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# Neurocognitive correlates of treatment response in children with Tourette's Disorder

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## Abstract

This paper examined neurocognitive functioning and its relationship to behavior treatment response among youth with [Tourette's Disorder](#) (TD) in a large [randomized controlled trial](#). Participants diagnosed with TD completed a brief neurocognitive battery assessing inhibitory functions, [working memory](#), and habit learning pre- and post-treatment with [behavior therapy](#) (CBIT, Comprehensive [Behavioral Intervention](#) for Tics) or [psychoeducation](#) plus supportive therapy (PST). At baseline, youth with tics and [Attention Deficit Hyperactivity Disorder](#) (ADHD) exhibited some evidence of impaired working memory and simple motor inhibition relative to youth with tics without [ADHD](#). Additionally, a small negative association was found between [antipsychotic medications](#) and youth's performance speed. Across treatment groups, greater baseline working memory and aspects of inhibitory functioning were associated with a positive treatment response; no between-group differences in neurocognitive functioning at post-treatment were identified. Within the behavior therapy group, pre-treatment neurocognitive status did not predict outcome, nor was behavior therapy associated significant change in neurocognitive functioning post-treatment. Findings suggest that co-occurring ADHD is associated with some impairments in neurocognitive functioning in youth with Tourette's Disorder. While neurocognitive predictors of behavior therapy were not found, participants who received behavior therapy exhibited significantly reduced tic severity without diminished cognitive functioning.

## Keywords

Neurocognition, Behavior therapy, Youth, Tourette, ADHD, Comorbidity

## 1. Introduction

[Tourette's Disorder](#) and Persistent [Tic Disorders](#) are [neurodevelopmental disorders](#) characterized by involuntary motor movements and/or vocalizations ([American Psychiatric Association, 2013](#)). These disorders (henceforth collectively referred to as Tourette's Disorder) develop in childhood and affect approximately 0.4–1.6% of youth ([Knight et al., 2012](#), [Scahill et al., 2014](#)). In addition to tics, youth with Tourette's Disorder commonly experience co-occurring

psychiatric conditions [e.g., [attention deficit hyperactivity disorder](#) (ADHD), [obsessive-compulsive disorder](#) (OCD), and anxiety disorders] ([Freeman et al., 2000](#), [Specht et al., 2011](#)), functional impairment ([Storch et al., 2007a](#)), and reduced quality of life ([Storch et al., 2007b](#), [Conelea et al., 2011](#)). Thus, efficient and effective treatments are important for youth with Tourette's Disorder. Traditionally, pharmacotherapy has been used to manage tic severity with [antipsychotic](#) and [alpha-2 agonist](#) medications yielding moderate reductions in tic severity ([Weisman et al., 2012](#)), although these medications are typically accompanied by adverse side effects and only partial response ([Scahill et al., 2006](#)). Meanwhile, behavioral interventions such as habit reversal training (HRT) and the Comprehensive [Behavioral Intervention](#) for Tics (CBIT) ([Woods et al., 2008](#)) have demonstrated moderate-to-large reductions in tic severity with no significant adverse effects or concerns of symptom substitution ([Piacentini et al., 2010](#), [McGuire et al., 2014](#), [Peterson et al., 2016](#)). Despite the proven efficacy of behavior treatments for tics, the neural mechanisms underlying their response remain largely unexamined and the limited neurocognitive research to date has produced mixed findings among youth with Tourette's Disorder.

Although the literature as a whole is inconsistent, dysfunction in inhibitory functioning, [working memory](#), and habit/procedural learning has been found across multiple studies of Tourette's Disorder. For instance, several studies have found that youth with Tourette's Disorder have significantly worse inhibitory functioning relative to unaffected controls across multiple tasks (e.g., Go/No-Go task, Stop-Signal task, [flanker task](#), visuospatial priming task, Stroop task) ([Swerdlow et al., 1996](#), [Casey et al., 2002](#), [Crawford et al., 2005](#)). Meanwhile, other studies have found no significant difference in inhibitory functioning between youth with tic disorders and unaffected controls ([Johannes et al., 2001](#), [Goudriaan et al., 2006](#), [Ray et al., 2006](#), [Roessner et al., 2007](#)). Similarly, when working memory has been studied as part of [executive functions](#) in Tourette's Disorder, findings are equivocal with some investigations reporting no significant differences in working memory relative to unaffected controls ([Channon et al., 2003](#), [Crawford et al., 2005](#)) and others suggesting some indication of poorer performance ([Chang et al., 2007](#)). With regard to habit or procedural learning, [Marsh et al. \(2007\)](#) found impairments in habit learning on the Weather Prediction Task (WPT) between youth with Tourette's Disorder and age-match unaffected controls, with the magnitude of impairment associated with tic symptom severity. Although findings are inconsistent and contradictory likely due to differing tasks and small sample sizes, some evidence suggests the possibility of deficits in inhibitory functions, working memory, and habit learning among youth with Tourette's Disorder.

Given the sustained attention demand required of most neurocognitive tasks, co-occurring [ADHD](#) may further complicate these results. For instance, co-occurring ADHD among youth with Tourette's Disorder has been associated with greater neurocognitive dysfunction and worse overall psychosocial functioning ([Chang et al., 2007](#), [Roessner et al., 2007](#), [Greimel et al., 2011](#)). Indeed, in the largest neurocognitive study of youth with Tourette's Disorder to date, [Sukhodolsky et al. \(2010\)](#) found that youth with tics + ADHD had deficits of sustained attention whereas the tics-ADHD group more closely resembled unaffected control participants. This finding is consistent with other studies indicating executive function-related inhibitory learning dysfunction among participants with tics+ADHD compared to tics-ADHD ([Ozonoff et al., 1998](#), [Channon et al., 2003](#)). Taken together, these studies suggest that youth with Tourette's

Disorder may have deficits in inhibitory functions, working memory, and habit learning that may be greater in the presence of co-occurring ADHD.

Aside from being implicated in the [pathophysiology](#) of Tourette's Disorder, inhibitory functioning, working memory, and habit learning may influence therapeutic outcomes for youth with Tourette's Disorder receiving [behavior therapy](#). For instance, youth with Tourette's who have greater dysfunction in inhibitory functions may have greater tic severity and/or greater difficulty engaging in tic suppression tasks. Meanwhile, youth with deficits in working memory may have greater difficulty retaining and/or recalling information presented in treatment sessions. Similarly, youth with habit learning deficits may experience greater difficulty implementing competing responses – a key feature of behavioral intervention.

Presently, only a handful of studies, all including adult participants, have directly explored the interplay between neurocognitive factors and behavior therapy. First, [Deckersbach et al. \(2006\)](#) examined predictors of response to behavioral interventions in 30 adults with Tourette's Disorder and found that greater baseline inhibitory functioning on a visuospatial priming task was associated greater treatment response. Second, a [meta-analysis](#) found greater ADHD co-occurrence was associated with attenuated treatment response to behavior therapy ([McGuire et al., 2014](#)), but other reports have not supported this findings ([Sukhodolsky et al., 2017](#)). Third, [O'Connor et al. \(2008\)](#) examined changes in neurocognitive functioning before and after a [cognitive-behavioral treatment](#) in 55 adults with Tourette's Disorder. Interestingly, [O'Connor et al. \(2008\)](#) found some evidence of improvement in executive functions and skilled motor performance after treatment. In contrast, a large trial of adults with Tourette's Disorder found that change in tic symptom severity and treatment response were not associated with neurocognitive performance on tests of inhibitory control, intellectual ability, or [motor function](#) for either the behavior therapy or supportive therapy conditions ([Abramovitch et al., 2017](#)). While no direct evaluation of the interplay between neurocognitive functioning and behavioral interventions exists among youth with Tourette's Disorder, there is some suggestion from a couple of small child studies that attention problems are associated with greater difficulty in tic suppression among youth with persistent tics ([Peterson et al., 1998](#), [Himle and Woods, 2005](#)).

Given the small sample sizes, inconsistent findings, and role of co-occurring ADHD found among previous neurocognitive investigations, further research is needed to clarify the possible impact of co-occurring ADHD in neurocognitive performance among youth with Tourette's Disorder. Moreover, it is important to understand neurocognitive functioning as both a predictor of treatment response and treatment outcome among youth with persistent tics. Such investigations may also clarify whether neurocognitive functioning in Tourette's Disorder may be malleable and responsive to intervention. Aside from advancing the etiological understanding of Tourette's Disorder among youth, findings may also be important for elucidating potential neural mechanisms of treatment response, identifying adjunct neurocognitive interventions, and optimizing treatment recommendations for individual patients based on neurocognitive predictors.

This study examined neurocognitive functioning in 126 youth with Tourette's Disorder at baseline and posttreatment in a [randomized controlled trial](#) of behavior therapy and a comparison condition ([Piacentini et al., 2010](#)). First, we examined whether youth with

Tics+ADHD differed in neurocognitive functioning relative to youth with Tics-ADHD at the baseline assessment. Based on the phenomenological and neurocognitive distinctions identified in smaller studies, we hypothesized that youth with Tics + ADHD would perform more poorly on tasks of inhibitory functions, working memory, and habit learning. We also examined the association between neurocognitive functioning and tic and ADHD symptom severity, and presence of antipsychotic medication at baseline. Second, we examined whether baseline inhibitory functioning, working memory, and habit learning predicted treatment response at mid- and post-treatment for youth receiving behavior therapy. Based on the findings by [Deckersbach et al. \(2006\)](#), we hypothesized that baseline inhibitory functioning would predict treatment response to behavior therapy. Third, we explored whether neurocognitive performance on tasks of inhibitory functions, working memory, and habit learning improved after treatment for youth receiving behavior therapy.

## 2. Methods

### 2.1. Participants

Participants were part of the Comprehensive [Behavioral Intervention](#) for Tics Study, a multi-site [randomized controlled trial](#) that compared the efficacy of a behavior intervention (Comprehensive Behavioral Intervention for Tics, CBIT) versus an active comparison treatment condition (Psychoeducation plus Supportive Therapy, PST) for the treatment of youth with [Tourette's Disorder](#). The background, rationale and procedures for the parent trial have been described in detail elsewhere ([Piacentini et al., 2010](#)).

Eligible participants were required to have a primary diagnosis of Tourette's Disorder or Persistent Motor Tics of moderate to greater severity, as measured by a Yale Global Tic Severity Scale Total Tic Score greater than 13 (> 9 for children with chronic motor or vocal tics only), English fluency, and IQ greater than 80. Co-occurring psychiatric conditions were allowed unless the disorder required immediate treatment or change in current treatment. Children receiving [psychotropic medications](#) for tics or other permissible psychiatric conditions were eligible if the dose was stable for 6 weeks prior to enrollment, with no planned changes during study participation. Exclusion criteria included an unstable medical condition, current diagnosis of substance abuse/dependence, lifetime diagnosis of [pervasive developmental disorder](#), mania or [psychosis](#), or four or more previous sessions of [behavior therapy](#) for tics.

Participants ( $N = 126$ ) ranged in age from 9 through 17 years (mean age = 11.7 years,  $SD = 2.3$  years); 99 (78.6%) were boys, 106 (84.1%) were white, and 93.7% (118) met criteria for Tourette's Disorder. Overall, 36.5% of youth who entered the trial were receiving stable tic medication, with 17% being on an [antipsychotic medication](#). There were no significant between-group differences in any baseline demographic or clinical characteristics, including IQ, tic medication status, [comorbidity](#) profile, and baseline tic severity ([Piacentini et al., 2010](#)). Sample sizes for each specific task are reported in [Table 1](#).

Table 1. Sample characteristics and comparisons with co-occurring [ADHD](#) in youth with [Tourette's Disorder](#).



	Total sample		Tics + ADHD		Tics-ADHD				
	<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>	<i>t</i>	<i>p-value</i>	<i>d</i>
<b>INHIBITORY FUNCTIONING</b>									
<b>Stroop Color-Word Test</b>									
Word Trial (T score)	125	47.22 (8.89)	32	47.28 (7.64)	93	47.19 (9.33)	- 0.05	0.96	0.01
Color Trial (T score)	124	45.45 (8.82)	32	44.22 (11.55)	92	45.88 (7.68)	0.92	0.36	0.19
Color-Word Trial (T score)	124	49.96 (9.57)	32	47.16 (11.90)	92	50.93 (8.47)	1.95	0.05	0.40
Interference (T score)	124	51.02 (7.71)	32	49.03 (6.97)	92	51.72 (7.87)	1.71	0.09	0.35
<b>Stop-signal Task</b>									
% Accuracy Go	99	89.16 (12.10)	24	84.85 (12.37)	75	90.54 (11.76)	2.04	0.04	0.48
% Accuracy Stop	98	52.29 (9.40)	25	47.54 (8.86)	73	53.92 (9.07)	3.05	0.003*	0.71
Go Reaction Time (ms)	101	738 (114)	25	691 (123)	76	753 (108)	2.43	0.02	0.55
Stop-signal Reaction Time (ms)	93	244 (62)	22	227 (84)	71	250 (52)	1.51	0.14	0.38
<b>Change-signal Task</b>									
% Accuracy Go	98	83.28 (13.76)	24	77.40 (14.90)	74	85.19 (12.90)	2.48	0.02	0.58
% Accuracy Stop	92	46.69 (11.50)	22	43.49 (11.27)	70	47.70 (11.46)	1.51	0.14	0.37
Go Reaction Time (ms)	100	750 (132)	25	753 (120)	75	749 (137)	- 0.16	0.87	0.03
Inhibit Delay	99	409 (151)	24	377 (158)	75	419 (148)	1.21	0.23	0.28
Change-Signal Reaction Time	87	292 (85)	22	289 (102)	65	294 (80)	0.22	0.83	0.06
<b>WORKING MEMORY</b>									
ACT Total Score	125	42.88 (7.58)	32	39.84 (8.21)	93	43.92 (7.10)	2.69	0.008*	0.55
<b>HABIT/PROCEDURAL LEARNING</b>									
Learning Coefficient (accuracy across blocks)	89	0.03 (0.13)	20	< - 0.01 (0.13)	69	0.03 (0.12)	1.11	0.27	0.16
Reaction Time Coefficient (speed across blocks)	89	- 85 (194)	20	- 159 (155)	69	- 63 (200)	1.97	0.05	0.50
<b>FULL SCALE IQ</b>									
WASI FSIQ	126	110.10 (13.84)	33	106.09 (15.21)	93	111.52 (13.11)	1.96	0.05	0.40

**Note:** Tourette Disorder includes Persistent [Tic Disorders](#); ADHD = [Attention Deficit Hyperactivity Disorder](#); ACT = Auditory Consonant Trigrams; [WASI](#) = Wechsler Abbreviated Scale of Intelligence.  
 \*Indicates statistical significance, which was set at  $p < 0.003$  for these comparisons due to Bonferroni correction.



## 2.2. Measures

### 2.2.1. Symptom assessments

#### 2.2.1.1. Anxiety Disorders Interview Schedule: Child and Parent Versions (ADIS–IV–C/P; [Silverman and Albano, 1996](#))

The ADIS–IV–C/P is a semi-structured psychiatric diagnostic interview administered separately to parent and child, which was modified to include a [tic disorders](#) diagnosis module. A clinical severity rating (CSR) of 4 or higher on a scale of 0–8 was considered indicative of a clinically significant disorder. The instrument has demonstrated sound [psychometric](#) properties in previous studies ([Silverman et al., 2001](#), [Wood et al., 2002](#)).

#### 2.2.1.2. Yale Global Tic Severity Scale (YGTSS; [Leckman et al., 1989](#))

The YGTSS is a clinician-rated scale used to assess tic severity. Motor and phonic tics are rated separately from 0 to 5 on several scales including number, frequency, intensity, complexity, and interference with the combined Total Tic Score ranging from 0 to 50. The YGTSS possesses excellent psychometric properties with good internal consistency, excellent inter-rater reliability, and excellent convergent and divergent validity ([Leckman et al., 1989](#), [Storch et al., 2005](#)). The change in the YGTSS Total Tic Score from baseline to mid-treatment and from baseline to post-treatment served as a measure of treatment outcome.

#### 2.2.1.3. Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS; [DuPaul et al., 1998](#))

The ADHD-RS is an 18-item scale derived from [ADHD](#) diagnostic criteria in the [Diagnostic and Statistical Manual of Mental Disorders](#) (4th edition). Each item is rated on a 4-point scale (0 = not present; 3 = severe). The ADHD-RS produces 3 scores: Inattentive score (9 items), Hyperactive score (9 items), and Total Score (18 items). The ADHD-RS Total Score has been shown to be sensitive to medication effects in children with Tourette's Disorder ([Scahill et al., 2001](#)).

#### 2.2.1.4. Clinical Global Impression-Improvement Scale (CGI-I; [Guy, 1976](#))

The CGI-I provides a global rating of clinical improvement from baseline with scores ranging from 1 (*very much improved*) to 7 (*very much worse*). The CGI-I is well validated in treatment studies of youth with PTD ([Storch et al., 2011](#), [Jeon et al., 2013](#)). Consistent with prior studies, a CGI-I rating of 1 (*very much improved*) or 2 (*much improved*) is considered to indicate a positive treatment response.

### 2.2.2. Neurocognitive assessments

#### 2.2.2.1. The Stroop Color Word Test ([Golden, 1978](#))

The Stroop Color Word Test is designed to assess cognitive inhibitory functions. The task consists of 3 consecutive trials: a word trial, a color trial, and a color-word trial. The number of words identified correctly in each trial generates the trial score. The interference score was calculated from the color-word trial and reflected the inhibition of a pre-potent response after accounting for baseline processing speed.

#### 2.2.2.2. The Stop-Signal Task (SST; [Logan, 1994](#); [Logan et al., 1997](#))

The SST is a computerized go/no-go paradigm that is used to assess aspects of inhibitory control. The SST produces two different types of inhibition related outcomes. First, simple motor inhibition is assessed and consists of go trials (e.g., press “1” when “X” appears or “2” when “O” appears), and stop trials (e.g., when “X” or “O” appears followed by a change to a red background, the stop signal, withhold previously learned response). The stop-signal reaction time or speed of inhibition was the outcome variable of interest. Second, the *stop-change condition* is a variation of a stop-signal task that assesses motor response flexibility. In this task, change trials are substituted for stop trials such that when the change signal (e.g., background changes to blue) is given, the subject is asked to perform an alternate response (e.g., instead of pressing “1” at signal, press “3”) instead of simply withholding the previously learned response as in the stop task. The change signal reaction time or the speed of inhibition plus execution of an alternate response serves as the primary task-dependent variable.

#### 2.2.2.3. Auditory Consonant Trigrams (ACT-child version; [Stuss et al., 1987](#); [Paniak et al., 1997](#))

The ACT evaluates verbal [working memory](#) and divided attention. Participants are verbally presented with a consonant trigram (e.g., BXY) and then given an interference task (counting backwards from a given number) to prevent explicit rehearsal. After varying time intervals (3, 9, and 18 s), participants are asked to recall the trigram. Total number of correct consonants retrieved correctly was used as the dependent variable. Average total scores for normative children aged 9–15 range from 37.1 to 47.4 ([Strauss et al., 2006](#)).

#### 2.2.2.4. The Weather Prediction Task (WPT; [Knowlton et al., 1994](#))

The WPT is a measure of habit or procedural learning that requires gradual acquisition of stimulus-response associations. Participants are asked to predict rain or sunshine based on the presentation of a varying combination of a set of four different cards on a computer screen by pressing one of two letters on the keyboard. Each card is independently and probabilistically related to the outcomes, each of which occurs equally often. Participants receive positive or [negative feedback](#) after each prediction via visual feedback on the computer screen. The task consists of 90 trials lasting approximately 15 min. Accuracy (% correct) and reaction time scores across six learning blocks were used as the outcome variables. The task has been shown to distinguish healthy control patients from those with [striatal](#) dysfunction such as [Parkinson's disease](#) and Tourette's Disorder ([Knowlton et al., 1996](#), [March et al., 2004](#), [Marsh et al., 2005](#)). More recently, differing perspectives on the validity of a dual memory system approach (implicit vs explicit) have questioned whether WPT should be considered an [implicit learning](#) task ([Newell et al., 2007](#)). However, for the sake of continuity with the tic research using this task ([Marsh et al., 2004](#), [Marsh et al., 2005](#)), we refer to the WPT as a habit learning task with these caveats in mind.

#### 2.2.2.5. Wechsler Abbreviated Scale of Intelligence (WASI; [Wechsler, 1999](#))

The [WASI](#) is a nationally standardized measure of intelligence for youth and adults, which is an abbreviated reliable and valid version of the Wechsler Adult Intelligence Scale-3 edition

(WAIS-III). The full-scale intelligence quotient (FSIQ) was used to measure overall intelligence. Individuals with a score  $\geq 80$  were deemed eligible to participate.

### 2.3. Procedure

Recruitment occurred across three clinical research centers: Johns Hopkins School of Medicine (N = 41), the University of Wisconsin-Milwaukee (N = 40), and the University of California Los Angeles (N = 45). Research protocols were approved by the local Institutional Review Boards. All participants provided written [informed consent and assent](#) for parents and youth, respectively. Afterward, participants completed a screening assessment to evaluate inclusion and exclusion criteria that included the administration of the ADIS-IV-C/P and YGTSS. [Clinical assessments](#) were completed by treatment-blind independent evaluators (IEs) trained to reliability and were supervised using a structured protocol ([Piacentini et al., 2010](#)). Eligible and interested participants returned for a baseline assessment that included YGTSS, the ADHD-RS, and the neurocognitive assessment battery (Stroop, SST, ACT, and WPT). Participants were randomized to receive either behavior therapy (CBIT: Comprehensive Behavior Intervention for Tics) or the control condition (PST: [Psychoeducation](#) + Social Support) immediately afterward. The behavior therapy condition consisted of a manualized intervention with habit reversal training as its core component plus a parent-focused functional intervention designed to identify and modify antecedent and consequent variables associated with tic expression and maintenance ([Woods et al., 2008](#)). Both treatment conditions consisted of eight sessions delivered over the course of 10 weeks. Participants were re-administered the YGTSS, the neurocognitive battery and the CGI-I at post-treatment by independent evaluators blinded to treatment condition ([Piacentini et al., 2010](#)). Participants were compensated for participation in the assessment portion of the study, with treatment provided free of charge.

### 2.4. Reliability of neurocognitive assessment

Neurocognitive certification procedures were established to maintain protocol reliability. Senior study personnel (SC) reviewed the initial videotaped administration of the neurocognitive battery and scored assessment materials for each examiner at the three study sites. After the initial certification, examiners were recertified on an annual basis following the same procedures. Administration and scoring issues were resolved on cross-site study calls on an ongoing and as-needed basis.

### 2.5. Analytic plan

First, descriptive statistics characterized the clinical and neurocognitive performance of the sample, and Pearson correlations examined the relationship between neurocognitive scores at baseline. Next, an independent sample *t*-test compared the baseline neurocognitive performance across inhibitory functions, working memory, and habit learning between youth with and without co-occurring ADHD. Pearson correlations examined the baseline association of neurocognitive performance and tic symptom severity, ADHD symptom severity, and antipsychotic medication status. Given the findings from previous studies noted above, comparisons between youth with and without ADHD may not be considered preliminary. Accordingly, a Bonferroni correction was applied to correct for multiple comparisons across

inhibitory functions, working memory, and habit learning variables (0.05/17 variables = 0.003). Since there were no meaningful between treatment group differences on clinical or neurocognitive characteristics at baseline, linear, step-wise, and logistic regression analyses were used to examine whether baseline neurocognitive functioning predicted the change in symptom severity at mid-treatment (Week 5) or post-treatment (Week 10) on the YGTSS and CGI-I. Finally, a paired *t*-test examined the pre- to- post-treatment change in neurocognitive functioning for the CBIT group, with an independent *t*-test comparing the pre- to- post-treatment change in neurocognitive functioning between treatment groups. Although the few prior studies of adults with Tourette's Disorder have found some association between neurocognitive factors and treatment response, no prior study has examined the relationship between neurocognitive functioning and behavior therapy in children with Tourette's Disorder. Given the exploratory nature of these comparisons, the statistical significance was set at 0.05 for tests examining the relationship of neurocognitive functioning and behavior therapy in youth with Tourette's Disorder.

[Table 1](#) presents the baseline neurocognitive functioning for inhibitory functions (Stroop and SST), [working memory](#) (ACT), habit learning (WPT), and IQ (WASI FSIQ) among youth [Tourette's Disorder](#) with and without co-occurring [ADHD](#). [Table 2](#) presents the intercorrelations between neurocognitive scores.

[illegible]

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
<b>8. Stop-signal Reaction Time (ms)</b>	– 0.05	0.00	– 0.01	0.03	0.20	0.50**	0.79**									
<b>Change-signal Task</b>																
<b>9. % Accuracy Go</b>	– 0.04	0.19	0.27**	0.26**	0.61**	0.48**	0.33**	0.14								
<b>10. % Accuracy Stop</b>	– 0.05	0.09	0.20	0.16	0.33**	0.67**	0.59**	0.32**	0.66**							
<b>11. Go Reaction Time (ms)</b>	0.01	– 0.09	– 0.07	– 0.03	0.07	0.49**	0.61**	0.43**	0.23*	0.68**						
<b>12. Inhibit Delay</b>	0.01	0.01	0.12	0.11	0.45**	0.66**	0.64**	0.25*	0.48**	0.87**	0.73**					
<b>13. Change-Signal Reaction Time</b>	0.02	0.02	– 0.08	– 0.06	– 0.07	0.21	0.40**	0.47**	0.17	0.34**	0.68**	0.11				
<b>WORKING MEMORY</b>																
<b>14. ACT Total Score</b>	0.13	0.24**	0.35**	0.31**	0.15	0.26**	0.05	– 0.16	0.25*	0.30**	– 0.07	0.17	– 0.18			
<b>HABIT LEARNING</b>																
<b>15. Learning Coefficient (accuracy across blocks)</b>	0.03	0.16	0.11	– 0.07	0.08	0.02	0.01	0.00	0.07	0.00	– 0.14	– 0.01	– 0.17	0.18		
<b>16. Reaction Time Coefficient (speed across blocks)</b>	0.04	– 0.04	– 0.05	0.07	– 0.16	– 0.04	– 0.04	–0.12	0.02	0.00	0.17	0.09	– 0.08	0.14	– 0.15	
<b>FULL SCALE IQ</b>																
<b>17. WASI FSIQ</b>	0.33**	0.37**	0.32**	0.01	0.15	0.17	0.12	0.22*	0.07	– 0.03	0.06	0.02	0.13	0.06	0.04	–0.09

**Note:** ACT = Auditory Consonant Trigrams; [WASI](#) = Wechsler Abbreviated Scale of Intelligence.

\* $p < .05$ .

\*\* $p < .01$ .

### 3.1. Baseline neurocognitive functioning with co-occurring ADHD

Youth with co-occurring ADHD had impaired working memory ( $p = 0.008$ ) relative to youth without ADHD. When examining inhibitory functions, youth with ADHD exhibited impaired inhibitory functioning on certain aspects of simple motor inhibition as measured by the SST (Accuracy Stop trials,  $p = 0.003$ ), but minimal impairment on the Stroop and SST motor response flexibility ( $p = 0.05$ – $0.96$ , see [Table 1](#)).

### 3.2. Baseline neurocognitive correlates with tic symptom severity, ADHD symptom severity, and antipsychotic medication

There were no associations between neurocognitive correlates and tic symptom severity ( $r = -0.16$  to  $0.15$ ,  $p = 0.13$ – $0.96$ ) or ADHD symptom severity (ADHD-RS;  $r = -0.17$  to  $0.24$ ,  $p = 0.02$ – $0.95$ ) at the baseline assessment. Meanwhile, there was a small negative association between the presence of [antipsychotic medication](#) and a Stroop variable representing processing speed (Stroop Word T-score,  $r = -0.24$ ,  $p < 0.006$ ). However, there were no other significant associations between neurocognitive variables antipsychotic medication status ( $r = -0.13$  to  $0.22$ ,  $p = 0.02$ – $0.91$ ).

### 3.3. Predicting treatment response from baseline neurocognitive performance

[Table 3](#) presents the baseline and change in neurocognitive performance between the two treatment groups (CBIT: Comprehensive Behavior Intervention for Tics; PST: [Psychoeducation + Social Support](#)). Although there were minor baseline differences on aspects of inhibitory functioning between groups (see [Table 3](#)), there were no significant differences on any other neurocognitive factors or the presence of co-occurring ADHD (CBIT = 20, PST = 13,  $\chi^2 = 2.66$ ,  $p = 0.10$ ,  $V = 0.15$ ).

Table 3. Pretreatment and posttreatment neurocognitive scores for the CBIT and PST groups.

	Pre-treatment						Change at post-treatment					
	CBIT (Behavior therapy)		PST (Education/Support)				CBIT (Behavior therapy)		PST (Education/Support)			
	<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>	<i>d</i>	<i>p</i>	<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>	<i>d</i>	<i>p</i>
INHIBITORY FUNCTIONING												
Stroop Color-Word Test												
Word Trial (T score)	60	48.53 (9.28)	65	46.00 (8.41)	0.28	0.11	54	- 1.28 (7.10)	58	- 3.66 (5.23)	0.38	0.05*
Color Trial (T score)	59	46.31 (9.77)	65	44.68 (7.85)	0.18	0.31	53	- 0.91 (6.71)	58	- 1.12 (5.54)	0.03	0.85
Color-Word Trial (T score)	59	51.27 (10.52)	65	48.77 (8.52)	0.26	0.15	53	- 2.04 (9.48)	58	- 2.03 (9.22)	0.00	1.00
Interference (T score)	59	51.41 (6.55)	65	50.68 (8.66)	0.09	0.60	53	- 1.38 (8.43)	58	- 1.28 (11.45)	0.01	0.96
Stop-signal Task												
% Accuracy Go	48	88.94 (12.05)	51	89.37 (12.26)	0.04	0.86	33	1.42 (10.28)	43	- 2.56 (11.53)	0.10	0.12

	Pre-treatment						Change at post-treatment					
	CBIT (Behavior therapy)		PST (Education/Support)		<i>d</i>	<i>p</i>	CBIT (Behavior therapy)		PST (Education/Support)		<i>d</i>	<i>p</i>
	<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>			<i>N</i>	<i>Mean (SD)</i>	<i>N</i>	<i>Mean (SD)</i>		
% Accuracy Stop	47	52.04 (8.48)	51	52.53 (10.25)	0.05	0.80	38	- 2.92 (11.07)	44	- 1.63 (7.46)	0.14	0.53
Go Reaction Time (ms)	49	729 (126)	52	746 (103)	0.15	0.46	38	- 25 (114)	45	- 22 (82)	0.03	0.87
Stop-signal Reaction Time (ms)	45	247 (65)	48	242 (59)	0.08	0.71	30	5 (58)	40	- 8 (65)	0.05	0.38
Change-signal Task												
% Accuracy Go	48	82.15 (14.67)	50	84.38 (12.87)	0.15	0.43	36	0.76 (11.51)	42	- 0.83 (9.71)	0.01	0.51
% Accuracy Stop	43	45.00 (9.78)	49	48 (12.73)	0.26	0.19	34	- 1.49 (9.99)	42	- 3.89 (8.88)	0.26	0.27
Go Reaction Time (ms)	49	723 (129)	51	775 (131)	0.40	0.05*	39	-17 (126)	44	- 9 (90)	0.07	0.74
Inhibit Delay	48	391 (149)	51	426 (152)	0.23	0.24	36	- 43 (154)	44	- 55 (103)	0.09	0.69
Change-Signal Reaction Time	43	275 (86)	43	304 (72)	0.37	0.05	31	5 (62)	35	29 (69)	0.36	0.15
WORKING MEMORY												
ACT Total Score	60	42.68 (7.86)	65	43.06 (7.37)	0.05	0.78	53	- 1.60 (6.08)	58	- 0.64 (4.96)	0.17	0.36
HABIT LEARNING												
Learning Coefficient(accuracy across blocks)	38	0.02 (0.12)	51	0.03 (0.13)	0.08	0.71	29	- 0.02 (0.15)	39	0.03 (0.19)	0.06	0.22
Reaction Time Coefficient (speed across blocks)	38	- 121 (179)	51	- 58 (201)	0.33	0.13	29	- 30 (242)	39	8 (311)	0.08	0.59
FULL SCALE IQ												
WASI FSIQ	61	111.74 (13.55)	65	108.55 (14.04)	0.23	0.20	-	-	-	-	-	-

Note: CBIT = Comprehensive Behavior Intervention for Tics; PST = [Psychoeducation](#) + [Social Support](#); ACT = Auditory Consonant Trigrams; [WASI](#) = Wechsler Abbreviated Scale of Intelligence.

\*Indicates statistical significance, which was set at  $p < 0.05$  for these comparisons due to their exploratory nature.



Subsequently, baseline neurocognitive predictors of treatment response were examined across treatment conditions for changes in tic severity at mid-treatment and post-treatment. The step-wise regression model that consisted of all neurocognitive predictors was significant ( $R^2 = 0.11$ ,  $F_{1,63} = 7.88$ ,  $p = 0.007$ ), and revealed that [full scale IQ](#) predicted reduction in tic severity from baseline to mid-treatment in the full sample ( $\beta = 0.33$ ,  $t_{1,63} = 2.81$ ,  $p = 0.007$ ). Meanwhile, a step-wise regression model that included all neurocognitive predictors found that working memory (ACT Total Score,  $\beta = 0.29$ ,  $t_{1,58} = 2.35$ ,  $p = 0.02$ ) and response time on a habit learning task (WPT reaction time,  $\beta = -0.26$ ,  $t_{1,58} = -2.11$ ,  $p = 0.04$ ) predicted the reduction in tic severity from baseline to post-treatment across groups ( $R^2 = 0.14$ ,  $F_{2,58} = 4.74$ ,  $p = 0.01$ ). However, a linear logistic regression model with all neurocognitive predictors found no significant predictors of baseline neurocognitive functioning and treatment response at Week 10 ( $\chi^2 = 12.02$ ,  $p = 0.85$ ).

When examining baseline neurocognitive predictors of treatment response within the [behavior therapy](#) group (CBIT), no single neurocognitive baseline predictor fulfilled the step-wise regression criteria likely due to the small sample size. Meanwhile, a linear regression model found no significant baseline neurocognitive predictors for either the change in tic severity from baseline to mid-treatment (Week 5,  $R^2 = 0.50$ ,  $F_{18,9} = 0.49$ ,  $p = 0.91$ ) or from baseline to post-treatment (Week 10,  $R^2 = 0.70$ ,  $F_{18,9} = 1.15$ ,  $p = 0.43$ ). Furthermore, a logistic regression found no significant predictors of baseline neurocognitive functioning and treatment response on the CGI-I at Week 10 for the behavior therapy CBIT group ( $\chi^2 = 13.86$ ,  $p = 0.74$ ).

### 3.4. Neurocognitive changes within CBIT and between treatment groups

A paired  $t$ -test explored changes in neurocognitive functioning in the behavior therapy CBIT group. Although findings suggested improvements in working memory after treatment ( $t_{52} = -1.92$ ,  $p = 0.06$ ,  $d = 0.26$ ), this change was not significant, and there was no significant change in neurocognitive functioning across inhibitory functions, working memory, or habit memory ( $p = 0.10$ – $0.69$ ,  $d = 0.08$ – $0.28$ ). When comparing performance change between treatment groups, no meaningful differences in the change in neurocognitive functioning were found between treatment groups (see [Table 3](#)).

## 4. Discussion

Few studies have examined neurocognitive functioning among youth with [Tourette's Disorder](#). The present study is the first to examine the neurocognitive correlates of behavior treatment outcome in a large sample of youth with Tourette's Disorder. The most robust neurocognitive findings involved the impact of co-occurring [ADHD](#), such that youth with Tics + ADHD demonstrated poorer baseline verbal [working memory](#) and simple motor inhibition compared to youth with Tics-ADHD. Specifically, the Tics + ADHD group exhibited lower accuracy on the SST stop trials relative to youth with Tics-ADHD, which suggests the possibility of [impulsivity](#) (commission errors). However, inhibitory functioning as measured by other SST variables and Stroop performance mostly indicated that there was no difference between the two groups, after controlling for multiple comparisons. Although a trend towards lower IQ and slower response speed on a habit learning task also characterized the Tics+ADHD group at baseline, this trend was also not statistically significant after controlling for multiple comparisons.

Collectively, these findings highlight the impact of [comorbid](#) ADHD on the neurocognitive profile of [pediatric](#) Tourette's Disorder, which is particularly relevant given their common co-occurrence. The baseline associations of ADHD symptom severity with poorer working memory, and simple motor inhibition are consistent with [cognitive dysfunction](#), primarily executive in nature, repeatedly identified in the ADHD literature ([Pitcher et al., 2003](#); [Mayes and Calhoun, 2007](#); [van der Oord et al., 2012](#)). Notably, the current findings also reflect that Tourette's Disorder on its own is not associated with meaningful neurocognitive impairment. Many previous studies of Tourette's Disorder across the age spectrum have suggested a profile of only subtle cognitive dysfunction, particularly in the case of tics uncomplicated by comorbidity ([Como, 2001](#); [Chang et al., 2007](#); [Sukhodolsky et al., 2010](#); [Greimel et al., 2011](#)). Similarly, in adult Tourette's samples, several studies examining [executive function](#) have shown no performance differences between Tourette's Disorder and unaffected controls ([Serrien et al., 2005](#), [Thibault et al., 2009](#), [Eddy and Cavanna, 2017](#), [Thomalla et al., 2014](#)).

Beyond the neurocognitive impairment associated with co-occurring ADHD, baseline examinations revealed a small significant association between [antipsychotic medication](#) and slower processing speed on the Stroop. Increased neurocognitive impairment among youth taking antipsychotic medications is consistent with other research in children with [neuropsychiatric disorders](#) (e.g., OCD; [Lewin et al., 2014](#)). While youth on antipsychotic medications may represent a more severe group of pediatric CTD, there were no associations between neurocognitive functioning and tic symptom severity at baseline. Thus, antipsychotic medication and its side effect profile (e.g., sedation) may adversely affect neurocognitive functioning in youth with CTD. Given the few number of youth taking antipsychotic medications in this sample (13.5%), future research should further examine whether these effects would be more robust in a larger medicated sample.

Although there were no baseline neurocognitive predictors significantly associated with treatment response to [behavior therapy](#), baseline working memory and habit learning response time were associated with reductions in tic severity from baseline to post-treatment across treatment conditions. While one prior study did find that a visuospatial priming task predicted reductions in tic severity for adults with Tourette's Disorder receiving habit reversal therapy, the primary therapeutic component of Comprehensive Behavior Intervention for Tics ([Deckersbach et al., 2006](#)), developmental differences between children and adults with Tourette's Disorder may influence potential predictors of therapeutic improvement. Specifically, adult with Tourette's Disorder may represent a more severe and persistent form of the disorder associated with greater neurocognitive impairment, which then may exert influence on treatment outcomes. This is in line with pediatric tic studies that document absent or mild behavioral dysfunction on neurocognitive measures ([Como, 2001](#); [Chang et al., 2007](#); [Sukhodolsky et al., 2010](#)). Moreover, two other large studies in adults with Tourette's Disorder found no relationship between performance on response inhibition tasks and treatment outcome ([Morand-Beaulieu et al., 2015](#), [Abramovitch et al., 2017](#)).

Beyond a lack of neurocognitive predictors, these results suggest that neurocognitive performance as assessed by inhibitory functions, working memory, and habit learning measures does not significantly change with treatment whether behavioral or supportive in nature. Although research examining the stability of neurocognitive functioning is absent in

pediatric tic studies, two findings in adult with Tourette's Disorder have found behavior treatment to be related to selective improvements in motor performance, which suggest some degree of malleability in neurocognitive functioning ([O'Connor et al., 2008](#), [Lavoie et al., 2011](#)). However, these studies were conducted by the same research group using different tasks than the ones used here. While specific aspects of neurocognitive functioning such as motor performance may be more malleable relative to other constructs such as executive functioning ([O'Connor et al., 2008](#)), it may be that the specific task and/or patient developmental level also plays a role. Future research should consider investigating whether neurocognitive impairments are stable across time in the absence of intervention.

While neurocognitive predictors of response to behavior therapy were not identified, youth receiving Comprehensive Behavior Intervention for Tics exhibited significantly reduced tic severity without any diminished cognitive functioning ([Piacentini et al., 2010](#)). This is important because some parents and clinicians express concern that implementing behavioral strategies for tics are likely to yield adverse effects on tics and increase the demand on children's cognitive resources ([Burd and Kerbeshian, 1987](#), [Woods et al., 2010](#), [Peterson et al., 2016](#)). Thus, these findings provide evidence that behavior therapy does not negatively impact neurocognitive functioning, relative to a non-tic specific treatment. Indeed, our findings along with other recent studies suggest that neither ADHD comorbidity nor its related neurocognitive dysfunction significantly reduces response to behavior therapy ([Abramovitch et al., 2017](#), [Sukhodolsky et al., 2017](#)). Furthermore, positive treatment response to behavior therapy was associated at 6-month post-treatment with improved [social functioning](#) and decreased anxiety, disruptive behavior, and family strain ([Woods et al., 2011](#)). Thus, these findings offer further support for recommendations of behavior therapy as a first-line intervention for Tourette's Disorder ([Murphy et al., 2013](#)).

While not specific to the behavior therapy group, working memory and WPT response latency predicted reductions in tic symptom severity across treatments. Specifically, poorer working memory and slower WPT response time were related to worse clinical outcomes across conditions. This suggests that better baseline working memory and processing speed have a predictive relationship to reductions in tic symptom severity that may be unrelated to specific treatment condition. While research into neurocognitive predictors of treatment response in other disorders has been inconsistent, there has been some evidence to suggest that executive functions such as working memory may function as a predictor of treatment response in pediatric OCD ([Flessner et al., 2010](#)). However, due to our lack of a no-treatment control group, we cannot entirely exclude the possibility that the association between baseline neurocognition and treatment response was not meaningful, but rather reflected the natural fluctuations of tics over time across both treatment conditions.

Despite clear strengths in methodology and sample size, a few limitations should be noted. First, this study did not include a matched unaffected control group, which made it difficult to assess the degree to which baseline neurocognitive performance in pediatric Tourette's Disorder varied from the normal range of functioning. However, when baseline measures of working memory (ACT) and inhibitory functioning (Stroop) were compared to published normative data, comparisons showed that youth with Tourette's Disorder fell within the average range of functioning ([Strauss et al., 2006](#)). In fact, inhibitory functions represented by the

[Stroop Interference](#) T-score was solidly in the average range (T-score range = 49–52) at baseline regardless of ADHD comorbidity and remained unchanged with treatment. Second, given the exploratory nature of the relationship between neurocognitive functioning and behavior therapy in youth with Tourette's Disorder, we did not correct for multiple comparisons for these analyses. Third, while the neurocognitive assessment battery was selected based on the theorized dysfunction in pediatric Tourette's Disorder, it may be that other aspects of neurocognitive functioning not captured in the present study serve as predictors of behavior therapy and/or may be more influenced by behavioral interventions. Future research should examine additional neurocognitive constructs in pediatric Tourette's. Beyond this, it would be beneficial to replicate the current findings with a different battery of neurocognitive tasks that capture the same broad constructs, to provide further assurance that findings are not task dependent.

In summary, this study found that co-occurring ADHD is associated with impaired cognitive functioning, including poorer verbal working memory and aspects of simple motor inhibition, in treatment-seeking youth with Tourette's Disorder. Although neurocognitive predictors of behavior therapy were not identified, youth who received Comprehensive Behavior Intervention for Tics exhibited significantly reduced tic severity without any diminishment in cognitive functioning. This finding effectively counters concerns regarding the potentially [iatrogenic effects](#) of behavior therapy on cognitive functioning; namely, that the cognitive resources required to engage in treatment (e.g., real-time monitoring of tic urge and contingent application of an incompatible behavior when urges are directed) may lead to greater impairment than the tics themselves ([Scahill et al., 2013](#)). Across treatment groups, youth with Tourette's Disorder demonstrating greater verbal working memory and response speed at baseline exhibited greater reductions in tic symptom severity. Finally, findings suggest that persistent tics may not be associated with appreciable neurocognitive dysfunction in youth, and if subtle impairments are present, they are not likely to change with treatment. Future research would benefit from the integration of multimodal evaluation of neurocognitive functioning that includes behavioral data and functional neuroimaging to comprehensively examine the neurocognitive mechanisms and predictors of treatment response in behavior therapy for children with Tourette's Disorder.

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## References

- 1 A. Abramovitch, L.S. Hallion, H.E. Reese, D.W. Woods, A. Peterson, J.T. Walkup, *et al.* **Neurocognitive predictors of treatment response to randomized treatment in adults with tic disorders**, *Prog. NeuroPsychopharmacol. Biol. Psychiatry*, 74 (2017), pp. 9-14.

- 2 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th ed), American Psychiatric Publishing, Arlington, VA (2013).
- 3 L. Burd, J. Kerbeshian. **Treatment-generated problems associated with behavior modification in Tourette disorder**, Dev. Med. Child Neurol., 29 (6) (1987), pp. 831-832.
- 4 B. Casey, N. Tottenham, J. Fossella. **Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control**, Dev. Psychobiol., 40 (2002), pp. 237-254.
- 5 S.W. Chang, J.T. McCracken, J.C. Piacentini. **Neurocognitive correlates of child obsessive compulsive disorder and Tourette syndrome**, J. Clin. Exp. Neuropsychol., 29 (2007), pp. 724-733.
- 6 S. Channon, P. Pratt, M.M. Robertson. **Executive function, memory, and learning in Tourette's syndrome**, Neuropsychology, 17 (2003), pp. 247-254.
- 7 P.G. Como. **Neuropsychological function in Tourette syndrome**, Adv. Neurol., 85 (2001), pp. 103-111.
- 8 C.A. Conelea, D.W. Woods, S.H. Zinner, C. Budman, T. Murphy, L.D. Scahill, *et al.* **Exploring the impact of chronic tic disorders on youth: results from the Tourette syndrome impact survey**, Child Psychiatry Hum. Dev., 42 (2011), pp. 219-242.
- 9 S. Crawford, S. Channon, M.M. Robertson. **Tourette's syndrome: performance on tests of behavioral inhibition, working memory and gambling**, J. Child Psychol. Psychiatry, 46 (2005), pp. 1327-1336.
- 10 T. Deckersbach, S. Rauch, U. Buhlmann, S. Wilhelm. **Habit reversal versus supportive psychotherapy in Tourette's disorder: a randomized controlled trial and predictors of treatment response**, Behav. Res. Ther., 44 (2006), pp. 1079-1090.
- 11 G. DuPaul, T. Power, A. Anastopoulos, R. Reid. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation, Guilford, New York, NY (1998).
- 12 C.M. Eddy, A.E. Cavanna. **Set-shifting deficits: a possible neurocognitive endophenotype for Tourette syndrome without ADHD**, J. Atten. Disord., 21 (10) (2017), pp. 824-834.
- 13 C.A. Flessner, A. Allgair, A. Garcia, J. Freeman, J. Sapyta, M.E. Franklin, *et al.* **The impact of neuropsychological functioning on treatment outcomes in pediatric obsessive compulsive disorder**, Depress. Anxiety, 27 (4) (2010), pp. 365-371.
- 14 R.D. Freeman, D.K. Fast, L. Burd, J. Kerbeshian, M.M. Robertson, P. Sandor. **An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries**, Dev. Med. Child Neurol., 42 (2000), pp. 436-447.
- 15 C.J. Golden Stroop Color and Word Test: A Manual for Clinical and Experimental Uses, Stoelting, Chicago (1978).
- 16 A.E. Goudriaan, J. Oosterlaan, E. De Beurs, W. Van Den Brink. **Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls**, Addiction, 101 (2006), pp. 534-547.

- 17 E. Greimel, S. Wanderer, A. Rothenberger, B. Herpertz-Dahlmann, K. Konrad, V. Roessner. **Attentional performance in children and adolescents with tic disorder and co-occurring attention-deficit/hyperactivity disorder: new insights from a 2 × 2 factorial design study**, *J. Abnorm. Child Psychol.*, 39 (2011), pp. 819-828.
- 18 W. Guy. **Clinical Global Impressions ECDEU Assessment Manual for Psychopharmacology (Vol. Revised DHEW Pub. (ADM))**, National Institute for Mental Health, Rockville, MD (1976), pp. 218-222.
- 19 M.B. Himle, D.W. Woods. **An experimental evaluation of tic suppression and the tic rebound effect**, *Behav. Res. Ther.*, 43 (2005), pp. 1443-1451.
- 20 S. Jeon, J.T. Walkup, D.W. Woods, A. Peterson, J. Piacentini, S. Wilhelm, *et al.* **Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods**, *Contemp. Clin. Trials*, 36 (2013), pp. 414-420.
- 21 S. Johannes, B. Wieringa, M. Mantey, W. Nager, D. Rada, K. Müller-Vahl, *et al.* **Altered inhibition of motor responses in Tourette syndrome and obsessive-compulsive disorder**, *Acta Neurol. Scand.*, 104 (2001), pp. 36-43.
- 22 T. Knight, T. Steeves, L. Day, M. Lowerison, N. Jette, T. Pringsheim. **Prevalence of tic disorders: a systematic review and meta-analysis**, *Pediatr. Neurol.*, 47 (2012), pp. 77-90.
- 23 B.J. Knowlton, J.A. Mangels, L.R. Squire. **A neostriatal habit learning system in humans**, *Science*, 273 (1996), pp. 1399-1402.
- 24 B.J. Knowlton, L.R. Squire, M.A. Gluck. **Probabilistic classification learning in amnesia**, *Learn. Mem.*, 1 (1994), pp. 106-120.
- 25 M.E. Lavoie, T.V. Imbriglio, E. Stip, K.P. O'Connor. **Neurocognitive changes following cognitive-behavioral treatment in Tourette syndrome and chronic tic disorder**, *Int. J. Cogn. Ther.*, 4 (1) (2011), pp. 34-50, [10.1521/ijct.2011.4.1.34](https://doi.org/10.1521/ijct.2011.4.1.34).
- 26 J.F. Leckman, M.A. Riddle, M.T. Hardin, S.I. Ort. **The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity**, *J. Am. Acad. Child Adolesc. Psychiatry*, 28 (1989), pp. 566-573.
- 27 A.B. Lewin, M.J. Larson, J.M. Park, J.F. McGuire, T.K. Murphy, E.A. Storch. **Neuropsychological functioning in youth with obsessive compulsive disorder: an examination of executive function and memory impairment**, *Psychiatry Res.*, 216 (1) (2014), pp. 108-115.
- 28 G.D. Logan. **On the ability to inhibit thought and action: a users' guide to the stop signal paradigm**
- 29 D. D, T.H. C (Eds.), *Inhibitory Processes in Attention, Memory, and Language*, Academic Press, San Diego, CA (1994), pp. 189-239.
- 30 G.D. Logan, R.J. Schachar, R. Tannock. **Impulsivity and inhibitory control**, *Psychol. Sci.*, 8 (1997), pp. 60-64.
- 31 J. March, S. Silva, S. Petrycki, J. Curry, K. Wells, J. Fairbank, *et al.* **Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for**



**Adolescents with Depression Study (TADS) randomized controlled trial**, JAMA, 292 (2004), pp. 807-820.

- 32 R. Marsh, G.M. Alexander, M.G. Packard, H. Zhu, J.C. Wingard, G. Quackenbush, *et al.* **Habit learning in Tourette syndrome: a translational neuroscience approach to a developmental psychopathology**, Arch. Gen. Psychiatry, 61 (2004), pp. 1259-1268.
- 33 R. Marsh, G.M. Alexander, M.G. Packard, H. Zhu, B.S. Peterson. **Perceptual-motor skill learning in Gilles de la Tourette syndrome. Evidence for multiple procedural learning and memory systems**, Neuropsychologia, 43 (10) (2005), pp. 456-465.
- 34 R. Marsh, H. Zhu, Z. Wang. **A developmental fMRI study of regulatory control in Tourette's syndrome**, Am. J. Psychiatry, 164 (2007), pp. 955-966.
- 35 S.D. Mayes, S.L. Calhoun. **Learning, attention, writing, and processing speed in typical children and children with ADHD, autism, depression, and oppositional-defiant disorder**, Child Neuropsychol., 13 (6) (2007), pp. 469-493.
- 36 J.F. McGuire, J. Piacentini, E.A. Brennan, A.B. Lewin, T.K. Murphy, Small, *et al.* (Eds.), A meta-analysis of behavior therapy for Tourette syndrome, J. Psychiatr. Res., 50 (2014), pp. 106-112.
- 37 S. Morand-Beaulieu, K.P. O'Connor, G. Sauve, P.J. Blanchet, M.E. Lavoie. **Cognitive behavioral therapy induces sensorimotor and specific electrocortical changes in chronic tic and Tourette's disorder**, Neuropsychologia, 79 (Pt B) (2015), pp. 310-321.
- 38 T.K. Murphy, A.B. Lewin, E.A. Storch, S. Stock. **Practice parameter for the assessment and treatment of children and adolescents with tic disorders**, J. Am. Acad. Child Adolesc. Psychiatry, 52 (12) (2013), pp. 1341-1359.
- 39 B.R. Newell, D.A. Lagnado, D.R. Shanks. **Challenging the role of implicit processes in probabilistic category learning**, Psychon. Bull. Rev., 14 (3) (2007), pp. 505-511.
- 40 K.P. O'Connor, M.E. Lavoie, E. Stip, F. Borgeat, A. Laverdure. **Cognitive-behaviour therapy and skilled motor performance in adults with chronic tic disorder**, Neuropsychol. Rehabil., 18 (2008), pp. 45-64.
- 41 S. Ozonoff, D.L. Strayer, W.M. McMahon, F. Filloux. **Inhibitory deficits in Tourette syndrome: a function of comorbidity and symptom severity**, J. Child Psychol. Psychiatry, 39 (1998), pp. 1109-1118.
- 42 C. Paniak, H.B. Miller, D. Murphy, A. Andrews, J. Flynn. **Consonant trigrams test for children: development and norms**, Clin. Neuropsychol., 11 (1997), pp. 198-200.
- 43 A.L. Peterson, J.F. McGuire, S. Wilhelm, J.C. Piacentini, D.W. Woods, J.T. Walkup, *et al.* **An empirical examination of symptom substitution associated with behavior therapy**, Behav. Ther., 47 (1) (2016), pp. 29-41.
- 44 B.S. Peterson, P. Skudlarski, A.W. Anderson, H. Zhang, J.C. Gatenby, C.M. Lacadie, *et al.* **A functional magnetic resonance imaging study of tic suppression in Tourette syndrome**, Arch. Gen. Psychiatry, 55 (1998), pp. 326-333.



- 45 J. Piacentini, D.W. Woods, L. Scahill, S. Wilhelm, A.L. Peterson, S. Chang, *et al.* **Behavior therapy for children with Tourette disorder: a randomized controlled trial**, JAMA, 303 (2010), pp. 1929-1937.
- 46 T.M. Pitcher, J.P. Piek, D.A. Hay. **Fine and gross motor ability in males with ADHD**, Dev. Med. Child Neurol., 45 (8) (2003), pp. 525-535.
- 47 C.-S. Ray Li, H.-L. Chang, Y.-P. Hsu, H.-S. Wang, N.-C. Ko. **Motor response inhibition in children with Tourette's disorder**, J. Neuropsychiatry Clin. Neurosci., 18 (2006), pp. 417-419.
- 48 V. Roessner, A. Becker, T. Banaschewski, R.D. Freeman, A. Rothenberger, T.S.I.D. Consortium. **Developmental psychopathology of children and adolescents with Tourette syndrome—impact of ADHD**, Eur. Child Adolesc. Psychiatry, 16 (2007), pp. 24-35.
- 49 L. Scahill, P.B. Chappell, Y.S. Kim, R.T. Schultz, L. Katsovich, E. Shepherd, *et al.* **A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder**, Am. J. Psychiatry, 158 (2001), pp. 1067-1074.
- 50 L. Scahill, G. Erenberg, C.M. Berlin Jr., C. Budman, B.J. Coffey, J. Jankovic, *et al.* **Contemporary assessment and pharmacotherapy of Tourette syndrome**, NeuroTherapeutics, 3 (2006), pp. 192-206.
- 51 L. Scahill, M. Specht, C. Page. **The prevalence of tic disorders and clinical characteristics in children**, J. Obsessive Compuls. Relat. Disord., 3 (2014), pp. 394-400.
- 52 L. Scahill, D.W. Woods, M.B. Himle, A.L. Peterson, S. Wilhelm, J.C. Piacentini, *et al.* **Current controversies on the role of behavior therapy in Tourette syndrome**, Mov. Disord., 28 (9) (2013), pp. 1179-1183.
- 53 D.J. Serrien, M. Orth, A.H. Evans, A.J. Lees, P. Brown. **Motor inhibition in patients with Gilles de la Tourette syndrome: functional activation patterns as revealed by EEG coherence**, Brain, 128 (Pt 1) (2005), pp. 116-125.
- 54 W.K. Silverman, A.M. Albano. **The Anxiety Disorders Interview Schedule for DSM-IV-Child and Parent Versions**, Graywinds Publications, San Antonio, TX (1996).
- 55 W.K. Silverman, L.M. Saavedra, A.A., Pina. **Test-retest reliability of anxiety symptoms and diagnoses with anxiety disorders interview schedule for DSM-IV: child and parent versions**, J. Am. Acad. Child Adolesc. Psychiatry, 40 (2001), pp. 937-944.
- 56 M.W. Specht, D.W. Woods, J. Piacentini, L. Scahill, S. Wilhelm, A.L. Peterson, *et al.* **Clinical characteristics of children and adolescents with a primary tic disorder**, J. Dev. Phys. Disabil., 23 (2011), pp. 15-31.
- 57 E. Strauss, E.M. Sherman, O. Spreen. **A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary**, Oxford University Press, New York (2006).
- 58 E.A. Storch, A.S. De Nadai, A.B. Lewin, J.F. McGuire, A.M. Jones, P.J. Mutch, *et al.* **Defining treatment response in pediatric tic disorders: a signal detection analysis of the Yale Global Tic Severity Scale**, J. Child Adolesc. Psychopharmacol., 21 (2011), pp. 621-627.

- 59 E.A. Storch, C.W. Lack, L.E. Simons, W.K. Goodman, T.K. Murphy, G.R. Geffken. **A measure of functional impairment in youth with Tourette's syndrome**, J. Pediatr. Psychol., 32 (2007), pp. 950-959.
- 60 E.A. Storch, L.J. Merlo, C. Lack, V.A. Milsom, G.R. Geffken, W.K. Goodman, *et al.* **Quality of life in youth with Tourette's syndrome and chronic tic disorder**, J. Clin. Child Adolesc. Psychol., 36 (2007), pp. 217-227.
- 61 E.A. Storch, T.K. Murphy, G.R. Geffken, M. Sajid, P. Allen, J.W. Roberti, *et al.* **Reliability and validity of the Yale Global Tic Severity Scale**, Psychol. Assess., 17 (2005), pp. 486-491.
- 62 D. Stuss, L. Stethem, C. Poirier. **Comparison of three tests of attention and rapid information processing across six age groups**, Clin. Neuropsychol., 1 (1987), pp. 139-152.
- 63 D.G. Sukhodolsky, A. Landeros-Weisenberger, L. Scahill, J.F. Leckman, R.T. Schultz. **Neuropsychological functioning in children with Tourette syndrome with and without attention-deficit/hyperactivity disorder**, J. Am. Acad. Child Adolesc. Psychiatry, 49 (2010), pp. 1155-1164.
- 64 D.G. Sukhodolsky, D.W. Woods, J. Piacentini, S. Wilhelm, A.L. Peterson, L. Katsoyich. **Moderators and predictors of response to behavior therapy for tics in Tourette syndrome**, Neurology, 88 (11) (2017), pp. 1029-1036.
- 65 N.R. Swerdlow, M. Magulac, D. Filion, S. Zinner. **Visuospatial priming and latent inhibition in children and adults with Tourette's disorder**, Neuropsychology, 10 (1996), pp. 485-494.
- 66 G. Thibault, K.P. O'Connor, E. Stip, M.E. Lavoie. **Electrophysiological manifestations of stimulus evaluation, response inhibition and motor processing in Tourette syndrome patients**, Psychiatry Res., 167 (3) (2009), pp. 202-220, [10.1016/j.psychres.2008.03.021](https://doi.org/10.1016/j.psychres.2008.03.021).
- 67 G. Thomalla, M. Jonas, T. Baumert, H.R. Seiner, K. Biermann-Ruben, C. Agnos, *et al.* **Costs of control: decreased motor cortex engagement during a Go/No-go task in Tourette's syndrome**, Brain, 137 (Pt 1) (2014), pp. 122-136, [10.1093/brain/awt288](https://doi.org/10.1093/brain/awt288).
- 68 S. van der Oord, H.M. Geurts, P.J. Prins, P.M. Emmelkamp, J. Oosterlaan. **Prepotent response inhibition predicts treatment outcome in attention deficit/hyperactivity disorder**, Child Neuropsychol., 18 (1) (2012), pp. 50-61.
- 69 D. Wechsler. **Manual for the Wechsler Abbreviated Intelligence Scale (WASI)**, Psychological Corporation, San Antonio, TX (1999).
- 70 H. Weisman, I.A. Qureshi, J.F. Leckman, L. Scahill, M.H. Bloch. **Systematic review: pharmacological treatment of tic disorders – efficacy of antipsychotic and alpha-2 adrenergic agonist agents**, Neurosci. Biobehav. Rev., 37 (6) (2012), pp. 1162-1171.
- 71 D.W. Woods, C.A. Conelea, M.B. Himle. **Behavior therapy for Tourette's disorder: utilization in a community sample and an emerging area of practice for psychologists**, Prof. Psychol. Res. Pract., 41 (6) (2010), pp. 518-525.
- 72 J.J. Wood, J.C. Piacentini, R.L. Bergman, J. McCracken, V. Barrios. **Concurrent validity of the anxiety disorders section of the anxiety disorders interview schedule for DSM-IV: child and parent versions**, J. Clin. Child Adolesc. Psychol., 31 (2002), pp. 335-342.

- 73 D.W. Woods, J. Piacentini, S.W. Chang, T. Deckersbach, G.S. Ginsburg, A.L. Peterson, *et al.* **Managing Tourette Syndrome: A Behavioral Intervention for Children and Adolescents**, Oxford University Press, New York (2008).
- 74 D.W. Woods, J. Piacentini, L. Scahill, A.L. Peterson, S. Wilhelm. **Behavior therapy for tics in children: acute and long-term effects on psychiatric and psychosocial functioning**, J. Child Neurol., 26 (7) (2011), pp. 858-865.