The relationship between motor response inhibition, tic severity and Attention Deficit Hyperactive Disorder (ADHD) in patients with Gilles de la Tourette Syndrome (GTS)

L. Lu (3520110)
Masterthesis Clinical and Health Psychology
Under supervision of dr. D.C. Cath and drs H.M. Huisman - van Dijk

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Abstract

Gilles de la Tourette Syndrome (GTS) is a neuropsychological developmental disorder characterized by tics. Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common comorbidities of GTS. There are suggestions that GTS and ADHD are etiologically related in the area of inhibition failure.

Method: To study whether serial response time, as measured by the serial response time task is associated with tic severity, and severity of co-morbid ADHD, and might serve as predictor of outcome, in total 28 GTS patients and 30 healthy control participants participated in the study. The GTS patients all finished the YGTSS, Y-BOCS, CAARS and the SRT and the control group finished the ticscreener, CAARS and the SRT. In the analyses, education level and gender were included as co-variates, since there were significant between-group differences on these measures.

Results: GTS patients with 1) higher ADHD severity and with 2) higher YGTSS tic severity showed at trend level- longer inhibition times compared to 1) GTS patients with low tic severity or 2) GTS + low ADHD scores, and controls. Other comparisons revealed no between-group differences. Gender en education level were significant predictors of response time, and education level was a predictor of the amount of errors on the SRT. Outcomes on the SRT neither predicted current tic severity nor change in tic severity over time in GTS patients.

Conclusions: in this study, longer response time was –at trend level – associated with current tic severity and with co-morbid ADHD, but does not seem to predict tic severity change. These findings need to be replicated in future studies, using larger sample size, wider range in age and a greader variation in tic severity

Keywords: Gilles de la Tourette Syndrome (GTS), motor response inhibition, response time (SSRT), Stop Signal Reactiontime Task (SRT), ADHD Severity, Tic severity, Tic severity over time, Age, Gender, Education level.

Preface

This master thesis is established in the context of the master program Clinical and Health Psychology at the University of Utrecht. As a subject we have chosen the Gilles de la Tourette Syndrome (GTS) study. The motivation to choose this subject is personal interest in the neuropsychological aspects of GTS. We want to expand our knowledge of GTS, get in touch with the

GTS patients in the clinical setting and we want to experience conducting neuropsychological tasks. We have chosen to investigate: “The relationship between motor response inhibition, tic severity and Attention Deficit Hyperactive Disorder (ADHD) in patients with Gilles de la Tourette Syndrome (GTS)”. In GTS patients uncontrollable motor movements (tics), are main symptoms. We became interested in the question whether it is possible to control tics. This has inspired us to choose for motor inhibition of tics. ADHD is chosen because of the high comorbidity with GTS and the related inhibitory problems. To answer the research question, we created several hypotheses.

To expand our knowledge as broad as possible and to both get insight in all investigated area’s, we chose to individually focus on different hypotheses whereby both researchers can get knowledge of all different subjects and statistical analyses within this research. A.M.Los had focused on the relation between tic severity in GTS patients and a healthy control group on motor response inhibition (hypothesis 2). Second she focused on the predictive value of motor response inhibition on change in tic severity over time (hypothesis 6). L.Lu had focused on tic severity over time and motor response inhibition (hypothesis 3). Second she focused on the predictive value of motor response inhibition on tic severity (hypothesis 5). The statistical analyses for the different hypotheses were performed separately and integrated into one thesis. The remaining hypothesis about the relation between ADHD severity of GTS patients and a healthy control group on motor response inhibition (hypothesis 1) and the relation between demographic variables and motor response inihibition (hypothesis 4) are written in cooperation. In the introduction A.M.Los has written alinea 7 and L.Lu alinea 8. The remaining part of the introduction was written in cooperation. In the discussion A.M.Los has written alniea 4, 6 and 8. L.Lu has written alinea 5, 7 and 9 from the discussion. The introduction of the discussion(alinea’s 1-3) and the conclusion (alinea 10), are written in cooperation.

We want to thank to dr. D.C. Cath for her professional supervision, guidance and for sharing her knowledge in writing these thesis. For the statistical part, we want to thank H.M. Huisman- van Dijk for her feedback and assistance. We also want to thank her for her willingness to explain and let us take part in the interviews with GTS patients and the conducted neuropsychological tasks.

GILLES DE LA TOURETTE: THE RELATIONSHIP OF ADHD SEVERITY AND TIC SEVERITY IN MOTOR RESPONSE INHIBITION IN GTS

Introduction

Gilles de la Tourette

At the end of the nineteenth century a new disease has been discovered by Georges Gilles de la Tourette. The disease has been characterized as a collection of symptoms that are manifested as uncontrollable muscle movements and in making noises, named Gilles de la Tourette Syndrome (GTS). GTS is a chronic childhood-onset neuropsychological disorder characterized by multiple motor, and one or more vocal (phonic) tics, lasting longer than a year and with no tic-free period of more than three successive months (American Psychiatric Association, 1994). Tics are sudden, repetitive nonrhythmic, stereotyped motor movements or vocalizations involving discrete muscle groups, and are categorized as motor and vocal tics (American Psychiatric Association, 1994). Examples of motor tics are eye blinking, head jerking, facial grimacing, or shoulder shrugging, and of phonic tics sounds or noises such as throat clearing, sniffing, or grunting (Freeman et al., 2000; Felling & Singer, 2011). GTS is usually diagnosed in early childhood with a mean age of onset of 6-7 years. GTS affects approximately 1% of the population. GTS has a genetic predisposition and is more common in men (Freeman et al., 2000; Robertson, 2008; Conelea, Woods & Brandt, 2011).

GTS has been linked to disturbances in several brain regions, in particular in the frontal parts of the brain. Basal ganglia abnormalities are found in both children and adults with GTS (Crawford, Channon & Robertson, 2005). There is also evidence found for impairments in executive functions in GTS patients such as working memory, regulation of motivation, and motor control (Barkley, 1997). The basal ganglia and executive functions are highly interrelated. Motor skills like motor response inhibition are dependent of both the basal ganglia and executive functions. Many GTS patients have problems with motor response inhibition (Verbruggen & Logan, 2008; DeLong & Wichmann, 2007; Cavanna, 2012). The movement difficulties in motor response inhibition are the inability to suppress inadequate motor responses and let them dominate by goal-directed behavior. However behavioral studies show improvement in performance of adolescents and young adults on tasks related to motor response inhibition increasing with age, as the frontal areas of the brain develops (Blakemore & Choudhury, 2006). At the same time from adolescence on, many GTS patients seem to suffer less from their tics as tic intensity and frequency diminishes, a development that is also linked to frontal lobe maturation. Presumably there is a link between motor response inhibition and the tics in GTS patients.

ADHD

Approximately 90% of the patients with GTS have comorbid neuropsychiatric disorders (Cavanna, Servo, Monaco & Robertson, 2009). One of the most common co-morbidity is Attention-Deficit Hyperactivity Disorder (ADHD) with a prevalence of 60%-80% (Freeman et al., 2000; Cavanna et al., 2009).

Comorbid ADHD often has a negative impact on concurrent social, academic and behavioral functioning and can have a negative impact on future quality of life and global psychosocial functioning (Bloch & Leckman, 2009). ADHD has a high prevalence rate. It affects 3-5% of the children and adolescents (Malfa, Lassi, Bertelli, Pallanti & Abertini, 2007). ADHD is characterized by symptoms like hyperactivity, impulsivity, a lack of attention and has an early age at onset (before age of 7 years; American Psychiatric Association, 2000). ADHD is more difficult to diagnose in adulthood, because of reduction of overall ADHD symptoms into adulthood. Although symptoms such as concentration problems persist in at least two-third of the persons into adulthood. The reported prevalence of ADHD in adults is between 2.9- 16.4%. ADHD is more common in men (Malfa et al., 2007).

Motor response inhibition related to GTS and ADHD

There have been suggestions that GTS and ADHD are genetically related (Lypszyc & Schachar, 2010). They appear to share the same symptomatology. Both GTS and ADHD are characterized by childhood onset and excessive motor activity. It is likely that there also is an overlap in neurological mechanisms. Structural neuroimaging studies have reported that both ADHD and GTS patients have abnormalities in brain regions implicated in inhibitory functions including motor inhibition (CSTC circuits; Sukhodolsky et al., 2010; Lypszyc & Schachar, 2010; Verbruggen & Logan, 2008). Presumably there is a link between motor response inhibition and GTS and ADHD.

OCD

Stop Signal Reaction Time Task

To measure motor response inhibition the neuropsychological Stop Signal Reaction Task (SRT) has widely been used. The SRT measures the ability to cancel an ongoing speeded motor response. The SRT is based on the "horse race" model (Jong, Coles, Logan & Gratton, 1990). This model involves a race between two sets of processes, the go process and the stop process. If the go process finishes first, the response will be executed. If the stop process finishes first, the response will be inhibited (Lypszyc & Schachar, 2010; Schachar & Logan, 1990; De Jong et al., 1990). The inhibition is shown by the outcome measure Stop Signal Reaction Time (SSRT). The SSRT provides an estimate of the latency of the inhibition process (Lypszyc & Schachar, 2010; Lijfijt, Kenemans, Verbaten & van Engeland, 2005). A slower response time (SSRT) on a trial implies less motor inhibition, while a faster response time (SSRT) implies better motor inhibition. The SRT also measures the percentage of commission errors (pressing for X when O was presented or vice versa), the percentage of omission errors (not responding to the primary task despite the absence of a stop signal).

Many studies have focused on the relationship between motor response inhibition measured by the SRT and ADHD (e.g. Lypzyc & Schachar, 2010; Verbruggen & Logan, 2008; Lijfijt et al., 2005; Kofler et al, 2013). A lack of motor response inhibition has been proposed as a component of

ADHD. However few studies focus on the link between GTS and motor response inhibition measured by the SRT. In the study of Crawford et al. (2005) GTS patients were less likely to respond as fast as the healthy control group. GTS patients also made more errors than the healthy control group. Results of the meta-analysis studied by Lipszyc and Schachar (2010) who used the SRT, showed an impaired inhibition in patients with ADHD. In the study of Lypszyc and Schachar (2010) the link between response inhibition and GTS (although investigated) remains unclear.

Both education level and gender are known to affect the inhibition. Several studies linked executive functions to academic performance and different academic domains in children (Hillman et al., 2012; Latzman, Elkovitch, Young & Clark, 2010). A more specific relationship was found between inhibition and academic achievement in middle childhood and preadolescent children (Thorell, Veleiro, Siu & Mohammadi, 2012; Clark, Pritchard & Woodward, 2010; Clair-Thompson & Gathercole, 2006). However, little is known about the relationship between education level and inhibition in adults. An fMRI study showed different activation patterns in different regions of the brain during the SRT between men and women (Li, Zhang, Duann, Yan, Sinha & Mazure 2009). Li et al. (2009) suggest in their study that this difference can be explained by the use of different strategies and the engagement in different neural pathways in men and women, during stop signal performance. This may help us to understand why men are more vulnerable to impulse control disorders.

This study aims at exploring motor response inhibition in GTS patients with high and low ADHD severity, GTS patients high and low tic severity and tic severity over time compared to a (healthy) control group. This study forms part of a naturalistic follow-up of GTS patients who have been pheotyped between 2000-2005 ni the scope of a large-scale genetic study. During the folow-up measurement the SRT has been taken as part of the test battery. Further, in the scope of this masterthesis a a healthy control group has been assessed. There are two main questions examined by several hypotheses:

(A) What are the differences and similarities between GTS patients with high versus low ADHD severity, GTS patients with high versus low tic severity, and GTS patients with an increase versus decrease in tic severity over time compared to a healthy control group in motor response inhibition on the SRT and the amount of errors on the SRT?

1. a) GTS patients with high ADHD severity have slower response time (SSRT; poorer inhibition) compared to GTS patients with low ADHD severity and the control group, and GTS patients with low ADHD severity will have a slower response time (SSRT) compared to the control group.

   b) GTS patients with high ADHD severity make more errors of omission (poorer inhibition) compared to GTS patients with low ADHD severity and the control group, and GTS patients

with low ADHD severity make more errors of omission (poorer inhibition) compared to the control group.

c) GTS patients with high ADHD severity make more errors of commission (poorer inhibition) than GTS patients with low ADHD severity and the control group, and GTS patients with low ADHD severity make more errors of commission (poorer inhibition) compared to the control group.

2. a) GTS patients with high tic severity score at FU will have a slower response time (SSRT) compared to GTS patients with low tic severity score at FU.

   b) GTS patients with high tic severity score at FU will have more errors of omission compared to GTS patients with low tic severity score at FU.

   c) GTS patients with high tic severity score at FU will have more errors of commission than GTS patients with low tic severity score at FU.

3. a) GTS patients with a decrease in tic severity from BM to FU will have faster response times (SSRT) than GTS patients with increase in tic severity.

   b) GTS patients with a decrease in tic severity from BM to FU will have less errors of omission than GTS patients with an increase in tic severity.

   c) GTS patients with a decrease in tic severity from BM to FU will have less errors of commission than GTS patients with an increase in tic severity.

(B) What are the predictors response time (SSRT) on the SRT, errors on the SRT, tic severity and change in tic severity over time?

4. Demographic variables, tic severity and ADHD are predictors of motor inhibition on the SRT.

a) Age will be a predictor of response time (SSRT), of errors of omission and of errors of commission on the SRT.

b) Gender will be a predictor of response time (SSRT), of errors of omission and of errors of commission on the SRT.

c) Education level will be a predictor of response time (SSRT), of errors of omission and of errors of commission on the SRT.

5. a) Response time (SSRT) on the SRT will be a predictor of tic severity in GTS patients.

   b) The amount of errors of omission on the SRT will be a predictor of tic severity in GTS patients.

   c) The amount of errors of commission on the SRT will be a predictor of tic severity in GTS patients.

6. a) Response time (SSRT) on the SRT will be a predictor of change in tic severity over time (from BM to FU) in GTS patients.

   b) The amount of errors of omission on the SRT will be a predictor of change in tic severity over time (from BM to FU) in GTS patients.

c) The amount of errors of commission on the SRT will be a predictor of change in tic severity over time (from BM to FU) in GTS patients.

Method

Participants

The baseline measurements (BM) between 2001 and 2008 consisted of 225 patients diagnosed with GTS and 350 family members . A follow up study (FU) with the same participants took place between 2008 and 2012 included 47 GTS patients. From the 47 GTS patients, 28 patients had received measurements of the SSRT and were included. They also finished the Yale Global Tic Severity Scale (YGTSS), Conners Adult ADHD Rating Scale (CAARS) and Yale-Brown Obsessvive Compulsive Scale (Y-BOCS) at baseline and Follow-up. In this group 18 persons were male (64.3%) and 10 were female (35.7%). Age at BM varied between 7 and 62 years (M=29.1; SD=16.2). At FU (± 7 years later) age varied between 14 and 70 years (M=34.7; SD=15.0). For the level of education, the Dutch school system is being used *(1= "Lager of basisschool onderwijs", 2 = "MAVO/ VMBO/ LTS/ LBO/MBO/ MEAO/ MTS ", 3= HAVO/ VWO/ Atheneum/ HBS HBO/ HEAO/ HTS / Universiteit).* Level of education in GTS patients at FU varies between 1 and 3 (M=2.44; SD=.75).

The control group (healthy patients) consisted of 30 patients without GTS. In this group 12 were male (40%) and 18 were female (60%). Age varied between 20 and 59 years (M=33.73; SD=13.90). level of education was M=2.56; SD=.66. The control group contained a convenience sample (students from the University of Utrecht and in the personal setting of the researchers).

Measures

Tic Severity

Tic severity was measured using the Dutch version of the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). The YGTSS is a semi-structured clinician-rated instrument that assesses the nature of motor and phonic tics over the week before the assessment and is a commonly used index of tic severity among children and adolescents. The clinician separately rates the severity of motor and vocal tics on five separate dimensions: number, frequency, intensity, complexity and interference. In addition, there is one question which measures the overall impairment in daily functioning due to tics (Leckman et al., 1989). The 10 items are rated on a 6-point ordinal scale (from 1=none to 6=severe). The YGTSS is a reliable and valid instrument with excellent internal consistency.

In this study the YGTSS is used to measure GTS severity. YGTSS scores of the GTS patients are divided to create different groups relating to different hypotheses. In the the first division YGTSS scores are divided in a group with high tic severity and a group with low tic severity. For this division a cutoff score of 21 (the mean score) is used. All GTS patients with a score of ≤ 21 on the YGTSS are

classified as the low tic severity group and all GTS patients with a score of >21 on the YGTSS are classified as the high tic severity group. In the second division YGTSS scores are divided on base of score differences from BM to FU (over time). All GTS patients with an increased tic severity score over time (from BM to FU) are classified as the increase tic severity group and all GTS patients with a decreased or unchanged score in tic severity over time (from BM to FU) are classified as the decrease tic severity group.

ADHD

To asses ADHD severity in adults the Dutch version of the Conners Adult ADHD Rating Scales (CAARS) was used. This instrument is designed for individuals aged 18 and older. The scales address ADHD symptoms as described in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV; American Psychiatric Association, 1994; Conners, Erhardt, & Sparrow, 1999). The version contains 30-items divided in Inattentive Symptoms and Hyperactive-Impulsive Symptoms. Items are rated on a 4 point likert scale (0=not at all to 3=completely). If participants scores 6 or higher on one scale, they will be classified as high-ADHD. When participants score less than 6 on a separate scale, they will be classified as low-ADHD. When participants scores 10 or higher as sum of both scales and at least 5 on both separate scales they will be classified as high-ADHD.

The CAARS has good psychometric properties and is a reliable and valid instrument for measuring ADHD symptomatology (Conner, Erhardt & Sparrow, 1999; Cleland, Magura, Foote, Rosenblum & Kosanke, 2006)

Obsessive Compulsive Disorder

To asses symptoms of Obsessive Compulsive Disorder a Dutch version of the Yale Brown Obsessive Compulsive Scale was used (Y-BOCS-ernst; Goodman 1989a,b; Moritz et al., 2002). The Y-BOCS is a clinician-administered semi-structured interview. It contains 16 core items scored on a five-step Likert scale (0–4, higher scores indicate greater disturbance). Only the first 10 items are used to compute the total score of the Y-BOCS. The first 5 items (1-5) represent obsession related symptomatology, the following 5 items (6-10) represent compulsion related symptomatology.

The Y-BOCS has excellent psychometric properties (Frost et al., 1995; Goodman et al., 1989a,b; Moritz et al., 2002). This instrument has good internal consistency (Cronbach's alpha, baseline .83, discharge .90 and baseline .79, discharge .88; Mortiz et al., 2002). An excellent inter-rater reliability for total scale (.93) and subscales (ranging from .74 to .91; Woody, Steketee & Chambless, 1995). The test-retest reliability of the Y-BOCS is acceptable for research purposes (total scale .61; Woody et al., 1995). Thereby the Y-BOCS has an excellent convergent validity (.74; Goodman et al., 1989b) and a poor divergent validity (Woody et al., 1995).

Motor response inhibition

The Stop Signal Reaction Time Task (SRT) is a computerized task used to measure motor response inhibition in a laboratory setting. The SRT consist of 4 blocks. In the first block patients

have to respond as fast as they can to symbols (X and O) presented on a computer screen. The second to fourth block a symbol is added randomly ($). In these blocks patients have to respond as fast as they can to symbols (X and O) presented on a computer screen and by the appearance of the $ the have to inhibit their response. The first two blocks are trial versions to learn to respond properly to X, O and $. This blocks consist of 126 trails. The last two blocks consist of 128 trails.

The SRT is based on the "horse race" model (Jong et al., 1990; Logan, 1994). This model involves a race between two sets of processes, the go process and the stop process. If the go process finishes first, the response will be executed. If the stop process finishes first, the response will be inhibited (Lypszyc & Schachar, 2010; Schachar & Logan, 1990).

In this study, three outcome viariables of the SRT are used: Stop Signal Reaction Time (SSRT), the ammount of commission errors (pressing for X when O was presented or vice versa) and the ammount of omission errors (not responding to the primary task despite the absence of a stop signal). Psychometric properties. Several studies have supported reliability and validity of the SRT as a measure of response inhibition (Oosterlaan, Logan & Sergeant, 1998; Kindlon, Mezzacappa & Ealrs, 1995; Tannock, Schacher, Carr, Chajczyk & Logan, 1989).

Procedure

Participants in the BM were recruited from 2001 to 2008 by MHC (GGZ) Buiten Amstel, the Dutch Tourette's syndrome patient association and the National Tourette days. Participants with GTS were invited for an assessment using self-report questionnaires and a semi-structured interview. After agreement of participation (informed consent) participants were sent self-report questionnaires consisting of the YGTSS, CAARS and the YBOCS and other measures. Participants were asked to bring the filled in forms to the interview. During the interview a trained employee assessed participants for co-morbid disorders.

Between 2008 and 2012, the GTS patients were re- invited (by letter and telephone) to participate. Participants at FU were re-measured using the same method as at BM. The FU patients completed the following questionnaires: Yale Global Tic Severity Scale (YGTSS), the Conner's Adult ADHD Rating Scale, and the Yale Brown Obsessive Compulsive Scale (YBOCS). This group additional finished several neuropsychological tasks, including the SRT.

The participants of the control group were recruited in 2013 at the University of Utrecht. In order to check the control group on tics, they completed a tic screener. The group also filled in the Conner's Adult ADHD Rating Scale (CAARS) and finished the SRT.

Groups

Main question A

For the first hypothesis the GTS patients with high ADHD severity and with low ADHD severity were compared to the control group in response time (SSRT) and amount of errors. For the second hypothesis the group of GTS patients with high tic severity and with low tic severity were compared to the control group in response time (SSRT) and amount of errors. For the third hypothesis GTS patients with an increase in tic severity over time and with a decrease in tic severity over time were compared to the control group on response time (SSRT) and amount of errors.

Main question B

For the fourth hypothesis the whole group of participants is used together (FU as well as the control group) to analyse the predictive value of age, gender and education level on the response time (SSRT) and amount of errors. For the fifth hypothesis, the YGTSS score of the group of GTS patients (FU) is used. There is no YGTSS score of the control group therefore the control group does not take part of the prediction. For the sixth hypothesis, the change in YGTSS score over time (from BM to FU) of the group of GTS patients is used.

Statistical analyses

All data were analyzed using the statistical analysis program SPSS (version 20.0). This study used a statistical significance level of $p < .05$.

First is checked for variables that influence the outcome variables response time (SSRT), errors of omission, errors of commission, tic severity and change in tic severity over time. Because in literature a strong link was found between GTS, ADHD and Obsessive Compulsive Disorder (OCD), a pearson correlation test was used to check for the influence for OCD. This analysis showed that OCD did not affect the response time (SSRT; $r = -.358$, $p = .062$), errors of omission ($r = .097$, $p = .632$), errors of commission ($r = -.165$, $p = .402$), tic severity ($r = .141$, $p = .482$) and tic severity over time ($r = .570$, $p = -.117$). Thereby there is checked for the influence for the influence of the demographic variables (age, gender and education level). Age did not influence response time ($F(1,56) = 1.21$, $p = .275$), errors of omission ($F(1,56) = .001$, $p = .275$), errors of commission ($F(1,56) = .053$, $p = .819$), tic severity ($r = -.133$, $p = .115$) and change in tic severity over time ($r = -.226$, $p = .267$). Gender did influence the response time ($F(1,56) = 4.60$, $p = .036$), but not the errors of omission ($F(1,56) = .250$, $p = 619$), the errors of commission ($F(1,56) = 1.11$, $p = .295$), tic severity ($r = .278$, $p = .161$) an change in tic severity over time ($r = .063$, $p = .761$). Education level did influence the response time ($F(1,55) = 5.21$, $p = .026$) as well as the errors of omission ($F(1,55) = 5.33$, $p = .004$) and errors of commission ($F(1,55) = 13.63$, $p = .001$), but not on tic severity ($F(1,23) = .354$, $p = .706$) and change in tic severity ($F(1,22) = .360$, $p = .702$). Before controlling for education level, there was a significant difference between the GTS patients with high ADHD and the control group ($p = .004$).

Main question A

An ANCOVA analysis was used to measure the first hypothesis (a), the comparison of the group of GTS patients with a high ADHD severity, the group of GTS patients with a low ADHD severity and the control group in response time (SSRT). For this part of the hypothesis gender and education level were used as a covariable. An ANCOVA analysis was used to measure the first hypothesis (b), the comparison of the group of GTS patients with a high ADHD severity, the group of GTS patients with a low ADHD severity and the control group in errors of omission. An ANCOVA analysis was used to measure the first hypothesis (c), the comparison of the group of GTS patients with a high ADHD severity, the group of GTS patients with a low ADHD severity and the control group in errors of commission. For part b and c of the hypothesis education level was used as a covariable.

An ANCOVA analysis was used to measure the second hypothesis (a), the comparison of the group of GTS patients with a high tic severity, the group of GTS patients with a low tic severity and the control group in response time (SSRT). For this part of the hypothesis gender and education level were used as a covariable. An ANCOVA analysis was used to measure the second hypothesis (b), the comparison of the group of GTS patients with a high tic severity, the group of GTS patients with a low tic severity and the control group in errors of omission. An ANCOVA analysis was used to measure the second hypothesis (c), the comparison of the group of GTS patients with a high tic severity, the group of GTS patients with a low tic severity and the control group in errors of commission. For part b and c of the hypothesis education level was used as a covariable.

An ANCOVA analysis was used to measure the third hypothesis (a), the comparison of the group of GTS patients with an increase in tic severity, the group of GTS patients with a decrease in tic severity and the control group in response time (SSRT). For this part of the hypothesis gender and education level were used as a covariable. An ANCOVA analysis was used to measure the third hypothesis (b), the comparison of the group of GTS patients with an increase in tic severity, the group of GTS patients with a decrease in tic severity and the control group in errors of omission. For this hypothesis education level are used as a covariable. An ANCOVA analysis was used to measure the third hypothesis (c), the comparison of the group of GTS patients with an increase in tic severity, the group of GTS patients with a decrease in tic severity and the control group in errors of commission. For part b and c of the hypothesis education level was used as a covariable.

Main question B

Linear regression analyses were used to measure the fourth hypothesis that age, gender and education level are predictors of response time (SSRT), the amount errors of omission and the amount of errors of commission. To further examine the direction of the predictive value for gender mean scores for men and women on the response time (SSRT) were compared. To further examine the direction of the predictive value for education level, mean scores on the response time (SSRT), amount of errors of omission and amount of errors of commission for all three levels were compared.

Linear regression analyses were used to measure the fifth hypothesis that response time (SSRT) on the SRT and the amount of errors of omission and commission on the SRT were predictors of tic severity in GTS patients.

Linear regression analyses were used to measure the sixth hypothesis that response time (SSRT) on the SRT and the amount of errors of omission and commission on the SRT were predictors of change in tic severity over time (from BM to FU) in GTS patients.

Results

Prior to the analysis the data have been checked on differences between groups. The group of GTS patients with a high tic severity did differ significantly in age from the group of GTS patienst with a low tic severity ($F(1,56)= 4.722$, $p=.014$, $\eta^2=.31$). The group of GTS patients with an increase in tic severity over time (from BM to FU) was older (M=34.63, SD=16.48 versus (M=33.73, SD=13.90) and contained more men (80%) than the control group (40%) ($\chi^2= 3.883$, df= 1, $p=.049$). Analysis on differences between groups and their level of education showed that GTS patients with a high ADHD severity differed significantly from the control group ($F(2,54)= 12.05$, $p=.000$, $\eta^2=.31$). GTS patients with a high tic severity had a lower education level (M=2.21, SD=.80) than the control group (M=2.89, SD=.31). Furthermore the group of GTS patients with an increase in tic severity over time (from BM to Fu) differed significantly from the control group in education level ($F(2,52)= 9.36$, $p=.001$, $\eta^2=.27$) as well as the group of GTS patients with a decrease in tic severity ($F(2,52)= 9.36$, $p=.034$, $\eta^2=.27$). Both the group of GTS patients with an increase in tic severity (M=2.13, SD=0.74) and the group of GTS patients with a decrease in tic severity (M=2.30, SD=0.82) had a lower education level than the control group (M=2.89, SD=0.31; see Table 1).

Hypothesis 1

There were trend-level between-group differences in response time (SSRT) outcome between the group GTS patients with high ADHD severity, the GTS group with low ADHD severity and the control group ($F(2,53)=3.006$, $p=.058$), with the GTS+ADHD group displaying increased inhibition times. Nor differences in amount of omission errors between the group of GTS patients with high ADHD severity, GTS patients with low ADHD severity and the control group ($F(2,53)=1.38$, $p=.26$) and differences in the amount of commission ($F(2,53)=.67$, $p=.52$; see Table 2).

Hypothesis 2

There were trend-level between-group differences in response times (SSRT) between GTS patients with high tic severity, with low tic severity and the control group ($F(2,51)=2.50$, $p=.092$), with the high tic severity group showing longer response times than the low tic severity group or controls. No differences in amount of omission or commission errors were found between GTS patients with high tic severity, GTS patients with low tic severity and the control group ($F(2,51)=1.22$, $p=.30$; $F(2,51)=1.14$, $p=.33$; see Table 2).

Table 1. Demographic data and distribution from the baseline measurement (BM) and the follow up measurement (FU) of GTS patients and the control group (control)

	N	Age		Gender	Education level		SSRT		Errors of omission		Errors of commission	
		M	*SD*	*% man*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
BM	28	29.07	16.20	64.30	-	-	-	-	-	-	-	-
FU	28	36.00	17.87	64.30	2.44	0.75	273.04	94.17	3.33	3.32	3.38	3.85
ADHD												
Low	11	46.55	15.06	61.50	2.40	0.70	272.69	99.36	2.08	1.16	3.52	2.85
High	13	48.00	18.36	66.70	2.12	0.78	273.33	92.96	4.79	4.11	4.05	2.95
Tic severity												
Low	12	44.83	17.14	66.70	2.25	0.75	271.92	85.10	4.38	4.33	3.37	2.70
High	15	28.07	12.37	60.00	2.21	0.80	280.53	103.21	2.55	1.29	4.12	3.00
Tic Severity (over time)												
Decrease	10	38.70	17.49	60.00	2.30	0.82	270.70	89.81	3.91	4.48	2.82	2.54
Increase	16	34.63	16.48	86.80	2.13	0.74	282.44	101.59	3.22	2.35	3.96	2.68
Control	30	33.73	13.90	40.00	2.89	0.31	209.17	48.81	.747	.679	.876	.698

Table 2. The results of the hypothesis of main question A, using ANOVA as statistical measuremen

	SSRT			**Errors of Omission**			**Errors of Commission**		
	F	*Df*	*P*	*F*	*df*	*p*	*F*	*df*	*p*
ADHD	3.01	2,53	.058	1.38	2,53	.26	0.67	2,53	.52
Tic severity high-low	2.50	2,52	.092	1.22	2,52	.30	1.14	2,52	.33
Tic severity decrease-increase	2.48	2,50	.094	1.75	2,50	.18	1.38	2,50	.26

Hypothesis 3

Between-group differences in response time (SSRT) outcome were found at trend level between the group GTS patients with an increase in tic severity over time (from BM to FU), the GTS group with a decrease in tic severity over time and the control group ($F(2,50)=2.48$, $p=.094$), with the tic severity increase group showing higher response times than the other groups. No differences were found in amount of omission errors between GTS patients with increase in tic severity over time, GTS patients with decrease in tic severity over time and the control group ($F(2,50)=1.75$, $p=.18$). Nor were between group differences found in the amount of commission errors ($F(2,50)=1.38$, $p=.26$).

Hypothesis 4

Age was not a predictor of response time (SSRT) on the SRT ($F(1, 56) = 4.604$, $p=.275$, $\beta= 0.146$, $R^2=.076$). Nor was age a predictor of the amount of errors of omission ($F(1, 56) = 1.215$, $p=.275$, $\beta= .146$, $R^2= .021$) and commission ($F(1, 56) = .053$, $p=.819$, $\beta= .031$, $R^2= .001$).

Gender was a predictor of response time (SSRT) on the SRT ($F(1, 56) = 4.604$, $p=.036$, $\beta= -.276$, $R^2=.076$). Being a man predicts a slower response time (SSRT; M=261.20, SD=91.21) than being a woman (M=217.29, SD=60.39). Gender was not a predictor of the amount of errors of omission ($F(1, 56) = .250$, $p=.619$, $\beta= .067$, $R^2=.004$) nor was gender a predictor of the amount of errors of commission ($F(1, 56) = 1.115$, $p=.295$, $\beta= -.140$, $R^2=.020$).

Education level was a predictor of response time (SSRT) on the SRT ($F(1, 55) = 5.218$, $p=.026$, $\beta= -.294$, $R^2=.087$). A higher education level predicts a faster response time (SSRT). Level 3 (M=224.20, SD=74.71) has a faster response time than level 2 (M=251.90, SD=75.12) and level 2 has a faster response time than level 1(M=317.20, SD 107.44; see Figure 1). Education level was also a predictor of the amount of errors of omission ($F(1, 55) = 5.331$, $p=.025$, $\beta= -.297$, $R^2=.088$), with lower education levels being predictors of more errors of omission. Level 2 has the highest amount of errors of omission (M=4.69, SD=8.09), followed by level 1 (M=3.54, SD 5.73) and level 3 had the lowest amount of errors of omission (M=.98, SD=.99; see Figure 2). Education level was also a predictor of the amount errors of commission ($F(1, 55) = 13.63$, $p=.001$, $\beta= -.446$, $R^2=.199$). A lower education level predicts a higher amount of errors of commission. Level 1 has the highest amount of errors of commission (M=3.54, SD 5.73), followed by level 2 (M=251.90, SD=75.12) and last level 3 (M=224.20, SD=74.71; see Figure 3; see Table l).

Hypothesis 5

Tic severity in GTS patients was not a predictor of response time (SSRT) on the SRT ($F(1, 25) = .000$, $p=.988$, $\beta= - .003$, $R^2=.000$). Nor was tic severity in GTS patients a predictor of the amount of errors of omission ($F(1, 25) = .056$, $p=.815$, $\beta= .047$, $R^2=.002$) and commission ($F(1, 25) = .713$, $p=.406$, $\beta= -.167$, $R^2=.028$; see Table 4).

Figure 1. The response time (SSRT) displayed by level of education

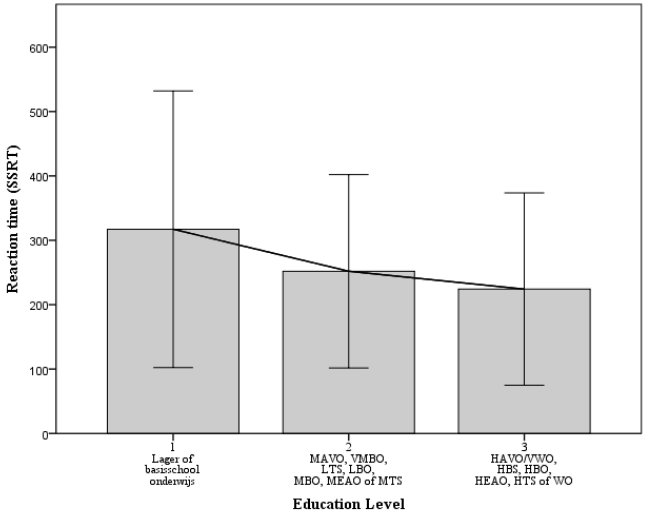

Figure 2. Errors of omission displayed by level of education

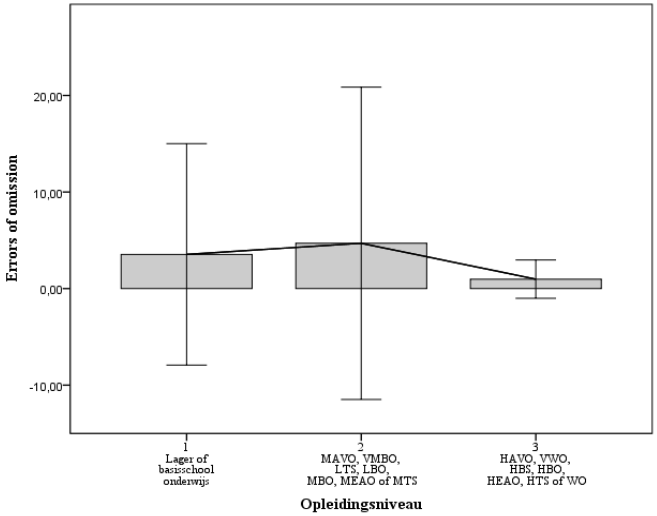

Figure 3. Errors of commission displayed by level of education

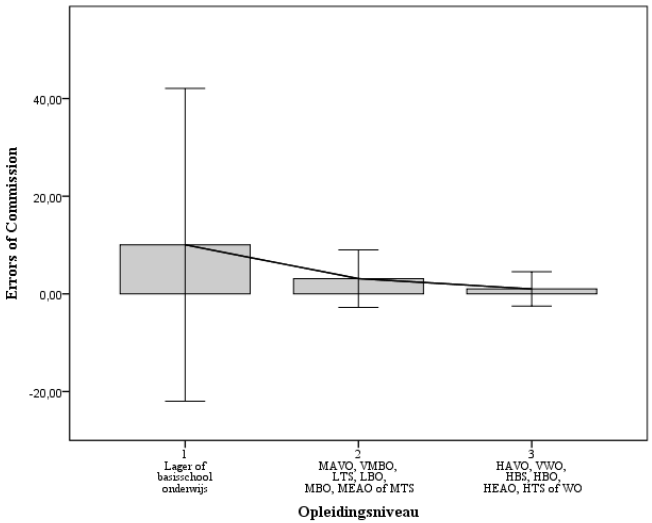

Table 3. Age gender and education level on SSRT, errors of omission and errors of commission

	SSRT						**Errors of omission**						**Errors of commission**					
	F	*df*	*β*	R^2	$R^2\Delta$	*p*	*F*	*df*	*B*	R^2	$R^2\Delta$	*p*	*F*	*df*	*β*	R^2	$R^2\Delta$	*p*
Age	1.215	1,56	.146	.046	.021	.275	.001	1,56	-.004	.000	.000	.979	.053	1,56	.031	.001	.001	.819
Gender	4.604	1,56	-.276	.076	.076	.036*	.250	1,56	.067	.004	.004	.619	1.115	1,56	-.140	.020	.020	.295
Education level	5.218	1,55	-.294	.087	.104	.026*	5.331	1,55	-.297	.088	.088	.025*	13.63	1,55	-.446	.199	.199	.001**

Note. *p>.05, **p>.01

Table 4. SSRT, errors of omission and errors of commission on tic severity and change in tic severity over time (from BM to FU)

	Tic severity						**Change tic severity over time**					
	F	*df*	*β*	R^2	$R^2\Delta$	*P*	*F*	*df*	*β*	R^2	$R^2\Delta$	*p*
SSRT	.000	1,25	-.003	.000	.000	.998	.069	1,24	-.054	.003	.003	.794
Errors of omisssion	.056	1,25	.047	.002	.002	.815	.964	1,24	-.196	.039	.039	.336
Errors of commission	.713	1,25	-.167	.028	.028	.406	2.100	1,24	.284	.080	.080	.169

Hypothesis 6

Response time (SSRT) on the SRT in GTS patients was not a predictor of change in tic severity over time ($F(1, 24) = .069$, $p=.794$, $\beta= -.054$, $R^2=.003$). Nor were the amount of errors of omission or commission predictors of change in tic severity over time in GTS patients ($F(1, 24) = .964$, $p=.336$, $\beta= -.196$, $R^2=.039$; $F(1, 24) = 2.100$, $p=.160$, $\beta= -.284$, $R^2=.080$; see Table 4).

Discussion

The first main question of this thesis has examined the differences and similarities between GTS patients with high versus low ADHD severity, with high versus low tic severity and with an increase versus decrease in tic severity over time compared to a healthy control group in response time (SSRT) on the SRT. The results show that GTS patients with high tic severity but also with high ADHD severity tended to show longer response times (analogous to more dysfunctional motor inhibition) compared to the low tic and ADHD severity groups and controls. A drawback of this study is that sample size did not allow for dividing the GTS group into more subgroups, i.e. of pure tic patients (without comorbid ADHD) with high versus low tic severity scores, and tic+ADHD patients, to sort out the specific contribution of tic severity to SRT times, apart from the contribution of ADHD.

The second main question examines the predictors of response time (SSRT) on the SRT. For all participants in this study, age was not a predictor of any of the response time (SSRT) measures. Furthermore, gender was a predictor of response time (SSRT). Being a man predicts a slower response time than being a woman, although gender was not a predictor of the amount of errors of omission and commission. Education level also predicted response time (SSRT). Participants with a higher education level had a faster response time (SSRT) than participants with a lower education level, and in general was higher education level associated with fewer errors of omission and comission

Several meta-analysis and reviews have found a relation between ADHD and motor response inhibition measured by the response time (SSRT) on the SRT in which patients with ADHD have a poorer motor response inhibition on the SRT than a (healthy) control group (e.g. Lypzyc & Schachar, 2010; Verbruggen & Logan, 2008; Lijfijt et al., 2005; Kofler et al, 2013). In contrast there are only few studies that measured the relation between motor response inhibition and GTS. The study of Crawford et al. (2005) found a poorer motor response inhibition in GTS patients than in a control group. Therefore the tendency to find poorer motor response inhibition in GTS patients with or without comorbid ADHD was fully in line with the literature. New of this study is that the current results were found in a predominantly adult patient group whereas the results of the main other study

by Crawford et al. (2005) was reported on adolescents (n=20) with GTS. Both trends in GTS patients on the SRT might turn into a significant result when measured in a larger sample.

GTS patients with an increase in tic severity over time did not differ from GTS patients with a decrease in tic severity over time nor from a control group. As it turns out, in adults tics and tic severity appear to be relatively stable. Therefore, maybe sub groups based on tic severity do not adequately reflect tic subgroups. Mostly change in tic severity in GTS patients takes place from adolescence to young adulthood (until approximately the age of 22), from then on the tics remain relatively stable. From adolescence to young adulthood also the maturation of the frontal lobe takes place, which is linked to better performance in executive functions including motor response inhibition (Blakemore & Choudhury, 2006; Verbruggen & Logan, 2008). In this study the age in the sample ranged from 14 to 70 years whereby 82.8% of the participants were above the age of 22 years in which frontal lobe has maturated. This probably explains the lack of a difference in motor response inhibition between the group of GTS patients with an increase and decrease in tic severity and a control group. This also explains why in this study age was not a predictor of motor response inhibition on the SRT.

The finding that education level had a predictive value of motor response inhibition is in line with findings in other research on other disorders (Hillman et al., 2012; Latzman, Elkovitch, Young & Clark, 2010). Although little is known about the relation between inhibition and academic achievement in adults, several studies linked executive functions to academic performance and different academic domains in children (Hillman et al., 2012; Latzman, Elkovitch, Young & Clark, 2010). A more specific relationship was found between inhibition and academic achievement in middle childhood and preadolescent children (Thorell, Veleiro, Siu & Mohammadi, 2012; Clark, Pritchard & Woodward, 2010; Clair-Thompson & Gathercole, 2006). This study confirmed that previous findings also apply to adults. Because of the predictive value of education level on motor response inhibition on the SRT, people with poorer academic achievement could be tested for potential inhibitory problems.

In this study a difference in motor response inhibition is found between men and women. The fMRI study of Li et al. (2009) showed that men and women have different activation patterns in different regions of the brain during the SRT. Li et al. (2009) suggest in their study that this difference can be explained by the use of different strategies and the engagement in different neural pathways in men and women, during stop signal performance. This may also help us to understand why men are more vulnerable to impulse control disorders (Li et al., 2009).

Previous meta-analyses and reviews, together with the trends found in this study suggest that there is a link between shared underlying neurological processes of GTS and ADHD on motor response inhibition (Lypzyc & Schachar, 2010; Verbruggen & Logan, 2008; Lijfijt et al., 2005; Kofler

et al, 2013). The present study confirms on a neuropsychological level shared etiologies between inhibition processes in GTS and ADHD (Lypszyc & Schachar, 2010).

A limitation in this study was that in this study ADHD was not diagnosed using structured interviews, only measured by a questionnaire that measures ADHD severity. For future research it would be interesting to use GTS patients with diagnosed comorbid ADHD for a more specific view of the relation between GTS with and without comorbid ADHD compared to a healthy sample on motor response inhibition.

Since there is a trend towards a difference between GTS patients with a high tic severity and a healthy control group, it would be interesting to use a larger sample to see if the results become significant. Furthermore it would be interesting to see if inhibition on the SRT can be used as a predictor of tic severity in GTS patients. In this study this prediction was not found, however the variation in tic severity was very small. For further research it may be interesting to see if by using sample with a large variation in tic severity (from none to high tic severity), a predictive value will be found.

In conclusion further research is needed to establish the exact underlying neurological and genetic relation between GTS and ADHD and motor response inhibition, to better understand the reason for the greater vulnerability to impulse control disorders in men and to better understand the relation between academic achievement and inhibitory problems.

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