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Executive function in children with Tourette syndrome and attention-deficit/hyperactivity disorder: Cross-disorder or unique impairments?

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ABSTRACT

Findings of executive functioning deficits in Tourette syndrome (TS) have so far been inconsistent, possibly due to methodological challenges of previous studies, such as the use of small sample sizes and not accounting for comorbid attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or medication use. We aimed to address these issues by examining several areas of executive functioning (response inhibition, attentional flexibility, cognitive control, and working memory) and psychomotor speed in 174 8-to-12-year-old children with TS [$n = 34$ without (TS−ADHD) and $n = 26$ with comorbid ADHD (TS+ADHD)], ADHD without tics (ADHD−TS; $n = 54$), and healthy controls ($n = 60$). We compared executive functioning measures and psychomotor speed between these groups and related these to ADHD severity across the whole sample, and tic severity across the TS groups. Children with TS+ADHD, but not TS−ADHD, made more errors on the cognitive control task than healthy children, while TS−ADHD had a slower psychomotor speed compared to healthy controls. The ADHD group showed impairment in cognitive control and working memory versus healthy controls. Moreover, higher ADHD severity was associated with poorer cognitive control and working memory across all groups; there was no relation between any of the executive functioning measures and tic severity. OCD severity or medication use did not influence our results. In conclusion, we found little evidence for executive function impairments inherent to TS. Executive function problems appear to manifest predominantly in relation to ADHD symptomatology, with

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both cross-disorder and unique features of neuropsychological functioning when cross-comparing TS and ADHD.

1. Introduction

Tourette syndrome (TS) is characterized by the presence of multiple motor tics and at least one vocal tic, and persistent (chronic) motor tic disorder only by motor tics, lasting at least one year and starting before the age of 18 years (American Psychiatric Association, 2000; Leckman, King, & Bloch, 2014). Although the precise etiology of TS is unknown, tics are presumed to originate from dysfunction in the cortico-–striato–thalamo–cortical (CSTC) circuits, possibly leading to disinhibition and other executive functioning deficits (Albin & Mink, 2006; Felling & Singer, 2011; Morand-Beaulieu, Leclerc et al., 2017; Peterson et al., 2003). Subcortical structures as the basal ganglia, which exerts inhibitory motor control, are reciprocally connected to the prefrontal cortex, including the anterior cingulate cortex, which are key areas implicated in cognitive functioning (Jung, Jackson, Parkinson, & Jackson, 2013; Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007; Mazzone et al., 2010; Van Velzen, Vriend, de Wit, & van den Heuvel, 2014). Impaired response inhibition, reflecting the ability to withhold a response, appears to be the most notable executive dysfunction in children and adults with TS, as shown by a recent meta-analysis (Morand-Beaulieu, Grot et al., 2017). Additionally, reduced attentional flexibility, which reflects the ability to adapt cognitive strategies and switch between task demands, has been observed in children and adults with TS (Lange, Seer, Müller-Vahl, & Kopp, 2017; Morand-Beaulieu, Leclerc et al., 2017); as have been deficits in working memory, which is the capacity to temporarily maintain and manipulate information in short-term memory (Eddy, Rizzo, & Cavanna, 2009).

Despite the vast number of studies examining executive functioning in TS over the past three decades and recent emerging meta-analyses (Kalsi, Tambelli, Aceto, & Lai, 2015; Lange et al., 2017; Morand-Beaulieu, Grot et al., 2017, Morand-Beaulieu, Leclerc et al., 2017), there is a need for studies addressing methodological limitations that are hampering existing research (Eddy et al., 2009; Morand-Beaulieu, Leclerc et al., 2017). A particular concern has been the use of small sample sizes. The majority of studies so far sampled fewer than 30 participants with TS (Channon, Pratt, & Robertson, 2003; Thibeault et al., 2016; Yaniv et al., 2017; see for a review; Morand-Beaulieu, Leclerc et al., 2017), resulting in only a few well-sized studies to date (between 50 and 101 children with TS; e.g. (Marsh et al., 2007; Schultz et al., 1998; Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, & Schultz, 2010). Also concerning are the use of wide age ranges. As TS is a neurodevelopment disorder with the most severe and disabling period of tics occurring around the age of 10 (Leckman et al., 1998), executive functioning measured in adolescents or adults may not be representative for the 'typical' patient with TS during childhood (Harris et al., 1995; Kalsi et al., 2015; Pépés, Draper, Jackson, & Jackson, 2016). Moreover, medication use or comorbid conditions, such as attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), in itself associated with impairments in executive functioning (Snyder, Kaiser, Warren, & Heller, 2015; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), have often not been taken into account, albeit increasingly recognized as important co-factors (Eddy et al., 2009; Morand-Beaulieu, Leclerc et al., 2017; Van Velzen et al., 2014). These limitations may explain the scattered and inconsistent findings for executive functioning deficits in TS so far.

Indeed, although the suggestion that specifically ADHD, which occurs in about 50% of individuals with TS (Hirschtritt et al., 2015), plays a predominant role in explaining executive dysfunction in TS is long-lasting (see e.g., Ozonoff, Strayer, McMahon, & Filloux, 1998; Pennington & Ozonoff, 1996), we still lack unequivocal evidence whether and to what degree potential deficits in different executive functioning domains in TS can be attributed to comorbid ADHD, or are intrinsic to TS without comorbid ADHD, due to the sparsity of well-sized studies. Similarly, it is not clear to what extent executive (dys)function in TS with comorbid ADHD is similar to that of ADHD without tics. Indeed, long-standing support for impairments in executive functioning has been found in children and adults with ADHD, most prominently response inhibition and working memory (Stevens, Quittner, Zuckerman, & Moore, 2010; Willcutt et al., 2005). Furthermore, a large number of studies suggests that comorbid ADHD in children and adolescents with TS is associated with worse performance in tasks measuring response inhibition, attentional flexibility, and working memory compared to TS without comorbid ADHD or healthy controls (Channon et al., 2003; Greimel et al., 2011; Lange et al., 2017; Ozonoff et al., 1998; Roessner, Becker, Banaschewski, & Rothenberger, 2007; Shin, Chung, & Hong, 2001; Thibeault et al., 2016). Yet, results are frequently inconsistent, with intact performances of children and adults with TS on the aforementioned tasks even in the presence of comorbid ADHD compared to healthy controls (Drury et al., 2012; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006; for review see Morand-Beaulieu, Grot et al., 2017, Morand-Beaulieu, Leclerc et al., 2017). Still, other studies found impairments in children and adolescents with TS without comorbid ADHD versus healthy controls in the domains of attentional flexibility, response inhibition, and working memory (Chang, McCracken, & Piacentini, 2007; Eddy & Cavanna, 2017; Jeter et al., 2015; Lange et al., 2017; Morand-Beaulieu, Leclerc et al., 2017).

Other aspects of executive functioning have been less commonly investigated in TS, such as cognitive control, referring to the ability to build expectations, override

impulses, and to adapt behavior to expected future action (Van Hulst, de Zeeuw, Rijks, Neggers, & Durston, 2017). For instance, it is not yet known whether impaired cognitive control, which has been associated with ADHD (Durston et al., 2007), is specific to comorbid ADHD in TS, or also manifests in TS without comorbid ADHD. Another under-investigated domain in TS is simple psychomotor functioning (Kalsi et al., 2015), which relates to executive functions and is often used to control for individual differences in processing speed to obtain a more specific measure of higher-level executive abilities (Cepeda, Blackwell, & Munakata, 2013). So far, there is little evidence for impairments in simple psychomotor functioning in TS compared to healthy controls (Georgiou, Bradshaw, Phillips, Cunnington, & Rogers, 1997), although findings have been inconsistent depending on the type and complexity of the motor task used (for review see Kalsi et al., 2015 and Morand-Beaulieu, Leclerc et al., 2017). A better understanding of these functions could help to further elucidate the unique deficits associated with TS.

Increasing efforts are being made to sub-phenotype TS based on the presence of comorbidities (Darrow et al., 2017; Grados et al., 2008); literature suggests that TS with and without comorbid ADHD may represent two distinct subtypes (Sukhodolsky et al., 2010). Moreover, some authors have proposed that comorbid ADHD in TS might not reflect the same phenomenon as ADHD without tics, in terms of clinical presentation, genetic background, and neuropsychological functioning (Gillberg et al., 2004; Harris et al., 1995; Morand-Beaulieu, Leclerc et al., 2017), whereas others have pointed to ADHD symptoms as a cross-disorder phenomenon (Huisman-van Dijk, van de Schoot, Rijkeboer, Mathews, & Cath, 2016; Van Hulst, de Zeeuw, Bos et al., 2017). To unravel the role of ADHD in TS it is important to not only compare different diagnostic groups, i.e., TS without comorbid ADHD, TS with comorbid ADHD, ADHD without tics, and healthy controls (Roessner et al., 2007), but also to explore dimensional phenotypic traits beyond diagnostic categories (Karalunas et al., 2018; Morand-Beaulieu, Leclerc et al., 2017).

In the present study, we therefore investigated several executive functioning domains (i.e., response inhibition, attentional flexibility, working memory, and cognitive control) and psychomotor speed in a sample of 174 8-12 year old children, at an age when tics are most prevalent (Cohen, Leckman, & Bloch, 2013). We compared four groups: TS without comorbid ADHD, TS with ADHD, ADHD without tics, and healthy controls. Additionally, we related executive functioning to ADHD severity across all groups, and tic severity across the TS groups. Our expectation was that possible executive functioning deficits in TS would primarily be explained by comorbid ADHD and that the TS without ADHD group would perform similar to healthy controls.

2. Methods

We here report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. The conditions of our ethics approval do not permit public archiving of individual anonymized study data. Readers seeking access to the data should contact the Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. There are no further conditions.

2.1. *Participants*

A total of 174 8-12 year old children participated in this study: $n = 60$ children with a chronic tic disorder [i.e., either TS ($n = 59$) or chronic motor tic disorder ($n = 1$), [TS]]: of whom $n = 34$ without ADHD [TS−ADHD] and $n = 26$ with comorbid ADHD [TS+ADHD], $n = 54$ children with ADHD without tics [ADHD−TS], and $n = 60$ healthy controls). The sample size was a priori determined. Affected children were recruited via child and adolescent psychiatry or neurology clinics and patient organizations throughout the Netherlands; healthy controls were recruited through local elementary schools. No part of the study procedures was pre-registered prior to the research being conducted. Inclusion criteria for all participants were established prior to data analysis, and included Caucasian decent (given that this study was part of a genetic cohort, see Naaijen, de Ruiter et al., 2016), IQ at least 70, no past or present head injuries or neurological disorders, and no major physical illness. Common comorbid psychiatric conditions, such as ADHD and OCD, were allowed in children with TS. In children with ADHD−TS, only comorbid oppositional defiant disorder (ODD), and conduct disorder (CD) were allowed (see Naaijen, Forde et al., 2016). Healthy controls had to be free of any psychiatric disorder, the absence of which was confirmed by the comprehensive and widely-used parent-administered Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997; Leffler, Riebel, & Hughes, 2014), based on DSM-IV-TR criteria (American Psychiatric Association, 2000), and by scores in the normal range on the Child Behavior Checklist and Teacher Report Form (CBCL, TRF; Achenbach et al., 2001). 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).

2.2. *Procedure and clinical measures*

Diagnostic interviews (+/− 1 h) with both the child and at least one parent present were carried out in cases and controls by trained study clinicians under supervision of board-certified clinicians, followed by neuropsychological assessments (+/− 1 h) and subsequent neuroimaging. Assessments took place on a single test day at the Radboud University Medical Center in Nijmegen, The Netherlands. Children were asked to refrain from using stimulant medication 48 h prior to the testing day, whereas other types of medication were allowed.

A clinical diagnosis of a chronic tic disorder according to DSM-IV-TR criteria (American Psychiatric Associaton 2000) was confirmed using the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989; Storch et al., 2005; https://www.kenniscentrum-kjp.nl/wp-content/uploads/2019/06/Vragenlijst-YGTSS-DCI.pdf). Tic severity was rated 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 (total YGTSS tic severity score, range 0–50). The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997; Storch et al., 2006; https://www.nji.nl/nl/Download-NJi/CY-BOCS-Vragenlijst-2009.pdf) was used to assess the presence of a comorbid OCD diagnosis and the severity of obsessive-compulsive symptoms, rating the time spent, interference, distressing nature, effort to resist, and level of control separately for obsessions and compulsions during the past week, each on a five-point Likert scale (total OCD severity score, range 0–40). Both the YGTSS and CY-BOCS are semi-structured clinical interviews representing the gold standard to rate tics and OCD symptoms. A clinical diagnosis of ADHD was confirmed by the K-SADS using DSM-IV-TR criteria (Kaufman et al., 1997; https://www.pediatricbipolar.pitt.edu/resources/instruments), one of the most effective and widely-used diagnostic interviews in research and clinical care (Leffler et al., 2014). Moreover, all children with ADHD–TS fell in the clinical range (all scores above the 97th percentile) as assessed by teacher report via the TRF (Achenbach et al., 2001). To rate ADHD severity, the Conners' Parent Rating Scale – Revised Long version was assessed (CPRS-RL; Conners, Sitarenios, Parker, & Epstein, 1998) calculating standardized T-scores (ADHD severity score, range 40–90). Readers seeking access to the CPRS-RL and TRF are advised to contact the copyright holders (https://www.aseba.nl/home; https://mhs.com).

None of the healthy controls met the cut-off for clinically significant ADHD symptoms (T-score $\geq$ 70) measured by the CPRS-RL, whereas 11 children (32%) of the TS–ADHD group scored in the clinically significant range of ADHD symptoms, but without a formal ADHD diagnosis as they did not meet all criteria of the DSM-IV-TR (American Psychiatric Association, 2000). The K-SADS (Kaufman et al., 1997) was furthermore used to establish a diagnosis of comorbid ODD and CD. IQ was estimated from four subtests (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.

2.3. *Executive functioning*

The cognitive assessments entailed computer-based tasks from the Amsterdam Neuropsychological Tasks (ANT; De Sonneville et al., 1999) program, the Cheese Timing Task (Davidson et al., 2004), and a verbal memory task (Digit Span; Wechsler, 2002), together assessing a range of executive functioning measures (i.e., response inhibition, attentional flexibility, cognitive control, and working memory) and psychomotor speed. The tasks are well-validated and have been found to be suitable to detect neuropsychological dysfunctions in patients with psychiatric conditions (Davidson et al., 2004; De Sonneville et al., 1999; Van Hulst, de Zeeuw, Rijks et al., 2017; Waters & Caplan, 2003). Legal copyright restrictions do not permit us to publicly archive the tasks used in this study. Readers seeking access to the ANT tasks or to the verbal memory task are advised to contact the copyright holder of the respective tasks (https://www.boomtestonderwijs.nl/productgroep/101-22_ANT; https://www.pearsonclinical.nl/wisc-iii-nl-wechsler-intelligence-scale-children). Readers seeking access to the Cheese Timing Task can go to https://www.sacklerinstitute.org/cornell/assays_and_tools/.

2.3.1. *Psychomotor speed*

Psychomotor speed was assessed with the baseline speed task from the ANT program (De Sonneville et al., 1999; Kalff et al., 2003), measuring simple visuo-motor reaction time. A white fixation cross is shown in the center of a computer screen, which changes unpredictably into a white square. Participants were instructed to respond as fast as possible by pressing a key once they see the square. The task consisted of two parts each with 32 trials. Responses were required within 150–4000 msec. The first part required a response with the non-dominant hand, and the second part a response with the dominant hand. The outcome measure was the mean reaction time in ms averaged across both hands.

2.3.2. *Attentional set shifting task*

The Shifting Attentional Set – Visual task from the ANT (Brunnekreef et al., 2007; De Sonneville et al., 1999) was used to measure response inhibition (i.e., the ability to inhibit prepotent responses) and attentional flexibility (i.e., the ability to switch between task demands), see also Supplement 1. The task was divided into three blocks. In each block a horizontal bar consisting of 10 grey squares was presented at the center of the computer screen. In *Block 1* a green colored square moved across the bar in either a right or left direction. Participants were asked to respond in a *compatible* way, by pressing the response button that corresponded to the direction in which the stimulus moved as quickly as possible. In *Block 2* a red colored square moved across the bar in a random direction. Participants were required to quickly respond in an *incompatible* way (mirroring) by pressing the response button that corresponded to the opposite direction of that in which the stimulus moved. In *Block 3* the color of the moving square alternated randomly between green and red, and both compatible and incompatible responses were required that were unpredictable. Block 1 and 2 consisted of 10 practice trials and 40 experimental trials, whereas Block 3 consisted of 16 practice trials and 80 experimental trials. Responses were required as quickly as possible; only responses between 150 and 5000 msec were used in the analyses.

Response inhibition, or the 'inhibition of prepotent responses', measures the output-related ability to inhibit an inappropriate, habitual response tendency, i.e., mirroring the direction of the moving square in Block 2 and inhibiting the more 'natural' response of copying it as in Block 1. It is computed by subtracting the mean reaction time and error rate of Block 1 (stimulus-response compatible situation) from the mean reaction time and error rate of Block 2 (stimulus-response incompatible situation).

Attentional flexibility reflects the central cognitive ability to mentally switch between two competing and unpredictable response sets. It is computed by subtracting the mean reaction time and error rate of the compatible responses of Block 1

from the mean reaction time and error rate of the compatible responses of Block 3. A lower reaction time (faster response) and lower error rate (more accurate response) indicate better response inhibition and attentional flexibility.

2.3.3. *Cheese timing task*

This task is a go/no-go task measuring cognitive control, in which participants are instructed to aid a mouse in its search for cheese (Davidson et al., 2004; Durston et al., 2007; Van Hulst, de Zeeuw, Rijks et al., 2017). A door on the screen opened regularly to reveal either a piece of cheese (go trials; 82% of 264 trials) or a cat (no-go trials; 18% of 264 trials), shown for 500 msec. Participants were instructed to press a key as fast as possible when a piece of cheese was shown, and to withhold their response when a cat was shown. In a majority of the trials (82%) the door was shown (closed) for 3500 msec (resulting in expected timing of the ensuing stimulus), and in a minority of trials (18%) the door was shown for 1500 msec (resulting in unexpected timing of the ensuing stimulus). We used four measures of cognitive control performance (i.e., the ability to build expectations, override impulses, and to adapt behavior to expected future action): (1) mean reaction time during expected go trials (where lower values indicate faster responses); (2) error rate of expected go trials (where lower values indicated better cognitive control performance); (3) reaction time variability, using the intra-individual Coefficient of Variation (ICV, which is the standard deviation of the reaction time divided by mean reaction time; higher values indicating greater response variability); and (4) response time benefit (defined as the reaction time during expected go trials minus the reaction time during unexpected go trials divided by the standard deviation of the reaction time of expected go trials [Durston et al., 2007]; a lower response time benefit indicates an impaired ability of children to benefit from trials at an expected time [De Zeeuw, Weusten, van Dijk, & Durston, 2012; Van Hulst, de Zeeuw, Rijks et al., 2017]).

2.3.4. *Digit span*

To assess verbal working memory (i.e., the ability to temporarily maintain and manipulate information in short-term memory needed to fulfill task demands), participants completed the widely used Digit Span subtest of the WISC-III (Waters & Caplan, 2003; Wechsler, 2002), consisting of the Forward and Backward Digit Span. The Forward Digit Span required participants to verbally repeat increasingly longer strings of digits (range 0–16), whereas the Backward Digit Span consisted of repeating sequences of numbers increasing in length in the opposite order to that presented (range 0–14). We used the combined Forward and Backward Digit Span total score as a measure of verbal working memory, with a higher total score indicating better working memory.

2.4. *Statistical analyses*

Statistical analyses were performed using SPSS version 23 (SPSS Inc., USA). Missing data (up to 4.2%) was imputed by means of the Expectation Maximization algorithm (Tabachnick & Fidell, 2001). All variables were checked for normal distribution and log transformed where appropriate (i.e., error rate of response inhibition, attentional flexibility, and cognitive control). The mean values reported are without a log transformation. To ensure correct task performance, children performing at a chance level of accuracy were excluded (i.e., making 50% or more errors on the task conditions of response inhibition and attentional flexibility [up to 4.6%], De Sonneville et al., 1999). Additionally, participants with outlier values (z-scores $\geq$ |3.0|) were removed from further analyses (up to 5.2%). See Supplement 2 for the final number of participants per task used for analysis. No part of the study analyses was pre-registered prior to the research being conducted.

Between-group differences (healthy controls, TS−ADHD, TS+ADHD, and ADHD−TS) regarding age were tested with the non-parametric Mann−Whitney *U* test, regarding sex through a Chi-square (χ^2) test, and regarding IQ by an analysis of variance (ANOVA). Possible speed-accuracy trade-offs (i.e., negative correlation) between the respective reaction time and error rate measures were checked with Pearson's *r* in all groups. One-way multivariate analysis of covariance (MANCOVA) was conducted with all executive performance measures and psychomotor speed in one model and group as a factor. We used one model since we noticed a few moderate inter-correlations between the respective executive functioning variables (reaction times: $r_{CC,AF} = .14$, $r_{CC,RI} = .12$, $r_{CC,RS} = .26$, $r_{AF,RI} = .40$, $r_{AF,RS} = .01$, $r_{RI,RS} = .07$; error rates: $r_{CC,AF} = .26$, $r_{CC,RI} = .06$, $r_{AF,RI} = .37$; CC = cognitive control, RI = response inhibition, AF = attentional flexibility, RS = response speed). To determine significance of group differences Bonferroni-corrected *p*-values were used with an alpha-level of .05. In addition, linear regression analyses were performed to investigate the relationship between the performance measures and tic severity in the TS sample ($n = 60$) and ADHD severity across all four groups to capture the full range of symptoms ($n = 174$), with age, sex and IQ included as covariates. The *p*-value indicating significance for all tests was <.05.

2.5. *Sensitivity analyses*

Analyses were repeated with three groups (healthy controls, TS irrespective of comorbid ADHD, and ADHD−TS) to make full use of the TS sample size and check whether results were similar. Furthermore, to control for current medication use, we excluded participants who were using medication during the assessment day ($n = 9$) in a four-group analysis. Additionally, analyses were repeated in the four groups with OCD severity as an extra covariate to check for the influence of OCD, and lastly in boys only to account for the unequal sex distribution across groups.

3. Results

3.1. *Sample characteristics*

See Table 1 for group characteristics. The TS−ADHD group consisted of significantly more boys compared to the ADHD−TS and healthy control groups. Further, healthy controls were slightly older compared to the TS+ADHD group, and IQ was higher in healthy controls than in

Table 1 – Group characteristics.

	HC ($n = 60$)	TS–ADHD ($n = 34$)	TS+ADHD ($n = 26$)	ADHD–TS ($n = 54$)	Test Statistic	
Male sex, *n* (%)	43 (71.7)	33 (97.1)	19 (73.1)	32 (59.3)	$X^2 = 4.14$[a]*	TS–ADHD > HC
					$X^2 = 9.64$[a]*	TS–ADHD > ADHD–TS
Age in years, M ± SD	10.50 ± 1.01	10.14 ± 1.41	10.05 ± 1.47	10.16 ± 1.25	$U = 817.50$[b]*	HC > TS+ADHD
IQ, M ± SD (range)	108.73 ± 12.2 (80.59–133.27)	107.79 ± 12.33 (80.59–127.73)	103.14 ± 11.99 (84.75–126.57)	102.18 ± 14.44 (79.43–135.43)	$F(3, 170) = 3.718$[c]*	HC > ADHD–TS
Tic severity, M ± SD	–	20.27 ± 8.03	23.00 ± 9.83	–	$T(58) = -1.174$[d]	
ADHD severity, M ± SD	45.32 ± 4.73	58.54 ± 11.41	69.70 ± 8.36	69.72 ± 11.36	$F(3, 170) = 79.086$[c]**	TS–ADHD > HC
						TS+ADHD > HC
						ADHD–TS > HC
						TS–ADHD < TS+ADHD
						TS–ADHD < ADHD–TS
OCD, *n*	0	8	4	0		
ODD/CD, *n*	0	2	1	4		
Medication, *n*	0	4	2	3		

*$p < .05$ **$p < .001$.
HC; healthy controls; TS, Tourette syndrome and chronic motor tic disorder; ADHD–TS, attention-deficit/hyperactivity disorder without tics; TS–ADHD, TS without comorbid 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); ADHD severity assessed by the Conners' Parent Rating Scale – Revised Long standardized T-score (Conners et al., 1998); 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.
[a] A Pearson's chi-squared test.
[b] Mann–Whitney *U* test.
[c] An analysis of variance.
[d] An independent T-test.

children with ADHD–TS, although IQ was within the normal range. There was no significant difference in tic severity between the two TS groups. ADHD severity was lowest in healthy controls compared to the diagnostic groups, lower in TS–ADHD compared to TS+ADHD and ADHD–TS, and not significantly different between the TS+ADHD and ADHD–TS groups.

About 35% of the children with TS, and 70% of the children in the ADHD–TS group without tics used medication (see Supplement 3). Three children with ADHD–TS did not comply with refraining from using stimulant medication 48 h prior to the testing day, while 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).

3.2. *Executive functioning between groups*

The MANCOVA indicated statistically significant differences in executive functioning performance between the four groups; see Table 2. We did not find speed-accuracy tradeoffs between reaction time performances and error rates of the children in any of the groups or tasks (all *p*'s > .05), indicating that a higher error rate is not explained by faster responses.

3.2.1. *Psychomotor speed*

Children with TS–ADHD responded significantly slower (i.e., had a mean longer reaction time) than healthy controls, which represented a medium sized effect. There were no other significant differences between the groups. Of notice, the reaction time values between the TS–ADHD, TS+ADHD, and ADHD–TS groups were in the similar range.

3.2.2. *Response inhibition and attentional flexibility*

No group differences were found regarding response inhibition and attentional flexibility.

3.2.3. *Cognitive control*

The ADHD–TS group differed significantly from the healthy control group showing slower responses (i.e., longer reaction times) on cognitive control, indicating poorer abilities to build expectations and act accordingly to predictable events. Moreover, both the ADHD–TS and the TS+ADHD groups made more errors on expected go trials compared to healthy controls, whereas TS–ADHD did not differ from healthy controls. Furthermore, the response time benefit was lower for the ADHD–TS group than for healthy controls, suggesting that children with ADHD–TS benefited less from the expected timing of trials. However, there were no differences in reaction time variability between groups. All significant effects were in the medium to large range.

3.2.4. *Working memory*

The TS groups did not differ from healthy controls in the ability to temporarily maintain and manipulate information in short-term memory. However, the ADHD–TS group displayed a significantly poorer verbal working memory as expressed by a lower total digit span score compared to healthy controls, TS–ADHD, and TS+ADHD, representing medium effect sizes.

Table 2 – Results of executive functioning performance measures.

	HC (n = 60)	TS−ADHD (n = 34)	TS+ADHD (n = 26)	ADHD−TS (n = 54)	Test statistic	(d)	
Psychomotor speed							
RT (SD)	311.90 (45.10)	341.31 (54.34)	333.76 (49.61)	331.89 (46.41)	F (3, 170) = 10.06*	.589	TS−ADHD > HC
Response inhibition							
RT (SD)	289.58 (195.17)	309.75 (214.80)	256.36 (211.87)	323.98 (256.89)	F (3, 170) = .67		
ER (SD)	5.69 (5.50)	3.46 (3.42)	4.82 (4.78)	6.62 (6.58)	F (3, 170) = 2.49		
Attentional flexibility							
RT (SD)	585.87 (269.17)	634.69 (260.16)	501.97 (204.77)	544.59 (359.73)	F (3, 170) = 2.76		
ER (SD)	8.29 (7.98)	6.72 (6.56)	4.09 (5.06)	8.71 (6.50)	F (3, 170) = 1.44		
Cognitive control							
RT (SD)	354.01 (24.13)	360.23 (22.71)	361.42 (18.05)	365.46 (30.61)	F (3, 170) = 4.93*	.415	ADHD−TS > HC
ICV	.24	.24	.24	.24	F (3, 170) = .65		
ER (SD)	38.26 (22.34)	52.45 (21.98)	62.28 (26.08)	59.32 (34.10)	F (3, 170) = 14.95**	.989	TS+ADHD > HC
						.731	ADHD−TS > HC
RT benefit (SD)	49.16 (21.85)	39.43 (51.08)	47.02 (27.24)	29.47 (48.41)	F (3, 170) = 3.51*	.524	ADHD−TS < HC
Working memory							
Total score (SD)	10.61 (3.55)	11.02 (3.28)	11.21 (3.27)	8.80 (3.17)	F (3, 170) = 6.76*	.538	ADHD−TS < HC
						.688	ADHD−TS < TS−ADHD
						.748	ADHD−TS < TS+ADHD

HC, healthy controls; TS, Tourette syndrome and chronic motor tic disorder; ADHD−TS, attention deficit/hyperactivity disorder without tics; TS−ADHD, TS without comorbid ADHD; TS+ADHD, TS with comorbid ADHD; RT, mean reaction time; ER, error rate; SD, standard deviation; ICV, reaction time variability; RT benefit, the ability of children to benefit from expected trials. Psychomotor speed measured by the baseline speed task (De Sonneville, 1999); response inhibition and attentional flexibility assessed by the Shifting Attentional Set – Visual (SSV) task (De Sonneville, 1999); cognitive control by the Cheese Timing Task (Davidson et al., 2004); working memory by the Digit Span (Wechsler, 2002); A one-way MANCOVA, followed by post hoc multiple comparisons with Bonferroni adjustment, was performed controlling for sex, age, and IQ; Effect sizes (d) are presented as Cohen's d (1988), with values between .2 and .5 considered as a small, between .5 and .8 as a medium, and above .8 as a large effect. The MANCOVA showed a significant difference in executive functioning performance between groups [$F(30,470) = 2.268$, $p < .001$; Wilk's $\Lambda = .669$, partial $\eta^2 = .13$]; $^*p < .05$ $^{**}p < .001$.

3.3. *Executive functioning in relation to tic and ADHD severity*

See Table 3 for results. Higher ADHD severity was related to slower responses (i.e., higher psychomotor speed reaction times) as measured by the baseline speed task and to lower cognitive control in terms of slower responses (i.e., higher reaction times), and making more errors. Finally, children with higher ADHD severity had poorer working memory as reflected by a lower total digit span score. We did not observe relationships between performance measures and tic severity in the TS sample.

3.4. *Sensitivity analyses*

The results remained similar after comparing three groups (healthy controls, combined TS group irrespective of comorbid ADHD, and ADHD−TS). Furthermore, using four groups (healthy controls, TS−ADHD, TS+ADHD and ADHD−TS), the results remained similar 1) when excluding the participants who were medicated at the time of assessment, 2) when including OCD severity as an extra covariate, and 3) when analyzing boys only.

4. Discussion

This study is one of the few larger-sized studies investigating executive functioning (response inhibition, attentional flexibility, cognitive control, and working memory) and psychomotor speed in children with TS with and without comorbid ADHD, compared to children with ADHD−TS and healthy controls. Overall, we found comparatively little evidence that executive functioning is inherently impaired in TS. except for poorer cognitive control in TS+ADHD compared to healthy controls. Furthermore, we observed slower responses on a basic psychomotor response task in TS−ADHD than in controls. Impairment in executive functioning, specifically cognitive control and working memory, manifested predominantly in children with ADHD−TS versus healthy controls and in relation to ADHD severity.

Children with TS+ADHD, but not those with TS−ADHD, showed more errors during the cognitive control task versus healthy controls, suggesting poorer ability to build expectations and act according to events in the future. We observed the same pattern in children with ADHD−TS as in those with TS+ADHD compared to healthy controls, as well as a lower reaction time and a reduced benefit of the expected timing of trials, consistent with previous findings in ADHD (Durston et al., 2007; Van Hulst, de Zeeuw, Rijks et al., 2017). Associations between higher ADHD severity and poorer cognitive control performance across groups supported these results. The lack of a significant difference between the TS+ADHD and TS−ADHD groups may have been due to the significantly higher ADHD severity in both groups compared to healthy controls. To conclude, also given a lack of an association between tic severity and cognitive control, our findings emphasize that comorbid ADHD underlies cognitive control deficits in TS, suggestive of a cross-disorder phenomenon.

Table 3 – Results of executive functioning performance measures associated with tic severity in the TS sample ($n = 60$) and with ADHD severity in the total study sample ($n = 174$).

	Tic severity		ADHD severity	
	B ± SE	*Beta*	B ± SE	*Beta*
Psychomotor speed				
RT	−.042 ± .032	−.230	.056 ± .025	.197*
Response inhibition				
RT	−.007 ± .007	−.169	.005 ± .005	.071
ER	−.080 ± .306	−.048	−.048 ± .153	−.023
Attentional flexibility				
RT	.003 ± .006	.081	−.001 ± .004	−.026
ER	.490 ± 1.588	.048	.000 ± .146	.000
Cognitive control				
RT	−.071 ± .076	−.152	.108 ± .044	.194*
ICV	36.913 ± 42.349	.129	7.801 ± 29.329	.020
ER	−.005 ± .062	−.015	.099 ± .038	.226*
RT benefit	−.068 ± .034	−.316	−.037 ± .027	−.106
Working memory				
Total score	−.281 ± .449	−.101	−1.056 ± .364	−.235**

TS, Tourette syndrome and chronic motor tic disorder; ADHD, attention deficit/hyperactivity disorder; RT, mean reaction time; ER, error rate; ICV, reaction time variability; RT benefit, the ability of children to benefit from expected trials; see Table 2 for further explanations. Linear regression analyses were performed with age, sex and IQ as covariates; *$p < .05$ **$p < .001$.

In contrast to our expectations and previous findings (Channon et al., 2003; Roessner et al., 2007; Shin et al., 2001), we did not observe other executive function impairments in TS+ADHD (i.e., response inhibition, attentional flexibility, working memory) compared to healthy controls. Neither did we find associations between tic severity and respective executive functioning measures, consistent with some (Eddy & Cavanna, 2017; Thibeault et al., 2016), but not other studies (Baym, Corbett, Wright, & Bunge, 2008; Jeter et al., 2015; Tharp et al., 2015). One possibility to explain discrepant results are differences in symptom severity; indeed, the mean YGTSS score (based on the preceding week) was lower in our study compared to previous studies (e.g., the mean past week YGTSS scores were 27–43 in the studies of Drury et al., 2012 and Channon et al., 2003 *vs* 20–23 in our study). Yet, similar or even lower mean tic severity scores have also been shown to be associated with executive dysfunction in TS+ADHD (Sukhodolsky et al., 2010; Termine et al., 2016). Other sources of variability that are related to tic severity include varying age ranges and the level of medication use across studies (Buse et al., 2012; Tharp et al., 2015; Yaniv et al., 2017). In this study only a minority (~35% in TS) was medicated in general, suggesting a less severely affected TS group. Additionally, as our age range (8–12 years) was chosen to capture an age where tics are most prevalent (Cohen et al., 2013), it may perhaps not directly compare with other studies using a broader age range (often between 6 and 18 years; Channon et al., 2003; Drury et al., 2012; Termine et al., 2016), as neuropsychological deficits may increase with age among children with TS (Bornstein, Carroll, & King, 1985; Jeter et al., 2015; Rasmussen, Soleimani, Caroll, & Hodlevskyy, 2009). However, studies using a similar age range to the current study have also shown associations between executive dysfunction and TS with and without comorbid ADHD (Harris et al., 1995; Rasmussen et al., 2009). Moreover, lack of controlling for current medication use (e.g., stimulants, antipsychotic medication) or other comorbid problems such as OCD has been criticized as a source of confounding effects in previous literature (Buse et al., 2012; Matsuda et al., 2012). However, these factors did not appear to impact on our findings. In sum, explaining the overall ambiguous literature remains challenging; perhaps it reflects the generally small-sized literature, which is often lacking a sound methodology (Morand-Beaulieu, Leclerc et al., 2017), or the heterogeneity in performance between the various tasks chosen to measure executive functioning.

Further, in line with our expectations, TS–ADHD showed largely similar performance in executive functioning as healthy controls. The only significant finding in those with TS–ADHD in our study was a longer response time during a simple motor speed task, suggesting that children with TS are characterized by slower psychomotor reactions compared to healthy controls. The sparse studies examining simple motor skills in TS so far largely indicated no deficits (Georgiou et al., 1997; Kalsi et al., 2015, although these studies concerned primarily adults with TS and were confined to small sample sizes. It has been suggested that previously reported impairments of (non-simple) motor skills in TS may not directly result from tics, but may depend on medication use or comorbidities (Buse et al., 2012). However, our results contradict this assumption, as the impaired simple psychomotor performance in the group of TS–ADHD was independent from medication use during the assessment day and OCD. Nevertheless, future studies are needed to confirm our findings. It is worth mentioning that motor performance in the TS+ADHD and ADHD–TS groups in our study appeared more similar to TS–ADHD than to healthy controls, suggesting that a slower motor speed may perhaps not be specific to TS–ADHD. Yet this observation was not significant; hence larger sample sizes may be needed to detect specific group differences, especially when the deficits are expected to be mild such as in simple motor tasks.

With regard to ADHD–TS, besides the aforementioned deficits in cognitive control, we observed poorer working memory performance compared to both TS groups and healthy controls. Results point to difficulties in holding relevant information in short-term memory for the purpose of completing a task, congruent with previous findings in ADHD (Rosenthal, Riccio, Gsanger, & Jarratt, 2006; Wells, Kofler, Soto, Schaefer, & Sarver, 2018). Interestingly, unlike for cognitive control, this effect appeared to be specific to the ADHD–TS group without tics (with similar working memory performance between TS+ADHD, TS–ADHD, and healthy controls, in line with the review of Morand-Beaulieu, Leclerc et al., 2017), even though ADHD symptom severity was similar in the TS + ADHD and ADHD–TS groups. In conclusion, despite a similar performance of cognitive control in ADHD–TS and TS+ADHD which may suggest a cross-disorder phenomenon, the discrepancy in results for working memory supports the notion that comorbid ADHD in TS and ADHD–TS may differ on some domains of cognitive functioning (Gillberg et al., 2004; Sherman, Shepard, Joschko, & Freeman, 1998; Sukhodolsky et al., 2010). Findings thus support partly

overlapping (i.e., explaining impairment through comorbidity) and partly unique neuropsychological effects of ADHD symptomatology in cross-disorder comparisons.

Finally, as previously described, we did not find deficits in response inhibition and attentional flexibility in TS or ADHD–TS compared to healthy controls. One possible explanation for the discrepancy in results compared to previous studies in TS and ADHD (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Morand-Beaulieu, Grot et al., 2017, Morand-Beaulieu, Leclerc et al., 2017; Sergeant, Geurts, & Oosterlaan, 2002; Van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007) may be that the various tasks differ markedly in cognitive demands and/or mechanisms involved in task performance (Halperin & Schulz, 2006; Rommelse et al., 2007; Sergeant et al., 2002). For example, the stop-signal task, a hallmark measure of response inhibition, requires explicitly withholding an already initiated response (Lipszyc & Schachar, 2010), whereas the ANT task used in this study does not (De Sonneville et al., 1999). Still, the ANT has generally been shown to be a sensitive instrument to measure response inhibition and attentional flexibility (Brunnekreef et al., 2007; De Sonneville et al., 1999), although null-findings have also been reported in other sizeable ADHD samples (Dietrich et al., 2012; Rommelse et al., 2007). Similarly, the Wisconsin Card Sorting test (Kongs, Thompson, Iverson, & Heaton, 2000), which is often used to (successfully) assess attentional flexibility, requires a subject to extract the (constantly changing) problem solving rules, whereas in our paradigm the problem solving rule is known and constant during the test (Rommelse et al., 2007). In sum, our non-findings with regard to response inhibition and attentional flexibility may perhaps be explained by differences in task-dependent cognitive demands.

Strengths of this study were the use of a sizeable sample of 8-12-year-old children with TS with and without ADHD, ADHD–TS, and healthy controls, the application of both group and dimensional analyses and conducting a number of sensitivity analyses controlling for medication use and OCD severity. Potential study limitations need to be addressed. First, it should be noted that the sample sizes of the TS groups were small in comparison with the other groups in this study, resulting in a lower power to detect small effects. Second, there was a high percentage of males in the TS group compared with the ADHD–TS and healthy control groups, although this was as expected as males are more frequently affected than females. Still, sensitivity analyses only in boys yielded similar results. Third, while this study focused on comorbid ADHD in TS and additionally controlled for comorbid OCD severity, we were unable to thoroughly explore the role of comorbid OCD (Chang et al., 2007) due to the low number of subjects with comorbid OCD. Fourth, some children did not comply with stopping medication 48 h prior to the assessments; however, removal of these children from the analysis did not change results. Fifth, the digit span task may be considered a simple working memory task and appears to place few demands on the central executive (i.e., the most versatile and driving component of working memory; Engle, Tuholski, Laughlin, & Conway, 1999); hence the multifaceted nature of working memory may need to be addressed in future TS studies using more enhanced measures. Sixth, our findings may not generalize to more severely affected TS groups given that our sample may have shown lower tic severity scores compared to some other studies investigating executive functioning in TS (Channon et al., 2003; Drury et al., 2012). Finally, future research may benefit from the use of various types of cognitive measures that are sensitive to different contexts including the child's executive function performance in daily life (see Hovik et al., 2014).

Overall, we found little support for impairments in executive functioning in TS, except for impaired cognitive control. Furthermore, we observed slower psychomotor performance in TS. Importantly, comorbid ADHD in TS appeared to drive cognitive control deficits. From a clinical perspective, this highlights the need to treat ADHD symptoms in children with TS to improve executive functioning. While these findings suggest ADHD-related impairment across disorders, we also found support for unique neuropsychological impairments in working memory performance in ADHD–TS versus TS. Further research is needed to disentangle the association of TS and ADHD, as well as of other comorbidities, using larger samples and a wide variety of tasks to examine task-dependent cognitive demands, preferably across different age ranges and varying degrees of symptom severity.

Declaration of Competing Interest

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Supplementary data

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