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The puzzling question of inhibitory control in Tourette syndrome: A meta-analysis

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ABSTRACT

Tourette syndrome (TS) is a neuropsychiatric disorder involving motor and phonic tics. Inhibitory control is a key issue in TS, and many disruptive or impulsive behaviors might arise from inhibitory deficits. However, conflicting findings regarding TS patients' inhibitory performance in neuropsychological tasks have been reported throughout the literature. Therefore, this meta-analysis aimed to evaluate inhibitory control through neuropsychological tasks, and to analyze the factors modulating inhibitory deficits.

To this end, a literature search was performed through MEDLINE and PsycINFO, to retrieve studies including neuropsychological tasks that assessed inhibitory control in TS patients. Of the 4020 studies identified, 61 were included in the meta-analysis, for a total of 1717 TS patients.

Our analyses revealed a small to medium effect in favor of inhibitory deficits in TS patients. This effect was larger in TS + ADHD patients, but pure TS patients also showed some inhibitory deficits. Therefore, deficits in inhibitory control seem to be an inherent component of TS, and are exacerbated when ADHD is concomitant.

1. Introduction

Tourette syndrome (TS) is a neuropsychiatric disorder involving motor and phonic tics. Those tics, are semi-voluntary, sudden and repetitive. Even though tics can be managed though behavioral therapy (Leclerc et al., 2016; McGuire et al., 2014; O'Connor et al., 2016; Wile and Pringsheim, 2013), the presence of such tics leads to think that inhibitory control could be impaired in TS. For example, thinking or talking about tics relates directly to tic onset due to anticipatory vigilance and psychological awareness, suggesting poor inhibition and impulse control in these patients (O'Connor et al., 2014). Furthermore, some individuals with TS have important socially disinhibited tics (Hirschtritt et al., 2016). Various disruptive and impulsive behaviors might also emerge from such impairment in inhibitory control (Stern et al., 2008; Wright et al., 2012).

1.1. Comorbidity and impulsive behavior in TS

In TS, comorbidity is the norm rather than the exception. Among comorbid disorders associated with TS, attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are the most common (Freeman, 2007; Freeman et al., 2000). It is frequently reported that only 10% of TS patients seen in clinical settings do not present any comorbid disorder (Cavanna et al., 2011; Freeman, 2007; Freeman et al., 2000; Ganos and Martino, 2015). However, this number might be overestimated, since TS patients who seek treatment are those showing more severe symptoms and most associated comorbid disorders. Results from the population-based Avon longitudinal study indicates a 20% prevalence for OCD or ADHD in children with TS (Scharf et al., 2012). Nonetheless, these authors mentioned that the instrument used to diagnose ADHD might underestimate the prevalence. Therefore, 20% should be considered as the minimum prevalence for comorbid ADHD in population-based samples of children with TS, but lower rates were also reported in adults with TS (Burd et al., 2001). Still, ADHD remains an important problem for TS patients seeking treatment, as 61% of children and 39% of adults with TS seen in clinical settings had ADHD (Freeman, 2007). Another issue when diagnosing

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Table 1
Neuropsychological tests measuring inhibitory control.

Test	Description	Outcome measure of inhibitory control
Circle tracing task	The participant must draw over a circle as slowly as possible. Faster drawing reflects a lack of inhibitory control (Bachorowski and Newman, 1985, 1990).	Latency
Continuous performance test (CPT)	In this task, participants are presented with a repetitive set of stimuli and they must maintain their attention over time in order to respond to target stimuli and to inhibit their responses when requested. Participants must press a key every time the letter "X" is presented (or when the letter "X" is preceded by the letter "A", in the AX variant) (Rosvold et al., 1956). More commission errors (i.e.: responding to any other letter than "X") and longer RT represent poor inhibitory control (Moeller et al., 2005; Shucard et al., 1997).	Commission errors & RT
Go/No-Go	Stimuli are presented to a participant; Go and No-Go. The participant must press a key every time a Go stimulus is presented, and must inhibit his response when a NoGo stimulus is presented. Commission errors (i.e.: pressing the key to a No-Go stimulus) and longer RT reflect poor inhibitory control (Bezdjian et al., 2009).	Commission errors & RT
Sentence completion	In sentence completion tests, such as the Hayling test, the examiner read a sentence aloud, with the last word missing. In the first part, the participant is simply asked to complete the sentence. In the second part, the participant must complete the sentence with a word that is not connected to the sentence. He must therefore inhibit his automatic response (Burgess and Shallice, 1997). More errors and longer latencies in sentence completion tasks reflect poor inhibitory control (Christodoulou et al., 2006).	Numbers of errors & latency
Stimulus-response compatibility paradigms	This group includes various tasks (Eriksen flanker task, Simon task, etc.) where the congruency between the stimulus and the response varies. These tasks include a compatible and an incompatible condition. In the compatible condition, the participant gives a response that is congruent with the stimulus. The incompatible condition creates a conflict between the stimulus and the response. For example, in a Simon task, a blue arrow pointing to the right would require a left-hand response. The participant must inhibit the automatic response (a right-hand response) (Eriksen and Eriksen, 1974; Simon and Wolf, 1963). More errors and longer RT in the incompatible condition represent deficits in inhibitory control (Wylie et al., 2012).	Accuracy & RT during the incompatible condition
Stop-signal task	The stop-signal task involves the ability to stop an already ongoing response. When stimuli are presented, the participant must press a key. On some trials, a stop-signal will appear, indicating the participant to stop the response that he just initiated (Logan, 1981). Less accuracy and longer SSRT are associated with poor inhibitory control (Castro-Meneses et al., 2015; Logan et al., 1997).	Accuracy & SSRT
Stroop	This test has three conditions. The first two conditions, where the participant must name colors and read words designating colors, serve as baseline measures. In the third (interference) condition, the words are printed in a color that does not match their significance (i.e.: "red" printed in green). The participant must name the color of the word without reading the word. (Stroop, 1935). Accrued latency in the interference condition reflects deficits in inhibitory control (Zaparniuk and Taylor, 1997).	Latency of the interference condition

***Note*:** SSRT: stop-signal reaction time; RT: reaction time

ADHD in TS patients is that some inherent features of TS might cause ADHD-like symptoms. Indeed, the ability to maintain attention could be impaired by the tics themselves, by efforts to inhibit the tics, or by distractions from comorbid anxiety or OCD (Erenberg, 2005).

TS also has a high rate of comorbidity with impulse control disorders, such as intermittent explosive disorder (IED), sexually inappropriate behavior, trichotillomania, self-injurious behavior or compulsive buying disorder (Frank et al., 2011; Freeman, 2007; Mathews et al., 2004; Wright et al., 2012). However, these disorders might not be solely impulsive disorders, but could also feature some compulsivity (Arzeno Ferrao et al., 2006; Flessner et al., 2012; Starcevic, 2015; Stein et al., 2002). For example, trichotillomania shares impulsive (pleasure and gratification obtained from hair pulling) and compulsive (hair pulling in response to negative affect) features (Flessner et al., 2012). This mix of impulsivity and compulsivity might explain why such disorders are often found in TS, which is a disorder characterized by both symptom clusters (Palumbo and Kurlan, 2007).

Impulsive behaviors are also common among TS patients, especially those with concomitant ADHD (Palumbo and Kurlan, 2007) or OCD (Budman et al., 2000; Freeman et al., 2000). These behaviors include argumentativeness, kicking and explosive outbursts (EO) (Alsobrook and Pauls, 2002). EO might be one of the most disturbing behaviors TS patients can experience. They consist of recurrent episodic rage attacks that seem unpredictable and lead the child to react in a disproportionate manner to a trigger stimulus (Budman et al., 2003; Stephens and Sandor, 1999; Sukhodolsky et al., 2003). These outbursts are similar to IED, but occur more frequently in TS patients than in the general population (Chen et al., 2013). Indeed, they affect between 25% and 70% of TS patients and occur more frequently in children than in adults (Budman et al., 2000), causing distress to both the patient and his surroundings (Budman et al., 2003). EO symptoms can take the form of a refusal (quickly gets angry), a lack of tolerance to frustration, a struggle in self-control, a social immaturity, and a disruptive behavior (Khalifa and von Knorring, 2006). The co-occurring presence of ADHD (Chen et al., 2013) or OCD (Budman et al., 2000) increases the risk of having such outbursts. While impaired impulse control is a factor favoring the occurrence of EO, they might also emerge from a deficit in emotional regulation (Fettich et al., 2015).

1.2. Inhibition and its relation to impulsivity: a neuropsychological perspective

Impulsivity is often conceptualized in three distinct dimensions: (1) the inability to use the available information to evaluate the consequence of someone's actions; (2) the inability to refuse an immediate smaller reward in favor of a delayed larger reward; (3) and impairment in suppressing prepotent motor responses (i.e.: lack of inhibitory control) (Bari and Robbins, 2013; Chamberlain and Sahakian, 2007; Torregrossa et al., 2008).

Neuropsychological tasks involving inhibitory control do not give a full picture of impulsivity, but they represent an objective assessment which is, at least in part, related to impulsivity. Furthermore, response inhibition deficits in neuropsychological tasks have been commonly found in ADHD, trichotillomania and substance abuse disorder, which represent archetypal impulsivity disorders (Chamberlain and Sahakian, 2007; Moeller et al., 2005; Swann et al., 2009). Poor response

inhibition has also been associated with impulsivity in remitted bipolar disorder patients (Christodoulou et al., 2006), binge eating disorder patients (Hege et al., 2015) and healthy controls (Aichert et al., 2012; Weidacker et al., 2017). The current meta-analysis focused particularly on motor and verbal inhibition tasks, since (1) response inhibition impairment is readily assessable through neuropsychological testing; (2) much data is available regarding these features in TS patients; (3) there is an important inconsistency regarding inhibitory control in the TS literature.

Many tests have been used to assess inhibition in TS, and conflicting findings have been reported. A description of these tests is given in Table 1. For instance, performances at the Go/No-Go task were not significantly affected in some studies (Delorme et al., 2016; Draper et al., 2015; Greimel et al., 2011; Ozonoff et al., 1994; Serrien et al., 2005), whereas other investigators found impaired performance (Goudriaan et al., 2005) or a trend toward more commission errors (Greimel et al., 2008) in TS patients. Also, few other Go/No-Go studies reported normal performance accompanied by delayed RTs in TS patients (Eichele et al., 2010; Shephard et al., 2016).

Other motor inhibition tasks, such as the Continuous performance test (CPT), provide a valuable piece of information to pinpoint inhibitory processes in TS. Impaired accuracy and delayed RTs were often reported in comorbid TS patients (Huckeba et al., 2008; Schultz et al., 1998), but some discrepancies exist throughout the TS literature. For instance, normal CPT performance has been found in comorbid and/or medicated TS patients (Matsuda et al., 2012; Sukhodolsky et al., 2010).

Some paradigms assessing response selection interference can also yield important information on inhibitory functions (Heym et al., 2014), but most investigations failed to report any consistent group difference in accuracy or RT at the flanker or at the stimulus-response compatibility (SRC) task (Channon et al., 2009; Channon et al., 2006; Morand-Beaulieu et al., 2015). Impaired Stroop task performance is often reported in TS patients (Chang et al., 2007; Channon et al., 2003; Eddy et al., 2012, 2014; Goudriaan et al., 2006). Nonetheless, intact (Drury et al., 2012; Lavoie et al., 2007; Ozonoff and Jensen, 1999) or even enhanced (Thibault et al., 2009) Stroop performance has also been found. Such discrepancies highlight the importance of the current meta-analysis.

Results from neuropsychological tasks involving inhibitory control may have been confounded by the presence of comorbidity and/or by psychiatric medications. For instance, many studies reported impairments in TS + ADHD patients, but not in pure TS patients (Sherman et al., 1998; Shin et al., 2001). As a matter of fact, many studies that excluded comorbid patients report intact inhibitory performance (Biermann-Ruben et al., 2012; Channon et al., 2009; Lavoie et al., 2007; Roessner et al., 2008a). However, impaired inhibitory performance has also been reported in non-comorbid patients, which makes it even more puzzling (Eddy et al., 2012, 2014). Also, many pharmacological treatments taken by TS patients to treat tics or other comorbid symptoms might also alter inhibitory performance. Indeed, neuroleptics and alpha-2 agonists are often prescribed to treat tic symptoms in TS patients (Scahill et al., 2006; Weisman et al., 2013). Previous research has shown that neuroleptics may also have an impact on inhibitory performance. For instance, pimozide was associated with reduced commission errors in CPT, while haloperidol had the opposite effect (Sallee et al., 1994). In addition, psychostimulants are sometimes given to TS patients to treat ADHD symptoms (Erenberg, 2005). In ADHD patients, psychostimulants have been shown to improve inhibitory performance in CPT (Riccio et al., 2001) or during the Stroop task (Langleben et al., 2006).

At this point, a meta-analysis is needed to gain a larger picture and get a grasp on the subtleties of inhibitory capacities in TS. As mentioned, impairments in inhibitory control may lead to unpredictable and/or explosive behaviors. Such behaviors can be disturbing for both the patient and his surroundings. However, many important discrepancies remain among the findings of neuropsychological tasks assessing inhibitory control. Therefore, the main goal of the current meta-analysis was to determine if TS patients genuinely display inhibitory deficits. Neuropsychological tasks were also analyzed separately, to examine if patients showed specific patterns of impairments in inhibitory control. Finally, comorbid disorders seem to act as major confounders when assessing inhibition in TS. Contrasting TS patients with and without comorbid disorders will be one of the principal benefits of the current meta-analysis, and will help to circumscribe the case of inhibitory control in TS. A particular accent was put on ADHD, since it is a frequent comorbidity of TS (Freeman, 2007; Scharf et al., 2012) and it is known be linked with various impulsive behaviors in TS patients (Palumbo and Kurlan, 2007; Yamamuro et al., 2015).

2. Methods

2.1. Literature search

A systematic search was conducted within the Tourette syndrome literature published up to March 2016, in Medline and PsycINFO databases. The following keywords were used: (Tourette* OR tic OR tics) AND (neuropsy* OR impuls* OR inhibit* OR task*).

2.2. Study selection

Studies were included in our meta-analysis if (1) they were published in French or English in a peer-reviewed journal; (2) they included a group of patients suffering from a tic disorder (Tourette syndrome or persistent [chronic] tic disorder) and (3) a comparison group of healthy controls; (4) they used a neuropsychological task requiring the inhibition of a motor or verbal response (see Section 2.3); (5) they reported sufficient results for meta-analysis purposes.

Studies were excluded if (1) they only reported results from non-parametric analyses; (2) they had been retracted after publication; (3) results were reported in a prior article.

The authors of 22 studies were contacted to provide further information about their results or to provide data that were missing. Nine authors responded, and six of them were able to provide data. The article selection process flowchart is shown in Fig. 1.

2.3. Inhibitory control assessment

Various tasks were used to assess inhibitory control in TS. For most of these tasks, the latency and response accuracy were calculated. The following measures were used in our meta-analysis: commission errors and reaction times (RT) in Go/No-Go paradigms and CPT, accuracy and RT during the incongruent condition of SRC paradigms (including Flanker and Simon tasks), Stroop test performance,[1] stop-signal tasks RT (SSRT) and accuracy, sentence completion tasks latency and accuracy, and the circle tracing task latency. For Go/No-Go, CPT, SRC, sentence completion and stop-signal tasks, latency and performance were both analyzed as a whole and separately.

2.4. Data analysis

The study data were analyzed with the Comprehensive Meta-analysis software (Borenstein et al., 2005). Cohen's d was calculated

[1] The clear majority of study using the Stroop test reported a score based on the time taken to complete the interference condition, or the time difference between the interference and baseline conditions. Only few studies reported a Stroop score that was based on the number of errors during the task, and that was mostly the case of the adapted version of the Stroop task (e.g.: for fMRI studies). Therefore, when both a latency based score and error count were reported, we chose the latency based score as our Stroop measure. If a study only reported an error count or a performance-based score, this score was used.

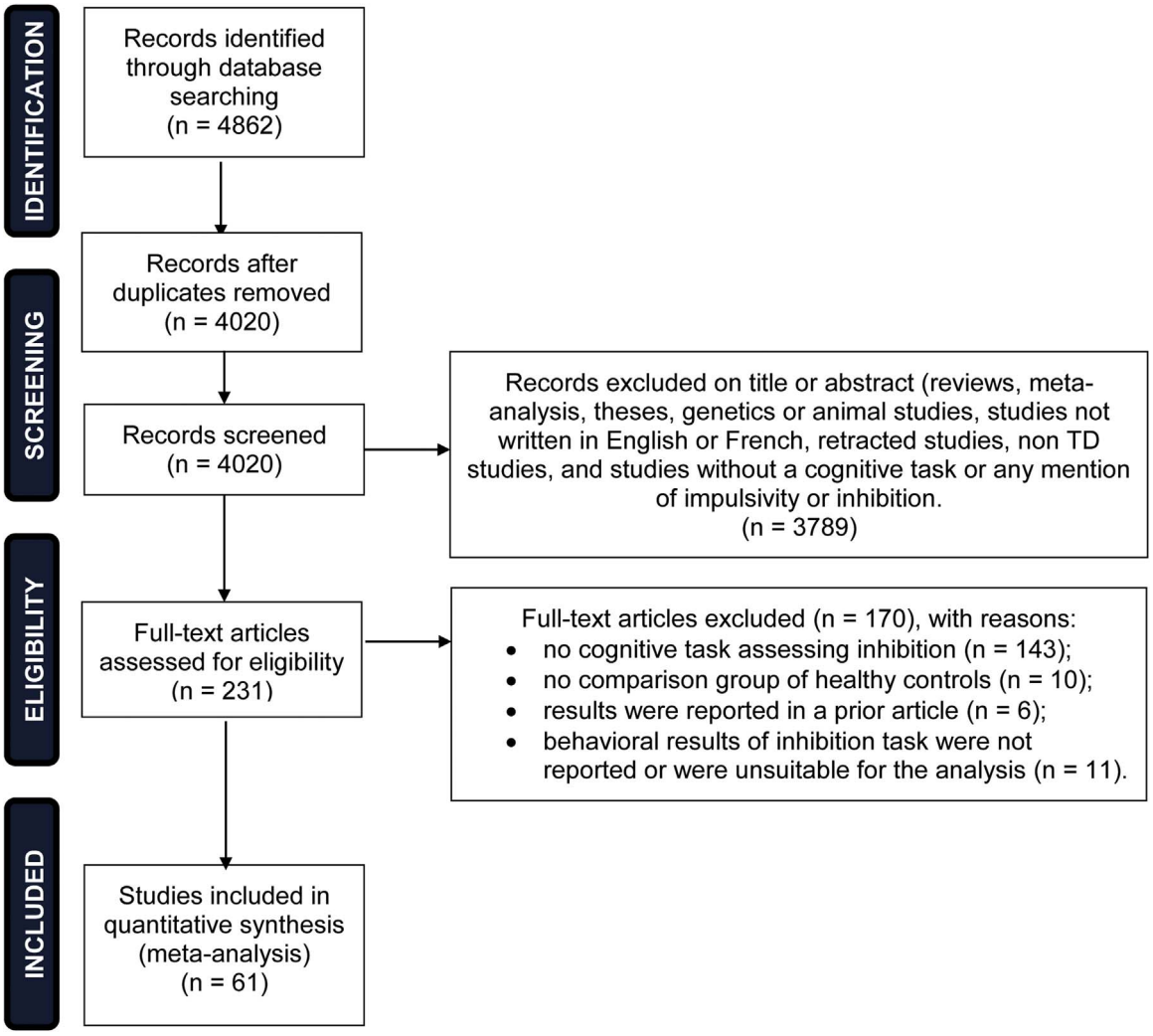

Fig. 1. Study selection flow chart.
Selection process of the studies included in the meta-analysis. The flow chart is based on PRISMA guidelines (Moher et al., 2009).

to determine effect sizes, which represent the standardized mean difference. They were computed by subtracting the mean score of patients from the mean score of healthy controls, which is then divided by the pooled standard deviation (SD). Preferentially, means and SD were used to compute effect sizes. When these data were not available, *t* values were used. In three studies, only median and range were reported; these scores were converted in means and standard deviation according to the formula from Hozo et al. (2005). Positive effect size reflects a better performance in healthy controls relative to TS patients (excepted for the supplementary analysis, where a positive effect size reflects a better performance in TS patients without ADHD relative to TS + ADHD patients). Conventionally, Cohen's d of 0.20, 0.50 and 0.80 are considered as being small, moderate and large effects, respectively (Cohen, 1988). A random-effect model was used to take into account between-study variability, and therefore provided a more conservative estimate of composite effect size (Cooper et al., 2009).

Heterogeneity between studies was evaluated with the Q and I^2 statistics. The I^2 is the proportion of inconsistency between studies' results attributable to heterogeneity. An I^2 value of 25%, 50% and 75% reflects a small, moderate or high degree of heterogeneity, respectively (Higgins et al., 2003). Publication bias was assessed with the Egger's regression intercept (Egger et al., 1997).

2.4.1. Task-specific analyses

Task-specific analyses were performed to determine if impairments were present in every task. Cohen's d was computed separately for each task (circle tracing, CPT, Go/No-Go, sentence completion, SRC, stop signal & Stroop).

2.4.2. Subgroup analyses

Four different subgroup analyses were performed. The first analysis aimed to evaluate the effects of comorbidity on inhibitory control, and comprised samples of TS + ADHD and pure TS patients. It was not possible to analyze a subgroup of TS + OCD patients, since the number of studies including a subgroup of OCD patients (n = 3) and the number of patients in these studies (n = 36) were too low to provide a thorough assessment of the impact of comorbid OCD on inhibition in TS. To be included in this analysis, the subgroup had to be characterized as either pure TS or TS + ADHD per each study criteria. Pure TS samples were considered as so if it was mentioned that comorbidity was excluded, with the explicit mention that no patient had comorbid ADHD and OCD. The second subgroup analysis was performed to evaluate the impact of psychiatric medication on inhibitory control. This analysis compared effect sizes between studies where medicated patients were excluded and those including medicated patients. The third subgroup analysis made a comparison between studies where a verbal response is given (sentence completion & Stroop) and those involving a motor response (circle tracing, CPT, Go/No-Go, Stimulus-response compatibility & Stop-signal). Finally, the fourth subgroup analysis made a comparison between samples including children and

those including adults. Cohen's d was calculated separately for each subgroup in these four subgroup analyses. For comparison purposes, the between-subgroup Q-statistic was calculated. A significant Q-statistic reflects a significant difference in effect size between subgroups.

2.4.3. Moderator analyses

Age and usage of psychiatric medication were added as moderators in our analyses. First, a meta-regression between Cohen's d and age was performed. Then, studies were split between adults and children, and meta-regressions between Cohen's d and age were performed for both subgroups. Finally, for studies reporting patients under psychiatric medication, a meta-regression was conducted between the Cohen's d and the proportion of medicated patients within the study. Meta-regressions were also conducted between Cohen's d and the proportion of patients under neuroleptics, and between Cohen's d and the proportion of patients under adrenergic agents (mainly clonidine and guanfacine). In studies that reported a YGTSS global score or a YGTSS total tic severity score, meta-regressions were conducted between those scores and Cohen's d.

2.4.4. Supplementary analysis

To quantify the contribution of ADHD to the inhibitory deficits of TS patients, we performed a supplementary analysis with studies that included two samples of TS patients, one with ADHD and one without. A systematic search was conducted with the full text articles assessed for eligibility and articles including a group of TS patients with ADHD and a group of TS patients without ADHD were selected. Therefore, studies that were not included because they did not present a comparison group of healthy controls (3rd inclusion criterion) might be included in this analysis if they had a group of TS patients with ADHD and one without. In each study, we computed the effect size between the two groups.

3. Results

3.1. Study characteristics

After excluding duplicates, our literature research identified 4020 potentially eligible studies, and 61 of them met our inclusion criteria (Fig. 1). Those 61 studies included a total of 1717 TS patients and 1399 healthy controls. The mean age of TS patients was 19.8 years. Our sample included both children and adults with TS. The mean age of children with TS was 11.6 (mean age ranged from 9.2 to 15.3), while the sample of adult TS patients had a mean age of 33.3 (mean age ranged from 24.7 to 38.0). The characteristics of each study selected in the meta-analysis are shown in Table 2.

The most frequently reported task is the Stroop, which was used in 25 studies. Other tasks were the Go/No-Go (n = 14), CPT (n = 13), sentence completion (n = 9), stimulus-response compatibility (n = 8), stop signal (n = 5) and circle tracing (n = 2).

3.2. Overall effect size

The overall pooling of 61 studies revealed a moderate effect size of d = 0.33, indicating more inhibitory deficits in TS patients, in comparison with healthy controls (Z = 6.40, p < 0.001) (Fig. 2). Between-study heterogeneity of the overall analysis reached significance level (Q = 142.92, p < 0.001, I^2 = 49.62). Egger's test for publication bias was not significant (Egger's regression intercept = 0.45, t[59] = 0.71, p = 0.48).

3.3. Task-specific analyses

Four of the seven task categories (sentence completion, circle tracing task, Stroop and CPT) revealed significant effect size regarding inhibitory deficits in TS patients. The sentence completion task yielded the most significant effect size (d = 0.54) between TS patients and control (Z = 3.73, p < 0.001). Effect sizes between TS patients and healthy controls were significant for both latency (d = 0.39, Z = 2.77, p < 0.01) and errors (d = 0.55, Z = 2.65, p < 0.01). There was also significant effect size, indicating more inhibitory deficits in TS patients, in the circle tracing task (d = 0.40, Z = 2.50, p < 0.05) and the Stroop test (d = 0.39, Z = 4.70, p < 0.001). TS patients also showed more inhibitory deficits during the CPT, as revealed by a significant effect size (d = 0.29, Z = 2.94, p < 0.005). Here, TS patients showed delayed RT (d = 0.32, Z = 2.52, p < 0.05) and made more commission errors (d = 0.37, Z = 3.15, p < 0.01) than healthy controls.

There was a trend toward a significant effect size in stop-signal paradigms (d = 0.29, Z = 1.88, p = 0.06). The trend regarded the SSRT (d = 0.30, Z = 1.71, p = 0.09), but not the accuracy (d = 0.11, Z = 0.58, p = 0.56).

There were no significant effect sizes regarding the incompatible part of SRC paradigms (overall: d = 0.23, Z = 1.19, p = 0.23; accuracy: d = 0.28, Z = 1.60, p = 0.11; RT: d = 0.17, Z = 0.71, p = 0.48). Overall performance (d = 0.13, Z = 1.31, p = 0.19) and accuracy (d = 0.14, Z = 0.09, p = 0.93) in Go/No-Go tasks were not significant either. However, a trend toward a small group difference in Go/No-Go RT was found (d = 0.15, Z = 1.63, p = 0.10). Task-specific results are shown in Fig. 3.

3.4. Subgroup analyses

3.4.1. The impact of comorbidity on inhibitory control

The first subgroup analysis assessed the impact of comorbidity on inhibitory control. Seventeen studies with a TS + ADHD subgroup, and 20 studies with pure TS samples were included in this subgroup analysis. Pure TS and TS + ADHD samples were separately compared with healthy controls. Among studies including a subgroup of TS + ADHD patients, ADHD status was either established based on clinician diagnosis (n = 6), clinical scale measuring ADHD (n = 3),[2] DSM and/or ICD criteria (n = 4), a combination of clinical scales and DSM criteria (n = 2) or a combination of clinician diagnosis and clinical scales (n = 3).

When comparing pure TS patients with healthy controls, there was a significant effect size, indicating more inhibitory deficits in pure TS patients (d = 0.26, Z = 2.80, p < 0.01). The analysis comparing TS + ADHD patients with healthy controls led to a significant group difference in favor of accrued inhibitory deficits in TS + ADHD patients (d = 0.51, Z = 6.03, p < 0.001) (Fig. 4). The heterogeneity test between both comparisons (Pure TS vs HC and TS + ADHD vs HC) was also significant (Q = 4.17, p < 0.05).

3.4.2. The impact of psychiatric medication on inhibitory control

Finally, analyses were performed to assess the role of psychiatric medication on TS patients' inhibitory capacities. Of the 61 studies included in the present meta-analysis, only 16 studies excluded TS patients under psychiatric medication. One study had a group of non-medicated TS patients, who were compared to medicated patients (Delorme et al., 2016). Thirty-eight studies included patients who were under psychiatric medication during testing. In those studies, the mean proportion of medicated patients was 46%. Medication status was not reported in six studies. In most cases, when children were prescribed methylphenidate or other stimulants, they were deposed prior to testing.

In studies that included medicated patients, there was a significant effect size between healthy controls and TS patients (d = 0.43, Z = 6.91, p < 0.001). However, inhibitory control in non-medicated TS patients did not differ from healthy controls (d = 0.06, Z = 0.66,

[2] In Roessner et al. (2007), ADHD was assessed with the Conners parent rating scale of ADHD in sample 1, and with ICD-10 and DSM-IV-TR in sample 2.

Table 2
Demographic and clinical data of studies on inhibition in Tourette syndrome.

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
Biermann-Ruben et al. (2012)	12	12	37.0	A	12 M:2F	Pure.	Patients were medication for at least 6 months (n = 1) or 1–10 years (n = 6).	Go/ NoGo	Go/NoGo commission errors & RT
Chang et al. (2007)	15	15	10.6	C	10 M:5F	Exclusion of OCD, but not ADHD.	7 patients were under medication, which was stable for at least 4 weeks prior to testing. Individual medication is not reported.	Stroop	Stroop performance
Channon et al. (1992)	19	22	32.7	A	12 M:7F	No explicit mention that ADHD or OCD is excluded.	8 patients were taking neuroleptics (haloperidol, sulpiride or pimozide) & 4 patients were taking antidepressants (fluvoxamine, clomimaprine or fluoxetine).	Stroop	Stroop performance
Channon et al. (2003a)	21	21	32.9	A	18 M:3F	Pure.	13 patients were under medication: antipsychotic (n = 6), SSRI (n = 1), antisympathetic (n = 1), antipsychotic & tricyclic (n = 2), antipsychotic & SSRI (n = 1), antipsychotic & SSRI & benzodiazepine (n = 1), antipsychotic & anticholinergic (n = 1).	Hayling	Sentence completion errors
Channon et al. (2003b)	29	21	13.6	C	19 M:10F	14 TS-only, 9 TS + ADHD, 6 TS + OCD. Data reported separately.	14 patients were under medication: 7 TS-only, 3 TS + ADHD, 4 TS + OCD. Medication type: antipsychotic (n = 5), SSRI (n = 2), antisympathetic (n = 2), tricyclic (n = 1), stimulant (n = 1), antipsychotic & SSRI (n = 2), antipsychotic & stimulant (n = 1).	Stroop & Hayling	Stroop performance, sentence completion errors
Channon et al. (2004)	15	23	33.9	A	11 M:4F	Pure.	N.R.	Hayling	Sentence completion errors
Channon et al. (2006)	20	25	31.1	A	13 M:7F	Pure.	10 patients were under medication: antipsychotic (n = 5), SSRI (n = 1), antipsychotic & SSRI (n = 3), antipsychotic & tricyclic	Flanker- & Sentence completion	SRC incompatible trials accuracy & RT, sentence completion

(continued on next page)

Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
							(n = 1).		errors & latency
Channon et al. (2009)	21	23	29.5	A	12 M:9F	Pure.	8 patients were under medication: antipsychotic (n = 4), tricyclic (n = 1), anxiolytic (n = 1), antipsychotic & SSRI (n = 1), antipsychotic & tricyclic (n = 1).	CPT, Flanker- & Stroop	CPT commission errors & RT, SRC incompatible trials accuracy & RT, Stroop performance
Channon et al. (2012)	20	20	33.5	A	15 M:5F	Pure.	9 patients were under medication: antipsychotic (n = 6), tricyclic (n = 1), antipsychotic & SSRI (n = 1), antipsychotic & benzodiazepine (n = 1).	Hayling	Sentence completion errors & latency
Church et al. (2009)	33	42	12.7	C	25 M:8F	ADHD & OCD were not excluded.	22 patients were under medication: centrally acting adrenergic agents (n = 13), atypical neuroleptics (n = 7), stimulants (n = 7), SSRI antidepressants (n = 6), benzodiazepines (n = 2), antiseizure medications (n = 2), SNRI (n = 2), β-blockers (n = 1), tetracyclic antidepressants (n = 1) (13 patients were taking more than one medication).	Stroop	Stroop performance
Crawford et al. (2005)	20	20	14.4	C	13 M:7F	Pure.	5 patients were under medication: pimozide (n = 3), haloperidol (n = 1), clonidine (n = 1).	Sentence completion & Flanker	SRC incompatible trials accuracy & RT, sentence completion errors & latency
Debes et al. (2011)	39	37	13.9	C	30 M:9F	20 TS-only, 5 TS + ADHD, 10 TS + OCD, 2 TS + ADHD + OCD. Data reported separately.	Medication stopped at least 6 months before testing.	Stroop & Go/ NoGo	Go/NoGo commission errors & RT, Stroop latency
Delorme et al. (2016)	34	17	31,1	A	24 M:10F	4 patients had comorbid OCD. ADHD is excluded.	1 group without medication, and 1 group taking antipsychotics for at least 4 weeks.	Go/ NoGo	Go/NoGo commission errors & RT

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
Draper et al. (2015)	10	10	15.3	C	9 M:1F	4 patients had comorbid disorders: 1 TS + ADHD, 3 TS + OCD.	4 patients were under medication: clonidine (n = 3), citalopram (n = 1).	Go/ NoGo	Go/NoGo commission errors & RT
Drury et al. (2012)	54	48	22,2	Both	39 M:15F	Experiment 1: 16 TS-only & 15 TS + ADHD. OCD is excluded. Data reported separately. Experiment 2: pure.	Experiment 1: 8 TS-only patients were under medication: antipsychotics (n = 4), antihypertensive (n = 2), antipsychotics & SSRI (n = 1), antipsychotics & antihypertensive (n = 1). 8 TS + ADHD patients were under medication: antipsychotics (n = 2), psychostimulant (n = 2), antihypertensive (n = 1), antipsychotics & SNRI (n = 2), antipsychotics & stimulant (n = 1). Experiment 2: 12 patients were under medication: antipsychotic (n = 6), tricyclic (n = 1), antipsychotic & SSRI (n = 3), antipsychotic & benzodiazepine (n = 1), tricyclic & benzodiazepine (n = 1).	Stroop	Stroop performance
Eddy et al. (2010a)	16	8	32.1	A	13 M:3F	4 patients had comorbid disorders: 1 TS + OCD, 2 TS + ADHD + OCD, 1 TS + OCD + anxiety disorder. 4 other patients had subthreshold OCD.	7 patients were under medication: risperidone (n = 3), aripiprazole (n = 2), sulpiride (n = 1), pimozide (n = 1).	Hayling	Sentence completion errors & latency
Eddy et al. (2010b)	18	10	24.7	A	9 M:9F	7 patients had comorbid disorders: 5 TS + OCD, 1 TS + ADHD, 1 TS + ADHD + OCD.	8 patients were under medication: risperidone (n = 4), haloperidol (n = 3), pimozide (n = 1).	Stroop & Hayling	Stroop performance, sentence completion errors & latency
Eddy et al. (2011)	18	20	26.8	A	13 M:5F	5 patients had comorbid OCD. ADHD is excluded.	9 patients were under medication: clonidine (n = 2), fluoxetine (n = 3), sertraline (n = 2),	Stroop	Stroop performance

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
							risperidone (n = 1), aripiprazole (n = 1).		
Eddy et al. (2012)	40	20	32	A	29 M:11F	Pure.	24 patients were under medication: risperidone (n = 6), aripiprazole (n = 6), haloperidol (n = 4), sulpiride (n = 3), clonidine (n = 2), haloperidol & clonidine (n = 1), aripiprazole & clonidine (n = 1), risperidone & pimozide & clonidine (n = 1).	Stroop	Stroop performance
Eddy et al. (2014)	18	18	31.7	A	13 M:5F	Pure.	11 patients were under medication: risperidone (n = 4), haloperidol (n = 2), clonidine (n = 1), sulpiride (n = 1), aripiprazole (n = 1), haloperidol & clonidine (n = 1), risperidone & pimozide & clonidine (n = 1).	Stroop	Stroop performance
Eddy and Cavanna (2014)	15	15	35.4	A	N.R.	ADHD and OCD scores are reported, but they are not used as exclusion criteria.	8 patients were under medication: aripiprazole (n = 2), risperidone (n = 2), sulpiride (n = 1), clonidine (n = 1), paroxetine (n = 1), citalopram (n = 1).	Hayling	Sentence completion latency
Eichele et al. (2010)	19	19	12.6	C	19 M:0F	9 patients had comorbid disorders: 5 TS + ADHD, 4 TS + OCD.	9 patients were under medication: neuroleptics (n = 4), alpha agonists (n = 2), stimulants (n = 2), SSRI (n = 1).	Go/ NoGo	Go/NoGo commission errors & RT
Ganos et al. (2014)	14	15	31.3	A	13 M:1F	Pure.	3 patients were under medication: tiapride (n = 2), aripiprazole (n = 1).	Stop-signal	Stop-signal accuracy & SSRT
Georgiou et al. (1995)	10	10	31	A	7 M:3F	Individual comorbidities are not reported, but authors found attention deficits and depression symptoms in patients.	5 patients were under medication (pimozide, thioridazine, haloperidol or fluoxetine).	SRC	SRC incompatible trials RT
Goudriaan et al. (2005)	47	49	37.0	A	32 M:15F	ADHD & OCD are not excluded.	Medication is not excluded. Individual medication is not reported.	Go/ NoGo	Go/NoGo commission errors
Goudriaan et al. (2006)	46	50	36.8	A	32 M:14F	12 patients had	Medication is not excluded.	Stroop,	Stroop

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
						comorbid disorders: 10 TS + OCD, 2 TS + ADHD.	Individual medication is not reported.	circle tracing & Stop-signal	performance, circle tracing latency, SSRT
Greimel et al. (2008)	20	20	11.3	C	14 M:6F	All TS patients (n = 20) had comorbid ADHD. OCD was excluded. The following comorbidities were reported: ODD (n = 8), specific developmental disorder (n = 4), anxiety (n = 2), affective disorder (n = 1).	6 patients were taking psychostimulants, which were deposed 48 h before testing. 3 children were taking tiapride during testing.	Go/ NoGo	Go/NoGo commission errors & RT
Greimel et al. (2011)	46	27	11.5	C	35 M:11F	21 TS without ADHD, 25 TS + ADHD. Data reported separately. OCD was excluded. Comorbidity among groups: TS-only: specific developmental disorder (n = 2), emotional disorder (n = 1), TS + ADHD: developmental disorder (n = 1), emotional disorder (n = 1), elimination disorder (n = 1), specific phobia (n = 1).	8 TS + ADHD patients were taking psychostimulants, which were deposed 48 h before testing.	Go/ NoGo	Go/NoGo commission errors & RT
Heintz et al. (2013)	16	22	33.4	A	13 M:3F	Pure.	5 patients were under medication: psychoactive medication (n = 2), other medication (N.R., n = 3). Patients taking psychoactive medication were asked to stop taking their medication 24 h before testing.	Stroop	Stroop performance
Hershey et al. (2004)	8	10	35.5	A	7 M:1F	4 patients had comorbid disorders: 3 TS + ADHD, 1 TS + ADHD + OCD.	2 patients were under medication: imipramine (n = 1), levodopa & carbidopa (n = 1). Medication was stopped 12 h before testing.	CPT	CPT commission errors
Huckeba et al. (2008)	47	17	11.6	C	43 M:4F	ADHD & OCD were	25 patients were under	TOVA-V	CPT

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
						not excluded.	medication: 9 patients took a single medication & 16 patients took multiple medications. Medication type is not specified.		commission errors & RT
Johannes et al. (2001)	10	10	34.4	A	9 M:1F	5 patients had comorbid disorders: 2 TS + ADHD, 2 TS + OCD, 1 TS + ADHD + OCD.	4 patients were taking neuroleptics.	Stop-signal	Stop-signal accuracy
Lavoie et al. (2007)	36	22	37	A	18 M:18F	OCD was excluded, but not ADHD.	Patients were free of any type of medication.	Stroop	Stroop performance
Li et al. (2006)	30	28	12.0	C	24 M:6F	13 patients had comorbid disorders: 5 TS + ADHD, 5 TS + OCD, 3 TS + ADHD + OCD.	12 patients were taking pergolide & 16 patients were taking clonidine.	Stop-signal	Stop-signal accuracy & SSRT
Mahone et al. (2002)	38	20	10.4	C	29 M:9F	21 TS-only, 17 TS + ADHD. Data reported separately. No OCD in both groups.	Patients were not on stimulant or tic-suppressing medication at the time of testing.	TOVA-V	CPT commission errrors & RT
Marsh et al. (2007)	66	70	26.7	Both	47 M:19F	Axis 1 disorders were excluded, but there is no explicit mention that ADHD or OCD is excluded.	N. R.	Stroop	Stroop performance
Matsuda et al. (2012)	33	18	18.0	Both	26 M:7F	12 patients had comorbid disorders: TS + ADHD (n = 5), TS + OCD (n = 7). OCS were present in 20 patients: aggression OCS (n = 11), sexual and religious OCS (n = 3), symmetry and counting OCS (n = 14) (8 patients had both aggression and symmetry OCS). Data for the aggression OCS subgroup is reported separately, but comorbidity is not excluded.	6 patients were taking antidepressants & 25 patients were taking antipsychotics.	Stroop & CPT (standard & AX task)	Stroop performance
Morand-Beaulieu et al. (2015)	20	20	38.0	A	13 M:7F	8 patients had comorbid disorders: 1 TS + ADHD, 1 TS + MDD, 5 TS	6 patients were under medication: clonidine (n = 1), SSRI (n = 1), SNRI (n = 1), benzodiazepine	SRC	SRC incompatible trials accuracy &

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
						+ social anxiety disorder, 1 TS + panic disorder.	(n = 1), benzodiazepine & SSRI (n = 1), benzodiazepine & SSRI & risperidone (n = 1).		RT
Muller et al. (2003)	14	14	29.2	A	13 M:1F	All TS patients (n = 20) had comorbid OCD. 3 patients also had comorbid ADHD.	8 patients were taking pimozide.	Go/ NoGo & Stroop	Go/NoGo commission errors & Stroop performance
Oades (2000)	11	14	11.9	C	10 M:1F	No comorbidity reported, but there is no explicit mention that ADHD or OCD is excluded.	5 patients were under medication: pimozide (n = 3), tiapride (n = 2).	CPT (standard & AX task)	CPT commission errors & RT
Ozonoff et al. (1994)	14	14	12.9	C	11 M:3F	Pure.	N.R.	Go/ NoGo & SRC	Go/NoGo commission errors & RT
Ozonoff et al. (1998)	46	22	11.9	C	41 M:5F	23 TS-only, 23 TS with comorbidities. Data reported separately. Comorbidities among comorbid group: TS + ADHD (n = 14), TS + OCD (n = 4), TS + ADHD + OCD (n = 5).	28 TS patients under medication: clonidine (n = 12), SSRI (n = 3), imipramine (n = 2), clomipramine (n = 1), haloperidol (n = 1), combination of medication (most commonly clonidine plus one of the medication listed above, n = 9).	Negative priming task	SRC incompatible trials accuracy & RT
Ozonoff and Jensen (1999)	30	29	12.6	C	N.R.	14 patients had comorbid disorders: 10 TS + ADHD, 1 TS + OCD, 3 TS + ADHD + OCD.	N.R.	Stroop	Stroop performance
Roessner et al. (2007)	66	37	11.4	C	61 M:5F	37 TS-only, 29 TS + ADHD. Data reported separately. OCD was excluded.	Medication naïve or medication free for at least 14 days before testing.	Stroop	Stroop performance
Roessner et al. (2008a)	20	15	12.5	C	20M	Pure.	Medication naïve.	Go/ NoGo	Go/NoGo commission errors & RT
Roessner et al. (2008b)	41	14	10.6	C	N.R.	22 TS, 19 TS + ADHD. Data reported separately. No mention of exclusion of OCD.	Patients using methylphenidate were free of medication for at least 48 h before testing. D2-blockers, SSRI and atomoxetine were continued.	Stroop	Stroop performance
Schuerholz et al. (1996)	65	27	10.1	C	56 M:9F	21 TS-only, 19 TS + ADHD, 25 TS ± ADHD (patients who don't	Medication free during the testing.	TOVA	CPT RT

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
						correspond to all criteria for ADHD diagnosis, but correspond to at least one criterion, and ADHD diagnosis is highly suspected). Data reported separately. No OCD among patients, but OCS were present.			
Schuerholz et al. (1998)	41	36	10.5	C	20 M:21F	18 TS & 23 TS + ADHD. Data reported separately. No mention of exclusion of OCD.	Medication free during the testing.	TOVA	CPT RT
Schultz et al. (1998)	50	23	10.8	C	35 M:15F	16 TS without ADHD & 34 TS + ADHD, Data reported separately. 6 patients also had comorbid OCD. In addition to OCD & ADHD, 27 patients had at least one other comorbid diagnosis, 15 had at least 2, 7 had at least 3, and 4 had 4 additional diagnoses.	Medication status available for 46 of 50 patients. 27 patients under medication: clonidine (n = 13), neuroleptic (n = 6), clomipramine (n = 2), desipramine (n = 3), neuroleptic & methylphenidate (n = 1), neuroleptic & clomipramine (n = 1), neuroleptic & clomipramine & benzotropine (n = 1).	CPT (standard & AX task)	CPT commission errors
Serrien et al. (2005)	9	9	28.0	A	7 M:2F	2 patients had comorbid disorders: 1 TS + ADHD, 1 TS + ADHD + OCD.	Unmedicated TS patients.	Go/ NoGo	Go/NoGo RT
Shephard et al. (2016)	34	20	12.8	C	29 M:5F	17 TS-only & 17 TS + ADHD. Data reported separately. Comorbidity among groups: TS-only: OCB (n = 4), depression (n = 3), anorexia (n = 1), TS + ADHD: OCD (n = 2), ODD (n = 5), generalized anxiety (n = 2), social phobia (n = 2), specific phobia (n = 2), separation anxiety (n = 2), dyslexia (n = 1).	6 TS-only patients were under medication: clonidine (n = 2), aripiprazole (n = 2), fluoxetine (n = 1), and citalopram (n = 1). 6 TS + ADHD were under medication: clonidine (n = 1), methylphenidate (n = 2), aripiprazole (n = 2), and fluoxetine (n = 1). Methylphenidate was stopped 24 h before testing, all other medications were continued.	Go/ NoGo	Go/NoGo commission errors & RT

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experimental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
Sherman et al. (1998)	35	18	10.8	C	N.R.	21 TS-only & 14 TS + ADHD. Data reported separately. None of the patients in this study had obsessive-compulsive symptoms that were severe enough to warrant a diagnosis of OCD.	5 patients were under medication: 2 TS-only & 3 TS + ADHD. TS-only: haloperidol (n = 1), imipramine (n = 1). TS + ADHD: haloperidol (n = 1), clonidine (n = 1), thioridazine (n = 1). 2 other TS + ADHD patients took methyphenidate, which was deposed 24 h before testing.	CPT	CPT commission errors & RT
Shin et al. (2001)	35	22	9.5	C	35M	16 TS & 19 TS + ADHD. Data reported separately. Patients had no other psychiatric disorder than TS or ADHD, but there is no explicit mention that OCD is excluded.	Patients were either unmedicated or had been free of medication for at least 4 weeks before testing.	CPT (signal detection)	CPT commission errors & RT
Shucard et al. (1997)	22	22	11.6	C	22M	ADHD & OCD were not excluded.	10 patients were under medication: clonidine (n = 4), imipramine (n = 2), pimozide (n = 2), methylphenidate (n = 1), fluoxetine (n = 1).	CPT (AX task)	CPT commission errors & RT
Silverstein et al. (1995)	17	17	32.0	A	9 M:8F	11 TS-only & 6 TS + ADHD. Data were reported separately. 12 patients also had comorbid OCD.	10 patients were under medication: antidepressants (n = 4), clonidine (n = 2), combination of neuroleptic and either antidepressant or clonidine (n = 4).	Stroop	Stroop performance
Sukhodolsky et al. (2010)	101	71	11.1	C	86 M:15F	56 TS without ADHD & 45 TS + ADHD. Data were reported separately. Comorbidity among TS-only: OCD (n = 18), ODD (n = 8), depression (n = 9), anxiety (n = 11). Comorbidity among TS + ADHD: OCD (n = 16), ODD (n = 14), depression (n = 11), anxiety (n = 5).	35 TS-only & 32 TS + ADHD patients: stimulants (n = 49), alpha-2 agonists (N = 45), SSRI (n = 32), antipsychotics (n = 32), anxiolytics (n = 5), mood stabilizers (n = 4), and tricyclic (n = 2) (47 patients were taking more than one type of medication). Patients taking stimulants were asked to skip their medication the morning before testing. The number of children receiving more than one type of medication did not	CPT & S-troop	CPT commission errors & RT, Stroop performance

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Table 2 *(continued)*

Study	TS patients (n)	Healthy controls (n)	TS patients' characteristics					Experim-ental task	Task category/ outcome
			Age	Adults/ children	Sex ratio	Comorbidity	Medication		
							differ across patient groups.		
Thibault et al. (2009)	15	20	37.0	A	8 M:7F	Other Axis 1 diagnoses were excluded, but there is no explicit mention that ADHD or OCD is excluded.	Patients were unmedicated. 6 patients had been medicated in the past: SSRI (n = 1), benzodiazepine (n = 1), tretrabenazine (n = 1), haloperidol & tetrabenazine (n = 1), medication not specified (n = 2).	SRC & S-troop	SRC incompatible trials accuracy & RT, Stroop performance
Thomalla et al. (2014)	15	15	34.0	A	13 M:2F	Pure.	Patients were either medication naïve or had stopped medication at least 3 weeks before testing.	Go/ NoGo	Go/NoGo commission errors & RT
Tulen et al. (1998)	9	9	25.8	A	7 M:2F	ADHD & OCD were not excluded.	Patients were medication free for at least 2 weeks before testing.	Stroop	Stroop performance
Verte et al. (2005)	24	47	10.0	C	20 M:4F	22 patients had comorbid disorders: 6 TS + ADHD, 8 TS + OCD, 8 TS + ADHD + OCD.	Patients were either medication free or discontinued their medication 20 h before testing.	Circle tracing & change task	Circle tracing latency, SSRT
Yamamuro et al. (2015)	10	10	9.2	C	10 M:0F	5 patients had comorbid ADHD. No patient had comorbid OCD.	3 patients were under medication: haloperidol (n = 2), risperidone (n = 1).	Stroop	Stroop performance

Note: ADHD: attention deficit hyperactivity disorder, CPT: continuous performance test, N.R.: not reported, OCB: obsessive-compulsive behaviors, OCD: obsessive-compulsive disorder, OCS: obsessive-compulsive symptoms, ODD: oppositional defiant disorder, RT: reaction time, SRC: stimulus-response compatibility, SNRI: selective norepinephrine reuptake inhibitors, SSRI: selective serotonin reuptake inhibitors, SSRT: stop-signal reaction time, TOVA: Test of Variables of Attention, TS: Tourette syndrome.

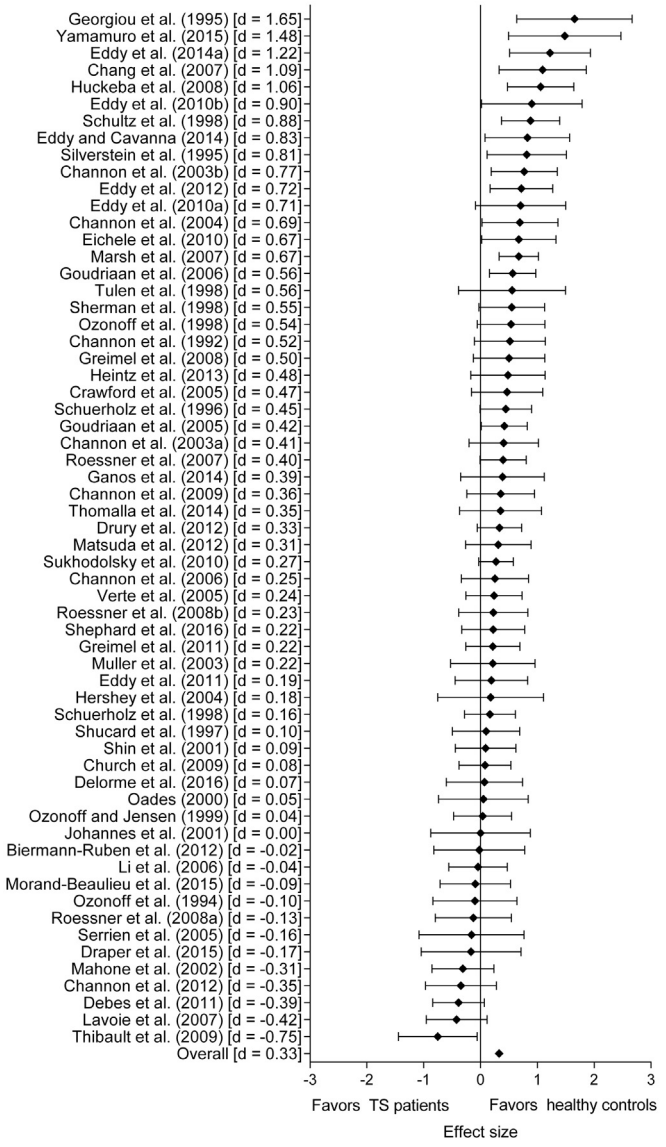

Fig. 2. Meta-analysis of inhibitory control in TS.
Globally, TS patients showed more inhibitory deficits than healthy controls. Diamond symbol represents the standard difference in means. Errors bars represent the 95% confidence interval.

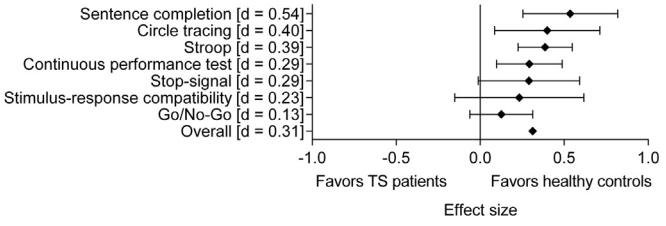

Fig. 3. Task-specific deficits.
TS patients had more inhibitory deficits in the following tasks: sentence completion, circle tracing, Stroop & CPT. There was a trend toward lower performance in the stop-signal task. TS patients' performance at the Go/Nogo and the incompatible portion of the SRC were unimpaired. Diamond symbol represents the standard difference in means. Errors bars represent the 95% confidence interval.

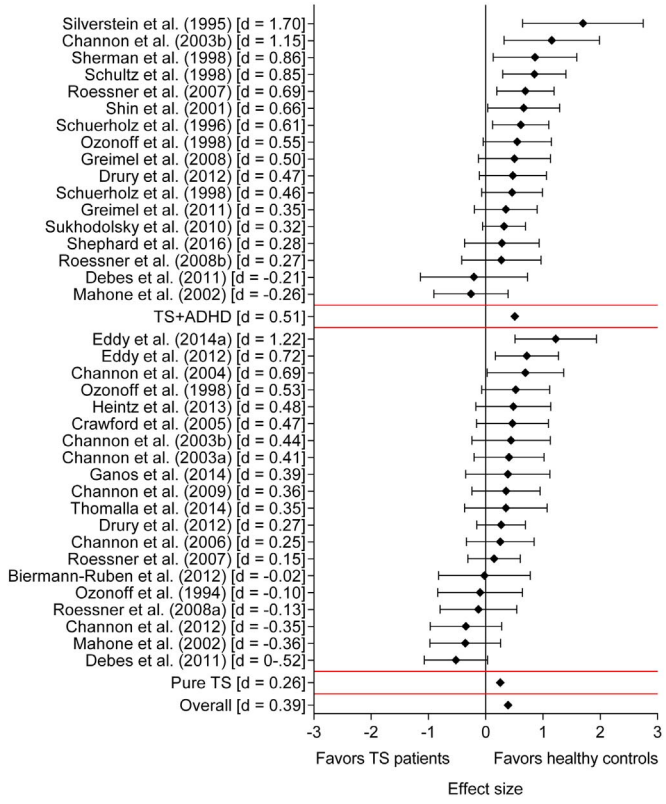

Fig. 4. Inhibition in pure TS and TS + ADHD patients.
Effects sizes show the differences in inhibitory control in pure TS and TS + ADHD patients when compared with healthy controls. Diamond symbol represents the standard difference in means. Errors bars represent the 95% confidence interval.

p = 0.51). The heterogeneity test between both comparisons was significant (Q = 12.72, p < 0.001), indicating more inhibitory deficits in studies that included medicated TS patients.

3.4.3. Comparison of verbal and motor responses

Taken as whole, motor (d = 0.23, Z = 4.04, p < 0.001) and verbal (d = 0.42, Z = 5.91, p < 0.001) responses were impaired, compared to healthy controls. However, inhibitory deficits were larger in tasks involving a verbal response than in those involving a motor response (Q = 4.14, p < 0.05).

3.4.4. Inhibitory deficits in children and adults

Inhibitory deficits were present in children (d = 0.30, Z = 4.20, p < 0.001) and adults (d = 0.35, Z = 4.07, p < 0.001). There was no difference between both subgroups (Q = 0.23, p = 0.63).

3.5. Moderators

Overall, the meta-regression between age and effect size in the total sample was not significant (p = 0.80). In studies including children, there was a trend toward a significant regression between effect size and age (β = −0.07, Z = −1.86, p = 0.06). In studies including adults, a similar trend toward a significant regression between effect size and age was also found (β = −0.04, Z = −1.89, p = 0.06).

Meta-regressions were also performed to assess the link between tic severity and inhibitory deficits. Among our sample, 32 studies reported YGTSS data: 21 reported the global score and 19 reported the total tic severity score (without the impairment scale). The meta-regression between YGTSS global score and effect size was not significant (p = 0.17), but there was a significant association between YGTSS total tic score and effect sizes (β = 0.07, Z = 3.60, p < 0.001).

Table 3
Demographic and clinical data of studies added to compare TS patients with and without comorbid ADHD.

Study	TS patients without comorbid ADHD (n)	TS + ADHD patients (n)	TS patients' characteristics					Experimental task	Task category/outcome
			Age	Adults/children	Sex ratio	Comorbidity	Medication		
Brand et al. (2002)	18	11	TS-only[a]: 11.7 TS + ADHD[a]: 10.1	C	TS-only[a]: 17 M:6F TS + ADHD[a]: 16 M:1F	Other comorbidities were not reported.	17 TS-only patients were under medication: neuroleptic (n = 10), clonidine (n = 5), neuroleptic & clonidine (n = 2)[a]. X TS + ADHD patients were under medication: neuroleptic (n = 4), clonidine (n = 3), neuroleptic & clonidine (n = 6)[a].	Stroop	Stroop performance
Harris et al. (1995)	10	32	TS-only: 11.6 TS + ADHD: 11.1	C	TS-only: 8 M:2F TS + ADHD: 30 M:2F	Other comorbidities were not reported.	Patients were not taking psychotropic or tic suppressing medication during testing.	TOVA	CPT RT & commission errors
Sallee et al. (1994)	44	22	Whole sample: 10.5	C	Whole sample: 60 M:6F	Other comorbidities were not reported.	Patients were allocated to 1 of 3 treatment condition: pimozide (TS without ADHD: n = 17, TS + ADHD: n = 7), haloperidol (TS without ADHD: n = 11, TS + ADHD: n = 6), unmedicated (TS without ADHD: n = 16, TS + ADHD: n = 9)	CPT	CPT RT & commission errors

Note: ADHD: attention deficit hyperactivity disorder, CPT: continuous performance test, RT: reaction time, TOVA: Test of Variables of Attention, TS: Tourette syndrome.
[a] Data was reported for a sample of 40 participants, but only 29 of them completed the Stroop task. Data specific to those 29 patients are not reported.

Fig. 5. The contribution of ADHD to inhibitory deficits in TS patients.
Effect sizes represent the difference in inhibitory control between TS patients with and without ADHD. Diamond symbol represents the standard difference in means. Errors bars represent the 95% confidence interval.

Finally, the meta-regression between effect size and the proportion of medicated patients within a study was not significant ($p = 0.90$). Meta-regressions between the effect size and the proportion of patients under neuroleptics ($p = 0.85$) or adrenergic agents ($p = 0.12$) were not significant either.

3.6. Supplementary analysis: a comparison of TS patients with and without ADHD

Among the 231 articles assessed for eligibility, 19 studies included subgroups of TS + ADHD and TS without ADHD patients, and were integrated in this supplementary analysis. Sixteen of these studies were included in the overall analysis. Three studies that were initially excluded because they lacked a healthy control comparison group were added for this analysis. In those three studies, ADHD status was established based on DSM criteria (n = 2) or the Diagnostic Interview Schedule for Children (n = 1). The characteristics of those three studies are shown in Table 3.

This analysis yielded a significant effect size, indicating more inhibitory deficits in TS + ADHD than in TS patients without ADHD ($d = 0.34$, $Z = 4.55$, $p < 0.001$) (Fig. 5).

4. Discussion

The main goal of the current meta-analysis was to assess the occurrence of inhibitory deficits in TS patients, through their performance in various neuropsychological tests involving inhibition of prepotent, automatic or ongoing responses. All in all, our results revealed a small to medium effect toward accrued inhibitory deficits in TS patients, in comparison with healthy controls. Another important goal was to address the contribution of comorbidity in the occurrence of inhibitory deficits of TS patients. While there were not enough studies with TS + OCD patients to provide a thorough assessment of the OCD symptoms' contribution to inhibitory deficits in TS patients, the role of ADHD was more clearly established. There was a medium effect when comparing TS + ADHD patients with healthy controls, and a small, yet significant, difference between pure TS patients and healthy controls. A direct comparison of TS patients with and without ADHD revealed a small effect in favor of TS + ADHD patients, which suggests that among TS patients, those with comorbid ADHD have more difficulty to inhibit their actions.

Overall, the results showed that inhibitory deficits were associated with tic severity, as assessed with the YGTSS total tic score. This indicates that patients with more severe tics are affected by more extensive impairments in inhibitory control. Interestingly, inhibitory

deficits were not associated with global TS severity. This might serve as an argument to provide the YGTSS total tic score separately from the global score, since the impairment subscale included in the global score is rather subjective (Eddy and Cavanna, 2014) and might be scored differently across clinicians.

4.1. Task-specific deficits

Largest effect sizes pointing toward inhibitory deficits in TS patients were found in tasks involving verbal responses (sentence completion & Stroop). While significant impairments were found in both motor and verbal responses, inhibitory deficits were larger in tasks involving a verbal response than those involving a motor response.

4.1.1. Verbal inhibition

We found significant impairments in verbal inhibition in TS patients, which are mainly reflected by poorer performance in sentence completion tasks. Patients took longer to respond and made more errors than healthy controls. Previous reviews already reported constant deficits at the Hayling test (Cavanna et al., 2009; Eddy et al., 2009). However, the analysis of 8 studies using sentence completion tasks allowed us to quantify this deficit in TS patients, which was the largest of all tasks included in our meta-analysis. These results also support the hypothesis that inhibitory deficits in TS are not strictly restricted to motor function, but also involve verbal inhibition. Of course, it is tempting to link this profile with coprolalia, the most noticeable verbal feature of TS, despite the fact that it only affects a very small percentage of patients (Freeman et al., 2009). Actually, a factor analysis of TS revealed that impulsivity, hyperactivity and aggressiveness, which could emerge from a lack of inhibition, were loaded on a different factor from coprolalia (Cavanna et al., 2011). While motor tics and those disinhibited behaviors were closely related, TS patients with coprolalia might suffer from a distinct form of TS. EO or IED might be more representative of verbal inhibition deficits in TS patients. Insults, coarse language and threats are common features of rage attacks that affect a significant part of TS patients (Budman et al., 2000). It is conceivable that the deficit in verbal inhibition impairs the patients' ability to refrain from expressing these things aloud, but this idea remains unclear.

4.1.2. Circle tracing task

After sentence completion tasks, the circle tracing task yielded the second-largest effect in TS patients. Only two studies used this task with TS groups, thus making it hard to draw a clear picture of TS patients' tracing performance. Poor circle tracing performance has also been linked with ODD (Avila et al., 2004) and ADHD (Scheres et al., 2004). These two conditions are often found in TS patients. Out of the 70 patients tested in the two studies using the circle tracing task, 16 patients (23%) had comorbid ADHD, but no ODD symptoms were reported. The presence of ADHD could have confounded the results. However, Goudriaan et al. (2006) reported a significant impairment in TS patients during the circle tracing task, and only two out of the 46 TS patients in their sample had comorbid ADHD. More studies are needed to generalize these results, but impaired circle tracing task performance might be a common feature in TS patients.

4.1.3. Stroop interference

The Stroop task revealed a similar effect size to what was obtained with the circle tracing task. It was the most frequently used (n = 25) among the bulk of neuropsychological tasks reported in our meta-analysis. Impairments in Stroop performance have been widely linked to impulsivity (Stahl et al., 2014). Indeed, in the interference condition of the Stroop task, the stimulus meaning and its color are incongruent, thus making it hard for impulsive individuals to perform effectively. Our results regarding the Stroop task could support the hypothesis that impulsivity in TS patients affects the control of interference from two alternative responses that compete. Accordingly, more interference at the Stroop task was also reported in other disorders that might have impulsive components, such as pathological gambling (Goudriaan et al., 2006; Kertzman et al., 2006), substance abuse disorder (Goudriaan et al., 2006; Verdejo-García et al., 2008) and ADHD (Lansbergen et al., 2007). Interestingly, Goudriaan et al. (2006) reported similar performance for TS patients, pathological gamblers and drug addicts, who were all outperformed by healthy controls at the Stroop interference. This suggests a potential common endophenotype for these groups.

4.1.4. Continuous performance test

The 13 studies using the CPT revealed a significant effect indicating inhibitory deficits in TS patients. Effect sizes in the CPT were significant for both RT and commission errors. CPT omission errors are traditionally associated with inattention, while commission errors are associated with impulsivity (Riccio et al., 2002). However, some authors argue that there are different subtypes of commission errors. Commission errors made with fast RTs are more specific to impulsivity, while commission errors with delayed RT are characteristic of inattention (Halperin et al., 1988). Also, with the AX CPT paradigm, a variant of that task, more types of commission errors can occur. Participants might respond to a random letter following the letter A, the letter X that was not preceded by the letter A, the letter A without another letter being presented before, or to any letter that is not an A or an X (Halperin et al., 1991). In this case, responding to a random letter following the letter A is the most common commission error, and is also closely associated with impulsivity (Halperin et al., 1988). Responding to the letter X that is not preceded by the letter A would represent inattention, while a certain proportion of response directly given to the letter A would be linked to impulsivity (Halperin et al., 1991). Most of the studies reported in the current meta-analysis did not necessarily use the CPT to directly assess inhibitory control in TS patients. Therefore, error subtypes and RT associated with commission errors were not systematically mentioned. Consequently, the current meta-analysis selected all CPT commission errors as a whole. More commission errors have been reported in various disorders characterized by impulsivity, such as disruptive behavior disorders (Dougherty et al., 2003), ADHD (Losier et al., 1996; Miranda et al., 2012) or substance abuse disorders (Moeller et al., 2005; Swann et al., 2004). The higher proportion of commission errors in TS patients could therefore be a marker of impulsivity.

4.1.5. Stop-signal task

Our analysis reported a trend toward an impairment in TS patients during stop-signal tasks, with a small to medium effect size. This task differs from most paradigms reported in this meta-analysis, since it requires to stop a response that is already initiated, while other paradigms mostly require to inhibit the initiation of an action. Therefore, inhibition deficits in TS patients might be present at stimulus presentation and during an ongoing response. Delayed SSRT has been linked with impulsive behavior and poor response inhibition capabilities (Castro-Meneses et al., 2015; Logan et al., 1997; Oosterlaan et al., 1998). Longer SSRT were also reported in hyperactive boys (Rubia et al., 1998). Among studies included in our meta-analysis, there were only five using the stop-signal task, and none of them made comparisons between TS and TS + ADHD patients. Of the 124 patients tested in those five studies, 27 (22%) of them had comorbid ADHD, which could have been a confounding factor.

4.1.6. SRC paradigms

In the SRC paradigm, the incompatible condition provides a context where irrelevant stimulus information can elicit a response that interferes with goal-directed action (van den Wildenberg et al., 2010). Thus, incorrect responses to incompatible stimuli in SRC

paradigms, such as the Simon or Eriksen flanker tasks, represent some form of deficits in inhibitory control. However, no significant differences were found between TS patients and healthy controls, neither for RTs nor for accuracy. Stahl et al. (2014) suggested that that Stroop and the SRC tasks involve different type of response-related interference. They argued that while the interference in response to the Stroop task is caused by the involuntary activation of a prepotent response, it is the consequence of the simultaneous activation of two candidate responses in SRC paradigms. This difference could explain why TS patients maintain normal performances in SRC paradigms, but showed impaired interference control during the Stroop task.

4.1.7. Go/No-Go task

Our results revealed a non-significant effect in the Go/No-Go task, which was the smallest of all effect sizes reported in the current meta-analysis. Intuitively, one might think that patients who have trouble inhibiting chronic motor tics would be challenged with motor inhibition tasks. However, some TS patients might use an adaptive mechanism, such as a speed-accuracy trade-off strategy, to maintain an effective inhibitory performance accuracy (Eichele et al., 2010; Shephard et al., 2016). This could reflect a compensatory tic control mechanism, since delayed RT might reflect increased regulation over motor output to facilitate tic control. For instance, Roessner et al. (2008a) found normal inhibitory performance in TS patients, and suggested that normal neuropsychological performance could be paired with neurophysiological features induced by a compensatory mechanism. In the same vein, Thomalla et al. (2014) reported delayed RT and more omission errors, but normal inhibition of No-Go stimuli. This was accompanied by a decrease in sensorimotor activation, which would act as a compensatory reorganization in fronto-parietal networks in response to overactivation of cortico-striato-thalamo-cortical circuits. This mechanism could thus enable TS patients to maintain efficient inhibitory control, but would come at the cost of delayed RT and more attentional errors. Yet, our results only showed a trend toward delayed RT, with a small effect size (d = 0.15). At this point, we cannot rule out the possibility that TS patients use a speed-accuracy trade-off mechanism.

4.2. The role of comorbid disorders in the inhibitory deficits of TS patients

An important feature of the meta-analysis is the assessment of the impact of comorbid disorders on inhibitory control in TS. As mentioned earlier, comorbidity is frequent in TS. Epidemiological data suggest that around 30% of patients have either ADHD or OCD (Scharf et al., 2012), while clinical studies report comorbidity rates up to 90% (Cavanna et al., 2011; Freeman, 2007; Freeman et al., 2000; Ganos and Martino, 2015). The literature on inhibitory control in TS is quite sparse, and this discrepancy could rely on comorbid disorders associated with TS. Among the 61 studies included in the current meta-analysis, 41 did not exclude TS patients with comorbid disorders. Our analyses revealed a small effect size (d = 0.26), indicating slightly more inhibitory deficits in pure TS patients than in healthy controls. The analysis comparing TS + ADHD patients and healthy controls revealed a medium effect size (d = 0.51), suggesting a significant inhibitory control impairment in TS + ADHD patients. The heterogeneity test between these two effect sizes revealed that TS + ADHD patients have more inhibitory deficits than pure TS patients.

Correspondingly, experiments including subgroups of TS patients with and without ADHD allowed to make a direct comparison between these patients, which revealed a small to medium effect size (d = 0.34). This supplementary analysis suggests that TS patients with comorbid ADHD are more prone to show impaired inhibition than TS patients without comorbid ADHD.

Our results imply that various levels of impairment in inhibitory control might be present in all TS patients, even when no comorbidity is present. The occurrence of comorbid ADHD seems to potentiate this effect, making inhibition deficits more important. Unfortunately, the number of studies including a subgroup of TS patients with comorbid OCD was not sufficient for valid analysis. Future studies should provide data separately for patients with comorbid OCD. OCD is believed to play a role in impulsive and aggressive behaviors (such as EO), which might be harder to manage when deficits in inhibitory control are present (Budman et al., 2003). Therefore, our findings could rely on the fact that impulsive and aggressive behaviors are closely linked with comorbid disorders. For instance, a multi-site study with over 3500 TS patients revealed that anger problems and self-injurious behavior were four times superior in comorbid than in pure TS patients (Freeman et al., 2000). While ADHD was the single comorbidity that was the most associated with anger problems, patients with the combination of TS, ADHD and OCD had the greatest risk (40%) of having EO.

4.3. Impact of psychiatric medication on inhibitory measures

Prescription of psychiatric medication is quite frequent in TS patients. Indeed, only 28% of the studies included in our meta-analysis comprised a group of non-medicated TS patients. This can be a confounding factor when it comes to assessing inhibitory control in TS. In fact, in a group of TS + ADHD patients, pimozide has been shown to lower commission errors during CPT, while haloperidol increased the amount of commission errors (Sallee et al., 1994). In other psychiatric disorders, such as borderline (Ripoll, 2013) and antisocial (Walker et al., 2003) personality disorder, neuroleptics have been proved to be efficient in decreasing impulsive behaviors. Methylphenidate has been shown to improve Stroop performance, both in healthy controls and in ADHD patients (Langleben et al., 2006). ADHD patients showed better performance during the CPT after administration of stimulant medication (Riccio et al., 2001). However, in most studies where stimulants were administered, they were discontinued prior to testing. Therefore, this should not affect our results.

More interestingly, our analyses showed that inhibition deficits were larger in studies that included medicated TS patients than in those that excluded them. Indeed, in the latter studies, there were no differences between TS patients and heathy controls. This is consistent with a previous study that found better Stroop performance in non-medicated TS patients (Eddy et al., 2012). This might be explained by the fact that TS patients who were under psychiatric medication could have to deal with more severe symptoms than patients who did not take any medication. Also, comorbidity plays an important role in inhibition deficits. For example, as our results show, TS + ADHD patients showed larger deficits than pure TS patients. Consequently, they are more likely to need medication to manage their symptoms. Furthermore, inhibition was not correlated to the proportion of patients under neuroleptics or adrenergic agents. Based on our results, psychiatric medication prescribed for tic symptoms does not seem efficient to improve inhibitory control. However, it is hard to draw conclusions from these results, since the proportion of medicated patients varied between studies. Future studies should target this aspect and compare medicated and non-medicated patients. In our sample, only one study made such comparison (Delorme et al., 2016). This study did not report a significant difference in Go/No-Go commission errors, which might be due to its relatively small sample size (n = 17). Also, apart from medication status, patients included in this study were otherwise very similar. This might explain the difference with our findings, since patients included in studies that did not control medication intake might have differed (more comorbidities, higher tic severity, etc.) from patients in studies that did make such control.

4.4. Inhibitory control and neurological correlates in TS

Many studies aimed at understanding how some TS patients can effectively manage their responses in tasks involving inhibitory control, and how this control could apply to tic management. Inhibitory control

over motor output seems to come with adaptive functional and structural changes in the prefrontal cortex (Jackson et al., 2011) and fronto-parietal networks, in response to overactivation of cortico-striato-thalamo-cortical circuits (Thomalla et al., 2014). Indeed, few electrophysiological studies reported a frontal shift of the electro-cortical activity related to the inhibition of No-Go stimuli in TS patients, in presence of a relatively intact inhibitory performance (Johannes et al., 2001; Morand-Beaulieu et al., 2015; Serrien et al., 2005; Thibault et al., 2009). Likewise, Marsh et al. (2007) reported that TS patients who strived the most during a Stroop task showed an important activation of prefrontal regions. This, per the authors, attests a mechanism used by TS patients to maintain their performance by engaging more attentional resources provided by the dorsolateral prefrontal cortex. Also, larger movement evoked fields in presence of normal Go/No-Go performance, were found in TS patients (Biermann-Ruben et al., 2012). This was attributed to enhanced sensory feedback, which might help TS patients in voluntary movement and tic control. Finally, fractional anisotropy of some prefrontal cortex tracts has been negatively correlated with behavioral task performance and negatively with motor tic severity (Jackson et al., 2011). This suggests that adaptive changes in prefrontal white matter microstructure could occur to provide better control over motor output. Such adaptive mechanism could partly explain some of the negative findings among studies included in the current meta-analysis (e.g.: Biermann-Ruben et al., 2012; Draper et al., 2015; Morand-Beaulieu et al., 2015; Serrien et al., 2005).

However, this view of the prefrontal cortex as the source of inhibitory control (for task performance and tic suppression) is challenged by Jung et al. (2013) who argue that overactivation of frontal cortex in TS patients might contribute to hyperexcitability of the motor cortex, and could therefore lead to the occurrence of tics, and poor tic control. Per that hypothesis, the proposed compensatory or adaptive mechanism for accrued inhibitory control would be more related to distribute local changes in cortical excitability.

So, even though our results showed inhibitory deficits in TS patients, it seems that some factors allow a performance that is close to what is found in healthy controls. Our data indicates that inhibitory control seems to improve as patients, both children and adults, get older. This could suggest that maturation of the frontal cortex helps to boost inhibitory control in these patients. However, most studies included exclusively children or adults, and there was almost no data available regarding the 15–25 year old range. This gap hinders our interpretations toward the developmental curve of inhibitory control with adolescents and young adults, who experience important stages of brain maturation (Johnson et al., 2009; Sowell et al., 1999).

4.5. Limitations

The current meta-analysis has some limitations. We did not have access to individual patient data, which made it impossible to compare the inhibitory performance of medicated and non-medicated patients. Also, YGTSS motor and vocal tics scores were not systematically reported in every study, which limited our analyses toward the impact of motor or vocal tics on motor of verbal task performance. It would be interesting, for example, to see how vocal tics could impact a patient's performance during the Stroop task. We encourage future studies to provide such scores when available. Another limitation is that the only comorbid disorder we could study was ADHD, given the important number of studies including a sample of TS + ADHD patients. Future studies should provide data on inhibitory control for TS + OCD patients, but also for TS patients with comorbid impulse control disorders, as it would help to better address the case of inhibitory control and impulsivity in TS.

5. Conclusion

The current findings have shown that inhibitory control deficits are present in TS patients, even in the absence of any comorbid disorder. Yet, the presence of comorbid ADHD has an increasing effect on these deficits. The effect size of inhibitory deficits in TS + ADHD patients was double of what was found in non-comorbid TS patients. Therefore, since they cause important inhibitory deficits, ADHD symptoms should systematically be addressed when dealing with TS in research and clinical settings. Recent developments in cognitive-behavioral therapies for tics revealed that certain tics respond better to treatment (McGuire et al., 2015), which opens the avenue for personalized treatment approach for patients with TS. In the same vein, the use of neurocognitive profiles in cognitive-behavioral treatment of TS could be useful. For instance, even though tic severity and/or impulsivity can be reduced in TS patients even when ADHD is not controlled (Leclerc et al., 2010; Leclerc et al., 2016; McGuire et al., 2014; O'Connor et al., 2016; Wile and Pringsheim, 2013), it seems plausible to propose that treatment response would increase with an approach that is tailored to a patient's neurocognitive profile. Therefore, one could offer ADHD treatment, cognitive remediation or biofeedback sessions targeted at inhibitory control prior to therapy. And since it was shown that cognitive-behavioral therapy improves certain neurocognitive functions (Lavoie et al., 2011; Morand-Beaulieu et al., 2016; Morand-Beaulieu et al., 2015), it might as well work bi-directionally, where a better understanding of neurocognitive functions could allow a better treatment response.

Finally, future research should also aim toward an ecological validation of these results, through systematic and quantitative analyses of disruptive and impulsive behaviors that might emerge from the inhibitory deficits of TS patients.

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