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## Impaired response inhibition during a stop-signal task in children with Tourette syndrome is related to ADHD symptoms: A functional magnetic resonance imaging study

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## Impaired response inhibition during a stop-signal task in children with Tourette syndrome is related to ADHD symptoms: A functional magnetic resonance imaging study

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### ABSTRACT

**Objectives:** Tourette syndrome (TS) is characterised by the presence of sudden, rapid movements and vocalizations (tics). The nature of tics suggests impairments in inhibitory control. However, findings of impaired inhibitory control have so far been inconsistent, possibly due to small sample sizes, wide age ranges, or not taking medication use or attention-deficit/hyperactivity disorder (ADHD) comorbidity into account.

**Methods:** We investigated group differences in response inhibition using an fMRI-based stop-signal task in 103 8 to 12-year-old children ( $n = 51$  with TS, of whom  $n = 28$  without comorbid ADHD [TS – ADHD] and  $n = 23$  with comorbid ADHD [TS + ADHD]; and  $n = 52$  healthy controls), and related these measures to tic and ADHD severity.

**Results:** We observed an impaired response inhibition performance in children with TS + ADHD, but not in those with TS – ADHD, relative to healthy controls, as evidenced by a slower stop-signal reaction time, slower mean reaction times, and larger variability of reaction times. Dimensional analyses implicated ADHD severity as the driving force in these findings. Neural activation during failed inhibition was stronger in the inferior frontal gyrus and temporal and parietal areas in TS + ADHD compared to healthy controls.

**Conclusions:** Impaired inhibitory performance and increased neural activity in TS appear to manifest predominantly in relation to ADHD symptomatology.

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### KEYWORDS

Tourette syndrome; comorbid ADHD; response inhibition; functional imaging; stop-signal task

## Introduction

Tourette syndrome (TS) is characterised by the presence of multiple motor tics and a minimum of one vocal tic, lasting for at least one year and starting before the age of 18 years (American Psychiatric Association 2013). While the neurophysiological basis of TS is currently unclear, a widely held view is that tics originate from dysfunction in the cortico-striato-thalamo-cortical (CSTC) circuits (Albin

and Mink 2006). Tics typically resemble ‘disinhibited’ behaviours, which suggest impairments in inhibitory control (i.e. the process of actively suppressing an ongoing or inappropriate response [Aron 2011; Mirabella 2014]). Indeed, a recent meta-analysis pointed to response inhibition impairments in TS (Morand-Beaulieu et al. 2017). However, the results of studies in inhibitory control are mixed; some studies identified impaired inhibitory performance in children and adults with TS compared with healthy controls

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(Goudriaan et al. 2006; Channon et al. 2009; Wylie et al. 2013; Yaniv et al. 2018), whereas other studies found no inhibitory impairment (Ray Li et al. 2006; Roessner et al. 2008; Eichele et al. 2010; Sukhodolsky et al. 2010; Mancini, Cardona, et al. 2018).

Few studies investigated the neural underpinnings of response inhibition in children and adults with TS, yielding mixed results. Brain regions typically implicated in response inhibition (in healthy subjects) include the inferior frontal gyrus, which is thought to have an inhibitory role during response execution (Cai et al. 2014); the insula, thought to be important for detecting behaviourally salient events (Cai et al. 2014); motor areas, including the primary motor cortex and the dorsal premotor cortex, involved in the suppression of pending movements (Coxon et al. 2006; Mirabella et al. 2011; Mattia et al. 2013), and temporal and parietal areas, linked to attentional redirection and task-set maintenance (Sharp et al. 2010). Further, a role in the inhibitory network is played by two subcortical nuclei, that is, the subthalamic nuclei (Mirabella et al. 2012, 2013; Mancini, Modugno, et al. 2018) and the striatum (Zandbelt and Vink 2010). In adolescents and adults with TS, increased activation in prefrontal regions has been found during inhibitory control tasks relative to healthy controls, often in the presence of a relatively intact inhibitory performance (Serrien et al. 2005; Marsh et al. 2007). This is suggested to reflect increased activation of the inhibitory pathway to inhibit actions, perhaps as a compensatory consequence of the frequent need to inhibit tics (Plessen et al. 2007). These results were, however, not replicated in more recent studies in children and adolescents (Debes et al. 2011; Jung et al. 2013).

Methodological limitations, such as the use of small sample sizes (mostly between  $n=18$  to  $n=75$ ; see Morand-Beaulieu et al. 2017 for review), with only a few well-sized studies to date ( $n>100$ ; Goudriaan et al. 2006; Marsh et al. 2007; Sukhodolsky et al. 2010; Drury et al. 2012), not taking medication use into account and including participants with wide age ranges probably explain the discrepant results observed so far. That is, inhibitory control measured in adolescents or adults may not be representative for a child with TS, as the majority of individuals with TS learn to effectively control and suppress their tics by early adulthood (Leckman et al. 1998). Furthermore, the wide variety of tasks used in previous studies may recruit different neural dynamics (Mostofsky et al. 2003; Simmonds et al. 2008; Zhang et al. 2017), and differ in cognitive requirements (Van Belle et al. 2014; Mancini, Cardona, et al. 2018) possibly resulting in

inconsistent outcomes. Additionally, another concern is that studies pointing to inhibition deficits in TS have often failed to exclude, or control for, comorbidities such as attention-deficit/hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD). This is of relevance, as previous studies found no impaired response inhibition in children and adolescents with TS without comorbidities (Ray Li et al. 2006; Roessner et al. 2008; Mancini, Cardona, et al. 2018; Mirabella et al. 2020). In line with this, a recent imaging study did not observe structural alterations in both grey and white matter volumes in brain regions associated with reactive inhibition in a paediatric unmedicated TS sample without comorbidities compared to healthy controls (Mirabella et al. 2020).

ADHD is the most frequently co-occurring disorder in TS (50–60%; Freeman 2007; Hirschtritt et al. 2015), and is in itself strongly associated with impaired inhibition performances and atypical neural activation in brain regions associated with response inhibition (Alderson et al. 2007; McCarthy et al. 2014; Van Rooij et al. 2015). Only one functional neuroimaging study to date directly examined the influence of comorbid ADHD on response inhibition in children with TS; observing no difference in brain activity patterns between children with and without comorbid ADHD (Debes et al. 2011). However, that study only included five children with TS and comorbid ADHD. At the behavioural level, a recent meta-analysis concluded small to medium inhibitory deficits in patients with TS, which was larger in individuals with TS and comorbid ADHD, but also present in those without comorbid ADHD (Morand-Beaulieu et al. 2017); the latter group may still have had subthreshold ADHD possibly explaining those results.

In sum, given the scattered findings in the literature utilising mostly small samples and a variety of inhibition tasks with wide age ranges, additional studies that employ both behavioural and neural analyses are necessary to further our understanding of the role of comorbid ADHD. In the present study, we investigated response inhibition in 8 to 12-year-old children with TS with and without comorbid ADHD in comparison to healthy controls. We used a key-press version of the stop-signal task, which measures so called reactive response inhibition, that is, the ability to stop an ongoing response when a stop instruction is presented (Verbruggen and Logan 2008), in contrast to proactive inhibition, which reflects the preparatory process that influences whether the response will be initiated (Aron 2011). We compared three groups: TS without comorbid ADHD, TS with comorbid ADHD

and healthy controls. As a sensitivity analysis, we compared the TS group irrespective of comorbid ADHD with the healthy controls, to allow for comparability with the literature and make full use of our data. Additionally, we related inhibitory performance to ADHD severity across all groups, and to tic severity across the TS groups. We hypothesised that the presence of comorbid ADHD in TS would largely explain the expected impaired behavioural inhibitory performance and atypical neural activation patterns.

## Materials and methods

### Study participants

Participants were 111 children between 8 and 12 years, of whom a total of 103 children remained eligible after exclusion based on low scan quality ( $n=7$ ), as checked with the Magnetic Resonance Imaging Quality Control tool (MRIQC; Esteban et al. 2017; <https://github.com/poldracklab/mriqc>) and one incidental finding ( $n=1$ ). This final sample consisted of a group and children with TS ( $n=51$  of whom  $n=28$  without comorbid ADHD [TS – ADHD] and  $n=23$  with comorbid ADHD [TS + ADHD]) and healthy controls ( $n=52$ ). Children with TS were recruited via child and adolescent psychiatry clinics, neurology departments and patient organisations throughout the Netherlands; healthy controls were recruited via elementary schools in the Nijmegen area (the Netherlands). Inclusion criteria for all participants included Caucasian descent (since this study was part of a cohort collected for genetic analyses, see Naaijen et al. 2017), an IQ of at least 70, no past or present head injuries or neurological disorders, and no major physical illness. Comorbid psychiatric conditions in children with TS (e.g. ADHD, OCD, oppositional defiant disorder [ODD] or conduct disorder [CD]) were allowed. The children were asked to stop stimulant medication 48 h prior to the testing day, whereas other types of medication were allowed during testing. Written informed consent was provided by the parents/guardians of the participant and by the child if 12 years of age; younger children provided oral assent. The study was approved by the regional ethics board (CMO Region Arnhem-Nijmegen, the Netherlands).

### Clinical measures

Children from the TS group met criteria for a diagnosis of a chronic tic disorder (TS or chronic tic disorder [motor type only]) according to the DSM-IV-TR (American Psychiatric Association 2000), as confirmed

with the Yale Global Tic Severity Scale (YGTSS; Leckman et al. 1989). The YGTSS is a semi-structured clinician-rated instrument that was also used to rate tic severity by assessing the number, frequency, intensity, complexity, and interference of motor and vocal tics over the past week, each scored on a six-point Likert scale (yielding a total YGTSS tic severity score, range 0–50). Healthy controls had to be free of any psychiatric disorder, the absence of which was confirmed by the parent-administered Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al. 1997), based on DSM-IV-TR criteria (American Psychiatric Association 2000), and by scores in the normal range on the Child Behaviour Checklist and Teacher Report Form (CBCL, TRF; Achenbach and Rescorla 2001). The K-SADS was used in participants of the TS group to assess the presence of ADHD, ODD, or CD, according to DSM-IV-TR criteria. To rate ADHD severity, we used the Conners' Parent Rating Scale-Revised Long version (CPRS-RL; Conners et al. 1998), with standardised T-scores accounting for age and sex (ADHD severity score, range 40–90). The semi-structured clinician-rated Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) was taken to assess comorbid OCD; we used a cut-off of 16 points to define an OCD diagnosis (Scahill et al. 1997). IQ was estimated from four sub-tests (block design, vocabulary, similarities, and picture completion) of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler 2002). Finally, parents reported on past and present medication use during the interview. Diagnostic interviews and functional magnetic resonance imaging (fMRI) assessments were carried out by trained investigators and took place during a single day.

### Stop-signal task

Response inhibition was measured by using a stop-signal task with fMRI (Logan et al. 1984; Van Rooij et al. 2015). Participants were required to respond as quickly as possible to visually presented Go-signals (Go-trials) by a manual button press, as indicated by an arrow to the left or right. In 25% of the trials the arrow to the left or the right was directly followed by an arrow pointing upwards, indicating the stop-signal (Stop-trials). In these Stop-trials subjects needed to withhold a prepotent motor response. To create a high expectancy to act, more Go-trials (234 trials) than Stop-trials (64 trials) were presented in a randomised order during approximately 10 minutes. Importantly, the delay between presentation of the Go and Stop stimulus

(the stop signal delay or SSD) was varied based on the participant's performance, to ensure each participant reached successful inhibition in approximately 50% of the Stop-trials. The task started with an SSD of 250 ms, and after each successful inhibition the delay was increased with 50 ms making successful inhibition more difficult, whereas after each failed inhibition the delay was decreased with 50 ms to facilitate inhibition on the next Stop-trial. Thus, in total, three different conditions could be distinguished: Go-success (when the participant correctly pushed the button), Stop-success (when the participant successfully withheld the response to push the button), and Stop-failed (when the participant failed to inhibit the response to push the button). Furthermore, during Go-trials, participants may also have failed to push the button, called Go-errors. The children were verbally instructed and subsequently offered the opportunity to practice the task in the dummy scanner.

### **Behavioural data**

Main dependent variables were (1) the stop-signal reaction time (SSRT) using the mean method, that is by subtracting the mean SSD from the mean reaction time (MRT), at which a participant was able to correctly inhibit a response (2) the MRT for Go-success and Stop-failed trials (3) the intra-individual variability of the MRT (SD-MRT) respectively for Go-success and Stop-failed trials, and (4) the error rate of participants during Go-trials (Go-error). The SSRT provides a measure of reactive inhibition, whereas the MRT, SD-MRT and Go-error provide an indication of cognitive performance not necessarily related to the response inhibition process.

### **MRI data acquisition**

All children were scanned with a 3 T Siemens Prisma scanner (Siemens, Erlangen, Germany) at the Donders Centre for Cognitive Neuroimaging in Nijmegen. During scanning their heads were stabilised with cushions and tape was placed across their foreheads to increase their awareness of movement and thus reduce movement during scanning.

Anatomical images were acquired using a T1-weighted magnetisation prepared rapid gradient echo (MPRAGE) sequence (TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; Field of View = 256 mm; flip angle = 9°; slice thickness = 1.20 mm; in plane resolution 1.0 × 1.0 mm; acceleration factor = 2; acquisition time 5:30 minutes). The functional images were acquired with an EPI

sequence (TR = 2100 ms; TE = 35.0 ms; Field of View = 192 mm; flip angle = 74°; slice thickness = 3.0 mm; in-plane resolution = 3.8 mm<sup>2</sup>; acceleration factor = 2; 36 axial slices; descending slice acquisition; 215 volumes; acquisition time ~10 min).

### **Pre-processing of functional MRI images**

Functional scans were pre-processed using a pipeline with integrated tools from FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl>). The first five volumes were removed to account for equilibration effects. The pipeline further involved head movement correction via realignment to the middle volume (MCFLIRT; Jenkinson et al. 2002), grand mean scaling, and spatial smoothing using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm. Furthermore, ICA-AROMA (Pruim, Mennes, Buitelaar, et al. 2015; Pruum, Mennes, van Rooij, et al. 2015) was applied to identify and eliminate signal components corresponding to secondary head motion-related artefacts. Also, nuisance regression and high-pass filtering (100 ms) were used. The images were co-registered to the anatomical T1 images per subject using boundary-based registration within FSL-FLIRT (Greve and Fischl 2009), and normalised to MNI152 standard space, a widely-used template adopted to define standard anatomy (Evans et al. 2001), which was refined by non-linear registration with FSL-FNIRT (Andersson et al. 2010). By applying the resulting warp fields to the functional image, this image was brought into standard space.

### **Statistical analyses**

#### **Behavioural data**

Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL). Missing data (up to 2.1%) was imputed by means of the Expectation Maximisation algorithm (Tabachnick and Fidell 2001). All variables were checked for normal distribution and log transformed where appropriate (i.e. SSRT, SD-MRT of Go-success and Stop-failed, and Go-error, resulting in a normalised distribution). The mean values reported are without a log transformation.

Differences in group characteristics were tested with the non-parametric Kruskal–Wallis test for age, a Chi-square ( $\chi^2$ ) test for sex, an analysis of variance (ANOVA) for IQ and ADHD and tic severity. Due to considerable inter-correlations between behavioural measures, we conducted a one-way multivariate analysis of covariance (MANCOVA,  $p < 0.05$ ) to evaluate

group differences in inhibitory performance with group as a factor, and age, sex, and IQ as covariates. This was followed by post-hoc analyses using a Bonferroni-adjusted  $p$ -value ( $p < 0.008$ ) to test between-group differences as per behavioural measure. In addition, linear regression analyses were performed to investigate the relationship between the behavioural measures and tic severity in the TS sample ( $n = 51$ ), and ADHD severity across the entire sample ( $n = 103$ ), with age, sex and IQ included as covariates. Effect sizes for the between-group analyses are presented as partial eta-squared ( $\eta^2_p$ ) and as  $R$ -squared ( $R^2$ ) for the dimensional analyses with 0.01–0.05 considered as a small, 0.06–0.13 as a medium, and  $\geq 0.14$  as a large effect (Cohen 1988).

### **fMRI first- and second-level analysis**

A first level analysis for each participant was conducted in Statistical Parametric Mapping software (SPM12; <http://www.fil.ion.ucl.ac.uk/spm/>). Regressors were generated for Go-success, Stop-success, and Stop-failed conditions, together with five rigid body head motion parameters as calculated by ICA-AROMA (Pruim, Mennes, Buitelaar, et al. 2015; Pruum, Mennes, van Rooij, et al. 2015), to account for residual head motion effects by convolving with a canonical hemodynamic response function estimated using a general linear model. Two first-level contrasts of interest were constructed: (1) Stop-success – Go-success, to isolate activation of successful inhibition, using successful Go trial activity as an explicit baseline; and (2) a Stop-failed – Stop-success contrast to model activation unique to the failed inhibition process.

First, whole-brain activation maps were made for the two contrasts (Stop-success – Go-success and Stop-failed – Stop-success) for all participants. Second, F-contrasts comparing the three groups (healthy controls, TS – ADHD, TS + ADHD) were applied, separately for the two contrasts. Significant activation was defined at default  $p < 0.05$  family-wise error-corrected, and regions were labelled by the xjView toolbox (<http://www.alivelearn.net/xjview>). Data was visualised using Slice Display (Zandbelt 2017; [https://github.com/bramzandbelt/slice\\_display](https://github.com/bramzandbelt/slice_display)). Finally, we investigated the association between tic severity and neural activation during failed inhibition in the TS groups, and between ADHD severity and neural activation during failed inhibition across the whole sample, by performing linear regression analyses. Age, gender and IQ were added as covariates for all analyses.

### **Sensitivity analyses**

The analyses were repeated with a two-group comparison (TS irrespective of comorbid ADHD versus healthy controls) to make full use of the TS sample size, enabling comparability with the literature, and to check whether results were in line with the three-group analyses. Furthermore, to check whether the behavioural results would remain consistent using a different method to compute the SSRT, we repeated the analyses with the SSRT as computed with the integration method instead of the mean method (Verbruggen and Logan 2009). Additionally, to control for comorbid OCD and current medication use, we added both separately as covariates in the three-group analyses (TS – ADHD, TS + ADHD and healthy controls).

## **Results**

### **Sample characteristics**

See Table 1 for group characteristics. Children with TS consisted of significantly more boys compared to healthy controls, this was specifically true for those with TS – ADHD. Children with TS, both TS – ADHD and TS + ADHD, had higher ADHD severity compared to healthy controls, and children with TS + ADHD had higher ADHD severity compared to TS – ADHD. No between-group differences were observed for age and IQ. Furthermore, TS – ADHD and TS + ADHD did not differ regarding tic severity.

About 29% of the children with TS – ADHD, and 61% of the children in the TS + ADHD group used some sort of medication (see Supplement 1). One child in the TS – ADHD did not comply with refraining from using stimulant medication 48 h prior to the testing day; six children used non-stimulant medication during the testing day (antipsychotics:  $n = 3$  children with TS – ADHD,  $n = 2$  with TS + ADHD; clonidine:  $n = 1$  child with TS – ADHD).

### **Behavioural results**

The MANCOVA indicated statistically significant differences in behavioural measures between the three groups; see Table 2. The post-hoc analyses as per behavioural measure are also presented in Table 2. Children with TS + ADHD had a longer SSRT compared to healthy controls, indicating a slower speed of the inhibition process, representing a medium effect. Of notice, the SSRT of children with TS – ADHD was more similar to those with TS + ADHD than to healthy

**Table 1.** Group characteristics.

	HC ( <i>n</i> = 52)	TS ( <i>n</i> = 51)	TS – ADHD ( <i>n</i> = 28)	TS + ADHD ( <i>n</i> = 23)	Test statistics	
Male sex, <i>n</i> (%)	37 (71.2)	45 (88.2)	27 (96.4)	18 (78.3)	$\chi^2(2) = 7.20^{a,*}$	TS > HC TS – ADHD > HC
Age in years, <i>M</i> ± <i>SD</i>	10.53 ± 0.10	10.23 ± 1.39	10.32 ± 1.29	10.14 ± 1.54	$\chi^2(2) = .87^b$	
IQ, <i>M</i> ± <i>SD</i>	108.72 ± 11.02	105.37 ± 12.51	106.81 ± 12.69	103.62 ± 12.35	$F(2, 100) = 1.50^c$	
Tic severity, <i>M</i> ± <i>SD</i>		21.02 ± 8.62	20.82 ± 7.30	21.26 ± 10.17	$T(49) = -1.184^d$	
ADHD severity, <i>M</i> ± <i>SD</i>	45.42 ± 4.36	64.12 ± 10.98	58.82 ± 9.43	69.78 ± 7.29	$F(2, 100) = 99.97^{c,**}$	TS > HC TS – ADHD > HC TS + ADHD > HC TS + ADHD > TS – ADHD
Comorbid OCD, <i>n</i> (%)	0	10 (19.6)	6 (21.4)	4 (17.4)		
Comorbid ODD or CD, <i>n</i> (%)	0	2 (3.9)	1 (3.6)	1 (4.3)		
Successful Stop trials, %	51.5	51	50.1	51.9		
Medication, <i>n</i> (%)	0	6 (11.8)	4 (14.3)	2 (8.7%)		

Values presented as *n*, percent or mean ± standard deviation.

HC: healthy controls; TS: Tourette syndrome; TS – ADHD: TS without comorbid attention-deficit/hyperactivity disorder [ADHD]; TS + ADHD: TS with comorbid ADHD; OCD: obsessive-compulsive disorder; ODD/CD: oppositional defiant disorder/conduct disorder.

Tic severity assessed by the Yale Global Tic Severity Scale (Leckman et al. 1989; range 0–50); ADHD severity assessed by the Conners' Parent Rating Scale – Revised Long standardised T-score (Conners et al. 1998; range 40–90); Medication denotes the number of children who did not comply with stopping medication 48 h prior to the assessment. Between-group differences were tested by <sup>a</sup>a Pearson's chi-squared test, <sup>b</sup>Kruskal–Wallis test, <sup>c</sup>an Analysis of Variance, and <sup>d</sup>an independent *t*-test; \* $p < 0.05$ ; \*\* $p < 0.001$ .

**Table 2.** Behavioural results during the stop-signal task for HC, TS – ADHD and TS + ADHD.

	HC ( <i>n</i> = 52)	TS – ADHD ( <i>n</i> = 28)	TS + ADHD ( <i>n</i> = 23)	Test-statistic	Direction	Effect size ( $\eta^2_p$ )
SSRT, ms	228.4 ± 58.1	258.1 ± 52.0	268.8 ± 62.5	$F(2, 100) = 4.75^*$	TS + ADHD > HC	0.08
MRT, ms						
Go-success	549.3 ± 60.9	565.6 ± 76.6	605.0 ± 75.4	$F(2, 100) = 5.23^*$	TS + ADHD > HC	0.11
Stop-failed	517.2 ± 56.0	517.5 ± 64.9	550.3 ± 63.5	$F(2, 100) = 2.68$		
SD-MRT, ms						
Go-success	139.0 ± 26.1	149.5 ± 33.8	174.1 ± 39.1	$F(2, 100) = 9.51^*$	TS + ADHD > HC TS + ADHD > TS – ADHD	0.16
Stop-failed	115.1 ± 51.9.2	129.0 ± 61.4	137.0 ± 51.6	$F(2, 100) = 2.09$	TS + ADHD > HC	
Error rate, <i>n</i>						
Go-error	10.2 ± 7.4	13.5 ± 11.5	11.5 ± 8.9	$F(2, 100) = 0.80$		

Values presented in milliseconds ± standard deviation, and as *n* (number of errors) ± standard deviation.

HC: healthy controls; TS: Tourette syndrome; TS – ADHD: TS without comorbid attention-deficit/hyperactivity disorder [ADHD]; TS + ADHD: TS with comorbid ADHD; SSRT: stop signal reaction time; MRT: mean reaction time; SD-MRT: standard deviation of the mean reaction time.

Effect sizes are presented as partial eta-squared ( $\eta^2_p$ ), with 0.01–0.05 considered as a small, 0.06–0.13 as a medium, and  $\geq 0.14$  as a large effect (Cohen, 1988). A one-way MANCOVA was performed controlling for sex, age, and IQ, showing a significant difference in behavioural measures between groups ( $F(18, 182) = 1.66$ ,  $p < 0.05$ , Pillai's Trace = 0.28, partial  $\eta^2 = 0.14$ ). The covariate sex was unequally distributed between groups ( $F = 4.00$  (2, 101),  $p = 0.02$ , partial  $\eta^2 = 0.08$ , see also Table 1), whereas age and IQ were not statistically significant ( $F = 0.77$  (2, 101),  $p = 0.47$ , partial  $\eta^2 = 0.02$  and  $F = 1.21$  (2, 101),  $p = 0.30$ , partial  $\eta^2 = 0.02$ , respectively). The presented results are from post-hoc analyses with a Bonferroni correction per behavioural measure; \* $p < 0.008$ .

controls. In children with TS + ADHD, we found slower reaction times (longer MRT) and a larger variability of reaction times during Go-success trials, indicating a higher variability in response readiness relative to healthy controls, representing medium to large effects. No differences between groups were observed in reaction time (variability) during Stop-failed trials or errors during Go-trials (Go-error).

### Dimensional analyses

Higher ADHD severity was related to slower reactions during Go-success trials and a larger reaction time variability during Go-success trials (see Table 3). Furthermore, a trend was observable between higher ADHD severity and a longer SSRT ( $p = 0.06$ ). We did not observe relationships between behavioural performance measures and tic severity in the TS sample.

### fMRI task activation

Group-differences in fMRI task activation indicated that children with TS – ADHD had increased brain activation in the left superior temporal gyrus in the Stop-success – Go-success contrast compared to TS + ADHD (see Table 4 and Supplement 2). In the Stop-failed – Stop-success contrast we observed enhanced brain activity in TS + ADHD compared to TS – ADHD in the left superior temporal gyrus (See Supplement 2 for results), and compared to healthy controls in the right superior and middle temporal gyrus, the right inferior frontal gyrus and the left insula (See Figure 1). Of note, the between-group differences involved a low number of voxels, indicating small differences between groups. See for results of neural activation across all participants using a whole brain approach Supplement 3. Furthermore, no associations were observed between neural activation and tic severity in the TS groups, or ADHD severity across the total sample (results not shown).



**Table 3.** Results of behavioural performance measures with tic severity in the TS group ( $n = 51$ ) and with ADHD severity in the total study sample ( $n = 103$ ) using linear regression analyses.

	Tic severity					ADHD severity				
		B $\pm$ SE	$\beta$	$t$	$R^2$	B $\pm$ SE	$\beta$	$t$	$R^2$	
SSRT		6.7 $\pm$ 236.5	0.01	0.03	0.04	372.9 $\pm$ 198.5	0.18	1.88 <sup>a</sup>	0.10	
MRT	Go-success	25.1 $\pm$ 182.3	0.02	0.14	0.04	405.9 $\pm$ 172.0	0.25	2.36*	0.15	
	Stop-failed	42.4 $\pm$ 211.8	0.03	0.20	0.04	251.8 $\pm$ 199.8	0.13	1.26	0.09	
SD-MRT	Go-success	66.5 $\pm$ 378.6	0.03	0.18	0.04	1096.2 $\pm$ 357.8	0.32	3.06*	0.12	
	Stop-failed	22.0 $\pm$ 225.2	0.01	0.10	0.04	210.8 $\pm$ 218.6	0.10	0.96	0.08	
Error rate	Go-failed	-0.1 $\pm$ 0.1	-0.08	-0.51	0.10	0.1 $\pm$ 0.1	0.05	0.48	0.07	

B: unstandardised beta; SE: standard error for the unstandardised beta;  $\beta$ : standardised beta;  $t$ :  $t$ -test statistic;  $R^2$ : explained variance; TS: Tourette syndrome; ADHD: attention-deficit/hyperactivity disorder; SSRT: stop-signal reaction time; MRT: mean reaction time; SD-MRT: standard deviation of the mean reaction time.

Age, sex and IQ were used as covariates.

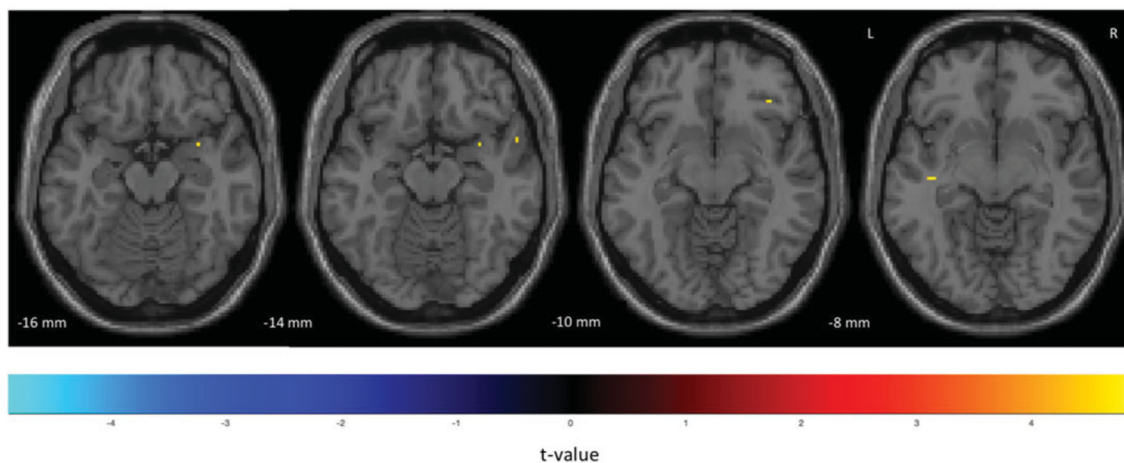
<sup>a</sup>nearly significant with  $p = 0.06$ ; \* $p < 0.05$ .

**Table 4.** Between-group differences in neural activation comparing TS – ADHD, TS + ADHD and healthy controls.

Condition Area	Side	Peak voxel			Brodmann area	Voxels			Direction
		$x$	$y$	$z$		$n$	$p$	$Z$	
Stop-success – Go-success									
Superior temporal gyrus	L	-44	-44	12	21	7	0.013	4.88	TS – ADHD > TS + ADHD
Stop-failed – Stop-success									
Superior temporal gyrus	L	-44	-46	12	21	6	0.009	4.96	TS + ADHD > TS – ADHD
Middle temporal gyrus	R	52	-4	-18	21	5	0.011	4.92	TS + ADHD > HC
Inferior frontal gyrus	R	38	32	-10	45	2	0.016	4.83	TS + ADHD > HC
Insula	L	-40	-18	-8	13	3	0.017	4.88	TS + ADHD > HC
Superior temporal gyrus	R	56	8	-14	21, 22	2	0.044	4.64	TS + ADHD > HC

TS – ADHD: TS without comorbid attention-deficit/hyperactivity disorder [ADHD]; TS + ADHD: TS with comorbid ADHD; HC: healthy controls.

Age, sex and IQ were used as covariates; corrections for multiple comparisons were performed using a Family Wise Error correction with a significance threshold of  $p < 0.05$ ; xjView was used to identify brain regions.

**Figure 1.** Differences in neural activation during the Stop-failed – Stop-success condition in a stop-signal task between TS + ADHD and healthy controls. Significant activation was defined at default  $p < 0.05$  family-wise error-corrected. xjView was used to identify brain regions.

### Sensitivity analyses

After comparing TS irrespective of comorbid ADHD with healthy controls for the behavioural analyses, we observed that the TS group had a slower inhibition process (longer SSRT) and a slower mean response speed (longer MRT) and higher variability of response time (SD-MRT) during Go-success trials compared to healthy controls, representing medium effects (See

Supplement 4 for results). Furthermore, the behavioural results remained significant after computing the SSRT with the integration method (instead of the mean method ( $F[2, 100] = 3.11$ ,  $p = 0.04$ )). Behavioural results thus confirmed a response inhibition deficit and broader cognitive impairments in the TS group irrespective of comorbid ADHD. Regarding functional brain activity, we observed no group differences in

task activation between TS (irrespective of comorbid ADHD) and healthy controls (results not shown). Finally, after adding comorbid OCD or current medication-use during the testing-day to the analyses, the results did not significantly change, indicating that comorbid OCD and medication use during the testing day did not have an effect on the results.

## Discussion

This is one of the few studies to date to investigate reactive response inhibition at a behavioural and neural level using a stop-signal task in children (8–12 years) with TS, with and without comorbid ADHD, compared with healthy controls. Overall, we observed an impaired inhibition process and overall cognitive task performance specifically in children with TS + ADHD, and not in those with TS – ADHD, compared to healthy controls. Additionally, dimensional analyses implicated comorbid ADHD as the driving force behind these findings. Furthermore, we observed atypical neural patterns during failed inhibition in children with TS + ADHD relative to healthy controls, and to those with TS – ADHD.

On a behavioural level, children with TS + ADHD had a slower stop-signal reaction time during response inhibition compared to healthy controls, independent from comorbid OCD and current medication use. The observed longer stop-signal reaction time indicates that children with TS + ADHD (but not those with TS – ADHD), needed more time to inhibit the response that they initiated, which is indicative of an overall impaired inhibition process compared to healthy controls (Castro-Meneses et al. 2015). Impaired response inhibition has been consistently found in children with ADHD as a core deficit (see for a review of meta-analyses Pievsky and McGrath 2018) and has also been implicated in children and adults with TS (Channon et al. 2003; Yaniv et al. 2017; for meta-analyses see Lipszyc and Schachar 2010; Morand-Beaulieu et al. 2017). However, our study results indicate that impaired response inhibition is primarily linked to comorbid ADHD in children with TS. This is in line with results of previous studies observing no response inhibition impairments in children and adolescents with TS when using strict criteria (i.e. unmedicated children and adolescents with TS without comorbidities [Ray Li et al. 2006; Roessner et al. 2008; Mancini, Cardona, et al. 2018; Mirabella et al. 2020]), suggesting that impaired inhibitory control is not a trait marker of TS. Also, our observed trend between higher ADHD severity and a longer stop-signal reaction time

suggests that comorbid ADHD is the driving force behind impaired response inhibition in children with TS, although further research may be needed to replicate these findings, also in relation to other frequently co-occurring disorders in TS (such as OCD or anxiety disorders).

Further in line with our expectations, we observed slower reaction times and larger response variability in reaction times during go trials, specifically in those with TS + ADHD, relative to healthy controls. While these performance measures do not specifically concern reactive inhibition, findings may relate to differences in proactive inhibition (Aron 2011). Also, these results do suggest broader cognitive impairments in TS + ADHD, consistent with previous findings in ADHD (for meta-analyses, see Lijffijt et al. 2005; Alderson et al. 2007). Associations between higher ADHD severity and poorer cognitive performance supported these results. Still, some level of cognitive impairment related to inhibition may be present in TS as such, even in the absence of ADHD comorbidity, as indicated by a recent meta-analysis (Morand-Beaulieu et al. 2017). Indeed, the performance of children with TS – ADHD during the stop-signal task were more similar to those with TS + ADHD than to healthy controls, despite not being significantly different from controls. However, this might still be due to co-occurring ADHD symptoms, as suggested by our result of higher ADHD severity in TS – ADHD compared to healthy controls, and, importantly, by the dimensional relationship between higher ADHD severity and performance measures, and a concomitant lack of association with tic severity in our study. In sum, we observed a specific response inhibition deficit and broader cognitive impairments in children with TS, which largely related to comorbid ADHD symptoms.

Regarding functional brain activity, we observed neural activation across all participants using a whole-brain approach during the task in areas associated with response inhibition (e.g. inferior and prefrontal gyri, insula and temporal gyri), in line with previous observations in healthy subjects (for meta-analyses, see Cieslik et al. 2015; Zhang et al. 2017). The between-group comparisons indicated increased activation during failed inhibition in the right inferior frontal gyrus and left insula only in children with TS + ADHD, but not of TS – ADHD, compared to healthy controls. Our findings are in contrast with previous observations, observing decreased activation of frontal gyri during failed inhibition in children with ADHD (McCarthy et al. 2014; Van Rooij et al. 2015), and in a large sample of adolescents with subclinical

ADHD (Whelan et al. 2012). However, in TS, hyperactivation of frontal regions has been suggested to be a consequence of the activity-dependent need to control tics in order to maintain a relatively normal level of performance (Marsh et al. 2007; Plessen et al. 2007). Additionally, activation of the left insula has been implicated in the suppression of urges (e.g. swallowing of yawning) in healthy subjects (Jackson et al. 2011), and associated with the urge-to-tic (premonitory urges) in TS (Tinaz et al. 2015). Given the lack of TS studies investigating inhibition in children with and without comorbid ADHD so far, we speculate that the hyperactivation of these areas in TS with comorbid ADHD may not only represent the effects of ADHD symptoms in TS during difficult conditions (e.g. failed inhibition), but perhaps also the combined, cumulative effects of controlling tics and associated premonitory urges. However, the observed differences between groups were small and we did not observe associations between neural activation and tic or ADHD severity. We also observed atypical neural patterns during successful stopping in children with TS – ADHD compared to those with TS + ADHD. Future research is warranted to confirm these findings.

Furthermore, we observed increased activation of the middle and superior temporal gyri during failed inhibition in TS + ADHD, and not TS – ADHD, compared to healthy subjects. Activation in these areas have previously been associated with inhibitory performance of typically developing children and adolescents, and not with adults (Tamm et al. 2002; Vara et al. 2014). Although inhibitory control has been suggested to rely on the cooperation between both brain hemispheres (Mirabella et al. 2017; Di Caprio et al. 2020), in general, healthy subjects are suggested to have predominantly right-lateralized activity during response inhibition (Cai et al. 2014), whereas more left-lateralized activity underlying response inhibition, as observed in our study in the superior temporal gyrus and insula, may be indicative of an immature neural network (Vara et al. 2014; Rahman et al. 2017). Children with TS, irrespective of comorbid ADHD, have previously been implicated to show functional brain immaturity ('a developmental delay'; Church et al. 2009), which is supported by our observations specifically in TS + ADHD. In sum, these findings underscore the possibility of an immature inhibitory network in children with TS + ADHD, which may lead to cognitive impairments (Church et al. 2009).

Strengths of this study were the use of one of the largest sample sizes of 8 to 12-year-old children with TS with and without comorbid ADHD and healthy

controls to date, combining both behavioural and neural measures in group and dimensional analyses. This allowed us to explore the role of comorbid ADHD in relation to TS, at an age when tics are most prevalent. Limitations of this study included, first, the use of only one inhibition task; future research may benefit from the use of multiple response inhibition tasks, as they differ markedly in cognitive demands and/or mechanisms involved in response inhibition (Zhang et al. 2017). Future studies may also include proactive inhibition (see Aron 2011); however, a recent study investigating this inhibition domain in TS indicated that impaired proactive inhibition was not related to the severity of tics, but to the severity of comorbid OCD symptoms (Mancini, Cardona, et al. 2018). As a second limitation, the low number of observed voxels may indicate that larger numbers of participants are needed to confirm our results. Third, results were not compared to an ADHD (without tics) group. Fourth, we were unable to fully address the role of comorbid OCD given the low prevalence in our sample. Fifth, it is possible that some children suppressed their tics during the inhibition task, which may have influenced the neural activation patterns (Ganos et al. 2014), although we did not observe differences in tic severity between our groups. Nevertheless, future research is warranted to investigate the effect of tic suppression during inhibition tasks.

To conclude, in children with TS + ADHD, we observed an impaired reactive inhibition process, an overall impaired cognitive task performance and atypical neural patterns compared to healthy controls, perhaps indicative of immature response inhibition processes. The association between ADHD severity and behavioural measures supports the notion that impaired response inhibition performance is largely driven by comorbid ADHD in TS. Furthermore, longitudinal fMRI research is needed, comparing different age ranges to investigate brain development in TS, preferably using larger sample sizes, and with the use of a greater variety of tasks to examine task-dependent inhibitory demands.

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