies, the strictest cut-off: at least 6 out of items 1-9 > 0 and at least 6 out of items 10-18 > 0).

1.3.6 Wender Utah Rating Scale Short Form (WURS-K)

ADHD symptoms were also rated on the German short version of the "Wender Utah Rating Scale" (WURS-K; (Ward, Wender, & Reimherr, 1993), the score ranges from 0 to 100 (cut-off = 30). The WURS-K asks patients to complete questions retrospectively regarding ADHD symptoms in childhood and has good psychometric properties (Ward et al., 1993).

1.3.7 Attention Deficit Hyperactivity Disorder Parent-Rating Scale (Fremdbeurteilungs-bogen; FBB-ADHD)

For two patients under the age of 18, scores were used from the German parent-rating scale (Döpfner, 2008). The scale comprises 20 items with a score from 0-3 (cut-off > .99).

1.3.8 Yale-Brown Obsessive Compulsive Disorder Scale (Y-BOCS)

OCD symptoms were rated on the interview version of the "Yale-Brown Obsessive Compulsive Disorder Scale" (Y-BOCS; (Goodman et al., 1989), ranging from 0 to 40 (cut-off = 16). The Y-BOCS encompasses 10 clinician-rated items assessing obsessive and compulsive symptom severity (thoughts and actions) with regard to time spent with OCD symptoms, distress, interference, resistance and degree of control over them (Goodman et al., 1989). The Y-BOCS has good psychometric properties and good sensitivity and specificity (Steketee, Frost, & Bogart, 1996). The Y-BOCS was treated as an ordinal scale for testing.

1.4 Ethics & consent

All studies were approved by the local ethics committee and conformed to the Declaration of Helsinki. All patients gave their written informed consent prior to the study.

1.5 Assumptions for statistical tests

The following assumptions were tested. For paired samples: normal distribution of the variables tested and the *difference* (variable 1-variable 2) between the variables tested where applicable. The Shapiro-Wilk test appears to be superior to the Kolmogorov-Smirnov test (Ghasemi & Zahediasl, 2012) and was therefore used for testing distributions. For independent sample: normal distribution of the variables was tested using the Shapiro-Wilk test and homogeneity of variance using Leven's test.

Some of the variables were not normally distributed (the video condition in study 2, chapter II, all of the suppression variables in study 3 chapter II and RT data in chapter III). In this case, the tests used in chapter II were also run for non-parametric data (Friedman test for

repeated measures analysis of variance (ANOVA) for paired samples, Wilcoxon test for comparing two means in a paired sample). However, where used, the non-parametric tests showed the same pattern of results (in terms of significance) as the parametric tests, hence I will report the results of the parametric tests for a more intuitive understanding for the reader. If assumptions for sphericity were violated, results from the Greenhouse Geisser test are reported. In chapter III, the RT data was log-transformed in order to achieve normal distribution.

Chapter II:

Attention to Own Tics Modulates Tic Frequency in Patients with Tourette Syndrome

2.1.1 Abstract

Despite the fact that GTS patients are asked to systematically pay attention to early warning signs of tics as part of the habit reversal therapy, and although it has been frequently reported that tics subside when patients pay attention to a task, it has never been systematically investigated how attention might modulate tic frequency in patients with GTS.

In study 1 and 2, tic frequency was determined in freely ticcing GTS patients while they were being filmed. In study 1, 12 patients were filmed i) alone in a room (baseline); ii) alone in front of a mirror (mirror condition). In study 2, these conditions were replicated in 16 patients with one additional condition: iii) patients were watching a video, in which they were shown not ticcing (video condition), in order to increase self-awareness without increasing awareness of tics, as in the mirror condition. In study 3, attention was systematically varied while patients were performing a motor task. Patients were asked to pay attention to i) whether they had executed any tics (tic attention condition), ii) which finger movements they had executed (finger attention condition), or iii) which colour a circle on the screen was (colour attention condition), in a pre-defined time frame. Additionally, patients were either allowed to tic freely or asked to suppress their tics during the task.

In study 1 and 2, tic frequency was significantly higher when patients watched themselves in a mirror compared to baseline. In contrast, tic frequency was significantly reduced in the video condition. In study 3, tic frequency was reduced overall during the motor task, compared to the baseline. Within the motor task, tic frequency was higher in the tic attention condition than in the finger attention condition or the colour attention condition. Tic suppression was equally good in all three conditions. Tic frequency in the finger attention condition did not differ from tic frequency under tic suppression.

Paying attention to one's own tics increases tic frequency when tics are not suppressed and appears to be specific for attention to tics, rather than attention to the self. Focusing attention on a motor task can reduce tic frequency overall. Different foci of attention during a motor task modulate tic frequency when patients tic freely but not when tics are suppressed, suggesting that tic suppression happens at a late stage of the motor output process. Interestingly, tic frequency can be decreased to the level of tic suppression by focus of attention without effortful tic suppression on part of the patient. This suggests that there are different possible mechanisms for tic reduction, which may have important implications for the development of new therapeutic interventions.

2.1.2 Theoretical background

As described in chapter I (paragraph 1.3.), GTS can be distinguished from other movement disorders by a bodily sensation, or premonitory urge, that is associated with most tics in approximately 80% of patients (M. M. Robertson, 2011). Premonitory urges are sometimes described as 'pressure-like,' or consisting of a tickling, cold, or warm sensation. They are subjectively experienced as occurring either at the location where a tic is about to occur, as a more generalized rising inner tension or anxiety, or both (Banaschewski et al., 2003). Because of these premonitory urges, the execution of tics is often experienced as a voluntary act with the goal of transiently relieving an increasingly uncomfortable sensation (Kwak et al., 2003).

Premonitory urges have been used to reduce tics in comprehensive behavioural interventions for tics. The HRT, a primary component of comprehensive behavioural interventions for tics, consists primarily of awareness training and competing-response training. During the awareness training, patients are taught to focus their attention on premonitory urges and become aware of them at an early stage. Competing-response training instructs the patient to perform a voluntary motor act that is incompatible with performing the tic. HRT has been investigated in several studies and seems to be effective in reducing tics, at least immediately following the treatment (Dutta & Cavanna, 2013; McGuire et al., 2014; Piacentini et al., 2010).

An alternative approach might be to provide patients with visual feedback about their tics. On the one hand, it could be hypothesized that increased awareness of one's own tics would lead to a decrease in symptoms, possibly through increased voluntary tic control, or deliberate relaxation mechanisms, which can underlie biofeedback. Biofeedback is a method that increases patients' awareness of physical processes, including heart rate, blood pressure, breathing patterns, or muscle activity. An uncontrolled single case study reported that symptoms in an adolescent GTS patient improved after EEG feedback training (Messerotti Benvenuti, Buodo, Leone, & Palomba, 2011).

On the other hand, visual feedback about one's own tics could lead to an increase in the tendency to perform tics. William James suggested that imagining a movement evokes the tendency to perform the movement to some degree (James, 1950), thereby extending the ideomotor action theory, originally developed by Carpenter (Carpenter, 1852). According to the ideomotor theory, actions are partly represented by their perceivable effects (such as sensory effects) and the activation of these action effects, for instance by imagining or anticipating an action (Elsner & Hommel, 2001), or by seeing someone else perform an already learned behaviour (Knuf, Aschersleben, & Prinz, 2001), activates motor tendencies to

perform the act that produces this effect (for a review see (Shin, Proctor, & Capaldi, 2010). A modern descendant of the ideomotor theory, the TEC, proposes that perception and action are not distinctly represented, but might be stored in common "event files" (Hommel et al., 2001). Hence, drawing the patients' attention to his/her own tics could lead to an increased activation of action-effect representations, and thereby to an increase in the tendency to tic.

The current study compared tics at a baseline condition to a condition, in which patients received immediate visual feedback about their tics. It was hypothesized that visual feedback might serve as biofeedback and thereby reduce tic frequency in GTS patients. To my knowledge, this is the first study investigating the effects of attention to tics on tic frequency, when tics are not suppressed.

2.1.3 Methods study 1

2.1.3.1 Clinical assessment study 1

In a pilot study, twelve GTS patients [mean age 29 years +/- 8.7 SD; 11 males; see Table 1], with a diagnosis of GTS according to DSM-5 criteria were tested (DSM-5, 2013). Mean YGTSS total tic severity was 17.31 +/- 8.3 SD; mean PUTS score was 25 +/-5.2 SD. Y-BOCS scores ranged from 0-10 (overall cut-off for OCD = 16). WURS-K scores were available from nine patients. For one additional patient WURS-K scores were extracted from a prior session, and two patients were assessed using a different questionnaire (FBB-ADHD; (Döpfner, 2008); for clinical data please also see Table 1). One patient fulfilled ADHD criteria according to the WURS-K (cut-off = 30) and another two patients fulfilled ADHD criteria according to the FBB-ADHD (cut-off = 1). This was in line with clinical data, indicating that those three patients fulfilled DSM-5 criteria for ADHD.

2.1.3.2 Task study 1

The task was modelled after the Modified Rush Video Protocol (Goetz et al., 1999), in which patients are filmed to evaluate current tic severity. This protocol consists of 60-second video ratings, but in this case, 120 seconds were used, in order to increase rating reliability. Patients were asked to tic freely under two conditions: i) alone in the room (baseline) and ii) alone in the room with a mirror placed in front of them (mirror condition). In the second condition, patients were instructed to watch their mirror image throughout the video recording. Patients were filmed during the whole study in order to ensure that they were watching themselves in the mirror, as well as for the purpose of tic frequency assessment.

Table 1: Demographic Data & Clinical Assessment for Studies 1, 2 & 3

	Study 1 (n = 12) Mean (range)	Clinical features	Study 2 & 3 (n = 17) Mean (range)	Clinical features
Age	29 (17-44)		31 (18-55)	
YGTSS total tic severity	17.3 (8-38)	12	16.7 (8-38)	17
YGTSS total score	26.1 (8-58)	12	25.5 (8-58)	17
PUTS	25 (17-32)	12	24.2 (12-33)	17
Total Y-BOCS	2.1 (0-10)	0	2.3 (0-11)	0
WURS-K/ FBB-ADHS	17.2 (3-38)	1/2	16.9 (0-44)	3
ADHD-SR			8.1 (0-24)	0
DSM-5 ADHD		3		2/1
DSM-5 OCD		0		0

Displayed are means and ranges for age, the Yale Global Tic Severity Scale (YGTSS), the Premonitory Urge for Tics Scale (PUTS), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Wender Utah Rating Scale short form (WURS-K), the parent-rated (Fremdbeurteilungsbogen) Attention-Deficit Hyperactivity Disorder (FBB-ADHD) and the number of patients who scored in the clinical range according to the cut-off values of the respective questionnaires or who have received a diagnosis for ADHD or obsessive compulsive disorder (OCD) according to the criteria provided by the Diagnostic and Statistical Manual of Mental disorders, 5th edition (DSM-5).

2.1.3.3 Rating procedure study 1

Every condition was filmed for approximately 2.5 minutes. For each video, tic frequency and tic categories (see Table 2; (Finis et al., 2012) were assessed for two minutes respectively by two independent, experienced raters. The tic rating started after the experimenter who turned on the camera had left the room. Both raters started counting tics at the same second for each video and counted for 120 seconds. The raters classified each tic according to the body part involved and time of occurrence. One rater was blind to the hypotheses.

2.1.3.4 Data analysis study 1

Three dependent variables were created: the variable "tic frequency" represents the number of tics per minute, while "tic variety" reflects the number of different tics in a given patient (e.g. eye blinking, nose wrinkling, etc.). As a third variable, "tic repetition" was introduced to assess whether the increase in tic frequency in the mirror condition (see below) was a consequence of echophenomena (see Finis et al., 2011). Thus, "tic repetition" represents events, during which a tic was immediately followed by the same tic.

The two conditions in study 1 (mirror, baseline) were compared by dependent samples *t*-tests for the variables tic frequency, tic variety, and tic repetition, respectively. All reported significance tests are two-tailed tests. Cohens *d* is reported as an effect size measure.

Total difference scores were created by subtracting tic frequency in the baseline condition from the mirror condition and by subtracting tic frequency in the baseline condition from the video condition. Thus, positive values reflect an increase in tic frequency, whereas negative values reflect a decrease. These difference scores were also calculated as percent difference (i.e. 100/baseline*mirror). Correlations between the tic count and the YGTSS, the PUTS, and the Y-BOCS as well as the inter-rater reliability were assessed using Pearson's r for parametric scales and Spearman's *rho* for ordinal scales.

2.1.4 Results study 1

Inter-rater reliability for tic frequency was very high, both for the baseline condition [$r = .98$, $p < .001$], and the mirror condition, [$r = .97$, $p < .001$]. Inter-rater reliability was also high for tic variety [$r = .89$, $p < .001$] and tic repetition [$r = .83$, $p = .001$] in the baseline condition, and for tic variety [$r = .71$, $p = .01$] and tic repetition [$r = .88$, $p < .001$] in the mirror condition. Tic frequency was significantly higher in the mirror condition than the baseline condition [$t(11) = -2.75$, $p = .02$, $d = -.65$] (see Figure 3).

Relative to the total number of tics, tic repetition did not differ between the baseline and the mirror conditions [$t(11) = 1.22$, $p = .25$]. Patients displayed a higher number of different tics in the mirror condition. The difference only reached marginal significance but the effect size was rather large [$t(11) = -2.67$, $p = .056$, $d = -.84$]. Correlations between the difference between the baseline tic frequency and the tic frequency in front of the mirror, relative to the tic frequency at baseline, and the total scores of the YGTSS, PUTS, WURS-K and Y-BOCS were not significant.

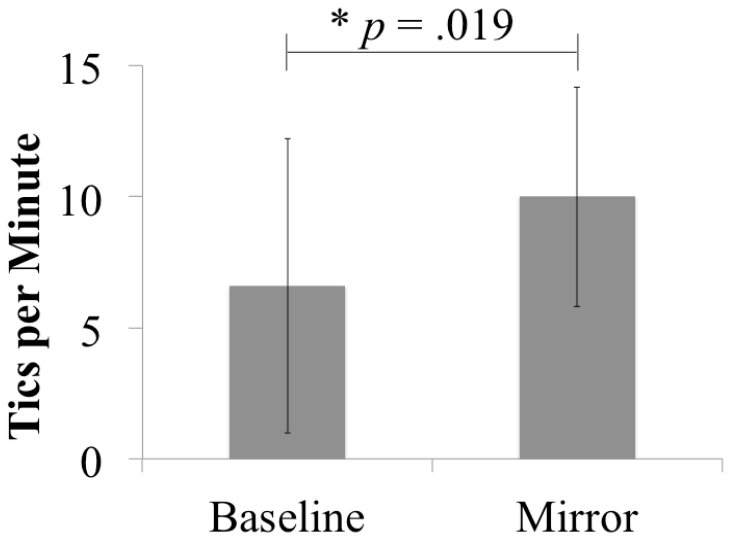


Figure 3: Number of Tics. *The number of tics per minute is shown for 12 GTS patients a) sitting alone in a room, b) sitting in front of a mirror. The tic frequency was significantly higher in the mirror condition compared to the baseline condition. Error bars represent standard deviations (+/- 1 SD).*
*Significance levels: *p < .05*

2.1.5 Discussion study 1

Originally, it was hypothesised that sitting in front of a mirror might serve as a form of intervention via feedback, increasing awareness of tics and thereby increasing tic control. Surprisingly, tic frequency increased when patients saw themselves tic in the mirror. However, research in social psychology has shown that seeing oneself in a mirror increases a person's self-awareness and thereby their awareness of social norms, which makes them more likely to adhere to those norms (Beaman, Klentz, Diener, & Svanum, 1979; Rochat, Broesch, & Jayne, 2012). Cooley introduced the concept of the "looking glass self," proposing that people construct their self-view by considering how they are perceived by other people.
On the basis of the results of study 1, it remained unclear whether tics occurred more frequently because of an increased attention to tics or merely because of increased self-awareness. In order to disentangle these effects, a second study was conducted. A condition was added in which the patient's self-awareness was boosted without drawing attention to concurrent tics. For the second study it was hypothesized that the tic frequency would increase in the mirror condition as compared to the baseline but not in the self-awareness condition without increased awareness of tics.

2.2.1 Methods study 2

2.2.1.1 Clinical assessment study 2

Seventeen GTS patients (mean age 31 +/- 9.9 SD; 15 males) participated in study 2. However, one had to be excluded from the mirror condition because they did not follow instructions and avoided looking in the mirror. Another patient had to be excluded entirely because they were chewing gum during the study, making the tic count impossible. Two of the remaining patients also fulfilled DSM-5 criteria for ADHD. All of the patients in study 1 were invited to participate again; eight of the sixteen patients included in study 2 had already participated in study 1.

Patients were unaware of the hypotheses as well as of the outcome of study 1. Patients in study 2 were also not included based on whether they had shown an increase in tics in the first study. There was no difference in tic increase between patients who participated again (mean increase = 2.38) and patients who did not return (mean increase = 5.13) [$t(10) = -1.09$, $p = .3$]. Mean YGTSS total tic severity was 16.71 +/- 7.5 SD; mean PUTS score was 24.18 +/- 6.48 SD. Y-BOCS values ranged from 0-11 with a mean of 2.29 +/- 3.79, WURS-K values ranged from 0-44 with a mean of 16.91 +/-11.62. According to the WURS-K (cut-off = 30), 3 patients scored in the clinical range of childhood ADHD. ADHD-SR scores ranged from 0-24 with a mean of 8.1 (+/- 6.8 SD). According to the ADHD-SR, none of the patients scored in the clinical range at the time of study (see Table 1).

2.2.1.2 Task study 2

The conditions from study 1 were replicated with one additional condition, in which patients were shown a video of a tic-free period of themselves, with the instruction that they should watch the video throughout the experiment (video condition). Video segments shown in the video condition were edited from tic-free phases of longer videos taken from patients in a "free ticcing" condition, recorded in previous studies (all patients had participated in studies before). A segment was selected, as long as possible, which was then looped for three minutes, in order to include natural eye blinking but avoid "jumping" of the video. For most patients it was possible to cut out a few consecutive seconds and loop them smoothly. Two patients were so severely affected that it was not possible to extract a longer tic-free phase, therefore the looped sequence was so short that it appeared like a still frame. However, a picture should also be sufficient to increase self-awareness (Joinson, 2001). The order of the three conditions in study 2 was pseudo-randomized to avoid order effects. Tics were assessed

by two independent raters (see Table 2). One rater was blind to the conditions and the hypotheses.

Table 2: Tic Categorization

Body parts	Movement category
Eye	Side/back, up/down, squinting, staring, blinking, winking
Eyebrow	Up, down/together, frowning
Nose	Nasal twitch, flare, sniffing, scratching, wrinkle
Mouth	Corners of mouth to side/up, smiling, mouth twitch, mouth to side, mouth down, mouth open, chewing, smacking, swallowing
Jaw	Jaw sideways / grinding, jaw clenching
Tongue	Licking lips, tongue protrusion
Lips	Purse lips, pouting, press lips together, lower lip twitch, upper lip up, grip on lips, bite lips
Chin	Chin down/forward
Head / Neck	Tilting, rotating, shaking, flexion, extension, nodding, head twitch, neck twitch / tensing neck muscles, scalp movements
Shoulder	Up/down, forward/backward
Trunk	Back stretching, abdominal tic

All tics were categorised according to "movement categories". The movement categories can be clustered into affected body parts but allow for narrower distinctions of tics than, for instance, the YGTSS.

2.2.1.3 Data analysis study 2

As in study 1, three dependent variables were created: the variable "tic frequency", i.e. number of tics per minute, "tic variety", i.e. number of different tics in a given patient, and "tic repetition", i.e. events during which a tic was followed immediately by the same tic. The three conditions in study 2 (mirror, baseline, video) were entered into a repeated measures ANOVA for the variables tic frequency, tic variety, and tic repetition, respectively. Paired sample *t*-tests between single conditions were used to determine which conditions differed significantly from one another. All significance tests reported are two-tailed tests. Cohens *d* is reported as an effect size measure. Total difference scores and difference scores relative to the baseline were created (i.e. 100/baseline*mirror). Correlations between the tic measures and the YGTSS, the PUTS and the Y-BOCS, as well as the inter-rater reliability, were assessed

using Pearson's *r* for parametric scales and Spearman's *rho* for ordinal scales.

2.2.3 Results study 2

Inter-rater reliability for tic frequency was very high for the baseline condition [$r = .97$, $p < .001$; n = 16], the mirror condition [$r = .97$, $p < .001$; n = 15] and the video condition [$r = .97$, $p < .001$; n = 16]. The order of conditions was neither significantly correlated with the difference in tic frequency between the baseline and the mirror condition [$r = .16$ $p = .58$], nor with the difference between the baseline and the video condition [$r = -.28$, $p = .32$].

A linear contrast using a repeated measures ANOVA (mirror, baseline, video) showed that tic frequency decreased significantly across the three conditions [$F(1, 14) = 7.43$, $p = .016$] (see Figure 4). Again, tic frequency was significantly higher in the mirror condition compared to the baseline condition, [$t(14) = -2.35$, $p = .034$, $d = -.27$]. However, tic frequency was not higher in the video condition compared to the baseline condition. In fact, tic frequency was reduced in this condition [$t(15) = 2.45$, $p = .027$, $d = .38$] (see Figure 4). Removing the two patients, whose videos appeared like a still frame, reduced significance to a trend-level. However the effect size remained the same [$t(13) = 2.08$, $p = .058$ $d = .4$].

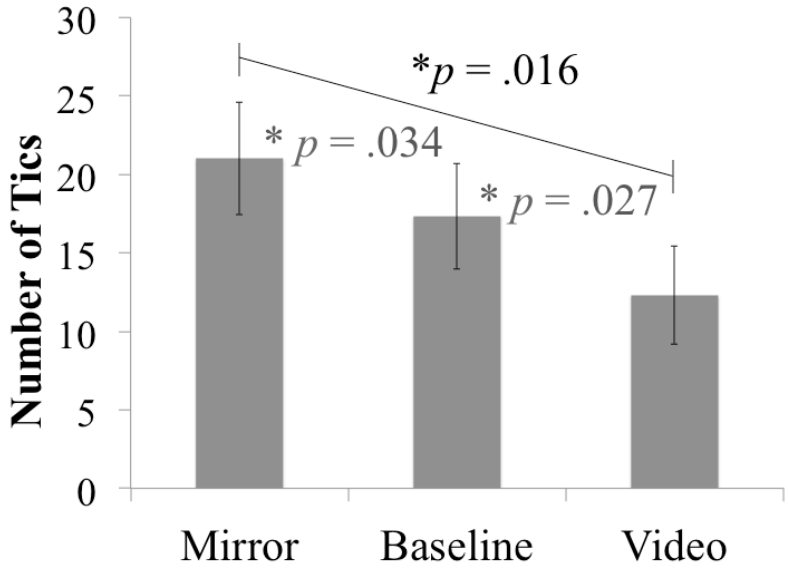


Figure 4: Number of Tics per Minute across Conditions. *The number of tics per minute is shown on the left for 16 GTS patients a) sitting in front of a mirror, b) sitting alone in a room, and c) watching a video of themselves not ticcing. Tic frequency decreased significantly across the three conditions. Post-hoc t-tests showed that tic frequency was significantly higher in the mirror condition compared to the baseline condition and significantly lower in the video condition compared to the baseline condition.*

*Error bars represent standard deviations (+/- 1 SD). Significance levels: *p < .05*

Moreover, removing those two patients increased the difference between the baseline and the mirror condition [$t(12) = -3.24$, $p = .007$ $d = -.42$], indicating that the patients added a "ceiling effect" to the data, i.e. their tic frequency was already extremely high in the baseline condition, so that it could not increase further in the mirror condition.

Again, repetition of the same tics, relative to tic frequency per minute, did not differ across conditions [$F(2, 28) = 1.82$, $p = .18$] (see Figure 5a). A repeated measures ANOVA (mirror, baseline, video) showed that tic variety differed significantly across conditions in a linear fashion [$F(1, 14) = 9.33$, $p = .001$] (see Figure 5b). Patients displayed a significantly larger variety of tics in the mirror condition than in the baseline condition [$t(14) = -2.21$, $p = .04$, $d = .31$] but not quite a smaller variety of tics in the video condition compared to the baseline condition [$t(15) = 1.73$, $p = .1$ $d = .28$]. Correlations were run between the difference measures (total difference and percent difference) and the total YGTSS score as well as motor and phonic symptom severity scores of the YGTSS, the total score of the PUTS, WURS-K and the Y-BOCS. The only significant correlation was found between percent change in tic frequency from the baseline to the mirror condition and the PUTS score ($r = .52$, $p = .05$). However, this correlation was not found in study 1, therefore it is unclear whether this association is meaningful.

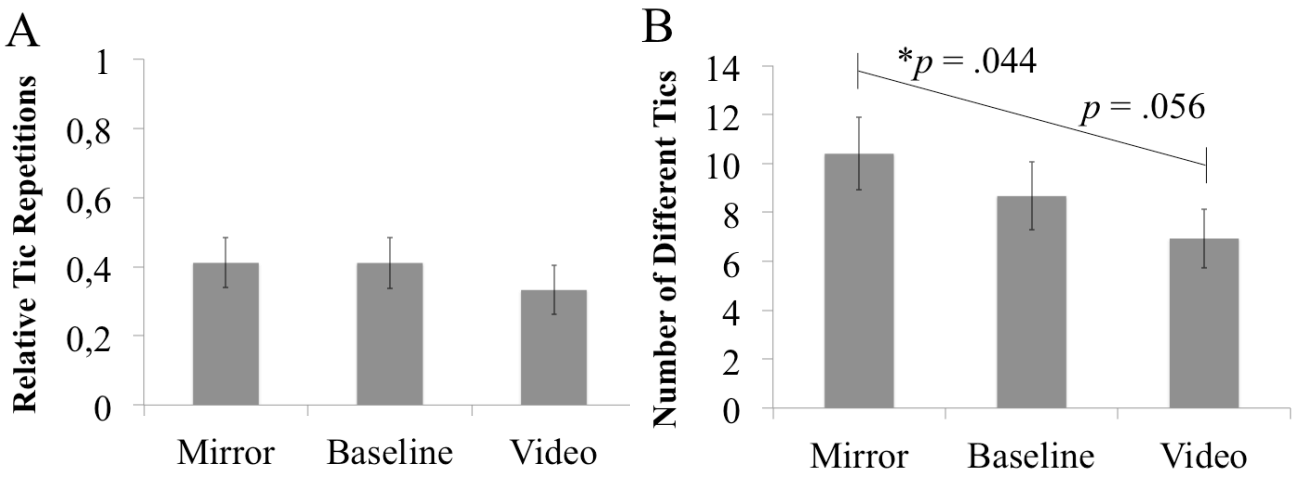


Figure 5: Different Tics across Conditions and Number of Tic Repetitions

A: *The number of repetition of the same tic did not differ across conditions.*

*Error bars represent standard deviations (+/- 1 SD). Significance levels: *p < .05*

B: *The number of different tics differed significantly across conditions.*

On average, patients displayed 51% of their tic repertoire as assessed by the YGTSS. Moreover, they had 16% additional tics that were not captured by the YGTSS. There were no significant differences between the conditions (see Table 3) in terms of tic repertoire. Additional tic categories were only included in this calculation if the tic occurred more than once, because tics can be difficult to judge for raters. Removing one outlier, who seemed to have difficulty giving information about his tic repertoire, changed the values to 53% and 8% respectively (see Table 3).

Table 3: Relation between Tic Repertoire and Tics Displayed in the Study

	% tics in the tic repertoire			% tics not in the tic repertoire		
	Baseline	Mirror	Video	Baseline	Mirror	Video
16 Patients	53	51	48	14	23	11
15 Patients	56	51	52	8	11	5

The left side of the table shows the average percentage of tics patients displayed, that were within their tic repertoire, while the right side of the table shows the average percentage of tics that were not within their tic repertoire, as assessed by the Yale Global Tic Severity Scale (YGTSS).

2.2.4 Discussion studies 1 & 2

The main results of study 1 suggest that paying attention to one's own tics increases tic frequency, if tics are not suppressed. However, it was unclear whether the increase in tic frequency was due to an increase in awareness of own tics or an increase in self-awareness. Therefore, tic frequency was determined in an additional condition in study 2, in which the patient's self-awareness was increased without drawing attention to concurrent tics, by showing them a tic-free video sequence of themselves. Interestingly, tics decreased compared to the baseline, when patients watched videos of themselves not ticcing. Thus, the "mirror effect" appears to be specific for attention to tics and not attention to the self.

Both results fit well with the ideomotor theory (James, 1950) and the TEC (Hommel et al., 2001). The ideomotor theory suggest that anticipating sensory effects of an action, that is part of a person's behavioural repertoire, establishes the tendency to perform that action, also termed "ideomotor response activation" (James, 1950). The TEC provides a theoretical explanation of how this mechanism may work, by assuming bidirectional associations

between codes for actions and perceptions (Hommel et al., 2001). If one of the codes is activated, the other one is automatically activated by association. A higher tic frequency in association with visual feedback may be the result of anticipated sensory effects of a tic, especially in association with an anticipated relief of premonitory urges.

As pointed out in chapter I, while the ideomotor response activation has been associated with activation in the SMA and the medial temporal lobe (Elsner & Hommel, 2001; Melcher et al., 2008), ideomotor learning (formation of action-effect associations), has been associated with activation in the medial temporal lobe, but also in the BG (Melcher et al., 2013). If tics are event files that are characterised by hyper-binding, anticipatory imagination may be a strong trigger for the activation of motor plans in the SMA and may, thus, lead to the activation and execution of further tics. This would also be in line with the BG Go/NoGo model, which proposes that urges might be caused by the activation of motor plans in the SMA and that states can serve as triggers (Maia & Frank, 2011). As a next step, it would be interesting to investigate whether tics can be more easily triggered than other movements.

Another explanation for an increased tic frequency is related to echophenomena. Echopraxia (repeating other people's movements) is a common phenomenon in GTS patients (Finis et al., 2012; Ganos, Ogrzal, et al., 2012). They tend to imitate movements or gestures of people surrounding them and also tend to imitate other patients' tics, sometimes integrating them into their own tic repertoire. Thus, one of the reasons why tic frequency was higher in the mirror condition could have been a form of echopraxia of one's own tics. However, patients did not repeat tics more often in the mirror condition than in the baseline condition. In contrast, patients displayed a higher variety of different tics, while the tic variety in the video condition was reduced nearly significantly compared to the baseline. Thus, the change in tic variety appears to be a consequence of altered tic frequency in general.

Another noteworthy result is that tic frequency was significantly reduced in study 2, when patients viewed themselves in a non-ticcing state as compared to the baseline. However, it is not clear whether the decrease in tic frequency in the video condition was due to a general shift of the focus of attention away from tics or due to increased attention to a non-ticcing self. In line with these results, it has been reported that tics subside when patients are focused on creative tasks, sports, or outdoor activities (Caurin, Serrano, Fernandez-Alvarez, Campistol, & Perez-Duenas, 2014).

2.2.5 Limitations

The main limitation of the present study is its small sample size, though finding an effect within a small sample suggests a strong effect. Further limitations include the partial overlap between the samples. However, the second study was not conducted to cross-validate the effect in a different sample but to add a condition that increases self-awareness without increasing awareness of tics (video condition). It should also be pointed out that the mirror condition and the video condition are not directly comparable because there are differences in temporal synchrony when watching oneself in a mirror as compared to watching oneself in a video. In a next step, it might be interesting to compare the tic frequency of patients, who watch a video of themselves while not ticcing, with the tic frequency of patients, who watch a video of themselves while ticcing.

In order to test the reliability of the results, the findings presented here will need to be replicated in a different, preferably larger sample. Premonitory urges should be assessed more systematically as a dependent variable, to determine possible interactions between attention to tics, premonitory urges, and tic frequency. Moreover, attention should be varied more systematically, while measuring its effects on tic frequency. It would be preferable to ensure shift of attention via a measurable, behavioural variable. Thus, a third study was conducted, controlling attention more systematically*.

**Study number 3 was developed and conducted in collaboration with Prof. Patrick Haggard, and his Ph.D. student Erman Misirlisoy, University College London.*

Contributions: based on the results of study 1, study 3 was conceptualized, designed and programmed by Erman Misirlisoy. The study was conducted (in Hamburg, at the same time as study 2) by Erman Misirlisoy as the leading junior investigator, and Valerie Brandt. The videos were rated and analysed independently by Erman Misirlisoy and Valerie Brandt. All data presented in this thesis was analysed by Valerie Brandt and interpreted mainly with regard to their association with study 2. Figure 6 was created by Erman Misirlisoy.

2.3.1 Methods study 3

2.3.1.1 Clinical assessment study 3

The sample was the same as described in "methods study 2" (see paragraph *2.2.1*). One participant was excluded from this study because they were aware of the main hypothesis (for clinical data please see Table 1). According to the Modified Rush Video protocol, patients showed on average 18.88 (+/- 13.19 SD) tics per minute when they were asked to tic freely, and 6.94 (+/- 9.43 SD) tics per minute when asked to suppress their tics.

2.3.1.2 Task study 3

In order to investigate the influence of attention on tic frequency more systematically, a paradigm was developed, which requires shifts of attention in different blocks of the task. Participants were seated in front of a computer and were asked to press one of their four fingers against their thumb every two seconds, in an alternating manner. Finger pressure sensors were attached to each of the four fingers of the dominant hand. Patients were asked not to follow patterns (for instance press 1-2-3-4, 1-2-3-4, etc.), and not to press the same finger against the thumb more than once.

Before starting the experiment, patients practiced the pacing of the task by pressing their fingers together in response to an auditory tone that was played every 2 seconds for a minute. Pressing a finger against the thumb triggered the appearance of a coloured circle (blue, green, red or orange) on the screen in front of the patient, lasting for 750ms. Appearance of colours was independent from the finger that was chosen to press against the thumb, and the order of colours was randomized, with the restriction of colours not being immediately repeated.

The task was divided into 1-minute blocks. In each block, patients were also presented with 3-5 auditory tones serving as memory cues, occurring randomly during the block. Each auditory cue would appear 250ms after the onset of a coloured circle. The information to be memorised was indicated prior to each block. There were 3 different attention conditions. In the first condition, patients were asked to focus on their finger movements and memorise the finger they had pressed against the thumb when they heard the auditory tone (finger condition). In the second condition, patients were asked to focus on the coloured circles, and, at the onset of the auditory cue, memorise the colour of the circle that was currently on the screen (colour condition). In the third condition, patients were asked to focus on their tics, and to memorise whether or not they had ticced in between the previous and the current coloured circle (tic condition; please see Figure 6 for experimental design).

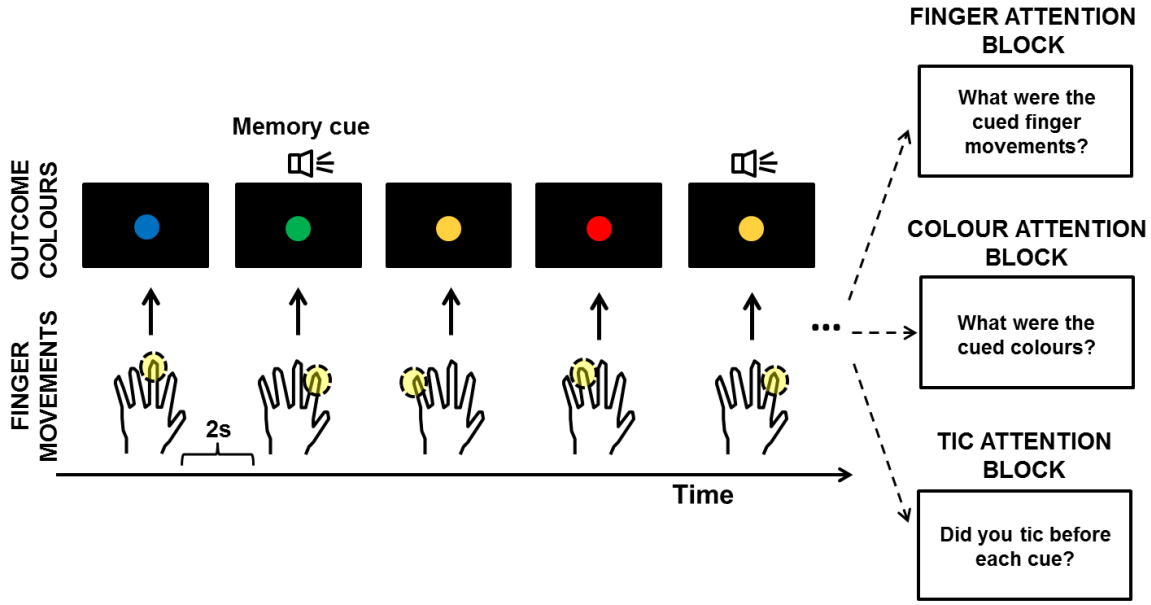


Figure 6: Experimental Design

Patients pressed one finger, selected endogenously at random, against the thumb, every 2 sec. Each finger press triggered a coloured circle to appear on the screen. At random times during each block, auditory cues occurred, instructing the patient to memorise a corresponding item. This was the finger moved, the colour displayed, or the occurrence of a tic, according to condition.

After the completion of each block, patients were asked to name the number of auditory cues that had occurred during the block. They were then asked to recall the task-related information they had memorised during the task and enter it into the computer in the correct order. For the colour condition, they were asked to enter the first letter of the colour words in the order of occurrence: 'r' for red, 'g' for green, 'b' for blue, or 'o' for orange. For instance, if the first auditory cue had coincided with a blue circle and the second auditory cue with an orange circle, the patient was asked to enter "b" and then "o" into the computer. Following the finger condition blocks, patients were asked to respond motorically, by pressing the respective finger against their thumb, indicating the fingers they had pressed together at the auditory cue. The occurrence of tics was indicted by entering 'j' for yes, and 'n' for no into the computer.

Each condition consisted of 9 consecutive 1-minute blocks and was once performed in a free ticcing state and once in a tic suppression state, resulting in a total of 54 blocks. The order of

conditions was pseudo-randomized across patients to avoid order effects in the task. During the whole experiment, patients were filmed in order to extract information about tic frequency.

2.3.1.3 Data Analysis Study 3

Tic frequency was rated by two independent raters. Both raters were blind to the conditions while ratings tics but were not blind to the hypotheses or the design of the experiment. All analyses were conducted with the mean of both raters. The baseline was technically the same as in study 2. However, for study 2, 120 seconds were rated and then divided by two to increase reliability of the rating, whereas in study 3 only 60 seconds were rated because all task-related blocks lasted 60 seconds. Furthermore, only one of the raters was the same person in studies 2 and 3 and out of the 17 patients participating in the study, one had to be excluded from study 2 and a different one had to be excluded from study 3.

Memory performance for the colour attention task and the finger attention task during free ticcing and tic suppression states was entered into a 2 x 2 repeated measures ANOVA. There is no objective possibility to assess accuracy for memory of tics because movements cannot be judged as tics or non-tics with absolute certainty by the raters. Furthermore, the video recording was only of the head and upper body, hence, tics in other body parts were not recorded. Thus, memory performance for tics was not included in this analysis. Tic frequency for attention to tics, fingers, and colours in a free ticcing state and a tic suppression state was assessed by a 3 x 2 repeated measures ANOVA. Paired samples *t*-tests served as post-hoc tests where applicable; cohens *d* is reported as an effect size measure. Correlations were run using Pearsons *r*. All significance tests were 2-tailed.

2.3.2 Results study 3

On average, patients pressed their fingers together every 1.8 seconds (+/- .30 SD). Repetitions of the same finger pressed against the thumb only occurred in 3.8% of all cases, indicating that patients were generally able to perform the task well. Memory was good for the finger condition during free ticcing (79%) and tic suppression (82%). It was also high for the colour condition during free ticcing (89%) and tic suppression (86%). A 2 (finger, colour) x 2 (free ticking, tic inhibition) repeated measures ANOVA on memory performance showed no main effect for attention condition [$F(1,15) = 2.9$, $p = 0.11$], no main effect for tic inhibition, [$F(1,15) = 0.02$, $p = 0.88$], and no significant interaction [$F(1,15) = 0.56$, $p = 0.46$], suggesting that there was no difference in task difficulty between the colour and finger

attention conditions, or between free ticcing and tic suppression states. The inter-rater reliability concerning tic frequency was very high across conditions ($r = 0.94$, $p < .001$). The mean of both raters was used for the following analyses.

A 3 (tic, finger, colour attention) x 2 (free ticcing, tic suppression) repeated measures ANOVA revealed a significant linear contrast for attention modulation [$F(1,15) = 11.35$, $p = .004$], a significant main effect for tic inhibition [$F(1,15) = 9.27$, $p = .008$] and a significant interaction between attention modulation and tic inhibition [$F(1.41, 21.09) = 5.31$, $p = 0.02$]. The significant main effect for tic inhibition indicates that patients successfully suppressed tics as compared to the baseline. Fourteen out of the sixteen patients had a lower tic count in the suppression condition than in the baseline condition. The tic count increased in the tic suppression condition in two patients.

Post-hoc *t*-tests for paired samples revealed that attention to tics resulted in the highest number of tics ($M = 128.5$), significantly higher than attention to colours [$t(15) = 2.17$, $p = 0.047$, $d = 0.34$; M = 97.75], which produced significantly more tics than attention to finger movements [$t(15) = 2.15$, $p = 0.048$, $d = 0.24$; M = 80.59]. There were no significant differences between the three conditions when patients were asked to suppress tics [all $t(15) < .55$, $p > 0.59$] (please see Figure 7).

Mean number of tics during the 1-minute baseline condition ($M = 18.88$) was significantly higher than mean number of tics per trial in the tic attention condition ($M = 14.28$ [$t(15) = 2.27$, $p = .04$]), indicating that any task, even the one with the highest tic count, reduced tic frequency significantly compared to the baseline. In contrast, there were no significant differences between any of the suppression conditions and the tic suppression baseline [all $t(15) < .18$, $p > .86$] (please see Figure 7).

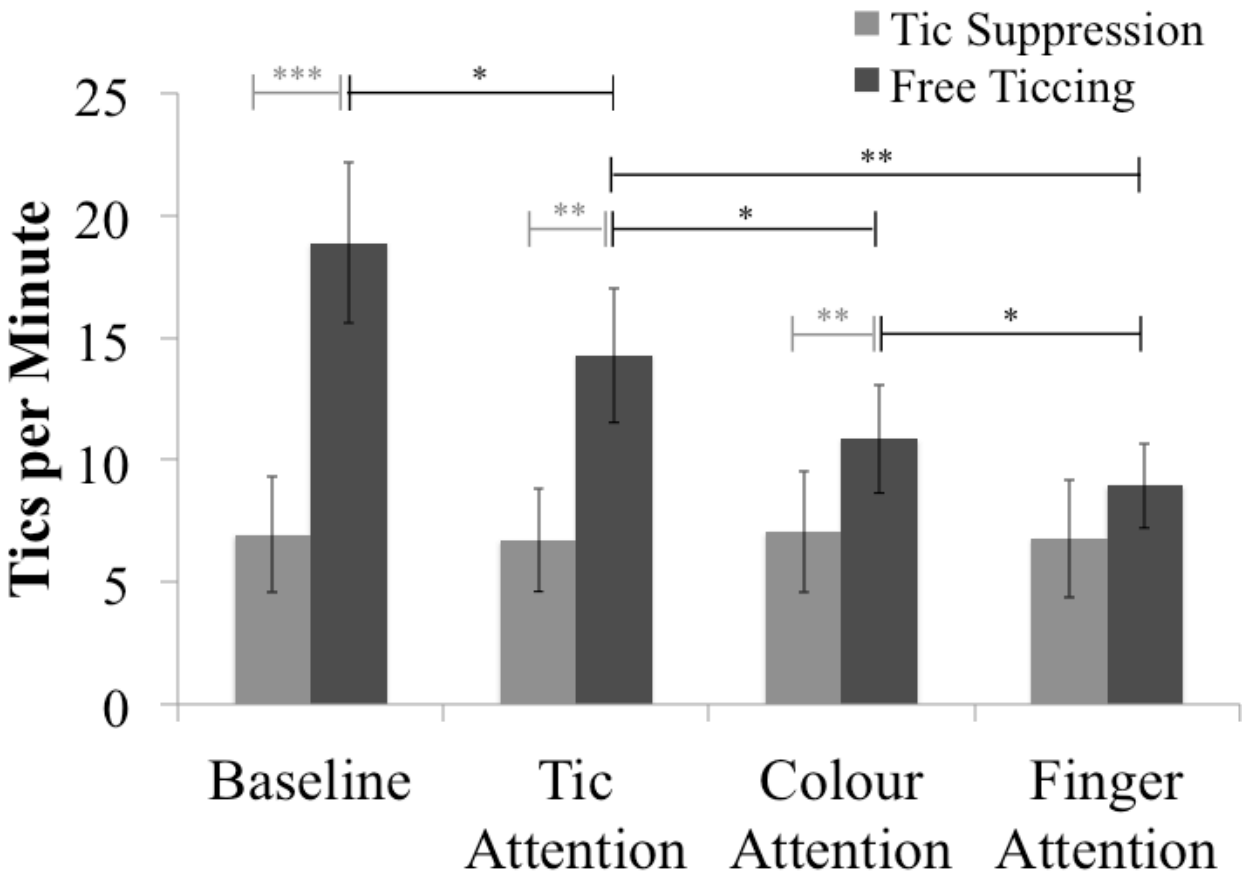


Figure 7: Mean Number of Tics per Block for each Task, Condition, and Baselines. *Black connecting lines indicate significant differences between free ticcing conditions and grey connecting lines indicate significant tic reductions when inhibiting tics within an attention condition (*p<0.05, **p<0.01). Tic frequency was significantly higher for the free ticcing baseline than all within-task free ticcing conditions (p < 0.05, Bonferroni corrected). There were no differences between baseline tic suppression and within-task tic suppression conditions.*

*Error bars represent standard deviations (+/- 1 SD). Significance levels: *p < .05, **p < .01*

Interestingly, there was no significant difference between the suppression baseline and the finger attention condition [$t(15)$ -1.18, p = .26]. There was also no difference between the video condition in study 2 and the tic attention condition in study 3 [$t(14)$ -.09, p = .93] (see Figure 8). Tic reduction from the baseline to the video condition in study 2 and tic reduction from the baseline to the tic attention task in study 3 were highly correlated (N = 15, r = .81, p < .001).

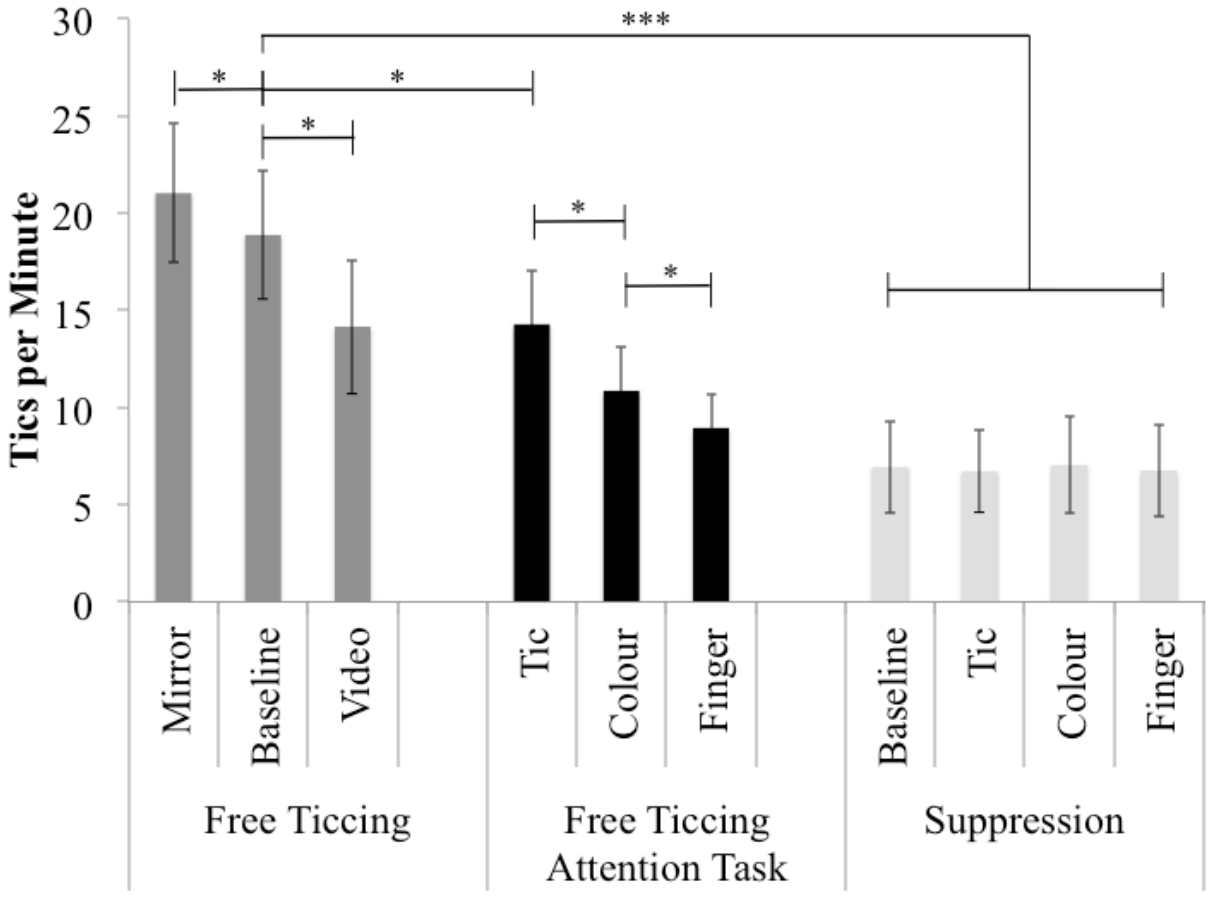


Figure 8: Tic Frequencies across all Conditions in Studies 2 & 3. *Data show tic frequency across all conditions in studies 2 and 3. On the left are tic frequencies for study 2. Tic frequency was significantly higher when patients viewed themselves in a mirror than at baseline. In contrast, tic frequency was significantly lower when patients watched videos of themselves while not ticcing compared to the baseline. Free ticcing attention conditions are displayed in the middle. The tic frequency in the tic attention condition in study 3 was not different from the tic frequency in the video condition in study 2. Tic frequency was significantly decreased in the colour attention condition as compared to the tic attention condition and significantly decreased in the finger attention condition compared to the colour attention condition. Tic frequency in all tic suppression conditions was significantly lower than the free ticcing baseline condition, but did not vary across the attention conditions. There was no difference in tic frequency between tic suppression and the finger attention condition.*

*Significance levels: *p < .05, **p < .01, *** p < .001*

2.3.3 Discussion study 3

Focusing attention on any of the three tasks reduced tic frequency compared to the baseline. Within the task, patients showed the highest tic frequency when focusing their attention on their own tics. Tic frequency was significantly lower in the colour condition, and even lower in the finger condition. These results corroborate the findings from the first two studies, indicating that focusing attention on tics increases tic frequency even without visual feedback.

The first interesting result with regard to attention is that any motor task requiring focused attention appears to reduce tic frequency. This is in line with anecdotal evidence reported by patients, describing that tic frequency decreases significantly in tasks requiring focused attention, such as playing a musical instrument or engaging in sportive activities (E. Nixon, Glazebrook, Hollis, & Jackson, 2014). In study 3, performance of the motor task reduced tic frequency even in the tic attention condition as compared to the free ticcing baseline. In study 2, tic frequency was reduced in the video condition, which shifted the focus of attention from ticcing to not ticcing but did not involve any motor task. The high correlation between those two difference measures implies that the reduction in tic frequency was comparable. Although no firm conclusion can be drawn as to the underlying processes, the correlation suggests that the decrease in tic frequency may have been due to a general shift of attention away from tics and not specifically to executing a motor task or focusing on a non-ticcing self.

,Shifting the focus of attention to external stimuli within the motor task, in this case colours, reduced tic frequency compared to focusing attention on own tics. Focusing attention on finger presses reduced tic frequency even more. It was originally hypothesised that tic frequency might be highest in the tic attention condition (internal, tic-related focus of attention), lower in the finger condition (internal, non-tic-related focus of attention) and lowest in the colour condition (external focus of attention).

The results could be interpreted in two ways. It has been proposed that, because most tics are voluntarily executed in response to an involuntary and uncontrollable urge, the boundaries between the experience of executing involuntary actions and executing planned motor actions, which are retrieved and selected voluntarily, are blurred in GTS (Cavanna & Nani, 2013). On the one hand, focusing on the generation of voluntary actions (finger presses) instead of involuntary actions (tics) may increase focused, controlled motor activation, thereby decreasing “noise” in the motor system. Previous research has shown that motor circuits in GTS patients show signs of disinhibition in an idle state (Heise et al., 2010; Orth, Amann, Robertson, & Rothwell, 2005); however, intracortical inhibition normalized prior to voluntary movements (Heise et al., 2010), and cortical excitability immediately prior to voluntary finger

movements was reduced in GTS patients compared to healthy controls, suggesting increased control over motor output (Jung et al., 2013). Attention to voluntary action selection and initiation of a voluntary movement may decrease the effects of "noise" created by BG overactivity, possibly by top-down control, and may therefore decrease the likelihood to tic. On the other hand, it has been shown that sensory stimulation such as pain (Riley & Lang, 1989), tactile, or proprioceptive (voluntary muscle contractions) stimulation (Wojcieszek & Lang, 1995) can relieves the urge to tic. Paying attention to finger pressing may have relieved some of the urge to perform tics.

Urges were not assessed online, therefore no conclusions can be drawn as to whether finger presses reduced the urge to tic or whether urges might mediate the relationship between attention and tic frequency. This would be an interesting study to conduct. However, it might be difficult to assess urges while, at the same time, attempting to vary attention to tics unless it would be possible to identify a physiological correlate of urges such as skin conductance or heart rate.

In line with previous research (Peterson, Skudlarski, et al., 1998; Serrien et al., 2005), the results of this study show that GTS patients were generally good at suppressing their tics. Only two out of sixteen patients were unable to suppress tics and experienced an increase in tic frequency in the suppression condition. Tic suppression during the task was at the same level as the suppression baseline and was not modulated by attention. This could either mean that tic suppression always requires a certain amount of attention and that tic frequency during suppression was not additionally modified by the task because all conditions are to some degree "tic attention" conditions. Or it could suggest that tic inhibition is not affected by effects of attention because the suppression of tics occurs at a late stage of motor output generation, i.e. when the tic is already "generated" and ready to be executed.

Interestingly, task performance was not influenced by tic suppression. This suggests that resources for tic suppression can be allocated independently from a motor task, further corroborating existing evidence for excellent executive functions in GTS patients (S. R. Jackson et al., 2011; S. R. Jackson et al., 2013).

2.3.3.1 General discussion

As pointed out before, it is generally assumed (although based on scarce evidence) that suppressing tics is associated with an increasing urge until the tic is executed and the urge is transiently relieved (Himle, Woods, Conelea, Bauer, & Rice, 2007). Focus of attention could play two important roles in this process. First, suppressing tics actually requires attention.

Although GTS patients are good at suppressing their tics when required, the long-term effects of continued tic suppression on tic frequency are unclear. Whether or not tic suppression is followed by a rebound effect is currently also under debate but systematic research suggests that it may be a subjective phenomenon (Himle & Woods, 2005; Hoogduin et al., 1997; Meidinger et al., 2005; Muller-Vahl, Riemann, & Bokemeyer, 2014; Specht et al., 2013; Verdellen et al., 2007). However, should the rebound effect exist, then it may be the result of increased attention to tics during tic suppression and immediately after tic suppression, until the urge to tic is relieved.

Second, a therapeutic concept based on diverting attention away from tics, instead of suppressing tics under an increasing urge, may be less aversive for the patient. The HRT is a behavioural approach, which mainly focuses on urges in order to detect early signs of a tic and increase tic control. The short-term benefits of HRT have been reported in some studies (Dutta & Cavanna, 2013; McGuire et al., 2014; Piacentini et al., 2010), though only very few are randomized, double-blind, and placebo-controlled. However, studies on the long-term effects of the HRT are rare and inconclusive (Dutta & Cavanna, 2013). Thus, it is unclear how increased attention to tics influences tic severity in the long run. It could be hypothesised that increased tic awareness over long periods of time may eventually lead to a permanent increase in tic severity.

2.3.3.2 Implications for treatment

Taken together, the results of all three studies may have important implications for behavioural interventions. The fact that there was no difference in tic frequency between active tic suppression and the finger attention task implies that tic frequency can be successfully reduced without effortful suppression on part of the patient. This reduction might happen at an earlier stage of the motor output process. It is possible that fewer tics are generated during distraction, which would make suppression unnecessary. Once a tic-motor plan is activated, execution of the motor plan may require effortful suppression. However, possible underlying mechanisms will need to be investigated more closely.

It might be worthwhile to develop and test interventions that stress attention to states, in which patients experience fewer tics, such as tasks focusing on voluntary actions rather than focusing on tics. Alternative therapeutic approaches might focus on (motor) skill training instead of tic suppression. An important question to address at this point would be whether tic reduction effects during motor tasks persist after the task and could thus generalize to

situations beyond the task. Practicing a certain skill in situations that normally lead to tic exacerbation (e.g. stress) may also help to ameliorate tics.

The results might eventually also be suitable to be incorporated into psychoeducation of parents and teachers. If the results can be replicated, parents and teachers should be informed about the detrimental effects of attention on tics, and the beneficial effects of motor skill development on tics. They may be advised to ignore tics in children with GTS and not draw unnecessary attention to them. Tics are often misinterpreted as misbehaviour and children are often berated for not sitting still and disrupting classes. However, more evidence will be needed in order to make recommendations to parents and teachers.

Moreover, these results challenge existing behavioural therapies for GTS. As mentioned in the introduction, exposure response prevention is based on the assumption that urges subside, similar to physiological arousal. However, this assumption has never been systematically tested. While HRT appears to be successful in the short run, the few long-term studies that exist show mixed results, with some treatment groups experiencing fewer symptoms than the control group a few months after treatment (Deckersbach, Rauch, Buhlmann, & Wilhelm, 2006), and some treatment groups experiencing more symptoms (Piacentini et al., 2010), or showing no difference (Wilhelm et al., 2003) compared to the control group. The results presented in this chapter could explain why this might be the case. Exposure response prevention and HRT increase attention to tics. Patients become more aware of early signs of tics and are better able to suppress them, or execute an incompatible response. Tics may initially subside because the therapy teaches tic suppression and suppression is a successful short-term strategy. However, in the long run, increased tic attention may lead to tic persistence or even deterioration. This hypothesis should be tested with care though before drawing treatment-relevant conclusions.

2.4 Limitations

There was no possibility of assessing urges online during the task. Thus, no conclusions can be drawn as to whether urges play a role in the relationship between attention and tic frequency. Moreover, task difficulty could influence tic frequency. However, there was no difference in performance between the colour attention task and the finger attention task. It was not possible to assess performance in the tic attention task but given the difference in tic frequency and the lack of difference in memory performance between the colour attention task and the finger attention task, it can be assumed that task difficulty did not influence tic frequency in this task.

2.5 Conclusions

Data from all three studies indicates that attention modulates tic frequency. Focusing attention on tics increases tic frequency in an idle state as well as during a motor task. Shifting attention away from tics leads to a reduction in tic frequency.

Chapter III

Event File Hyper-binding in Tourette Syndrome: Execution of Facial Tic-like Movements is not Decelerated by Incompatible Visual Stimuli

3.1 Abstract

Tic can be triggered in GTS patients by watching tics of other patients or single voluntary movements of healthy controls. This automatic imitation of movements is termed "echopraxia" and has been ascribed to a failure to inhibit normal imitation tendencies. However, inhibition is not typically impaired in GTS patients. The TEC proposes that different parts of an event, such as perceiving a stimulus and responding to it, are stored in action and perception codes, which are bound into a common event file. The aim of this study was to investigate whether tics might be viewed as event files that are characterised by hyper-binding. If so, it should be possible to trigger them with less interference from competing visual information, because they are movements that are represented and interconnected more strongly than other movements. It has previously been shown that expert dancers have stronger representations of movements occurring in their own dance style than movements occurring in a different dance style.

The present study investigated 16 GTS patients (mean age 29.19 years +/- 9.58 SD; 14 males) and 21 healthy controls (mean age 28.14 years +- 5.38 SD; 17 males), using an adapted version of the imitation-inhibition paradigm. Patients were asked to respond to two different auditory cues with either a facial movement that was part of their tic repertoire (tic-like movement) or a facial movement that was not (non-tic movement). At the same time, patients were presented with behaviourally irrelevant videos of the same two facial movements, which were either compatible or incompatible with the movement executed by the patient. Movements in healthy controls were matched to patients.

Healthy participants responded faster in compatible than in incompatible trials. GTS patients showed the same effect for non-tic movements. However, their responses were equally fast in incompatible and compatible trials, when the movement they were asked to execute was a tic-like movement. Patients did not make more errors than healthy participants, regardless of whether the cued movement was a tic-like movement or a non-tic movement.

The results suggest that tic-like movements are highly overlearned responses that can be triggered without interference by external, incompatible, visual movement stimuli. They also indicate that GTS patients do not have difficulties inhibiting movements if the task requires them to, not even when they are part of their own tic repertoire. Hence, the results are in line with the assumption that it might be useful to conceptualize tics as excessively bound event files, rather than a failure in inhibition.

3.2 Introduction

The studies presented in chapter II showed that paying attention to own tics increases tic frequency. This is in accordance with the ideomotor theory, which proposes that the anticipatory imagination of action effects can evoke the tendency to execute the respective action (James, 1950). The TEC provides an information processing mechanism that explains how this might work. The TEC proposes that events are stored in event files and that motor and perception components belonging to a common event are represented by bi-directionally linked codes. If one of these codes is activated, the other code becomes automatically activated by association (Hommel et al., 2001).

The neurobiological equivalent of the ideomotor theory and the TEC would be the activation of action representations in the brain by anticipating and thereby activating their sensory effects. Indeed, an fMRI study confirmed that presenting part of a newly created event file (e.g. a visual stimulus in a stimulus-response paradigm), automatically activated the cortical representation of the other part of the event file (e.g. the motor area for the respective response) (Kuhn et al., 2011).

Action representations are also activated when actions are observed in others. According to the action observation/execution matching model, an observer can immediately and automatically understand a behaviour that is part of their own motor repertoire because observing actions in others activates the same neuronal networks in the observer that are necessary for performing the observed action. This mechanism is thought to rely on the mirror neuron system, which describes neurons that are activated both in action execution and action observation (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). Thus, humans (and some animals) show an automatic tendency to imitate behaviour, which can, for instance, express itself as contagious laughing, coughing, yawning or very subtle mimicking of facial expressions in a conversation (Hatfield, Cacioppo, & Rapson, 1994; Rizzolatti, Fadiga, Fogassi, & Gallese, 1999). However, overt automatic imitation of complex motor behaviour such as gestures or facial movements (echopraxia) is not commonly found in healthy adults but can occur in certain disorders such as GTS (Finis et al., 2012).

More subtle automatic imitation tendencies can be assessed using behavioural paradigms such as the imitation-inhibition paradigm (Brass, Bekkering, Wohlschlager, & Prinz, 2000). One variation of the imitation-inhibition paradigm requires participants to lift the little finger or the index finger in response to a tone, while watching biological (finger) or non-biological (dot) movements that can be either compatible or incompatible with their own movement.

Motor responses in an observer can be facilitated when watching a compatible movement (i.e. prepotent response), probably because of the activation of corresponding action representations in the observer during action observation. This has been shown both in healthy adults (Biermann-Ruben et al., 2008; Jonas et al., 2007) and adults with GTS (Jonas et al., 2010). While healthy adults respond faster to biological movements than to non-biological movements when the movement is compatible with a simultaneously presented auditory cue, GTS patients do not show the same RT advantage but show increased interference in response to incompatible biological movements as compared to incompatible non-biological movements (Jonas et al., 2010). It has been hypothesized that this is a consequence of GTS patients exerting increased inhibitory control over motor behaviour in potentially "echogenic" situations (Ganos, Ogrzal, et al., 2012; Jonas et al., 2010).

However, GTS patients tend to "echo what they tic", i.e. they are more likely to imitate movements if they are part of their own tic repertoire (Finis et al., 2012). These results suggest that echopraxia might not simply be a result of decreased inhibitory capacities. A number of studies has failed to show that GTS patients display deficits in motor inhibition on the behavioural level (Eichele et al., 2010; Ganos, Kuhn, et al., 2014; Johannes et al., 2001; Ray Li, Chang, Hsu, Wang, & Ko, 2006; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008; Roessner, Becker, Banaschewski, & Rothenberger, 2007; Serrien et al., 2005; Thomalla et al., 2014). Moreover, there are a number of studies showing that GTS patients exhibit superior performance in certain motor tasks requiring high levels of cognitive control (G. M. Jackson et al., 2007; Jung et al., 2013; S. C. Mueller et al., 2006). Echopraxia may not be the results of decreased inhibitory control but may be the result of hyper-binding of tic-related event files.

I proposed in chapter I that tics may be event files, in which actions are excessively bound to perceptions, attention, and intentions. So far, no phenomenological (Paszek et al., 2010) or electrophysiological (Flanagan et al., 1999) differences could be identified between single voluntary movements and single tics. However, if tics are hyper-bound event files, they should be distinguishable from other, similar movements. If representations of tics are more strongly bound, there should be less interference by the activation of other movement representations, i.e. activation caused by watching another person perform a movement.

To test this assumption, the imitation-inhibition paradigm was adapted accordingly. Patients were asked to respond to an auditory cue by performing a facial movement that was part of their tic repertoire (tic-like movement) and to a different auditory cue by performing a movement that was not in their tic repertoire (non-tic movement). At the same time, patients

watched behaviourally irrelevant movements, which could be either compatible or incompatible with the movement they were instructed to execute.

If patients made more errors in the non-tic condition while watching movements that were part of their own tic repertoire, this would be indicative of reduced inhibitory capacities concerning tics because patients would not be able to suppress the prepotent response (tic) in favour of a different movement. In contrast, faster RTs in compatible tic movement trials compared to healthy participants would be an indicator of stronger cortical motor representations of tics. If RTs for tic-like movements compared to non-tic movements were not slowed down by incompatible movement videos in GTS patients, this would suggest hyper-binding and stimulus features and action features in tic-event files.

3.3 Methods

3.3.1 Participants

The study included 16 patients (mean age 29.19 years +/- 9.58 SD; 14 males) with a diagnosis of GTS according to DSM-5 criteria (DSM-5, 2013) and 21 healthy controls (mean age 28.14 years +- 5.38 SD; 17 males). None of the patients fulfilled criteria for OCD or ADHD according to DSM-5 criteria (DSM-5, 2013). However, one of the patients scored above a strict DSM-5 cut-off (at least 6 out of items 1-9 > 0 and at least 6 out of items 10-18 > 0) according to the ADHD-SR (Rosler et al., 2004).

Mean YGTSS total tic severity was 18 +/- 7.8 SD, mean PUTS score was 24.8 +/- 5.2 SD. Mean DCI score was 52.8 +/- 16.3 and Y-BOCS scores had a mean of 2.7 +/- 3.7. WURS-K scores were available from 15 patients with a mean of 20.4 +/- 13.6. ADHD-SR data was available for 15 patients with a mean of 12.7 +/- 9.7 (for clinical data please also see Table 4).

3.3.2 Task

Most GTS patients have at least one or two facial tics. The patients who participated in the study were asked to indicate a facial tic that was part of their current tic repertoire and to select one facial movement that was not, neither currently nor in the past. The experimenter then selected two videos from a pool of 3-second videos of single facial/head tics, showing the two movements named by the patient. The videos were previously collected from 7 different patients (6 male, 1 female) with their permission to use the videos for research purposes.

Patients were then asked to respond to a high- or a low-pitched auditory cue respectively by either executing their tic-like movement or by executing the non-tic movement. Patients were

asked to execute the tic-like movement so that it would feel as similar to their tic as possible. Patients often execute tics to achieve a just-right feeling (Cavanna & Nani, 2013), hence, the respective movement, for instance squinting, needs to be executed in a particular way to achieve this feeling. Patients were asked to do just this rather than simply squint.

Table 4: Clinical Assessment Study 4

	GTS patients (n = 16)	**Healthy controls (n = 21)**
	Mean +/- SD (range)	Mean +/- SD (range)
YGTSS total tic severity (0-50)	18 +/- 7.8 (10-38)	0
YGTSS total score (0-100)	26.1 +/- 10.5 (14-58)	0
DCI	52.8 +/- 16.3 (34-100)	0
PUTS	24.8 +/- 5.2 (16-33)	0
Y-BOCS	2.7 +/- 3.7 (0-10)	0.5 +/- 2.2 (0-10)
WURS-K	20.4 +/- 13.6 (0-44)	23.5 +/- 11.9 (5-42)
ADHD-SR	12.7 +/- 9.7 (0-30)	11.4 +/- 8.5 (2-30)

Data are means, standard deviations (SD) and ranges for the Yale Global Tic Severity Scale (YGTSS), the Diagnostic Confidence Index (DCI), the Premonitory Urge for Tics Scale (PUTS), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for 16 Gilles de la Tourette syndrome (GTS) patients, the Wender Utah Rating Scale short form (WURS-K) and the Attention-Deficit Hyperactivity Disorder self-rating scale (ADHD-SR), for 15 GTS patients.

Whether the tic-like movement was assigned to the high- or the low-pitched tone was counter-balanced across patients. At tone onset, patients viewed videos of either the tic-like movement or the non-tic movement. The videos were either compatible or incompatible with the movement executed by the participant. Each participant responded to 40 trials, presented in a pseudo-randomized order, with an equal likelihood of tic-like vs. non-tic movements and compatible vs. incompatible trials (please see Figure 9 for study design).

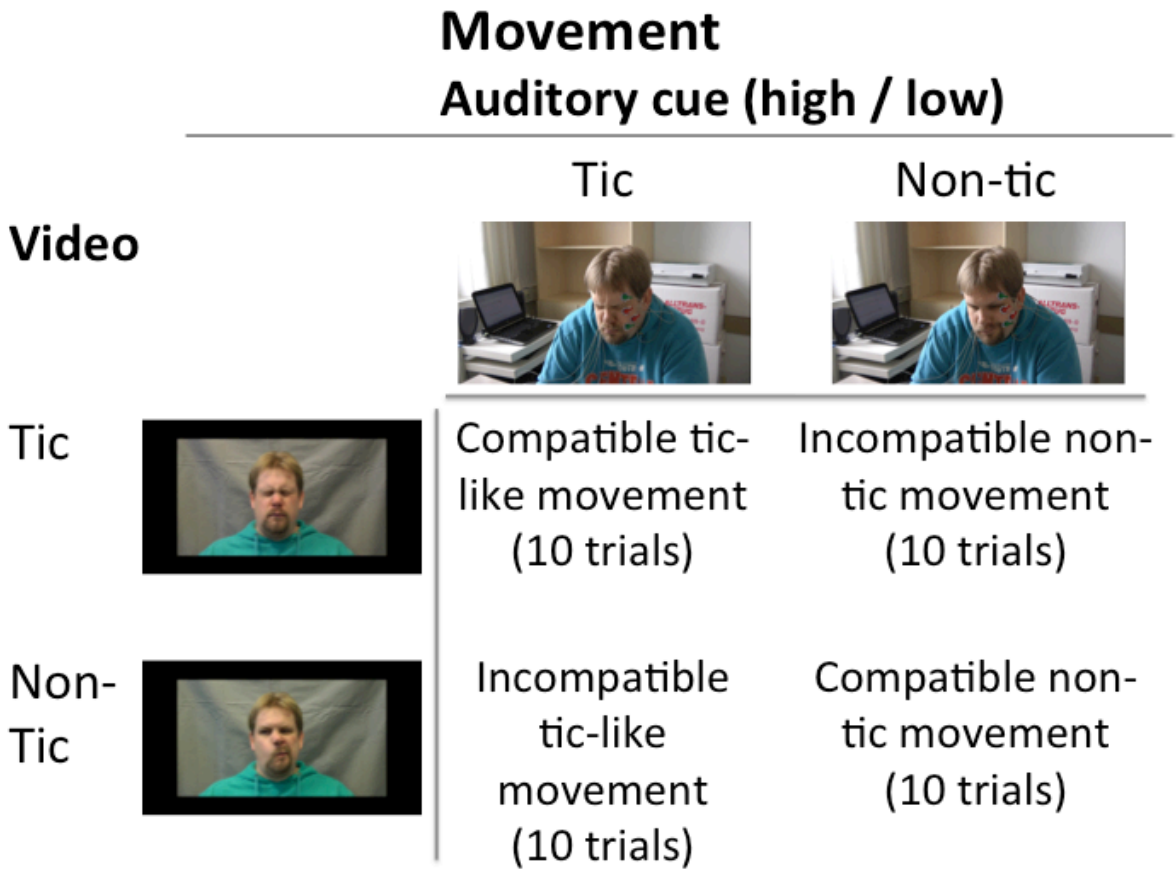


Figure 9: Study Design. *Participants were instructed to respond to an auditory cue by executing one of two facial movements. For patients, one was a tic-like movement the other a non-tic movement. Additionally, videos of the same movements were presented simultaneously at tone onset and were either compatible or incompatible with the movement executed by the participant.*

Thirteen of the healthy controls were exactly matched to thirteen GTS patients concerning the two facial movements, the assignment of the tone to the respective movement and the order of trial presentation. All other healthy participants were matched to the tic-like movement of at least one GTS patient. Each GTS patient had at least one healthy match for the tic-like movement (for all movements please see Table 5).

Table 5: Tic-like Movement and Non-tic Movement Categories

Tic-like movements (GTS patients / healthy controls)	Non-tic movements (GTS patients / healthy controls)
Headshake (5 / 6)	Headshake (1 / 1)
Mouth to side (1 / 2)	Mouth to side (2 / 3)
Blinking (2 / 2)	Blinking (1 / 1)
One corner of mouth up (2 / 2)	One corner of mouth up (4 / 5)
Squinting (4 / 4)	Squinting (0 /1)
Nose wrinkling (2 / 2)	Nose wrinkling (2 / 4)
Eyebrow up (0 / 3)	Eyebrow up (4 / 4)
	Pouting (1 / 1)
	Open mouth (1 / 1)

Types of movements and the number of Gilles de la Tourette syndrome (GTS) patients who displayed them as well as the number of healthy controls who were assigned to the respective movements.

Participants were instructed to watch the videos presented on the screen but to ignore them and only react to the auditory cue. All participants were aware that they were filmed during the whole task to ensure that they viewed the movements on the screen while performing the task and to extract errors. RTs were measured using surface electromyography (EMG) recordings with 2 electrodes placed over the respective muscles and a reference electrode at the mastoid. EMG signals were amplified and filtered (20 Hz to 1kHz). The signals were sampled at 5000 Hz and digitized using an analogue-digital converter (Micro1401, Cambridge Electronics Design (CED), Cambridge, UK). EMG-data was acquired with the Signal software (Cambridge Electronics Design, Version 3.10).

3.3.3 Data analysis

RTs < 50 ms and RTs associated with errors were excluded from the analysis (there were no RTs > 2000 ms). RT was defined as the difference between the onset of the auditory cue and the first detectable muscle activity in the EMG recording (for an example please see Figure 10). Missing data points (9.9%) due to noise in the recordings were not replaced by mean values or by other imputation techniques. It was not possible to obtain EMG recordings for four of the patients. For those patients, video recordings were used to extract RTs (25 frames

per second were re-sampled into ms). Accordingly, video analysis was also used for the four matched healthy controls.

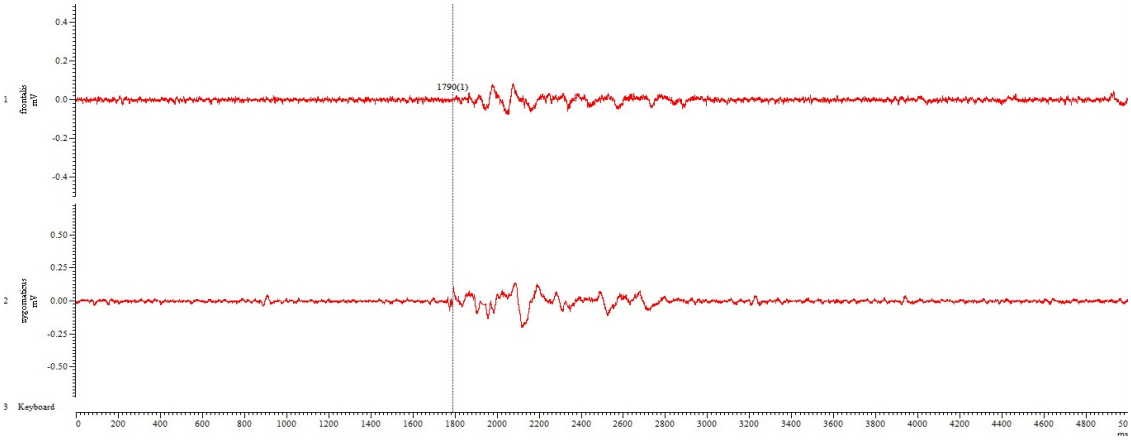


Figure 10: Example of one frame of an electromyography recording. *The upper and the lower line represent two different channels, i.e. muscle activity of two different muscles.*

RTs were then log-transformed in order to achieve a normal distribution for parametric testing. The variables tic vs. non-tic movements ("type of movement"), compatible vs. incompatible videos ("compatibility"), GTS patients vs. healthy controls ("group") and all interactions between the variables were included as fixed effects factors in a linear mixed models analysis, single trials were treated as random effects. RTs and errors were tested as dependent variables. Furthermore, types of error (false reaction, omission, tic) were tested using a chi-square test. Correlations between RTs and clinical scores were performed using Pearsons *r* for the WURS-K, the ADHD-SR, the YGTSS and the PUTS and with Spearman's *rho* for the DCI.

3.4 Results

A 2 ("type of movement") x 2 ("compatibility") x 2 ("group") linear mixed models analysis with RT as a the dependent variable showed no main effect for type of movement [$F(1,1291) = 1.19$, $p = .28$], indicating that there was no overall RT difference between tic-like movements and non-tic movements, a significant main effect for compatibility [$F(1,1291) = 20$, $p < .001$], indicating that both groups responded faster to compatible than to incompatible trials, no significant main effect for group [$F(1,35) = .08$, $p = .78$], indicating that there was no significant RT difference between GTS patients and healthy controls overall, a significant interaction of type of movement x compatibility [$F(1,1291) = 10.13$, $p = .001$], indicating that participants reacted significantly faster to compatible non-tic movements than incompatible

non-tic movements but that there was no significant difference between compatible and incompatible tic-like movements. There was also a significant interaction of type of movement x group [$F(1,1291) = 7$, $p = .008$], indicating that GTS patients reacted significantly faster when they performed tic-like movements than non-tic movements but that there was no difference between those movement categories in healthy controls, and a marginally significant 3-way interaction between type of movement x compatibility x group [$F(1,1291) = 2.94$, $p = .087$].

A hypothesis-driven 2 ("type of movement") x 2 ("compatibility") linear mixed models analysis for the GTS group alone revealed a significant main effect for type of movement [$F(1,546) = 6$, $p = .015$], indicating that RTs associated with tic-like movements were shorter than RTs associated with non-tic movements, a significant main effect for compatibility [$F(1,546) = 5.28$, $p = .022$], indicating that RTs associated with compatible trials were shorter than RTs associated with incompatible trials and a significant interaction of type of movement x compatibility [$F(1,548) = 10.29$, $p = .001$]. Post-hoc LSD tests revealed that the interaction was driven by GTS patients responding significantly slower in incompatible than in compatible trials when they had to perform movements that were not in their tic repertoire [$F(1, 546) = 15.43$, $p < .001$] but that they did not respond significantly slower in incompatible trials than in compatible trials when the movement they performed was a tic movement [$F(1, 546) = .4$, $p = .53$]. GTS patients responded faster in incompatible trials when they were instructed to perform a tic movement than when they were instructed to perform a non-tic movement [$F(1, 546) = 15.26$, $p < .001$] (see Figure 11).

A 2 ("type of movement") x 2 ("compatibility") linear mixed models analysis for the healthy group revealed no significant main effect for type of movement [$F(1,745) = 1.44$, $p = .23$], indicating that there was no difference in RT associated with the movements that were matched to tics and non-tics in GTS patients, a significant main effect for compatibility [$F(1,745) = 17.6$, $p < .001$], indicating faster responses to compatible than to incompatible stimuli and no significant interaction of type of movement x compatibility [$F(1,745) = 1.28$, $p = .26$] (see Figure 11).

GTS patients made 8.8% errors and healthy participants 7.4%. A 2 ("type of movement") x 2 ("compatibility") x 2 ("group") linear mixed models analysis with errors as the dependent variable showed no significant main effect for type of movement [$F(1,1426) = .002$, $p = .96$], a significant main effect for compatibility [$F(1,1425) = 19.9$, $p < .001$], indicating that all participants made more errors in incompatible trials than in compatible trials, no significant main effect for group [$F(1,35) = .49$, $p = .49$], and no significant interactions. There was no

difference between the groups in the types of error committed (wrong reaction vs. omission) [$\chi^2(3) = 1.89$, $p = .6$]. There were only two cases of omission per group overall.

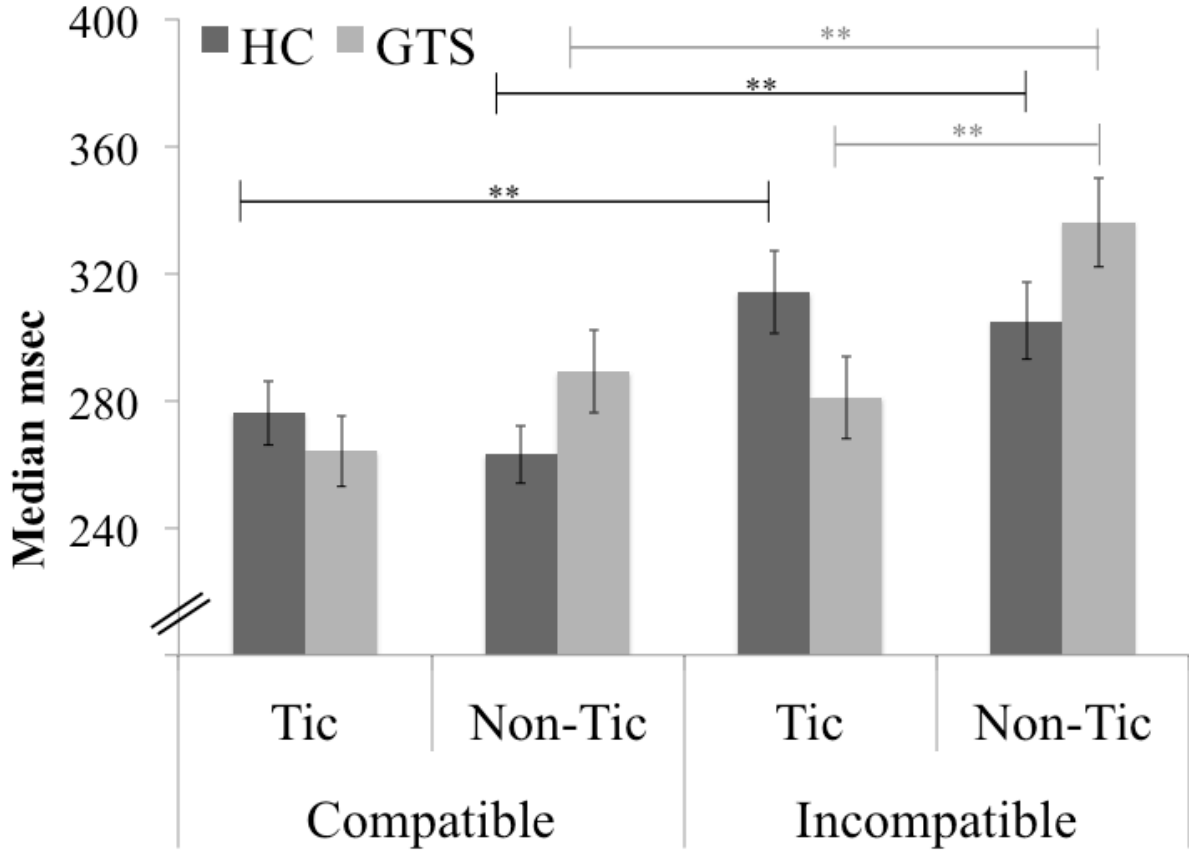


Figure 11: Reaction Time Data for Tourette's Patients and Healthy Controls. *Reaction times (ms) for tic-like movements and non-tic movements in compatible and incompatible trials in Gilles de la Tourette syndrome (GTS) patients and for matched movements in compatible and incompatible trials in healthy controls (HC). Data are displayed as medians because ms are more intuitive than log-transformed data.*
Error bars display +/- 1 SEM. Significance levels: ** $p < .01$

A difference variable subtracting compatible non-tic movements from incompatible non-tic movements showed no difference between GTS patients and healthy controls [$t(35) = .79$, $p = .44$], suggesting, together with the errors, that GTS patients did not have difficulties inhibiting the tendency to imitate a tic movement in order to perform a non-tic response if required by the task. Overall, RT correlated negatively with number of errors both in GTS patients ($r = -.68$, $p = .004$) and healthy controls ($r = -.5$, $p = .02$), suggesting a speed-accuracy trade-off. Many of the clinical measures were correlated with RT and errors (for correlations please see Table 6).

Table 6: Correlations between Clinical Scores and Errors / Reaction Times

	WURS-K	**ADHD-SR**	**PUTS**	**Y-BOCS**	**YGTSS motor**	**YGTSS phonic**	**DCI**
Errors	*r* = .54*	*r* = .58*	*r* =.65*	*rho* =.49	*r* =.37	*r* = -.06	*rho* =.36
RT	*r* = -.66*	*r* = -.55*	*r* = -.57	*rho* = -.6*	*r* = -.35	*r* = -.19	*rho* = -.66*

Data show correlations between the number of errors and log-transformed reaction times (RT) and the Wender Utah Rating Scale short form (WURS-K), rating symptoms of attention deficit hyperactivity disorder (ADHD) retrospectively for childhood, the ADHD self rating scale (ADHD-SR), rating ADHD symptoms in adulthood, the Premonitory Urge for Tics Scale (PUTS), the Yale-Brown Obsessive Compulsiveness scale (Y-BOCS), the severity of motor and phonic tics according to the Yale Global Tic Severity Scale (YGTSS) and the Diagnostic Confidence Index (DCI), assessing the lifetime likelihood of having Tourette syndrome.
*Significance levels: * p < .05, **p < .01, ***p < .001*

Hence, a stepwise linear regression was performed, including WURS-K, ADHD-SR, and the PUTS, as independent variables and RT as a dependent variable, showing that the best predictors for variation in RTs were the WURS-K score and the PUTS score (please see Table 7), indicating that higher ADHD scores in childhood and stronger urges were associated with faster RTs.

Table 7: **Results for Stepwise Regression with Reaction Time as the Dependent Variable**

	B	SE B	ß
Step 1			
Constant	6.12	.056	
WURS-K	-.014	.002	-.88***
Step 2			
Constant	6.53	.15	
WURS-K	-.012	.002	-.73***
PUTS	-.017	.006	-.36*

Note: R^2 = .78 for step 1, ΔR^2 = .88 for step 2 (p < .001).
** p < .05, **p < .01, ***p < .001*

3.5 Discussion

The main finding of this study was that GTS patients did not show an interference effect by incompatible visual stimuli when executing a movement that was part of their own tic repertoire, indicating that the execution of the triggered tic-like movement was not immediately influenced by visual stimuli. However, when GTS patients were asked to execute a movement that was *not* part of their tic repertoire, they did respond more slowly to an auditory cue while watching an incompatible movement than while watching a compatible movement. Hence, GTS patients showed a "normal" interference effect in response to incompatible movements if they were instructed to execute non-tic movements. Research on interference of finger movements in adult GTS patients also suggests that RT interference by biological stimuli is typically at least as strong in GTS patients as it is in healthy adults (Jonas et al., 2010). Overall, these findings could be interpreted as hyper-binding of tic-event files.

The negative correlation between ADHD scores and RT is perhaps not surprising. More interesting is the finding that stronger urges were related to quicker reactions. Urges have been hypothesized to occur because a certain state triggers the motor plan for a certain movement, which is then active in the SMA and produces the urge to execute the movement (Maia & Frank, 2011). It is conceivable that individuals, who experience stronger hyper-binding of event files, would also experience stronger urges and faster activation of the corresponding action code, because action plan and action code would be more strongly linked.

The results presented here suggest that tics might have such highly overlapping sensory and action codes, that they can be triggered without interference by an incompatible visual stimulus. Moreover, healthy controls showed normal interference in incompatible trials for both matched tic-like movements and non-tic movements, suggesting that the effect was not due to tic-like movements being movements that can generally be performed more quickly or easily than movements that tend not to be in GTS patients' tic repertoire. Interestingly, GTS patients did not make more errors when instructed to execute non-tic movements while watching tic movements than vice versa or in comparison to healthy controls. Thus, it appears that although GTS patients tend to "echo what they tic" (Finis et al., 2012), they do not have difficulties in suppressing response tendencies when watching a movement that belongs to their own tic repertoire if the task requires them to do so. Therefore, voluntary control appears to be normal in GTS patients, or perhaps even enhanced, if tic movements require enhanced top-down inhibition. These results are in line with studies showing that young GTS patients exhibit increased top-down behavioural control over automatic motor response tendencies (G.

M. Jackson et al., 2007; Jung et al., 2013; S. C. Mueller et al., 2006), and studies showing normalisation of intracortical inhibition prior to action execution in GTS patients (Orth, Munchau, & Rothwell, 2008).

3.5.1 Prepotency of actions

Responding equally fast to an auditory cue triggering a tic-like movement irrespective of the visual stimulus observed, indicates that the tic-like movement represents a prepotent response in GTS patients. Similar effects can be found in healthy controls in the "stroop" task, in which the response to the stimulus (which colour is the word?) requires inhibition of an overlearned response, which is automatically triggered despite the task (reading the word).

It has been pointed out that prepotent responses have been defined in the literature in two different ways (Brass, Derrfuss, & von Cramon, 2005). On the one hand, there are automatically triggered imitative response tendencies such as echopraxia (Finis et al., 2012), or an RT advantage in a finger-lifting task when watching biologically compatible finger movements as compared to non-biological movements (imitation-inhibition paradigm) (Biermann-Ruben et al., 2008; Jonas et al., 2007; Jonas et al., 2010). On the other hand, there are overlearned behaviours, such as automatically reading the word stimulus in the stroop task.

In a double dissociation study, Brass and colleagues (2005) were able to show that, while the inhibition of overlearned responses was associated with activation in prefrontal cortex, the pre-SMA and the inferior frontal gyrus (Brass et al., 2005), structures typically associated with interference control and task management; the imitation-inhibition paradigm was associated with activity in the fronto-median cortex and the temporo-parietal junction (Brass et al., 2005), areas which have previously been found in tasks on perspective taking and self-agency. Activation for both tasks overlapped in the fusiform gyrus and the right inferior frontal gyrus (Brass et al., 2005).

Tics can be considered prepotent responses in both ways described above. First of all, tics are overlearned movements. They are repeated many times a day, often over years. It appears that GTS patients do not have difficulties inhibiting tic movements (prepotent response) as they do so very often voluntarily but that tic-like movements are triggered faster, or more easily, with no interference by incompatible visual stimuli. Secondly, their imitation can be automatically triggered by an external stimulus (Finis et al., 2012).

3.5.2 Possible neural mechanisms for tics as excessively bound event files

When previously learned event files consisting of an auditory cue and a motor response are re-activated by presenting the tone, areas comprising premotor and somatosensory cortices, the SMA and the cerebellum become active (Melcher et al., 2008). Based on the TEC, it would be assumed that in the task presented here, the auditory cues would form new event files with tic-like and non-tic movements. Assuming that tic-related information in the SMA, the somatosensory cortex, the motor cortex, and possibly other areas of the brain might be very strongly interconnected, the activation triggered by the tic-related auditory cue might either spread faster, or might be stronger than activation triggered by a non-tic cue. Tics could be viewed as a form of expertise and may be represented more dominantly in a patients' action-repertoire than other movements, due to excessive "practise" effects. A study conducted by Calvo-Merino and colleagues (2005), involving ballet and capoeira dancers, suggests that expert dancers have stronger representations of movements belonging to their own dance style, than movements belonging to a different dance style (Calvo-Merino, Glaser, Grezes, Passingham, & Haggard, 2005).

Information about competing visual stimuli may spread more slowly or may simply not interfere with movement execution, if the triggered movement is more strongly represented than the competing movement. The fact that patients with stronger urges responded faster overall, would support this notion. It is plausible that patients, in whom hyper-binding of event files is stronger, would also experience stronger urges and faster activation of the motor code, the tic. However, the underlying neural mechanisms will need to be tested with fMRI or EEG; preferably both, because in addition to the strength of the activation of the respective brain areas and the question which modulatory role the hippocampus and the BG might play, the timing of cortical activation might be interesting.

The fact that there was no behavioural difference between tic-like movements and non-tic movements in healthy controls raises the question, why some movements become tics in GTS patients in the first place. If tics are viewed as event files that are characterized by hyper-binding, it has to be considered what the underlying mechanisms of hyper-binding might be. While the retrieval of an event files is associated with activation in cortical areas and the hippocampus (Melcher et al., 2008), the BG appear to be involved in the acquisition of new event files (Melcher et al., 2013).

The BG Go/NoGo model suggests that tics are excess movements that initially occur randomly because of BG hyperactivity (Maia & Frank, 2011). The involvement of the BG in tics, and an imbalance in their inhibitory/excitatory pathways has been corroborated by a

wealth of studies in humans and animals (Bronfeld et al., 2011; Bronfeld, Israelashvili, & Bar-Gad, 2012; Bronfeld et al., 2013; Kalanithi et al., 2005; Kataoka et al., 2010; Muller-Vahl et al., 2011; Worbe et al., 2010; Worbe et al., 2012). Once a tic has occurred several times in a certain state, it may become coupled with the state, and, due to cortico-striatal, Hebbian learning mechanisms, can be triggered by those states. This would suggest, that tics are initially caused by BG hyperactivity and are then "transferred" to cortical areas. There might be excessively strong connections between the BG, the SMA, pre-motor, and sensorimotor cortices for tic-event files, possibly due to abnormal striatal DA levels, leading to excessive reinforcement in motor sequence learning (Bronfeld et al., 2011; Palminteri et al., 2011). Those connections would form the basis of Hebbian learning (long-term potentiation), which can be facilitated by higher DA levels up to a certain point (inverted U-shape association) (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010). The association of cholinergic activation in the striatum with tic movements corroborates the assumption of a reward-related component in tics. Based on BG and DA hyper-activation, GTS patients may be excellent motor learners. The results presented here would support this assumption. This may foster tics on the one hand, but the potential for outstanding motor performance on the other hand (Palminteri et al., 2011; Sacks, 1985, 1992, 2007).

3.6 Limitations & future directions

One limitation of this study is the small sample size. This reduces generalizability across patients. Furthermore, the results can only be applied to uncomplicated GTS patients, without relevant comorbidities such as ADHD and OCD. Particularly ADHD may influence the results as even sub-clinical scores correlated with RT and errors in this sample.

Moreover, the interpretation of the data only relies on RTs. There was no direct measure of the strength of movement representations, such as fMRI data. It would be interesting to use functional imaging to investigate whether tic movements in GTS patients are more strongly represented than non-tic movements (Calvo-Merino et al., 2005; Calvo-Merino, Grezes, Glaser, Passingham, & Haggard, 2006). Furthermore, it would be interesting to create event file as was done in this study, and to investigate how activation patterns for tic-like movements and non-tic movements might differ if activated by the auditory cue. It would also be interesting whether suppressing the second part of an event file requires more effort and cognitive control, if it concerns a tic-movement, and whether this would be reflected by neural activation, such as additional prefrontal activation. However, this study might be difficult to implement as an imaging study because the individual tic repertoire varies

between patients. It may be possible to recruit a sample of individuals who are not diagnosed with GTS but who share a common tic, such as eye blinking.

Finally, investigating the neural mechanisms of motor learning in GTS patients, using transcranial magnetic stimulation (TMS), might be useful in order to investigate whether GTS patients show abnormally high long-term potentiation-like plasticity in motor areas. This could be the neural basis for excessive event file binding.

6.7 Conclusions

To summarise, the results suggest that tics in GTS are overlearned actions, possibly characterised by strong representations in the motor system and resistance to external interference, thus resembling expert actions. A brain with a propensity to tic may also be particularly capable of outstanding motor performance, which has in fact been repeatedly reported (Sacks, 1985, 1992, 2007). The results indicate that tics may be event files that are characterised by hyper-binding but will need further corroboration.

Chapter IV

Altered Synaptic Plasticity in Tourette Syndrome and its Relationship to Motor Skill Learning

4.1 Abstract

Learning motor skills involves implicit and explicit processes, which can vary in their degree, depending on the task. While many tics are explicitly executed to relieve a premonitory urge, the acquisition of tics appears to be an implicit process, i.e. GTS patients do not aim to "learn" and practise tics. It has been shown that GTS patients exhibit superior performance in some motor learning tasks, but inferior performance in others. Moreover, synaptic plasticity, the neural basis of motor leaning, appears to be abnormal in GTS patents. However, it has not been investigated whether altered synaptic plasticity is directly linked to motor skill acquisition in GTS patients. In this study, cortical plasticity was assessed by measuring motor-evoked potentials before and after paired associative stimulation in 14 Tourette patients (13 male; age 18 – 39) and 15 healthy controls (12 male; age 18 – 33). Tic and urge severity were assessed using the Yale Global Tic Severity Scale and the Premonitory Urges for Tics Scale. Visuo-motor integration (explicit motor learning) was assessed 45 minutes after inducing synaptic plasticity and 9 months later, using the rotary pursuit task. Additionally, acquisition of an implicitly learned stimulus sequence was assessed using the serial reaction time task.

On average, long-term potentiation-like effects in response to the paired associative stimulation were present in healthy controls but not in patients. Instead, synaptic plasticity was found to be bi-directional, with the majority of GTS patients showing long-term depression-like effects. Moreover, long-term potentiation-like effects were associated with more and long-term depression-like effects with less severe urges and tics. While motor learning in the rotary pursuit task did not differ between patients and healthy controls 45 min after inducing synaptic plasticity, the learning curve of the healthy controls started at a significantly higher level than the GTS patients' 9 months later. Induced synaptic plasticity correlated positively with motor skills in healthy controls 9 months later and negatively with motor learning skills in GTS patients immediately after inducing synaptic plasticity and 9 months later. For the serial reaction time task, the pattern was nearly reversed. The groups did not differ with regard to implicit learning 45 min after inducing synaptic plasticity. Nine months later, GTS patients, but not healthy controls, were already significantly faster in the first implicit block compared to the first random block, albeit not significantly faster than the healthy controls. Induced synaptic plasticity correlated positively with implicit learning in the serial reaction time task across both groups immediately after inducing synaptic plasticity, but not 9 months later. Furthermore, GTS patients who were better at implicit learning had more severe symptoms.

The present study confirms previously found long-term improvements in the rotary pursuit task after induced long-term potentiation in healthy controls but not in GTS patients. Moreover, GTS patients showed reduced levels of motor skill consolidation after 9 months in the rotary pursuit task, confirming a relationship between synaptic plasticity and long-term consolidation of explicitly learned motor skills, with a disadvantage in GTS patients. Even more interesting is the finding that synaptic plasticity was related to implicit motor learning but also to symptom severity in GTS patients. The finding that long-term depression-like effects in GTS patients were associated with fewer symptoms, a better performance in explicit motor learning and slower implicit learning, suggest a compensatory mechanism on the neural level.

4.2 Introduction

The results presented in chapter III suggest that GTS patients may differ from healthy controls, at least in some respects, with regard to the acquisition, consolidation and retrieval of motor sequences, and possibly the neural basis of motor learning. Chapter II and III support the assumption that tics might be event files that are characterised by hyper-binding and can, thus, be more easily triggered than other movements by activating part of a tic-event file; either by paying attention to action effects (study 1, 2 & 3), or by an auditory cue that triggers activation of the motor part of the event file (study 4). It was proposed, that hyper-binding may be caused by abnormal cortico-striatal synaptic plasticity in GTS patients. Hence, the aim of the study presented in chapter IV was to test the synaptic plasticity of the M1 in GTS patients and a healthy control group, and its relationship with implicit and explicit motor learning.

Synaptic plasticity refers to the capacity of nerve cells to alter their structural and functional properties, such as strengthening of a synapse by long-term potentiation (LTP). LTP is defined as an activity dependent, long lasting enhancement of synaptic transmission, while long-term depression (LTD) refers to a long lasting attenuation of synaptic transmission; both LTP and LTD are referred to as synaptic plasticity, and are thought to constitute the neuronal basis for learning and memory (Doyere & Laroche, 1992; Morris, Davis, & Butcher, 1990). Synaptic plasticity can be induced via temporally correlated pre- and post-synaptic activation. The relative timing of this activation determines whether the synapse is strengthened or weakened. In many neuronal systems, LTP occurs if the presynaptic neuron fires in a critical interval prior to the post-synaptic neuron; and LTD occurs if the post-synaptic neuron fires prior to the pre-synaptic neuron (Bi & Poo, 1998). Activation dependent plasticity is also called "Hebbian" learning, and is based on an enhanced influx of calcium through *N*-methyl-D-aspartate (NMDA) receptor gated channels (Bliss & Collingridge, 1993; Schiller, Schiller, & Clapham, 1998), or by activation of voltage-dependent calcium channels (Humeau et al., 2005). This leads to a change in the number of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Citri & Malenka, 2008). Studies in single cells and animals suggest that LTP is expressed via inactive, postsynaptic AMPA receptors diffusing into the synaptic cleft, thereby strengthening synaptic transmission, while LTD is likely expressed by a reduction in postsynaptic AMPA receptors via endocytosis (Citri & Malenka, 2008). Accordingly, synaptic plasticity does not occur if NMDA receptors are blocked (Bi & Poo, 1998; Bliss & Collingridge, 1993; Bliss & Lomo, 1973).

LTP– and LTD-like neuroplasticity can be induced in the M1 in humans using techniques such as repetitive TMS protocols including theta burst stimulation (TBS), high frequency stimulation (HFS) and paired associative stimulation (PAS). It has been shown that PAS induces synaptic plasticity more effectively than TBS, at least in healthy participants (Player, Taylor, Alonzo, & Loo, 2012).

In the PAS protocol, an electrical, peripheral stimulus is applied to the wrist, before a TMS stimulus is delivered to the contralateral M1. The PAS protocol displays properties that are also associated with synaptic plasticity induced in single cells. First of all, if the peripheral, afferent stimulus arrives at the same time or shortly before the TMS stimulus in M1 (approx. 25 ms interval between the stimuli – PAS_{25}), corticospinal excitability increases (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000); if the afferent stimulus arrives after the TMS stimulus (approx. 10 ms interval – PAS_{10}), excitability decreases (Wolters et al., 2003). Second, the change in excitability is specific to the cortical representation of the stimulated cutaneous region (Stefan et al., 2000; Weise, Schramm, Beck, Reiners, & Classen, 2011; Wolters et al., 2003). Third, both LTP-like and LTD-like plasticity is likely mediated by synapses of excitatory neurons (Elahi, Gunraj, & Chen, 2012; Weise et al., 2013), and cannot be induced if NMDA receptors are blocked (Muller-Dahlhaus, Ziemann, & Classen, 2010; Wolters et al., 2003). Instead of using a default 25 ms interval for the excitatory PAS protocol, the interstimulus interval can also be determined on an individual basis by measuring how long an electrical stimulus takes to travel form the wrist to the cortex (N20 latency - PAS_{N20}).

Motor evoked potentials (MEPs) are commonly measured as the dependent variable in TMS paradigms inducing synaptic plasticity, because they reflect corticospinal excitability. Studies in healthy participants show an increase in MEP amplitudes after PAS_{25} and a decrease after PAS_{10} (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002; Stefan et al., 2000; Wolters et al., 2003). It has to be kept in mind though that altered MEP amplitudes at the same stimulus intensity could be the consequence of changes in the synaptic weights at excitatory neurons or inhibitory neurons. However, it has been repeatedly been shown that the effects of PAS on inhibitory synapses is not strong enough to induce long lasting excitability changes (Di Lazzaro et al., 2011; Russmann, Lamy, Shamim, Meunier, & Hallett, 2009; Weise et al., 2013).

There is a large variety of motor tasks, testing different aspects of motor behaviour, often in combination with other skills, such as executive functions. Two of those tasks appeared to be the most useful tasks to test in combination with synaptic plasticity. An explicit motor

learning task, the rotary pursuit task, and its short-term and long-term associations with synaptic plasticity, has previously been tested in healthy participants (Rajji et al., 2011). The data suggests that long-term consolidation of performance levels in the rotary pursuit task can be directly related to synaptic plasticity. Moreover, an association between PAS_{25}-induced LTP and motor learning in the rotary pursuit task has been further demonstrated in a sample of healthy controls and schizophrenia patients (Frantseva et al., 2008). While the execution of the rotary pursuit task engages a wide network of brain regions located in the cortex, the striatum and the cerebellum, motor learning is correlated with increased activity over time in contralateral M1, SMA and pulvinar of the thalamus (Grafton et al., 1992), hence synaptic plasticity in M1 and motor learning in the rotary pursuit task should be associated.

Implicit sequence learning, which is relevant for the second task, the serial reaction time task (SRTT), has been widely studied in health and disease in humans and in animals and appears to recruit striatal areas more than explicit motor learning (Destrebecqz et al., 2005; Karabanov et al., 2010). Tics are essentially motor sequences, which might be learned implicitly (Maia & Frank, 2011). Striatal DA appears to modulate synaptic plasticity and might thereby influence motor sequence learning (Garraux, Peigneux, Carson, & Hallett, 2007; Karabanov et al., 2010; Matsumoto, Hanakawa, Maki, Graybiel, & Kimura, 1999). Tics have also been associated with dopaminergic abnormalities in frontal and striatal areas (Minzer et al., 2004; Yoon et al., 2007). Hence, implicit sequence learning may be comparable to tic learning and was therefore of particular interest in this study.

Learning in the SRTT has been associated with activation in the prefrontal cortex, the striatum and the cerebellum (Pascual-Leone et al., 1993; E. M. Robertson, Tormos, Maeda, & Pascual-Leone, 2001; Torriero, Oliveri, Koch, Caltagirone, & Petrosini, 2004). Goal-based learning during the SRTT (the sequence of buttons that needs to be pressed, irrespective of the fingers pressing them) appears to engage parietal and prefrontal areas, whereas movement – based learning (learning an implicit finger sequence, irrespective of the buttons) primarily recruits M1 (Grafton, Hazeltine, & Ivry, 1998; Hikosaka, Nakamura, Sakai, & Nakahara, 2002). Moreover, excitatory stimulation of the contralateral M1 during the performance of an SRTT results in increase performance in healthy adults (Nitsche et al., 2003). A recent study, investigating the neural basis of the acquisition of implicit knowledge, suggests that learning in the acquisition stage of the SRTT might be associated with modulating activation in the M1 to cerebellum connections (Tzvi, Munte, & Kramer, 2014). This stage likely requires kinematic adjustments of the sensory inputs associated with the task. In later stages, once a

plateau is reached, performance functions more automatically and has been associated with activation in the CSTC-loops (Doyon, Penhune, & Ungerleider, 2003; Hikosaka et al., 2002).
If tics were highly bound event files, this would suggest abnormal implicit motor learning in GTS patients, on a behavioural, and on a neural level. The underlying mechanism of hyper-binding of event files may be increased long-term potentiation in cortico-striatal synapses in GTS patients. Abnormal striatal DA levels in GTS patients may be associated with abnormal synaptic plasticity, leading to increased motor sequence learning and increased long-term potentiation. In line with this assumption, a study combining the SRTT with rewards showed that unmedicated GTS patients displayed superior performance levels in implicit sequence learning compared to healthy controls and medicated GTS patients, if the sequence was followed by a significant reward (1 Euro) but not, if the sequence was followed by a non-significant reward (1 cent) (Palminteri et al., 2011).
Evidence on performance levels in different explicit motor tasks in GTS patients is conflicting. Several studies indicate that GTS patients display deficits in tasks of visuo-motor integration. However, most studies did not control for comorbid ADHD (Como, 2005). Performance in the rotary pursuit task was not shown to be impaired in GTS patients compared to healthy controls (Marsh, Alexander, Packard, Zhu, & Peterson, 2005). Neither children (Bornstein, 1991; Bornstein, Stefl, & Hammond, 1990; Yeates & Bornstein, 1994), nor adults (Neuner et al., 2012) with GTS show deficits in simple motor speed tasks but both display deficits in fine motor skill tasks requiring visuo-motor integration (Bornstein, 1991; Bornstein et al., 1990; Neuner et al., 2012; Yeates & Bornstein, 1994). Although it has already been shown that deficits in fine motor skills in childhood can predict tic severity in adult GTS patients (Bloch et al., 2006), there are no published studies investigating long-term consolidation of motor skills in GTS.
Previous studies, employing TBS and HFS, have found reduced synaptic plasticity in GTS patients as compared to healthy controls (Suppa et al., 2011; S. W. Wu & Gilbert, 2012). These findings have important implications for understanding which neural processes may cause GTS patients to experience difficulties in some motor learning tasks (Bloch et al., 2006; Serrien et al., 2002), but have to be regarded with some care because both studies included GTS patients with comorbid OCD or ADHD. In contrast to previous studies, the present study only included patients without clinically relevant comorbidities. Also, the paradigm used in the present study, the adapted PAS protocol as described by Ziemann and colleagues (2004) (Ziemann, 2004), has been shown to induce synaptic plasticity more effectively than the paradigm used in previous studies (Player et al., 2012). Finally, it was explored whether

synaptic plasticity in GTS patients and healthy controls can be directly linked to short-term and long-term motor learning using the rotary pursuit task and the SRTT.

Resulting effects of PAS_{N20} were determined on the basis of MEP amplitudes and cortico-spinal excitability measured by input-output (IO) curve changes (Ziemann & Siebner, 2008). While MEP changes have mainly been associated with short-term effects of cortical plasticity, changes in IO curves are thought to reflect more long-term changes in cortical plasticity, likely connected to consolidation processes through synaptogenesis (Rosenkranz, Kacar, & Rothwell, 2007). The aim of this study was to corroborate findings of altered synaptic plasticity in uncomplicated GTS patients and relate synaptic plasticity directly to the ability to acquire and consolidate motor skills.

4.3 Materials and Methods

4.3.1 Participants

Fourteen patients (mean age 25.6 years, SD = 5.9; 13 males) with a diagnosis of GTS according to DSM-IV-TR criteria were recruited from the University hospital Hamburg-Eppendorf in Hamburg. Patients fulfilling criteria for OCD according to the structured clinical interview for DSM-IV Axis I disorders (SCID-I), ADHD according to DSM-IV-TR or other neurological or psychiatric comorbidities were excluded from the study. Thus, all patients had uncomplicated GTS exhibiting no clinically relevant comorbidities.

At the time of the study, all patients reported motor tics and an additional 5 reported having phonic tics. Mean disease duration was 19.7 +/- 6.7 years. Mean DCI score was 47.8 +/- 7.9, mean YGTSS total tic severity was 15.71 +/- 5.8, mean YGTSS motor tic severity was 12.42 +/- 4.3 and mean YGTSS phonic tic severity was 3.29 +/- 4.2. Four patients were taking medication at the time of the study (please see Table 8). Information about premonitory urges, assessed by the validated German version of the PUTS (Rössner et al., 2010) was available for 12 patients (M = 23.3 +/- 4.7). The PUTS was originally developed for children but has recently been validated also in adult GTS patients (Crossley, Seri, Stern, Robertson, & Cavanna, 2013; Woods et al., 2005).

Fifteen healthy, age-matched individuals (mean age of 25.7 years SD = 4.4; 12 males) without a history of psychiatric disorders or neurological diseases were recruited as a control group. All participants were tested between 1-7 pm to avoid confounding effects of circadian rhythm. All participants were right-handed, as assessed by the Edinburgh handedness Inventory (Oldfield, 1971), and gave their written informed consent prior to the study. This study,

including all measures and interventions, was reviewed and approved by the ethics committee of the "Ärtzekammer Hamburg" and conformed to the Declaration of Helsinki.

Table 8: Demographic Data & Clinical Assessment

	Gender (M:F)	Age (years) Mean (SD)	DCI	YGTSS Phonic Tic Severity	YGTSS Motor Tic Severity	YGTSS Total Tic Severity	Medication
Healthy controls	12:3	25.7 (4.4)	0			0	0
GTS patients	13:1	25.6 (5.9)	47.8 (7.9)	3.29 (4.2)	12.43 (4.3)	15.71 (5.8)	4: Amisulprid, Tegretol retard, Tiapridex, Tiaprid

Data shown are means and standard deviations (SD) for age, Diagnostic Confidence Index (DCI) and the Yale Global Tic Severity Scale (YGTSS); GTS = Gilles de la Tourette syndrome

Before the start of the experiment, all participants completed a TMS safety screening. None of the participants had a family history of epilepsy, or had undergone neurosurgery. Thereafter, the PAS_{N20} protocol was administered. MEPs were measured before PAS_{N20}, immediately after PAS_{N20}, and 30 min after PAS_{N20}. Participants were given a 10 min break and were then asked to complete 12 trials of the rotary pursuit task and 12 blocks of the SRTT, overall 45 min after administration of the PAS_{N20} protocol. Additionally, all participants were invited for a second testing session of the rotary pursuit task and the SRTT 9 months later. Of the 29 participants, 12 patients and 12 healthy controls were able to attend the second testing session. However, only 10 patients could be tested with the rotary pursuit task, due to software problems.

4.3.2 *Experimental procedure*

Participants were seated in a comfortable reclining chair with their hands resting on a table, and were asked to relax and keep their eyes open. To insure that all participants stayed alert during the whole TMS procedure, a standardized attention test was administered (Krivanekova, Lu, Bliem, & Ziemann, 2011). Participants were instructed to look at the stimulated hand, count light stimuli projected onto this hand during the experiment (produced

with a laser pointer), and later report how many stimuli they had counted overall. The number of light stimuli ranged from 5 to 7 in all participants.

The optimal location for the magnetic coil was defined as the site where the largest MEPs in the right abductor pollicis brevis (APB) muscle could be produced by slightly suprathreshold stimulation of the contralateral M1. The location and orientation of the coil was then marked on the scalp with a soft pen. Next, the resting motor threshold was determined as the lowest stimulus intensity capable of inducing peak-to-peak MEPs with amplitudes of more than 50 μV in the relaxed APB in at least 5 out of 10 consecutive trials. TMS stimulus intensities are generally reported as percentage of maximum stimulator output (100%). The test stimulus intensities applied during all following stimulations were adjusted to evoke peak-to-peak MEP amplitudes of approximately 1 mV in each participant. The sensory perception threshold for peripheral stimulation was defined as the least intense electrical stimulus that could be perceived by each participant, and was assessed by increasing and decreasing stimulus intensity 10 times around the first noticeable stimulus.

Somatosensory evoked potentials were then obtained from each participant to assess how long it takes for an electrical stimulus to travel from the median nerve at the wrist to the cortex. For this purpose, 300 electrical stimuli (200 μs duration, 3 x sensory perception threshold) were applied to the right median nerve and the average response time was measured over the sensorimotor cortex (at C3, as the active electrode and Fz, as the reference electrode). For reliability purposes, somatosensory evoked potentials were measured twice and results were averaged. Based on this method, the interval between the electrical stimulus applied to the wrist and the magnetic stimulus applied to the cortex in the PAS protocol, can be individualised and thus optimised for each participant.

4.3.3 Paired-Associative Stimulation (PAS) Protocol

PAS is a conditioning paradigm. Peripheral, electrical stimulation at the wrist, and central, TMS stimulation over M1 are repeatedly combined in such a way, that both stimuli arrive in the cortex simultaneously, which should result in a transient strengthening of the synapses involved. The PAS_{N20} consisted of 225 pairs of single, peripheral, electrical stimuli at the median nerve (300% of the sensory perception threshold), and suprathreshold TMS over the hand area of the contralateral M1 (adapted from (Muller-Dahlhaus, Orekhov, Liu, & Ziemann, 2008; Ziemann, Ilic, Pauli, Meintzschel, & Ruge, 2004). Individual interstimulus intervals between the peripheral and the cortical stimulus were adjusted according to the respective result of the somatosensory evoked potentials. These paired peripheral and cortical

stimuli were delivered at 0.25 Hz for 15 min. Peak-to-peak amplitudes of MEPs were measured prior to PAS_{N20} (T1; average of 10 MEPs, given at a rate of 0.1 Hz with an inter-trial interval variability of 25%), immediately after PAS_{N20} (T2) and 30 min later (T3; for the timeline please see Figure 12).

IO curves were determined three times, subsequent to each MEP measurement. IO curves constitute the relationship between TMS stimuli applied at different intensities and biological responses, and provide additional information about cortico-spinal excitability at different intensities. To this end, MEPs were determined at five different stimulus intensities (100%, 110%, 120%, 130%, 140 % of the resting motor threshold). The measured output slope of IO curves is sensitive to the order in which the stimulus intensities are applied (ascending or descending), hence, five single pulses per intensity were delivered twice in an ascending order of stimulus intensity.

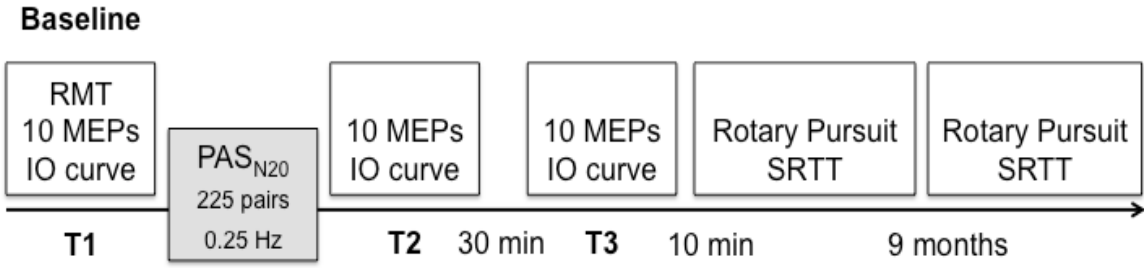


Figure 12: Experimental Design. *Ten motor evoked potentials (MEPs), and input-output (IO) curves, at five different intensities, served as dependent variables. They were assessed three times: before the application of the paired associative stimulation (PAS_{N20}) paradigm, immediately after PAS_{N20}, and 30 min later. The rotary pursuit task and the SRTT were carried out following TMS measurements 45 min after PAS_{N20}, and 9 months later.*

4.3.4 Transcranial magnetic stimulation

Surface electromyography (EMG) recordings were made with silver surface electrodes, placed over the right APB, using a tendon-belly montage. EMG signals were amplified and filtered (20 Hz to 1kHz). The signals were sampled at 5000 Hz, and digitized, using an analogue-digital converter (Micro1401, Cambridge Electronics Design (CED), Cambridge, UK). Off-line data analysis was performed with the Signal software (Cambridge Electronics Design, Version 3.10). Auditory feedback about muscle relaxation was provided by loudspeaker, connected to the EMG channel.

All TMS measurements were performed with a Magstim 200 magnetic stimulator (Magstim Company, Whitland, Dyfed, UK). A figure-of-eight coil with an outer diameter of 70 mm (Magstim Company) was held tangentially over the scalp at a 45° angle to the sagittal plane, with a coil orientation inducing posterior-anterior currents in the brain. Electrical stimulation for somatosensory evoked potentials measurements and during the administration of the PAS_{N20} protocol was applied over the median nerve at the wrist with a standard stimulation block (cathode proximal) at a stimulation width of 200 μs, and a duration of 1 ms.

4.3.5 Rotary Pursuit Task

The visuo-motor integration task consisted of a computerized version of the rotary pursuit task (S. T. Mueller, 2012). Participants were asked to keep a tracking arrow on top of a red dot, which moved around on a circle (see Figure 13). The dependent measure was "time on target", i.e. the duration per trial a participant was able to keep the curser of the mouse on the red dot. Each trial lasted 15 sec. Participants completed 3 blocks, each consisting of 4 trials.

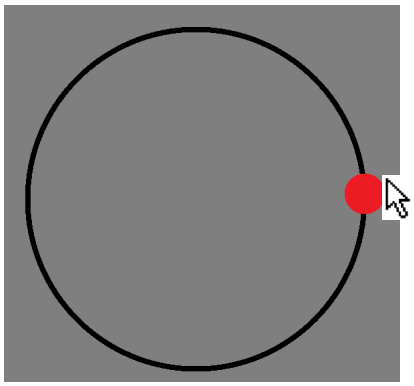


Figure 13: Rotary Pursuit Task. *The red dot (the target) travels around the circle twice within 15 seconds. Participants are asked to keep the curser on the red dot as accurately as possible. The dependent variable is "time on target"*

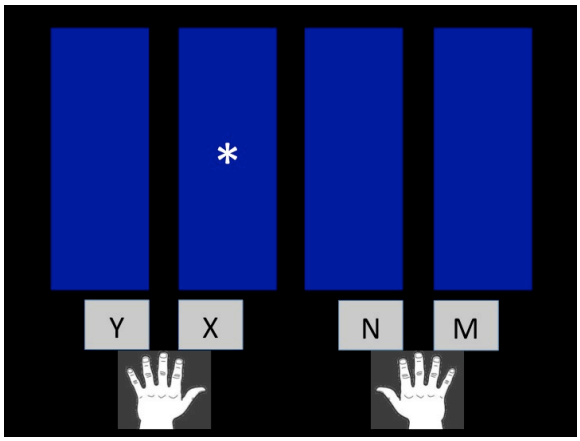
4.3.6 Serial Reaction Time Task

Participants were asked to react as fast as possible to a visual cue, which could appear in one of four spatial locations on the screen. Each of the locations was assigned to a key on the keyboard in front of the participant. Participants were asked to use the index and middle finger of their left and right hand to react to the stimuli, appearing consecutively on the screen (see Figure 14). A trial started, when a cue appeared on the screen. Each trial lasted for 1 sec if the participant did not react. If the participant reacted, the next stimulus appeared 200 ms after the button press. First, participants completed a baseline block, consisting of 96 trials in a random order. They then completed 12 alternating blocks of random trials, and trials

repeatedly containing a sequence of 12 stimuli. Random blocks contained 24 random trials; non-random blocks contained 72 trials, consisting of 6 sequences of 12 non-random stimuli. After each block, there was a 3 sec break. After 6 alternating random and implicit blocks, participants were given a 5 min break, during which they could see the number of mistakes they had made in the first half of the task.

Figure 14: Serial Reaction Time Task

In each trial a cue (the white asterisk) appeared in one of the four blue boxes. Participants were asked to react to the cue as quickly and accurately as possible by pressing the according key with their left or right index or middle finger.



Participants do not typically realize that there is a sequence embedded in the task, because 12 stimuli in a non-random order are difficult to detect. However, participants typically become faster when responding to the sequence. After completing the task, participants were asked whether they had recognized a sequence, and if so, to repeat as much of the sequence as they could remember. At the second testing session, nine months after the first testing session, all participants knew that the task included a sequence, thus, learning effects in the second SRTT were not strictly implicit. However, the sequence was different and the breaks between the blocks had been removed to make the task more difficult. The implicit learning task was programmed in "presentation" (www.neurobs.com).

4.3.7 Data Analysis

MEP amplitudes were measured semi-automatically, peak-to-peak, for each frame, using "Signal" software (customized script). Mean values were calculated for each participant by averaging the MEP amplitudes, excluding single trials that deviated more than 2.5 SDs from the mean. The data pre-processing was also conducted by script.

Repeated measures analyses of variance (ANOVA) were carried out with time (T1, T2, T3) as a within-subjects factor, and group as a between-subjects factor, to detect differences in mean

MEP amplitude in response to PAS_{N20}. In case of a violation of the sphericity assumption, the Greenhouse-Geisser correction was chosen. Post-hoc tests, if applicable, were conducted using independent samples *t*-tests and paired-samples *t*-tests. Results were considered significant if $p < 0.05$, and near-significant if $p < 0.1$. An "MEP change" variable was calculated by subtracting mean MEP amplitude values at T2 from values at T1, so that positive values represent LTP-like changes, and negative values represent LTD-like changes. In addition, to determine synaptic plasticity independent of the direction (LTP or LTD), absolute values of MEP changes from time 1 to time 2 (|MEP T2-T1|) were compared between the groups by an independent samples *t*-test.

To evaluate PAS_{N20} effects on IO curves, 3 x 5 repeated measures ANOVAs with time (T1, T2, T3) and stimulus intensity (100%, 110%, 120%, 130%, 140%) as within-subjects factors were carried out for both groups. Slopes of each curve were assessed for each participant by fitting the data to a linear regression function. The slope values were then entered into a repeated measures ANOVA with time (T1, T2, T3) as a within subjects factor and group as a between-subjects factor. Hypothesis-driven correlations were performed in patients between clinical scores, MEP change, IO curve slopes, resting motor threshold, and strength of test stimulus. Correlations were performed with Pearson's *r*.

To investigate differences in motor learning between the groups, a repeated measures ANOVA was carried out with trial (1-12) and time (rotary pursuit 1, rotary pursuit 2) as within-subjects factors and group as a between subjects factor. Further, MEP change was correlated with motor performance. Two healthy controls had 4 missing data points at rotary pursuit 1. The missing data points were replaced by the mean values of all other healthy controls for the respective trial. For correlation analyses, the 4 trials of the 3 blocks were averaged for time 1 and 2 respectively.

For the SRTT, a repeated measures ANOVA was carried out with block (1-6), condition (implicit sequence, random sequence) and time (implicit learning 1, implicit learning 2) as within-subjects factors and group as a between subjects factor. A "learning" variable was created by subtracting the decrease in RT across the sequence blocks (random block 1 – random block 6) from the decrease in RT across random blocks (sequence 1 – sequence 6) so that higher negative values reflect faster RTs associated with the implicit sequence relative to the overall decrease in RTs due to non-specific learning effects.

4.4 Results

4.4.1 Paired Associative Stimulation

Healthy controls and GTS patients performed equally well in the attention test, administered during PAS_{N20} [$t(27) = .21$, $p = .84$]. MEPs before, and after PAS_{N20}, were obtained from 14 GTS patients and 15 healthy controls. IO curve data were not available from one GTS patient, because this patient experienced higher stimulation intensities as uncomfortable. Groups did not differ with respect to gender or mean age (see Table 9). Also, mean resting motor threshold, strength of test stimulus, somatosensory evoked potentials latencies, and sensory perception thresholds did not differ significantly between the groups (Table 9). Age was neither correlated with MEP size at T1 ($r = .08$), nor with MEP change from T1 to T2 ($r = -.07$).

Table 9: TMS Parameters

	Somatosensory evoked potentials (ms)	Resting motor threshold (% stimulator output)	Test stimulus (% stimulator output)	Sensory perception threshold (mA)
Healthy controls	22.4 (1.5)	44.0 (5.8)	56.3 (8.4)	2.4 (1.1)
GTS patients	21.8 (1.2)	47.1 (8.6)	58.1 (11.6)	2.2 (0.6)

Means and standard deviations (SD) of somatosensory evoked potentials, resting motor threshold, test stimulus intensity, and the sensory perception threshold during paired associative stimulation (PAS) are shown; GTS = Gilles de la Tourette syndrome

A repeated measures ANOVA (T1, T2, T3) with „group“ as a between-subjects factor (n = 29) revealed a significant interaction between time and group [$F(2, 54) = 4.79$, $p = .01$], indicating that healthy controls had significantly higher MEP amplitudes immediately following PAS, compared to the baseline and 30 min after PAS, but that GTS patients showed no change over time in MEP amplitudes. Post-hoc *t*-tests showed that MEP amplitudes at baseline did not differ between the groups [$t(27) = -.55$, $p = .59$]. MEP amplitudes increased from T1 to T2 [$t(14) = -2.41$, $p = .03$, $d = .45$] and decreased from T2 to T3 in healthy controls [$t(14) = 2.44$, $p = .03$, $d = .38$]. In contrast, there was no mean MEP amplitude difference between T1 and T2 [$t(13) = 1.07$, $p = .3$, $d = .24$], or between T2 and T3 [$t(13) = -1.35$, $p = .2$, $d = .32$] in GTS patients (see Figure 15). Excluding the 4 patients who were taking medication did not change the results in GTS patients (T1 to T2 [$t(9) = 1.16$, $p = .28$]

and T2 to T3 [$t(9) = -.27$, $p = .79$]). T1 and T3 did not differ significantly from each other in either group, indicating that the PAS_{N20} effect had worn off after 30 min (see Figure 15).

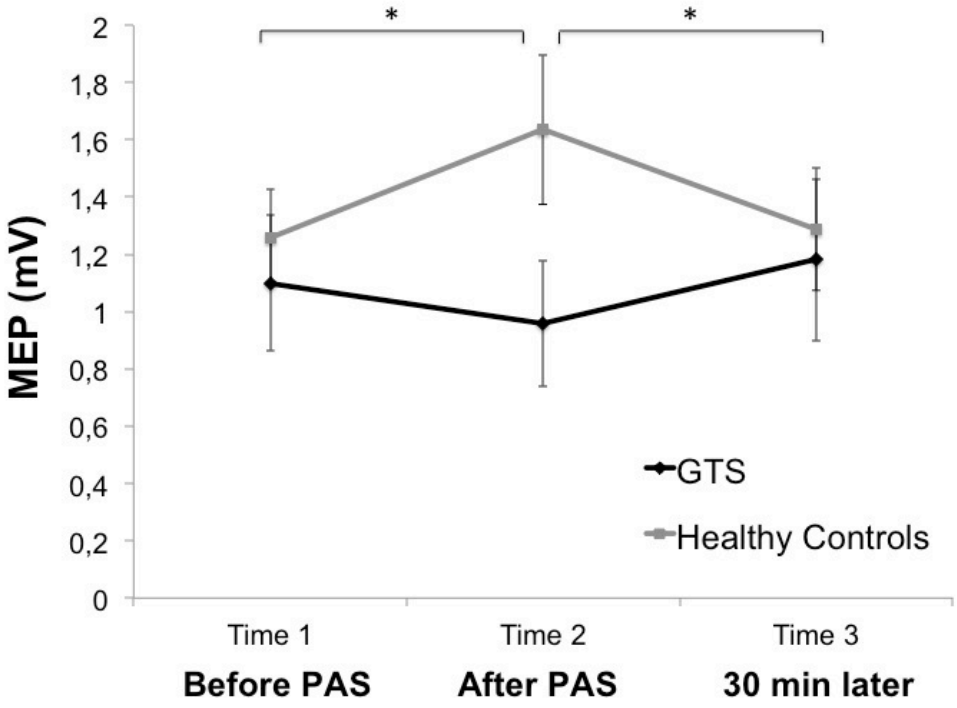


Figure 15: Mean MEP Amplitudes at T1, T2, and T3. *Data shown are mean values +/- standard error of the mean (SEM). There was no significant change between the three time points in Gilles de la Tourette syndrome (GTS) patients, whereas healthy controls showed the expected facilitatory effect after paired associative stimulation (PAS_{N20}), immediately following PAS_{N20} (T2).*
*Significance levels: *p < .05*

Concerning the IO curve data, the 3 x 5 repeated measures ANOVA („time“ x „stimulus intensity“) with “group” as a between-subjects factor did not reveal any significant interactions involving “group”. As expected, there was a significant main effect for stimulus intensity [$F(1, 26) = 72.54$, $p < .001$], indicating higher MEP amplitudes in response to higher stimulus intensities. Despite the lack of significant interactions, an ANOVA, based on a-priori hypotheses, was then conducted for each group separately to explore whether there was a detectable effect of PAS_{N20} in one of the groups.
The 3 x 5 repeated measures ANOVA („time“ x „stimulus intensity“) revealed no significant interaction between time and stimulus intensities for IO curve data in controls. As expected,

there was a significant main effect for stimulus intensity with higher intensities eliciting higher MEP amplitudes [$F(1, 56) = 44.07$, $p < .001$] and a marginally significant effect for time [$F(1, 28) = 3.07$, $p = .06$], suggesting overall higher MEP amplitudes immediately after PAS_{N20}. Explorative post-hoc *t*-tests showed, that overall mean MEP amplitudes at T2 were significantly larger than those at T1 [$t(27) = -5.59$, $p = .02$], indicating a general increase in cortico-spinal excitability after PAS_{N20} for most intensities in the control group, corroborating the results from the main experiment (see Figure 16). The same 3 x 5 repeated measures ANOVA („time" x „stimulus intensity"), run for the GTS group, only yielded significant results for stimulus intensity [$F(1, 24) = 22.76$, $p < .001$], indicating a normal ascending response of MEPs to higher intensities,but no PAS_{N20} effect in GTS patients (see Figure 16).

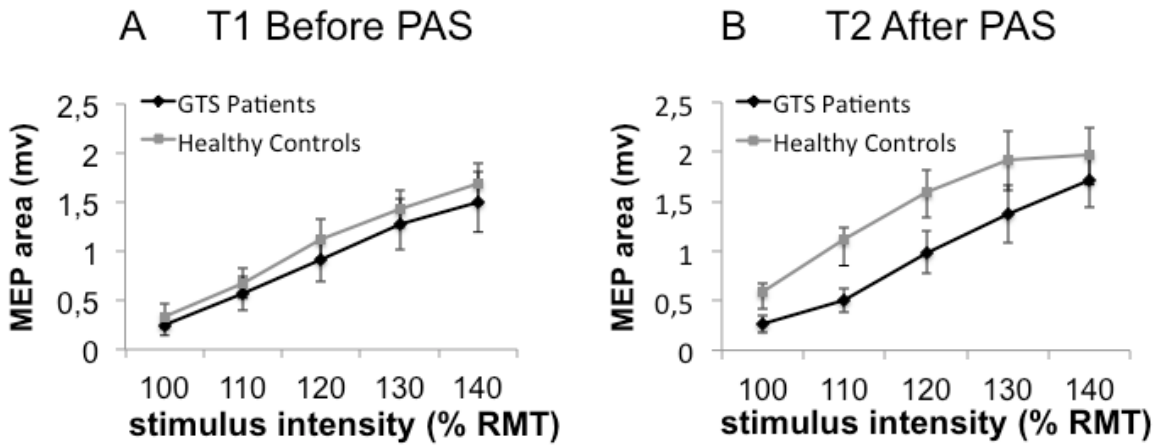


Figure 16: Input-Output Curves at T1 and T2. *Data shown are mean values +/ - SEM.*
A *Time 1, before paired associative stimulation (PAS_{N20}): motor evoked potential (MEP) amplitudes increased significantly in both groups with increasing stimulus intensity. There was no difference between the slopes of the groups at baseline.*
B *Time 2, after PAS_{N20}: MEP amplitudes of the IO curve increased significantly with increasing stimulus intensity. GTS patients' IO curve after PAS did not differ from baseline, while healthy controls showed a marginally significant increase in the IO curve after PAS.*

The amount of MEP change following PAS_{N20}, irrespective of the direction of change (|MEP T2-T1|), did not differ between GTS patients and healthy controls [$t(27) = -1.04$, $p = .31$],

indicating that overall, plasticity effects were comparable. However, more GTS patients than healthy controls (57% compared to 33%) showed an LTD-like change in response to PAS_{N20}. The mean resting motor threshold did not differ between the groups. However, variability was higher in GTS patients (min = 35; max = 62) than in healthy controls (min = 33; max = 52). YGTSS scores (total tic severity) correlated positively with resting motor threshold (r = .56, p = .04), i.e. higher tic severity was associated with lower cortical excitability, suggesting a decreasing resting motor excitability in more severely affected GTS patients. Moreover, total tic severity correlated positively with MEP change from T1 to T2 (r = .56, p = .04), indicating LTP-like plasticity changes in more severely affected patients, and LTD-like plasticity changes in patients with fewer tics (see Figure 17a). Correlations between the resting motor threshold, and MEP change with clinical measures are reported in Table 10.

Table 10: Correlations with Clinical Scores

	MEP change T2 – T1	Resting motor threshold
YGTSS total tic frequency	r = .53, p = .05	r = .69, p = .007**
YGTSS total tic intensity	r = .63, p = .02*	r = .59, p = .03*
YGTSS total tic severity (phonic & motor tic severity)	r = .56, p = .04*	r = .56, p = .04*
YGTSS impairment	r = -.08, p = .8	r = .54, p = .047*
Total YGTSS score (total tic severity & impairment)	r = .25, n.s.	r = .67, p = .008**
DCI	*rho* = -.39, p = .17	*rho* = -.03, p = .93
PUTS	r = .82, p = .001**	r = .53, p = .08

Correlations (r/rho) between motor evoked potential (MEP) changes caused by paired associative stimulation (PAS) / resting motor threshold and symptom severity as measured by sub-scales of the Yale Global Tic Severity Scale (YGTSS), the Diagnostic Confidence Index (DCI) (n = 14), and the Premonitory Urge for Tics Scale (n = 12) in Gilles de la Tourette syndrome (GTS) patients.
*Significance levels: *p < .05, **p < .01*

Correlations between MEP change, and resting motor threshold with the IO curves are reported in Table 11

Table 11: Correlations between Physiological Measures

	MEP Change T2 – T1		Resting Motor Threshold	
	GTS	Healthy	GTS	Healthy
IO Slope 1	r = -.45, p = .12	r = .16, p = .58	r = -.68, p = .01*	r = .11, p = .7
IO Slope 2	r = -.2, p = .52	r = .21, p = .46	r = -.68, p = .01*	r = -.23, p = .41
IO Slope 3	r = -.19, p = .53	r = .2, p = .48	r = -.68, p = .01*	r = .19, p = .49

Correlations between the input-output (IO) slopes before the paired associative stimulation (PAS; time 1), immediately after PAS (time 2), and 30 min after PAS (time 3) and motor evoked potential (MEP) changes from time 1 to time 2, as well as the resting motor threshold in Gilles de la Tourette (GTS) patients and healthy controls.

*Significance levels: *p < .05*

Information about premonitory urges was obtained from 12 patients. Patients with stronger premonitory urges also had a higher tic severity (r = .63, p = .04). Moreover, the strength of premonitory urges was highly correlated with MEP change (r = .82, p = .001), indicating that patients with higher LTP-like changes had stronger premonitory urges, while patients with stronger LTD-like responses reported fewer, or less severe, urges (see Figure 17b). There was no correlation between MEP change and current intake of medication (r = .02, p = .96) or previous intake of medication (r = -.18, p = .61).

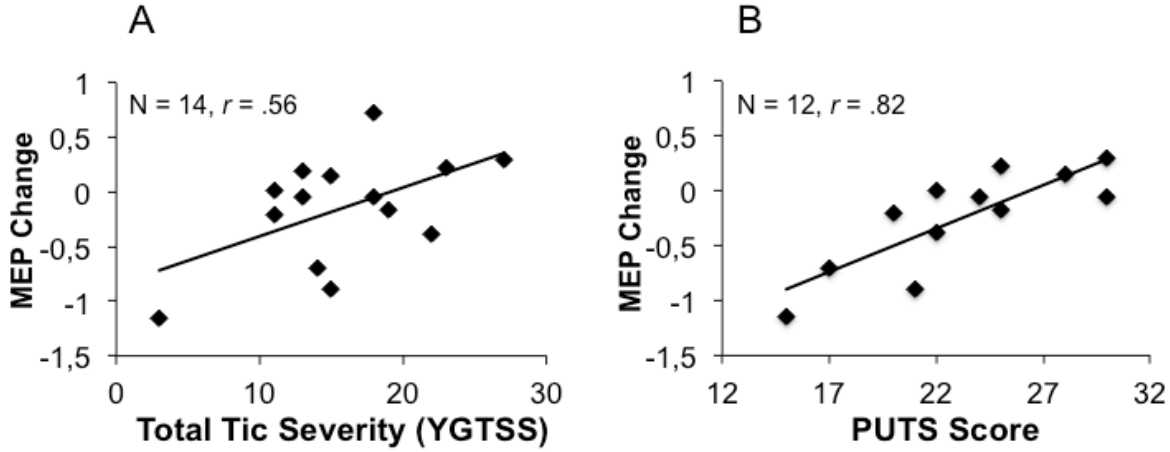


Figure 17: Correlations between Induced Synaptic Plasticity and Clinical Measures

A *Correlation between total tic severity, as determined by the Yale Global Tic Severity Scale (YGTSS; score = 0-50), and change in motor evoked potentials (MEP) from T1 to T2.*

B *Correlation between premonitory urges, as determined by the Premonitory Urges for Tics Scale (PUTS; score = 10-40), and MEP change from T1 to T2 in patients.*

4.4.2 Behavioural Results

4.4.2.1 Rotary Pursuit Task

Patients and healthy controls showed a normal learning curve at time 1 (see Figure 18a). A repeated measures ANOVA ("trial" x "time" x "group") showed a significant linear contrast for learning in both groups, at both times, during the rotary pursuit task [$F(1, 20) = 69.75$, $p < .001$], indicating that both groups spent progressively more time on the target across the 12 trials immediately after PAS, as well as 9 months later. The assumption of sphericity was violated for the within subjects tests. The multivariate tests showed that the only significant result, apart from the linear learning across trials, was a significant three-way interaction between learning curve, time, and group [$F(11, 10) = 3.67$, $p = .03$]. Post hoc *t*-tests revealed that, while there was no difference between patients and healthy controls in the first trial of the rotary pursuit task at time 1 [$t(27) = .61$, $p = .55$], healthy controls started their second learning curve (time 2) at a significantly higher level than GTS patients [$t(20) = 2.23$, $p = .037$, $d = 1$] (see Figure 18c).

Mean learning in block 1 and 3 at time 1 was significantly negatively correlated with MEP change in GTS patients [$r = -.65$, $p = .01$ for block 1; $r = -.39$, $p = .17$ for block 2; $r = -.59$, $p = .03$ for block 3], indicating better performance in GTS patients with LTD-like plasticity (see Figure 18b), whereas learning at time 1 was not significantly correlated with MEP amplitude change in healthy controls [$r = .19$, $p = .49$; $r = .19$, $p = .51$; $r = .36$, $p = .19$] (see Figure 18b).

Healthy controls showed an association between the extent of LTP induced at time 1 and motor learning 9 months later. The size of LTP-like changes correlated significantly with mean time on target in block 2 and 3 of the rotary pursuit task at time 2 [$r = .33$, $p = .23$; $r = .58$, $p = .05$; $r = .63$, $p = .03$] (see Figure 18d). In contrast, MEP change and time on target measured 9 months later, were not significantly correlated in any of the blocks in GTS patients [$r = -.51$, $p = .14$; $r = -.4$, $p = .25$; $r = -.42$, $p = .23$] (see Figure 18d). The size of the correlations for GTS patients at time 2 is similar to the correlations at time 1. Correlations may have missed significance because the sample may have been underpowered. Therefore, I will report the variance in motor performance (r^2) at time 1 and 2 that can be explained by variance in synaptic plasticity. In healthy controls, 7% of the variance in motor learning in the rotary pursuit task 1 can be explained by PAS_{N20}-related synaptic plasticity. In contrast, 31% of the variance in motor learning in the rotary pursuit task 2 can be explained by synaptic plasticity, induced 9 months earlier. In GTS patients, 33% of the variance in the rotary pursuit task 1 and 26% of the variance in the rotary pursuit task 2 can be accounted for by changes in

synaptic plasticity induced by PAS_{N20}. This measure does not reflect causality but merely assesses the size of the association without taking sample size into account. According to these results, there is a difference in the association between motor learning and synaptic plasticity between time 1 and 2 in GTS patients, but it is not as clear as in healthy controls.

Performance in the rotary pursuit task 1 and the rotary pursuit task 2 did not correlate significantly with the total YGTSS score or premonitory urges.

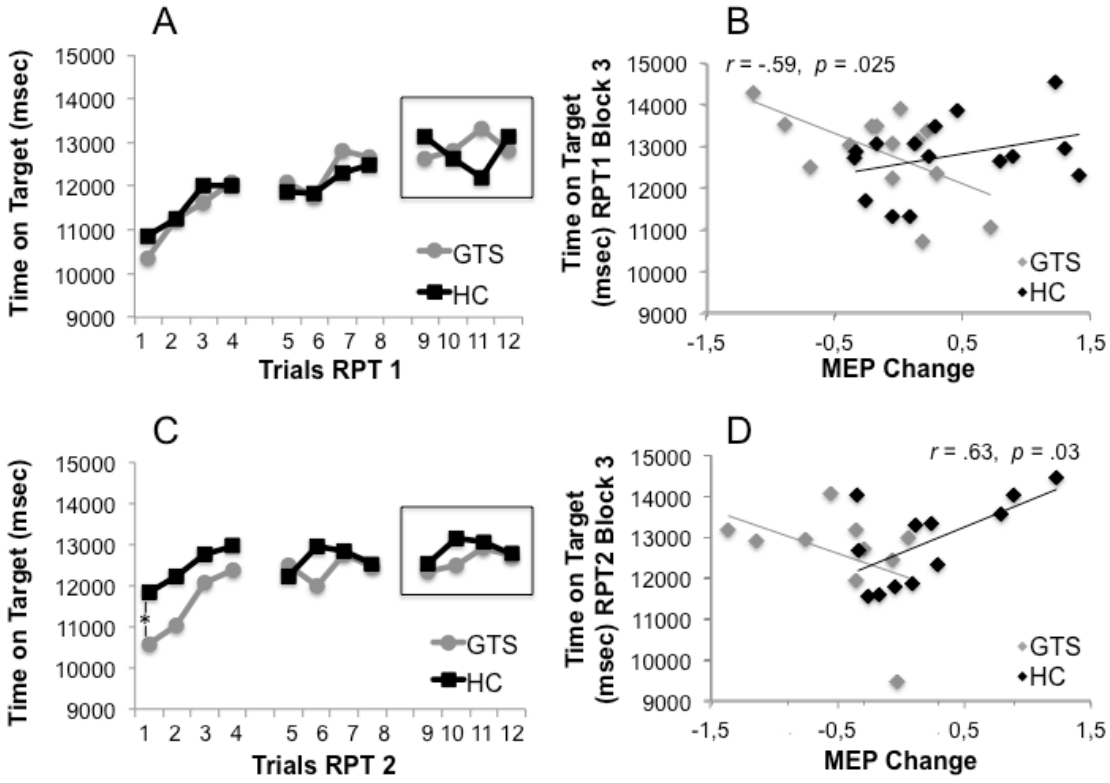


Figure 18: Association between Acquisition and Consolidation of Visuo-motor Integration Skills, Measured by the Rotary Pursuit Task, and Synaptic Plasticity

A *Learning curves at time 1, immediately after the paired associative stimulation paradigm (PAS_{N20}), of Gilles de la Tourette syndrome (GTS) patients and healthy controls (HC) in the rotary pursuit task (RPT) across 3 blocks, consisting of 4 trials respectively.*

B *Mean values of the last block of the learning curves at time 1, immediately after PAS_{N20}, correlated significantly negatively with MEP change in GTS patients (n = 14), but not in healthy controls (n = 15).*

C *Learning curves of the RPT in both groups at time 2, 9 months after PAS_{N20}. HCs started at a significantly higher level than GTS patients ($p < .05$).*

D *Mean values of the last block of the learning curves correlated significantly positively with MEP change in healthy controls (n = 12), but not in GTS patients (n = 10).*

4.4.2.2 Implicit Sequence-learning

A repeated measures ANOVA ("block" x "sequence" x "time" x "group") showed a significant linear contrast for block in both groups at both times [$F(1, 22) = 13.03$, $p = .002$], indicating that all participants increased significantly in speed overall at time 1 and 2, a main effect of condition [$F(1, 22) = 39.23$, $p < .001$], indicating that RTs associated with the implicit sequence were shorter than RTs associated with the random sequence, a main effect of time [$F(1, 22) = 16.81$, $p < .001$], indicating slower RTs at time 2 than time 1, a significant interaction of block and condition [$F(5, 110) = 12.79$, $p < .001$], indicating that RTs decreased more across implicit blocks than random blocks, a significant interaction between block and time [$F(5, 110) = 7.15$, $p < .001$], indicating that RTs decreased more at time 1 than time 2, a significant interaction between condition and time [$F(1, 22) = 12.9$, $p = .002$], indicating that the difference in RT, between time 1 and time 2, was overall larger for the random blocks than the implicit blocks, a significant interaction between block, condition and time [$F(5, 110) = 3.59$, $p = .005$], indicating that RTs decreased in both conditions at time 1 but only in the implicit condition at time 2, and a significant interaction of block, condition, and group [$F(5, 110) = 2.67$, $p = .03$], indicating that GTS patients' RTs across random blocks decreased more than the healthy controls', but that there was no difference between the groups across implicit blocks.

A repeated measures ANOVA for GTS patients showed a significant main effect of block [$F(1.8, 20) = 4.51$, $p = .03$], a main effect of condition [$F(1, 11) = 20.8$, $p = .001$], a main effect of time [$F(1, 11) = 8.66$, $p = .01$], a significant interaction between block and condition [$F(5, 55) = 9.26$, $p < .001$], and a significant interaction between block and time [$F(5, 55) = 3.71$, $p = .006$].

Looking more closely at the interaction terms, post-hoc *t*-tests for implicit learning at time 1 revealed that GTS patients reacted significantly faster to the last block of the implicit sequence than the first block [$t(13) = 4.1$, $p = .001$, $d = .91$] and significantly faster to the last block of the random sequence than the first block [$t(13) = 4.59$, $p = .001$, $d = .8$]. Furthermore, GTS patients reacted significantly faster to the last block of the implicit sequence than to the last block of the random sequence [$t(13) = 2.46$, $p = .03$, $d = .43$], indicating that RTs decreased more across implicit blocks than across random blocks (see Figure 19a). At time 2, GTS patients did not react significantly faster to the last block of the implicit sequence than the first block [$t(11) = .33$, $p = .75$], and not significantly faster to the last block of the random sequence than the first block [$t(11) = .24$, $p = .82$], but significantly faster to the last block of the implicit sequence than to the last block of the random sequence

[$t(11) = 2.7$, $p = .02$, $d = .47$], indicating that RTs did not decrease across implicit or random blocks at time 2, but that implicit blocks were still associated with an RT advantage compared to random blocks (see Figure 19c). GTS patients already reacted faster to the first implicit block at time 2 than the first random block [$t(11) = 3.12$, $p = .01$, $d = .6$]; hence, the absence of a learning effect was due to a significant difference that was already present at the beginning of the task.

Patients reacted significantly faster during the second baseline than during the first baseline [$t(11)= -3.15$, $p = .009$, $d = 1.1$], but significantly faster during the last random block at time 1 than time 2 [$t(11) = -3$, $p = .01$, $d = .6$], and significantly faster during the last implicit sequence block at time 1 than time 2 [$t(11) = 2.21$, $p = .05$, $d = .52$], reflecting increased task difficulty at time 2. However, there was no difference between block 4 at time 2 and the last block at time 1 [$t(11) = -1.69$, $p = .12$], indicating that GTS patients did reach the same speed at time 2 as they did at time 1, and then became slower towards the end of the task.

A repeated measures ANOVA for healthy controls showed a significant main effect of block [$F(5, 55) = 3.35$, $p = .01$], a main effect of condition [$F(1, 11) = 18.43$, $p = .001$], a main effect of time [$F(1, 11) = 8.47$, $p = .01$], a significant interaction between block and condition [$F(5, 55) = 6.29$, $p < .001$], a significant interaction between block and time [$F(5, 55) = 4.37$, $p = .002$], a significant interaction between condition and time [$F(1, 11) = 17.26$, $p = .002$], and a significant interaction between block, condition, and time [$F(5, 55) = 2.91$, $p = .02$].

Post-hoc *t*-tests for time 1 revealed that healthy controls reacted significantly faster to the last block of the implicit sequence than the first block [$t(14)= 4.16$, $p = .001$, $d = .85$] and significantly faster to the last block of the random sequence than the first block [$t(14)= 3.05$, $p = .009$, $d = .58$]. Furthermore, healthy controls reacted significantly faster to the last block of the implicit sequence than to the last block of the random sequence [$t(14)= 4.43$, $p = .001$, $d = .67$], indicating that RTs decreased more across implicit blocks than across random blocks (see Figure 19b). One healthy participant was able to repeat more than 4 stimuli in the correct sequence. He was not excluded from all analyses because at time 2, all participants knew that there was a sequence embedded in the task. However, post-hoc tests for time 1 were run again, excluding that participant from the analysis, but the pattern of results did not change (all $p < .05$).

At time 2, healthy controls reacted significantly faster to the last block of the implicit sequence than the first block [$t(11) = 2.35$, $p = .04$, $d = .38$], but not significantly faster to the last block of the random sequence than the first block [$t(11) = -1.31$, $p = .22$], and significantly faster to the last block of the implicit sequence than to the last block of the

random sequence [$t(11) = 3.6$, $p = .004$, $d = .85$], but only marginally significantly faster to the first block of the implicit sequence than the first block of the random sequence [$t(11) = 1.97$, $p = .08$, $d = .28$] (see Figure 19d), indicating a significant decrease in RTs for both random and implicit blocks at time 1 but only for implicit blocks at time 2.

Healthy controls reacted significantly faster during the second baseline than during the first baseline [$t(11) = -4.03$, $p = .002$, $d = .71$], not significantly faster during the last implicit sequence block at time 1 than time 2 [$t(11) = 1.79$, $p = .1$], and significantly faster during the last random block at time 1 than time 2 [$t(11) = -2.85$, $p = .02$, $d = 1.1$]. There were no significant differences between the groups at baseline at time 1 [$t(27) = .78$, $p = .44$] or time 2 [$t(22) = -.15$, $p = .89$], and no significant differences between the groups in the last implicit [$t(27) = .1$, $p = .92$], or random block [$t(27) = -.18$, $p = .86$] at time 1 or time 2 [$t(22) = -.04$, $p = .97$; $t(22) = -1.1$, $p = .28$]. Overall, learning did not differ between the groups at time 1 [$t(27) = .55$, $p = .59$] or time 2 [$t(22) = 1.69$, $p = .11$]. Excluding 4 patients, who were taking medication for their tics, and one healthy control, who had noticed that there was a sequence embedded in the task, did not change the results for time 1 [$t(22) = 1.3$, $p = .21$] or time 2 [$t(18) = 1.14$, $p = .27$].

GTS patients made 4.7% errors at time 1, and 4.8% errors at time 2. Healthy controls made 3.6% errors at timer 1, and 2.7% errors at time 2. Due to the low overall number of errors, no further analyses were conducted.

Overall learning across all participants at time 1 showed a small trend-level correlation with MEP change ($r = -.32$, $p = .093$). Additionally, GTS patients showed a medium but non-significant correlation with the PUTS ($r = -.41$, $p = .19$), and a significant correlation with complexity of phonic tics ($r = -.57$, $p = .035$). Learning at time 2 only showed a near-significant correlation with phonic tic severity ($r = -.51$, $p = .09$). There were no significant correlations found between clinical scores or MEP change, and learning at time 2.

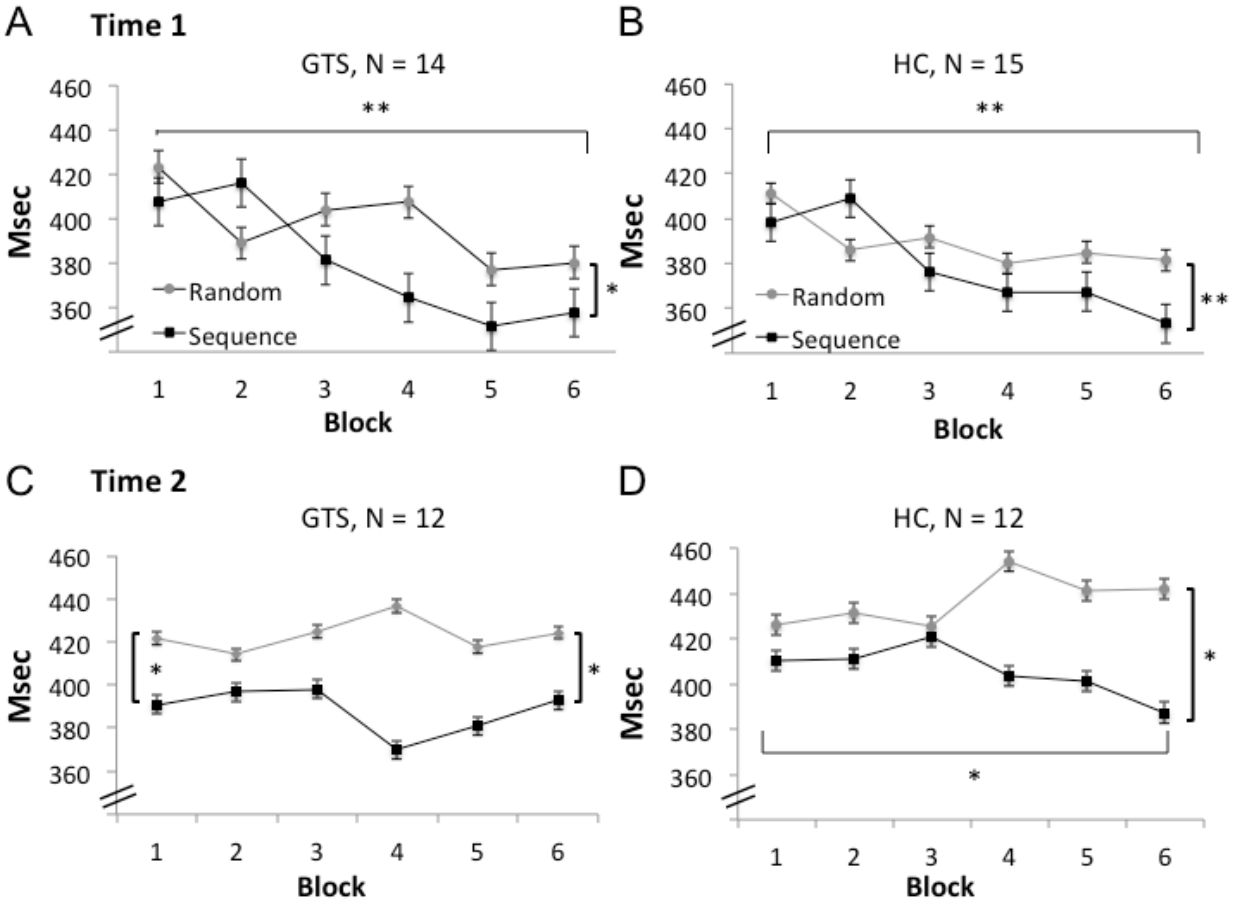


Figure 19: Implicit Motor Learning in the Serial Reaction Time Task at Time 1 & 2

A *Learning curves across 6 random and 6 implicit blocks of Gilles de la Tourette syndrome (GTS) patients at time 1, immediately after the paired associative stimulation paradigm (PAS_{N20}). GTS patients' reaction times (RTs) decreased significantly more across the implicit blocks than the random blocks, suggesting implicit learning of the stimulus sequence.*

B *Learning curves across 6 random and 6 implicit blocks of healthy controls (HC) at time 1, immediately after the PAS_{N20}, Healthy participants' RTs decreased significantly more across the implicit blocks than the random blocks, suggesting implicit learning of the sequence.*

C *Learning curves of GTS patients across 6 random and 6 implicit blocks at time 2, 9 months after the PAS_{N20}. RTs did not decrease across blocks, but were significantly faster in implicit blocks than in random blocks from the beginning, suggesting consolidated motor knowledge of SRTT-specific skills.*

D *Learning curves of HCs across 6 random and 6 implicit blocks at time 2, 9 months after the PAS_{N20}. RTs decreased across implicit blocks, but not random block, and were significantly faster in the last implicit block as compared to the last the random block, indicating that healthy controls learned in the implicit condition, but not the random condition.*

*Significance levels: *p < .05, **p < .01*

4.5 Discussion

4.5.1 Main findings

The main finding of this study is, that M1 synaptic plasticity in adults with uncomplicated GTS differs from healthy controls. As expected, mean MEP amplitudes following PAS_{N20} increased in healthy controls (Rosenkranz et al., 2007), whereas there was no overall change in GTS patients. However, if the absolute MEP amplitude change was taken into account, rather than the mean change, synaptic plasticity was not reduced in GTS, but bi-directional. More GTS patients than healthy controls showed an LTD-like effect following PAS_{N20}, which was correlated with less severe urges and fewer tics. Both groups performed equally well in the motor tasks immediately following PAS_{N20}. However, healthy controls performed significantly better than GTS patients in the first trial of the rotary pursuit task 9 months later, indicating that long-term consolidation processes differed between the two groups. In contrast, GTS patients were significantly faster in the first implicit sequence block compared to the first random block at time 2, while this difference only reached marginal significance in healthy controls. However, GTS patients did not start the implicit sequence at time 2 faster than the healthy control group.

4.5.2 Synaptic plasticity induced by TMS

Two studies, using iTBS and HFS, have previously shown reduced synaptic plasticity in GTS patients with comorbidities, compared to healthy controls (Suppa et al., 2011; S. W. Wu & Gilbert, 2012). The results presented here confirm those findings in patients with uncomplicated GTS, and extend them by showing that plasticity is not reduced on the individual level, but that the majority of patients show LTD-like plasticity in response to PAS_{N20}. Wu & Gilbert (2012) also reported "substantial variability" in their GTS sample using iTBS to induce LTP-like plasticity, but did not report whether absolute changes in amplitude were similar in GTS patients and healthy controls (S. W. Wu & Gilbert, 2012).

4.5.3 Visuo-motor learning in the rotary pursuit task and its association with synaptic plasticity

The main question addressed in the present study was whether synaptic plasticity can be related to motor learning in GTS patients. The data show that aberrant synaptic plasticity in GTS was related to reduced long-term consolidation of motor skills in the rotary pursuit task. Rajji and colleagues (2011) found that TMS-induced LTP did not enhance performance in the rotary pursuit task 45 min after PAS_{25}, but that it enhanced motor learning one week later

(Rajji et al., 2011). Synaptic plasticity can be divided into short-term effects, lasting from a couple of minutes up to hours, and long-term effects, lasting from hours to months (Park et al., 2014). Short-term LTP is likely achieved by a modification in the likelihood of transmitter release, while long-term LTP might be related to more persistent postsynaptic, structural changes (Park et al., 2014). Based on the established biological mechanisms, Rajji and colleagues (2011) proposed that long-term improvements in the rotary pursuit task, beyond practise effects, might be achieved by PAS_{25}-induced, long-term structural changes in M1. The present study confirms this finding by showing that in healthy controls, synaptic plasticity was unrelated to motor learning 45 min after PAS_{N20}, but correlated positively with motor learning 9 months after PAS_{N20}. The results indicate a long-term beneficial effect of induced LTP-like plasticity in healthy controls. However, GTS patients did not express LTP-like changes in response to PAS_{N20}.

Although motor skill acquisition in the rotary pursuit task was normal in GTS patients (Marsh et al., 2005), they started their learning curve at a significantly lower level than the control group in the second motor learning session, 9 months after PAS_{N20}. In other words, long-term consolidation of motor learning appeared to be stronger in healthy controls than in GTS patients. These results could be accounted for in two different ways. Either long-term consolidation of motor learning in GTS patients is impaired in general, or GTS patients did not benefit from PAS_{N20}, because no LTP was induced. However, if long-term consolidation of motor learning is generally impaired in GTS patients, this may also be related to aberrant synaptic plasticity. TMS-induced LTP is thought to rely on the same biological processes as learning experiences in a natural environment (Citri & Malenka, 2008). If GTS patients show LTD-like plasticity instead of LTP-like plasticity in response to PAS_{N20}, they may also differ with respect to biological processes in motor learning tasks. This would be an interesting question to address in an independent experiment.

4.5.4 Implicit motor learning in the serial reaction time task

First of all, it is noteworthy that GTS patients performed on the same level as healthy controls in the SRTT at time 1 and at time 2. It has previously been shown that unmedicated GTS patients display superior performance in the SRTT, compared to healthy controls, if the sequence is associated with a relevant reward, and that both medicated and unmedicated GTS patients show inferior performance, as compared to healthy controls, if the sequence is associated with a negligible reward (Palminteri et al., 2011). It was hypothesised that GTS patients off medication experience excessive reinforcement as a result of an overactive DA

system and are therefore better at learning motor sequences associated with rewards (Palminteri et al., 2011). The results reported here do not confirm the inferior performance. As a group, GTS patients performed on the same level as healthy controls.

In order to optimize their behavior, humans (and at least some animals) make predictions about future events and their reward value. If those predictions are erroneous, either in a positive or a negative direction, they have committed a "prediction error". Prediction errors are probably encoded by dopamine-release in the striatum (Bayer & Glimcher, 2005; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Zaghloul et al., 2009). Assuming a high reward was related to a positive prediction error (i.e. the reward was higher than expected), it could be also assumed that a low reward was associated with a negative prediction error (i.e. the reward was lower than expected). Both positive and negative prediction errors are likely coded for by subcortical dopaminergic activity (Hart, Rutledge, Glimcher, & Phillips, 2014). "Inferior" performance, i.e. longer response times in the low reward condition of the SRTT in GTS patients, as found by Palminteri et al. (2011), could also be interpreted as a learning effect, because the sequence might have been associated with a negative prediction error.

Another explanation for the difference between the findings presented here and the findings by Palminteri and colleagues (2011) may be that all implicit learning processes rely, at least partly, on DA, as has been indicated by a large body of research, but that these processes can be modulated by reward. A PET study showed, for instance, that D2 receptor density in the striatum is differentially related to implicit and explicit sequence learning (Karabanov et al., 2010). Furthermore, the amount of implicitly acquired knowledge, as opposed to explicit knowledge, has been associated with activation in the striatum (Destrebecqz et al., 2005). Even more persuasive are results showing that DA agonists enhance implicit sequence learning in healthy controls (without rewards), whereas DA antagonists impair performance in the SRTT (Kumari et al., 1997).

It has been proposed that individual movements in the SRTT may become coupled with implicit predictions about the sequence and may be mostly erroneous (random blocks) or correct (implicit sequence) (Penhune & Steele, 2012). This part of the learning process may be more pronounced in unmedicated GTS patients due to increased DA activity in the striatum (Minzer et al., 2004; Yoon et al., 2007). There were no differences between medicated and unmedicated patients in this study. However, the sample was too small to find a difference if it was there. It would be interesting to test implicit learning without external rewards in a larger sample of GTS patients.

It should be noted that learning in the second SRTT cannot be considered implicit learning because explicit knowledge about stimulus sequences had to be assessed after the first SRTT, hence, participants were aware that there was a sequence embedded in the task. This makes learning in the second SRTT difficult to interpret.

4.5.5 Differences between implicit and explicit motor learning

The second interesting finding with regard to the SRTT was that GTS patients reacted significantly faster in the first implicit sequence block as compared to the first random block at time 2, while healthy participants did not. Although GTS patients were not significantly faster than healthy controls, this is an interesting point. It shows, that, contrary to visuo-motor learning, GTS patients did not have difficulties consolidating sequence learning.

The performance difference between the two motor tasks may be the result of different underlying mechanisms. The rotary pursuit task is an explicit motor learning task, the SRTT an implicit motor learning task. While the rotary pursuit task requires the continuous integration of visual and motor information, i.e. hand-eye coordination, and is regarded as a fine-motor skill task, the SRTT requires fast reactions to single stimuli, which can be automatically anticipated during implicit blocks by a quick formation of motor memory, and is considered a procedural learning task. Ashe and colleagues (2006) developed a model, proposing that subcortical structures might be associated with automatic behaviour, while activation in M1 (element-to-element associations within sequence), SMA (temporal representation of already learned sequences) and the pre-SMA (temporal representation of new sequences) may be predominantly associated with implicit motor learning, and prefrontal cortex (rehearsal) and posterior parietal cortex (abstract representation) might be involved in explicit learning processes (Ashe, Lungu, Basford, & Lu, 2006).

Superior learning in the rotary pursuit task has been predicted in a sample of healthy participants by higher connectivity between M1 and parietal cortex, pointing to the importance of the spatial component in the task (J. Wu, Srinivasan, Kaur, & Cramer, 2014). Furthermore, several motor areas including M1, the cerebellum, the putamen, parietal cortex, and premotor areas appear to be involved in the acquisition and consolidation of visuo-motor integration skills, in the rotary pursuit task (Grafton, Woods, & Tyszka, 1994; Raz, Williamson, Gunning-Dixon, Head, & Acker, 2000), underlining their involvement in explicit motor learning. Reduced volume of the putamen is a predictor for poorer performance during skill acquisition in healthy controls (Raz et al., 2000), a structure that has also been implicated in tic generation (Muller-Vahl, Grosskreutz, et al., 2014). The results found in this study

suggest that abnormalities in M1 plasticity may be one of the factors explaining inferior long-term consolidation of explicit motor learning in the rotary pursuit task in GTS patients. However, interactions with other brain areas may play a role, which could be more efficiently investigated using fMRI.

In contrast, implicit motor sequence learning appears to recruit striatal areas more than explicit motor learning (Destrebecqz et al., 2005; Karabanov et al., 2010). Striatal abnormalities may be the key difference between performances in the two tasks in GTS patients. This assumption is in line with evidence suggesting that the acquisition stage of implicit sequence-learning in the SRTT might be associated with activation in cortical motor areas, the parietal cortex, and the cerebellum, while consolidation of those skills appears to be related to activation levels in the striatum (Lehericy et al., 2005; Seidler et al., 2005; Steele & Penhune, 2010). Studies in monkeys suggest that the cerebellum plays a crucial role in automatizing motor sequences (P. D. Nixon & Passingham, 2000). Areas in the BG, which belong to the associative loop, are primarily active during the acquisition of new motor sequences, while areas in the sensorimotor areas of the BG (striatum and posterior putamen) are preferentially active during the execution of already overlearned motor sequences (Miyachi, Hikosaka, & Lu, 2002). Interestingly, the sensorimotor part of the CSTC-loop has been associated with the development of tics in humans (Singer, 2005; Worbe et al., 2010). Although GTS patients showed reversed synaptic plasticity in M1, an increased DA activity in the striatum, and aberrant cortico-striatal interaction patterns (possibly increased plasticity in cortico-striatal synapses) may lead to a better performance in implicit motor learning than explicit motor learning. However, this is a rather speculative assumption at this point. It might be interesting to investigate though, especially with regard to the point that GTS patients did not show deficits in explicit or implicit motor learning per sé, despite their abnormal M1 plasticity.

4.5.6. Implicit motor learning, and its association with synaptic plasticity

Also of interest is a near significant correlation between MEP change and learning at time 1 across all participants. The correlation suggests that participants with a higher LTP-like response to PAS_{N20} are also better at learning an implicit motor sequence. Moreover, there was a medium but non-significant correlation between implicit motor learning immediately after PAS and premonitory urges, as well as a significant correlation with phonic tic complexity. The results suggest that patients who show higher synaptic plasticity are better at motor sequence learning and have more severe premonitory urges and phonic tics, pointing

towards an association between sequence learning and symptom severity. The patients who participated in this study reflect the lower end of the GTS spectrum (max. YGTSS score of 30 out of 50), mainly because the quality of the TMS data might suffer if patients tic a lot during the procedure. However, Palomar and colleagues (2014) tested severely affected GTS patients with the PAS_{25} paradigm and found that very severely affected patients show increased LTP-like effects in response to PAS, compared to healthy controls. They were also able to replicate the finding that synaptic plasticity is associated with tic und urge severity (Palomar et al., 2014).

Taken together, the findings suggest that synaptic plasticity in M1 in severely affected GTS patients is higher than in healthy controls, while synaptic plasticity in M1 is reversed in mildly affected patients. On the one hand, these results further corroborate the assumption that tics may be characterized by hyper-binding and that the underlying mechanism might be cortico-striatal synaptic plasticity. On the other hand, they suggest a compensatory mechanism. Patients who show LTD-like responses to PAS_{N20} are worse at learning implicit motor sequences and are therefore probably worse at "learning" tics. Although cause and effect cannot be disentangled on the basis of correlational data, the data may serve as a useful indication for future research.

To summarize, interpreting the results reported by Palminteri et al. (2011), Palomar et al. (2014, and the results found in this study in terms of hyper-binding, GTS patients show normal motor sequence learning, if it is not followed by external rewards. However, if it is followed by significant rewards, unmedicated GTS patients outperform healthy controls, suggesting hyper-binding when rewards are movement related. Phasic dopamine activity may support long-term potentiation in cortico-striatal connections and thereby increases the likelihood, that an action, which was associated with a positive prediction error, will be selected again in the future. Tics have been repeatedly associated with abnormalities / hyperactivity of the basal ganglia (BG) but also with cholinergic activation in the BG (Bronfeld et al., 2011), pointing towards a role of reward-related processes in the development of tics. The underlying mechanism of hyper-binding might be synaptic plasticity. The findings in this study suggest an association between synaptic plasticity in M1 and learning in the SRTT, as well as urge and tic severity. Combined with data recently presented by Palomar and colleagues (Palomar et al., 2014), it can be concluded that severely affected GTS patients might show increased LTP-like plasticity in M1 compared with healthy controls, possibly reflecting increased binding of motor sequences. LTD-like responses to PAS_{N20} in mildly affected patients may reflect compensatory mechanisms on a neural level.

4.5.7 General discussion

Suppa and colleagues (2011), and Wu and colleagues (2012) have pointed out that synaptic plasticity in GTS patients may be altered because of meta-plasticity effects, which may occur as a consequence of tics (Suppa et al., 2011; S. W. Wu & Gilbert, 2012). The excitability of a neuron depends, in part, on its firing history (Rutherford, DeWan, Lauer, & Turrigiano, 1997; Turrigiano, 1999; Turrigiano, Leslie, Desai, Rutherford, & Nelson, 1998). If a neuron has been highly active, self-regulatory feedback mechanisms can scale the excitability of the neuron down (Turrigiano et al., 1998). Although this assumption has been raised twice, there is no detailed account of how meta-plasticity may affect synaptic plasticity in GTS patients. I would like to discuss a theoretical framework that could account for the results. However, it should be clearly stated that all results in the present study are based on correlational analyses and cannot provide any information about causality.

According to the Bienenstock-Cooper-Munro rule, there is a floating threshold, which determines the amount of activity needed to elicit LTP or LTD. The activation needed is a function of the average postsynaptic activity levels (Bienenstock, Cooper, & Munro, 1982), i.e. neurons that have been relatively over-active are more likely to decrease their synaptic weight. Although it is difficult to apply these homeostatic effects found in single cells to a complex system that develops over many years, it can be speculated that GTS brains that have adapted to an over-active striatal system, may react differently to PAS_{N20} stimulation than healthy brains. Similarly reversed effects of TMS protocols that normally induce LTP, such as PAS, occur in healthy volunteers, if cortico-spinal excitability is altered at baseline, and have been attributed to homeostatic meta-plasticity (Abbott & Nelson, 2000; Potter-Nerger et al., 2009). For instance, Potter-Nerger and colleagues (2009) applied low-intensity rTMS over the premotor cortex of 10 healthy participants to produce an increase in corticospinal excitability in ipsilateral M1, before applying a PAS protocol. Subsequent PAS caused a decrease in cortico-spinal excitability instead of a further increase (Potter-Nerger et al., 2009).

If there is a long-term compensatory mechanism, it might not be as simple as single cell threshold adaptation though. Most GTS patients gain increased control over their symptoms during adolescence (Leckman, 2002), thus, compensatory effects may be associated with the development of the prefrontal cortex. This hypothesis is supported by several studies, showing that tic severity was associated with enhanced cognitive control and structural changes in the prefrontal cortex (G. M. Jackson et al., 2007; S. R. Jackson et al., 2011). The prefrontal cortex might not exert inhibitory control, but may serve to bias response competition in motor areas (Munakata et al., 2011; Sumner et al., 2007). Based on this

assumption, Jeyong et al. (2013) have proposed that the prefrontal cortex may be hyperactive in GTS patients and that this hyperactivity may be compensated for in adolescence, by structural and functional changes in the long-range neural pathways, that link the prefrontal cortex to those motor areas (Jung et al., 2013). Another result of those compensatory mechanisms could be an overall change in synaptic weights in M1, thereby creating a bias towards LTD-like plasticity in response to excitatory stimulation. However, the assumptions described should be addressed in a longitudinal study.

Several findings in the present study would support the assumption of a compensatory mechanism. Remarkably, LTD-like changes were strongly associated with fewer premonitory urges and fewer tics. Fewer tics were in turn associated with fewer premonitory urges. LTP-like changes were associated with superior performance in the SRTT at time 1, indicating that participants with higher LTP-like changes were better at learning a motor sequence, even without knowing that they were learning it. In turn, this means that participants with LTD-like changes were less prone to picking up the motor sequence. Moreover, those GTS patients who reacted with LTD-like plasticity instead of LTP-like plasticity were better at motor skill acquisition and consolidation in the rotary pursuit task. If LTD-like plasticity were indeed a compensatory mechanism, then these results would indicate that patients who compensate more successfully for their tics and urges may also develop strategies in dealing with explicit motor learning more successfully.

An alternative explanation for LTD-like plasticity in GTS would have been an increased cortical excitability at baseline, reflecting a homeostatic reaction of an „overexcited“ brain. Reversed effects of TMS protocols that normally induce LTP, such as PAS, occur in healthy volunteers if cortico-spinal excitability is altered at baseline and have been attributed to homeostatic meta-plasticity (Abbott & Nelson, 2000; Potter-Nerger et al., 2009). However, in this study there was no correlation between resting motor threshold and MEP change, suggesting no direct association between LTD-like changes and heightened baseline cortical excitability. On the contrary, correlations between resting motor threshold and tic severity showed that more severely affected patients had lower cortical excitability at baseline than less severely affected patients, although in keeping with previous studies, mean resting motor threshold at baseline did not differ significantly between GTS and healthy controls (Orth et al., 2005; Ziemann, Paulus, & Rothenberger, 1997).

4.5.9 IO curves

Another finding in this study was that IO curves did not differ between the groups at baseline, which is an interesting result with respect to previous inconsistent IO findings in GTS. While one study found a shallower slope in GTS patients as compared to healthy participants, suggesting reduced cortico-spinal excitability at rest (Orth et al., 2008), another study could not replicate this difference at rest, but found shallower IO slopes in GTS patients during movement preparation (Heise et al., 2010). However, tic severity was much higher in the sample investigated by Orth and et al. (2008) than in the study by Heise et al. (2010), hence, discrepancies between studies may be attributable to clinical differences in the populations investigated, such as tic severity or efforts to control tics (Orth & Munchau, 2013). The finding that tic severity was positively correlated with resting motor threshold, i.e. reduced excitability at rest, corroborates the assumption that tic severity might be associated with cortical excitability. However, it remains unclear whether this is a short-term effect, possibly due to the necessity to control tics for the duration of the experiment.

4.5.8 Limitations & future research

The main limitation of this study is its small sample size. The population investigated was very homogeneous though, making it more likely that the results can be generalized to other uncomplicated GTS patients despite the sample size. However, approximately 90% of GTS patients suffer from comorbidities (M. M. Robertson, 2011), hence, the findings reported in this study might not be valid for the whole population of GTS patients. Further limitations of this study include the possibility that past and present intake of medication may have influenced the results. Although controlling for present intake of medication did not alter the results and neither present nor past intake of medication correlated with MEP change, the sample might have been too small to detect medication effects. Future research should investigate whether unmedicated patients would perform better in the SRTT without external rewards, and whether this might be associated with higher LTP-like changes induced by PAS_{N20}. It would further be interesting to investigate whether medication changes the response to PAS as well as the performance in the motor tasks in GTS patients, as has been suggested previously (Palminteri et al., 2011).

Also, right hand or finger tics during MEP measurements could have influenced PAS_{N20} responses but this is unlikely because no tics occurred during the assessments of MEPs and IO curves. The possibility cannot be excluded that ticcing or tic suppression at other times during the experimental procedure may have influenced results. Furthermore, it cannot be

deduced whether the difference in long-term consolidation between the groups is a general problem in GTS or whether it was due to the absence of induced LTP at time 1. Further research will be needed to determine whether motor skill consolidation is generally impaired in GTS patients. Moreover, inducing synaptic plasticity in children with GTS might clarify whether they show a normal response to PAS. If our findings of aberrant plasticity in GTS reflect a compensatory mechanism associated with the PFC, it should not be present before puberty.

4.5.10 Conclusions

Synaptic plasticity in response to PAS_{N20} differed between a small sample of GTS patients and healthy controls. The majority of patients responded with LTD-like changes, while the majority of healthy participants responded with LTP-like changes. Patients also showed reduced motor skill consolidation as compared to healthy controls 9 months after PAS_{N20} but normal acquisition and possibly increased consolidation of motor sequence learning. Although LTP was artificially induced in this study these results may help to explain abnormalities in cortex-based motor learning in GTS patients more generally. Moreover, GTS patients with strong premonitory urges and more severe tics tended to show physiological LTP-like plasticity, which was in turn associated with better implicit learning of the motor sequence embedded in the SRTT. In contrast, less severely affected patients had LTD-like responses and a less pronounced learning effect of the motor sequence in the SRTT, suggesting a compensatory mechanism. This study provides first indications of the neural basis of binding of tics as event files. However, to draw stronger conclusions from the data, a larger sample of GTS patients, covering the whole range of symptom severity and allowing for testing of medication effects will need to be investigated.

Chapter V:

Integration and Discussion of Results

5.1.1 Summary of chapters II & III

Chapter II described three behavioural studies investigating the influence of attention on tic frequency. In study 1, patients were asked to tic freely a) alone in a room (baseline condition) and b) in front of a mirror (mirror condition). The results showed that tic frequency increases when patients view themselves in a "free ticcing" state in a mirror as compared to the baseline. In study 2, patients were asked to tic freely a) alone in a room (baseline condition), b) in front of a mirror (mirror condition), and c) in front of a video showing the patient without tics (video condition). Again, tic frequency significantly increased in front of the mirror compared to the baseline and significantly decreased in the video condition compared to the baseline. These results clarify that the increase in tic frequency was due to an increase in awareness of tics, not an increase in self-awareness in general.

In study 3, patients heard auditory cues, which instructed them to memorize a) which finger they had pressed against their thumb, b) which colour the circle on the screen was, or c) whether they had executed a tic in the previous 2 seconds. Compared to the baseline (the same baseline as in study 2), tic frequency was decreased during all three tasks, which confirms anecdotal evidence that focusing attention on any motor task decreases tic frequency compared to an idle state. The results also showed that tic frequency varied between the three motor conditions in the task when patients were not suppressing tics. Tic frequency was highest when patients were focusing their attention on their own tics compared to focusing attention on finger movements or stimuli on the screen.

The condition effect was abolished when patients suppressed their tics during the task. Attention did not have an additional effect under tic suppression as compared to the tic suppression baseline (sitting in a room alone, suppressing tics as much as possible). The decrease in tic frequency from the baseline condition to the video condition in study 2 correlated highly with the decrease in tic frequency from the baseline condition to the tic attention condition in study 3. This suggests that the decrease in tic frequency in study 2 was due to a general shift of attention away from tics and not specifically due to attention to a non-ticcing self. Another important point to note is that tic frequency was comparable between the tic suppression baseline and the free ticcing attention conditions, in which patients were asked to pay attention to their own finger movements. This result points to the possibility of reducing tics via interventions that do not require active tic suppression.

In summary, the results of all three studies suggest that tic frequency increases when patients pay attention to their own tics or receive immediate visual feedback about their tics and that

tic frequency decreases when patients shift their focus of attention away from tics. However, the ability to suppress tics does not appear to be influenced by these shifts of attention.

Chapter III introduced a study in which patients were asked to respond to auditory cues by either executing a facial/head movement that was part of their tic repertoire (tic-like movements), or a facial/head movement that was not part of their tic repertoire (non-tic movements) while watching behaviourally irrelevant videos of compatible (same movement) or incompatible (different movement) facial/head movements. Movements in healthy participants were matched to the patients' movements.

When patients executed non-tic movements they showed a normal interference effect by incompatible visual stimuli. However, GTS patients did not show an interference effect for tic-like movements, while healthy controls showed interference effects for both types of movements. These results suggest that tics in GTS patients are highly overlearned, prepotent responses that can be triggered automatically, without interference from incompatible visual stimuli. GTS patients did not experience any difficulties inhibiting incorrect responses, irrespective of whether they were tic-like movements or non-tic movements. Hence, tics might be viewed as highly bound event files that can be triggered without interference by incompatible visual stimuli, rather than a failure of inhibition.

5.1.2 Discussion of chapters II & III

Results from both chapters II and III are consistent with the ideomotor theory and the "TEC", which suggests that anticipating sensory effects of an action triggers the tendency to execute the movement (Hommel et al., 2001; James, 1950). Looking in a mirror seeing oneself execute tics as in studies 1 and 2 of chapter II, or merely thinking about tics as in study 3 of chapter II might be enough to trigger these actions. This is particularly true if tics are more strongly represented and interconnected than other comparable movements, as results presented in chapter III would suggest.

At this point I can only speculate with regard to the underlying mechanisms but will attempt to integrate the results into an overarching theoretical framework. The results can be interpreted in terms of "hyper-binding". The TEC suggests that event files bind information about single events, such as an action and the action-related perceptions (Hommel et al., 2001). On the one hand, actions are commonly followed by the perception of their effect. On the other hand, actions are also typically executed with some anticipation of their sensory consequences (P. A. Chouinard, Leonard, & Paus, 2005). Activating one code in this event

file, for instance anticipatory sensory effects of a tic, automatically activates motor codes in this event file by association.

Tics might be event files that are characterised by hyper-binding, i.e. certain actions, and their perceptions are more strongly bound than others. As a consequence, perceptions associated with the execution of tics might trigger tics more easily. Seeing oneself tic in a mirror or focusing on tics might lead GTS patients to anticipate the sensory effect created by executing tics. This effect may be even more prominent because most tics are preceded by urges (Leckman et al., 1993). Therefore, anticipating the sensory effects of a tic means anticipating relief from an unpleasant urge.

The BG Go/NoGo model proposed by Maia and Frank (2011) suggests that certain internal and external states become associated with tics via Hebbian learning and can then serve as triggers for tics (Maia & Frank, 2011). Certain states, for instance stress, may activate the representation of certain actions, thus creating the urge to execute the action. Combined with the TEC, this would imply that thinking about tics, or attending to own tics, might also be a trigger state for increased ticcing. In fact, increased awareness of own tics may be an extremely potent trigger because thinking about tics or paying attention to own tics should immediately activate motor plans associated with tics. Anticipating the relief from an urge could activate a whole variety of tic-action plans, which would explain why patients showed an increased variety of *different* tics in the mirror condition of studies 1 and 2 of chapter II.

Hyper-binding in GTS may, at least partly, be based on excessive DA transmission (Buse et al., 2012). Findings from a study investigating motor sequence learning in combination with rewards in GTS patients on and off medication suggest that GTS patients off medication outperform healthy controls at implicitly learning a motor sequence (Palminteri et al., 2011). The authors concluded that GTS patients off medication might learn motor sequences more quickly because of excessive reinforcement based on an overactive DA system (Palminteri et al., 2011). The results imply that GTS patients may be gifted with the ability to learn motor sequences exceptionally quickly, especially when they are reward-related. The ability to learn motor sequences quickly may lead to outstanding achievements, such as playing a musical instrument, sports, or performing surgeries exceptionally well. Anecdotal evidence for this has been repeatedly reported by Oliver Sacks (Sacks, 1985, 1992, 2007). The curse that accompanies the gift, however, might be that GTS patients also tend to learn motor sequences exceptionally well that are mostly context-independent, i.e. tics.

The results presented in chapter III indicate that tics are indeed not influenced by an incompatible context. Frequent repetition of certain motor sequences may lead to particularly

strong representations of those motor sequences, comparable to expert actions (Calvo-Merino et al., 2005; Calvo-Merino et al., 2006). Based on these results, it could be hypothesized that tics and echopraxia are not the result of inhibitory problems in GTS patients. On the contrary, GTS patients have been shown to possess excellent cognitive control (G. M. Jackson et al., 2007). The results of both chapters confirm that most GTS patients can, on the one hand, successfully suppress most of their tics. On the other hand, they were equally good at suppressing tic-like movements and non-tic movements when seeing an incompatible visual stimulus, contradicting assumptions of inhibition failure associated with tics. They also performed on the same level as healthy controls at suppressing responses tendencies, which are automatically triggered by incompatible stimuli, contradicting inhibition failure in general (Brass et al., 2005; Jonas et al., 2007; Jonas et al., 2010).

Instead, tic-like movements may be more easily triggered because their action representations might be more dominantly represented in the brain and because the codes of the different components may be very strongly interconnected. Anecdotal and systematic findings concerning echopraxia and suggestibility of tics support the assumption of stronger interconnectedness of tic-event files. First of all, patients tend to "echo what they tic", i.e. automatic imitation of movements that are part of a patient's tic repertoire are more likely than automatic imitation of movements that are not (Finis et al., 2012). Secondly, tics are suggestible (Jankovic, 1997). Simply asking a GTS patient about certain tics (for instance: "have you ever had a nose-twitching tic?") can prompt the patient to execute the tic mentioned to him/her.

Overall, the data presented in chapter II and III imply that echopraxia and the occurrence of tics may not reflect difficulties with inhibition but may be a result of hyper-binding of actions and perceptions. This leads to the question what the neural basis for hyper-binding might be. The most likely candidate is long-term potentiation, which is assumed to be the neural basis for learning and memory. Hence, in chapter IV I investigated synaptic plasticity in GTS and its relationship to explicit and implicit motor learning.

5.1.3 Summary of chapter IV

Synaptic plasticity was induced in GTS patients and healthy controls by using a TMS paradigm that has been shown to be particularly effective at inducing increased synaptic excitability. While healthy controls responded with LTP-like changes as expected, the majority of GTS patients showed LTD-like changes in response to PAS_{N20}. LTD-like changes where associated with lower symptom severity and fewer premonitory urges.

Furthermore, GTS patients showed normal explicit motor learning in the rotary pursuit task and the SRTT immediately after PAS as well as 9 months later. However, 9 months after PAS_{N20} GTS patients started their learning curve in the rotary pursuit task at a significantly lower level than healthy controls but showed an RT advantage in the first sequence-learning block of the SRTT as compared to the first random block, which healthy controls did not show.

Visuo-motor learning in the rotary pursuit task 9 months after PAS_{N20} correlated positively with LTP-like changes in healthy controls, while visuo-motor learning immediately after PAS_{N20} and 9 months later correlated negatively with LTP-like changes in GTS patients. In contrast, LTP-like changes correlated positively with implicit motor learning immediately after PAS_{N20} across all participants but did not correlate with learning in the SRTT 9 months later. However, it has to be kept in mind that the second SRTT cannot be considered implicit learning because participants were already familiar with the task.

Overall, the results suggest a compensatory mechanism in GTS patients on the synaptic level. Patients displaying LTD-like changes in response to an excitatory stimulation tended to have fewer symptoms and premonitory urges showed less pronounced implicit sequence-learning effects in the SRTT but performed better in the visuo-motor integration task.

5.1.4 General discussion of chapters II, III & IV

Taken together, the results show that tics can be triggered by paying attention to them and that they can be reduced by diverting attention away from them. Furthermore, tics can be triggered without interference by external, incompatible, visual stimuli. At the same time, GTS patients were able to suppress tics and performed at the same level as healthy participants when suppressing prepotent, incorrect motor reactions triggered by visual stimuli. These results imply that tics do not surface because GTS patients cannot inhibit an overactive motor system. Instead, tics might be strongly represented in GTS patients' motor repertoire, possibly because of DA-related hyper-binding of actions and perceptions, and may therefore be more easily triggered either by external cues or by anticipating their sensory effects.

Assuming that synaptic plasticity, induced by TMS, reflects learning mechanisms on a cell level, it can be concluded that GTS patients who are good learners on a synaptic level are also good learners on a behavioural level. Results from the SRTT confirmed a medium but non-significant correlation (r = -.41) between implicit learning and premonitory urges, a significant correlation (r = -.57) between the SRTT and complex phonic tics, and a trend-level association between implicit sequence learning and synaptic plasticity. In the study presented

in chapter IV, GTS patients did not outperform healthy controls in the SRTT, although they appeared to have stronger consolidation effects of the implicit sequence as compared to the random sequence. However, the sample was small and suffers from a lack of power, especially when effects of medication and age also need to be controlled for. Moreover, GTS patients showed reduced synaptic plasticity rather than enhanced plasticity but only covered the lower end of the GTS spectrum (YGTSS score < 30). Thus, the conclusions that can be drawn from the results in chapter IV with regard to behavioural and neural hyper-binding are limited, mostly because of the sample size.

However, in combination with results reported by Palomar et al. (2014), it can be shown that severely affected patients indeed show increased synaptic plasticity in M1 compared with healthy controls, whereas mildly affected patients show LTD-like plasticity effects in response to inducing excitatory synaptic plasticity (Palomar et al., 2014). Overall, synaptic plasticity correlates with tic and urge severity across both this sample and the data collected by Palomar et al. (2014). Synaptic plasticity also correlated with implicit motor sequence learning, corroborating the assumption that synaptic plasticity may be the neural basis of event-file binding. Patients who successfully reverse the neural mechanism have fewer symptoms. Reversing synaptic plasticity effects can be achieved due to meta-plasticity (Kim & Yoon, 1998). Meta-plasticity effects and their relationship with tics should be investigated in a separate study.

Although correlations cannot be interpreted in terms of causality, the results are in line with the BG Go/NoGo model, which assumes that Hebbian learning processes moderate the strength of the association between states and activation of motor plans in the SMA, which may cause premonitory urges. GTS patients do not only experience “internal overactivation” due to an excitatory-inhibitory imbalance in the BG (Bronfeld & Bar-Gad, 2013), they are also more sensitive to external stimulation. Tics can sometimes be triggered by external sensory stimuli, such as labels in clothes (Depboylu, Oertel, & Münchau, 2012; Münchau, 2012). Furthermore, GTS patients show an enhanced physiological response to external stressors (Chappell et al., 1994). These factors may contribute to hyper-binding of certain perceptions and actions in GTS. GTS patients are better at learning reward-related motor sequences (Palminteri et al., 2011) and may therefore be especially good at learning or consolidating tics. A successful compensatory mechanism of the brain might be to down-regulate learning on the synaptic level. If responses within synaptically connected sensorimotor networks to both intrinsically arising and externally derived sensory input, spontaneous motor fluctuations, or both are attenuated or even reversed over time, the

likelihood of urges and associated unwanted tic events may be reduced. This, however, may come at a price, such as reduced visuo-motor integration.

An open question in this logic would be how tics are related to subjectively experienced reward compared other movements. The answer may be given by the BG Go/NoGo theory. The theory assumes that tics initially occur randomly and are then coupled to states because of Hebbian learning mechanisms. These mechanisms are also responsible for the experience of urges because the motor plan becomes couples with the state and is therefore activated by the state. It could be hypothesized that this is a relatively normal process. However, individuals who experience the release of a movement as particularly rewarding may be prone to consolidate the binding between state, motor plan, and motor execution in a vicious circle. The experience of reward may be mediated by BG/DA hyperactivity. The next open question would then be how this vicious circle can be reversed by compensatory mechanisms. Or, more precisely, why and how compensatory mechanisms occur at some point. This may be related to brain maturation and the development of the prefrontal cortex and associated changes between prefrontal cortex and sensorimotor areas (Jung et al., 2013). However, these assumptions are purely speculative at this point.

5.2 Future research

Overall, the results suggest that certain motor learning and consolidation processes differ between GTS patients and healthy controls. GTS patients may be exceptionally good reward learners, possibly because of increased DA transmission. Therefore, tic-event files may become abnormally strongly bound. The relationship between implicit motor learning and cortical synaptic plasticity should be investigated in a larger, uncomplicated, non-medicated GTS sample covering the whole range of symptom severity.

It might also be worthwhile to study acquisition and consolidation of learning in the SRTT in GTS patients using fMRI in order to investigate how BG-modulated consolidation mechanisms may differ between healthy controls and GTS patients. Furthermore, meta-plasticity effects could be studied in more detail using TMS. It would be interesting to investigate whether inducing increased excitability in GTS patients could reverse long-term potentiation-like effects in severely affected patients. However, an association with symptom severity might be difficult to investigate because synaptic plasticity effects can only be induced locally (e.g. in the hand).

Moreover, it would be interesting to investigate whether tic movements are more strongly represented than other, comparable movements, using fMRI. Building on the TEC, it might be

interesting to investigate how GTS patients acquire and bind event files compared to healthy controls. There are a number of behavioural paradigms that have been used to investigate the acquisition and structure of event files (Colzato, Warrens, & Hommel, 2006; Hommel, 2004, 2007; Zmigrod & Hommel, 2009). Employing these paradigms, it would be possible to test the assumption that event-files become more strongly bound in GTS patients than in healthy controls. Should this not be the case, then the hypothesis of tics as hyper-bound event files will be rejected.

Developmental questions, i.e. whether tics are acquired because of an overactive striatal reward system, or whether tics become rewarding over time, possibly due to a relief of premonitory urges, and also when and how compensatory mechanisms at the neural basis become active, are much more difficult to address. These questions would require long-term studies starting in high-risk children (parents affected) before the age of four.

Effects of attention should be studied in more detail. Studies 1 and 2 should be replicated, adding a condition in which patients view a video of themselves while ticcing. This might clarify whether immediate visual feedback about own tics plays a role in increasing tic-frequency. Moreover, study 3 could be adapted to investigate how attention by others might modulate tic frequency in GTS patients. Patients could be asked to perform one of the tasks, e.g. memorizing coloured circles, while they are informed that a third party a) performs the same task next to them (attention away), b) counts their mistakes in the task (attention on the patient), or c) counts their tics (attention on tics).

Finally, tic-interference effects might be investigated by adding a second tic-like category to the task, in order to find out how the visual perception of a tic that belongs to the patients' tic-repertoire might influence the execution of a tic-like movement.

5.3 Implications for behavioural treatment

Once generated, the majority of tics can be suppressed before being executed at the cost of experiencing an increase in urges. However, the possibility to trigger tics more easily than other movements appears to be the underlying problem. One possibility of influencing tic frequency would be to modulate attention. Paying attention to a task appears to decrease tic frequency. Motor skill training might be a good opportunity to decrease tic frequency without the aversive effects of having to suppress tics. Patients might even enjoy practising certain motor skills.

TMS-based interventions might be possible but will require more detailed investigation of the underlying mechanisms of tic-related synaptic plasticity, particularly if they are counter-

intuitive, for instance increasing cortical excitability in order to prompt the brain to induce meta-plasticity effects. Three TMS studies have attempted tic reduction in the past by applying low-frequency repetitive TMS over the pre-motor cortex, the motor cortex (Munchau et al., 2002), and the SMA (Kwon et al., 2011; Mantovani et al., 2007). Stimulation of the SMA caused a significant decrease in symptom severity.

5.4 Conclusions

The data presented in this thesis provide first evidence that tics might be viewed as event-files that are characterised by hyper-binding. A shift in the perception of tics away from inhibition failure towards an integration into a framework for both motor and perception processing might be helpful for future research, behavioural therapies, and GTS patients' perspective on their on tics. The results will need to be confirmed or refuted with regard to hyper-binding, based on paradigms that can investigate single aspects of event files more specifically.

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Abbreviations

α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid – AMPA
Abductor pollicis brevis - APB
Analyses of variance - ANOVA
Attention deficit hyperactivity disorder – ADHD
The Attention Deficit Hyperactivity Disorder Self-Rating - ADHD-SR
Attention Deficit Hyperactivity Disorder Fremdbeurteilungsbogen - FBB-ADHD
Basal ganglia –BG
Cortico-striatal-thalamo-cortical - CSTC
Diagnostic Confidence Index - DCI
Diagnostic Statistical Manual – DSM
Dopamine – DA
Functional magnetic resonance imaging - FMRI
Gamma-Aminobutyric acid - GABA
Genome-wide association studies - GWAS
Gilles de la Tourette syndrome – GTS
Habit reversal therapy - HRT
High frequency stimulation – HFS
Input-output curve - IO curves
Long-term depression – LTD
Long-term potentiation - LTP
Motor evoked potentials – MEP
N-methyl-D-aspartate - NMDA
Obsessive–compulsive disorder - OCD
Paired associative stimulation – PAS
Positron emission tomography - PET
Premonitory Urge for Tics Scale - PUTS
Primary motor cortex – M1
Repetitive Transcranial magnetic stimulation – rTMS
Serial reaction time task – SRTT
Single-photon emission computed tomography – SPECT
Standard deviation - SD
Standard error of the mean - SEM

Supplementary motor area – SMA

Theory of event coding - TEC

Theta burst stimulation – TBS

Transcranial magnetic stimulation – TMS

Wender-Utah Rating Scale – WURS

Yale-Brown Obsessive Compulsive Disorder Scale (Y-BOCS)

Yale Global Tic Severity Scale- YGTSS