Neuropsychological functioning in children with Tourette Syndrome with and without Attention-Deficit/Hyperactivity Disorder

Denis G. Sukhodolsky, Ph.D., **Angeli Landeros-Weisenberger, M.D.**, **Lawrence Scahill, M.S.N., Ph.D.**, **James F. Leckman, M.D.**, and **Robert T. Schultz, Ph.D.**
Drs. Sukhodolsky, Landeros-Weisenberger, and Leckman are with the Yale Child Study Center. Dr. Scahill is with the Yale Child Study Center and Yale School of Nursing. Dr. Schultz is with the University of Pennsylvania and Children's Hospital of Philadelphia

Abstract

Objective—Neuropsychological functioning in children with Tourette Syndrome (TS) has been characterized by subtle deficits in response inhibition, visual-motor integration and fine-motor coordination. The association of these deficits with the tics of the TS versus co-occurring attention-deficit/hyperactivity disorder (ADHD) has not been well understood due to small sample sizes and lack of adequate control conditions. We examined neuropsychological functioning in relatively large and well-characterized samples of children with TS, TS-plus-ADHD, ADHD, and unaffected controls.

Method—Fifty-six children with TS-only, 45 with TS-plus-ADHD, 64 with ADHD and 71 healthy community control subjects were assessed on a battery of neuropsychological measures including the Connors' Continuous Performance Test (CPT), the Stroop Color-Word Interference Test (Stroop), the Beery Visual-Motor Integration Test (VMI), and the Purdue Pegboard Test.

Results—There were no differences between children with TS-only and unaffected controls on the measures of response inhibition and visual-motor integration. Boys with TS-only but not girls with TS-only were impaired in the dominant hand Purdue performance. Children with ADHD were impaired on all study measures. Children with TS-plus-ADHD revealed no deficits on the Stroop, VMI and Purdue tests but were impaired on the sustained attention portion of the CPT.

Correspondence to: Dr. Denis G. Sukhodolsky, Yale Child Study Center, 230 South Frontage Road, P.O. Box 207900, New Haven, CT 06520-7900. Tel: 203-785-6446; fax: 203-785-7611; denis.sukhodolsky@yale.edu or to Dr. Robert T. Schultz, Center for Autism Research, Children's Hospital of Philadelphia, 3535 Market Street, 8th floor, Suite 860, Philadelphia, PA 19104. Tel: 267-426-7907; fax: 267-426-7590; schultzrt@chop.edu..

Conclusions—These results indicate that co-occurring ADHD may be responsible for the neuropsychological deficits, or at least those assessed in the present study, in children with TS. Explanations in terms of neurobiological mechanisms of co-occurring TS and ADHD as well as possible compensatory mechanisms in children with TS are discussed.

INTRODUCTION

Tourette syndrome (TS) is a disorder of childhood onset characterized by chronic motor and phonic tics. The worldwide prevalence of TS in children and adolescents ranges from 1 to 10 per 1000. [1] The prevalence of diagnosed cases in the US is estimated at 3 per 1000, suggesting that many cases escape detection. [2] Tics usually first appear between the ages of 5 and 7 years and follow a fluctuating course with common worsening between 9 and 12 years. In up to 80 percent of patients tics decline by late adolescence. [3, 4] Fifty to 90 percent of clinically-referred children and adolescents with TS have co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD).[5] Similar rates have been reported in population-based samples. [6] Both TS and ADHD are characterized by childhood onset, excessive motor activity, and abnormalities in the cortical–striatal–thalamo–cortical (CSTC) circuits. [7] This study investigates whether neuropsychological impairments in children with TS are associated with co-occurring ADHD.

Although the etiology of TS is unknown, tics are presumed to originate from the aberrant striatal activity which leads to disinhibition, via the thalamus, of cortical motor areas. [8] This CSTC model is supported by the anatomical MRI findings of reduced caudate volumes [9] and thinning of sensorimotor cortices, [10] and electrophysiological findings of reduced cortical inhibition in the motor circuitry in individuals with TS.[11] Neuroimaging studies have also detected abnormalities in the CSTC circuitry during performance of inhibitory control tasks in individuals with TS. Specifically, the normal levels of behavioral performance on the Stroop [12] and GoNoGo [13] were paralleled by greater levels of brain activation in the frontal cortical regions. It was suggested that this increased activation may reflect a mechanism that compensate for the inefficient recruitment of neural resources that subserve response inhibition.

In agreement with the CSTC model, subtle impairments in two domains of neuropsychological functioning – motor skills and response inhibition – have been reported in TS.[14] However, the association of these deficits with TS versus co-occurring ADHD has not been well understood due to small sample sizes and lack of adequate control conditions. Fine-motor coordination deficits in TS subjects have been demonstrated on the Grooved Pegboard and Purdue Pegboard tests. [15-17] Early studies in children and adults with TS revealed deficits in visual-motor integration as measured by the Bender-Gesalt Test and the Beery Visual-Motor Integration Test (VMI) [17-19] but later studies reported normal level of performance on VMI. [20, 21] In the domain of response inhibition, impaired performance in children with TS was reported on the Flanker, [22] the Hayling, [23] and Visuospatial Priming [24] tasks. By contrast, no difference was found between children with TS and unaffected controls on the stop-signal reaction time [25] and the signal detection version of the continuous performance test. [26] Conflicting results were reported on the Stroop. [21, 23] It was suggested that response inhibition deficits in TS can be attributable to co-occurring ADHD. [26-29] To address the constraints posed by small sample sizes and lack of adequate control groups in earlier studies, we examined neuropsychological functioning in the domains of motor skills and response inhibition in a large, well-characterized sample of children with TS with and without ADHD.

METHOD

Subjects

Subjects included 236 children and adolescents (172 boys, 64 girls, mean age=11.37 years; SD=2.58) who participated in one or more studies of childhood neuropsychiatric disorders conducted at the Yale Child Study Center. Fifty-six subjects were diagnosed with TS-only and 45 were diagnosed with TS+ADHD. Also included were 64 children with ADHD and 71 unaffected control children. The TS sample was ascertained through the Yale Tic Disorders Specialty Clinic and through the local chapter of the Tourette Syndrome Association. Subjects with a primary diagnosis of ADHD were recruited either through the Yale outpatient clinic or through a local chapter of Children and Adults with Attention Deficit Disorder (CHADD). Unaffected control children were recruited from randomly selected names on a telemarketing list of approximately 10,000 families in the local community and matched on a group basis for age, income and ethnicity. Approximately 10 percent of families who were contacted participated and received the same diagnostic evaluation as other subjects. Children with a history of neurological illness, past seizures or history of head trauma with loss of consciousness, mental retardation, pervasive developmental disorder, psychosis, or severe major depression were excluded. Additional exclusionary criteria for unaffected control subjects were any history of OCD, ADHD, tic disorder, or current Axis I disorder. Socioeconomic status was estimated with the Hollingshead four-factor index [30] and the majority of families were middle to upper-middle class. After a complete description of the study was given to the subjects, written informed consent was obtained from the parents and assent was obtained from children.

Procedures

All subjects were evaluated using the Schedule for Tourette and Other Behavioral Syndromes, [31] which includes the Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version (K-SADS-PL) [32] and extended modules on TS and associated disorders. The kappa statistics were evaluated in the earlier study and were 1.0 for TS and OCD and 0.66 for ADHD modules. [17] The Yale Global Tic Severity Scale (YGTSS) [33] and the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), [34] administered by an experienced master-level clinician as an interview with child and parent, were used to evaluate tics and OCD symptoms, respectively. YGTSS provides separate ratings on a 0 to 5 scale for the number, frequency, intensity, complexity, and interference of motor and phonic tics with a Total Tic Score in the range from 0 to 50. CY-BOCS yields separate scores, ranging from 0 to 20, for obsessions and compulsions, with a combined total of 0 to 40. The parents' scale of the Conners' Teachers and Parents Rating Scales [35] was used to obtain the 10-item hyperactivity index. Intelligence was evaluated with the Block Design and Vocabulary subtest of the Wechsler Intelligence Scale for Children (WISC-III). [36] Following a review of all available information, two senior clinicians independently assigned DSM-IV diagnoses using the best-estimate procedure. [37] All subjects also completed a battery of neuropsychological measures. Research assistants administering these measures were blind to the diagnostic status of the subjects. During these evaluation procedures, medicated children remained on their usual dose and type of medication. However, children on stimulant medications were required to skip their medications the morning of testing and any subsequent dose during their study assessments.

Neuropsychological measures

The battery of neuropsychological measures included well-known standardized measures that have been commonly used in TS research and reflect the domains of motor skills and response inhibition presumed to be affected in TS.

The Conners' Continuous Performance Test (CPT; version 3.0) [38] is a measure of sustained attention and inhibitory control, which requires the subject to respond to the target letters by a button press and to withhold the response to the nontarget letter "X". There is a total of 360 trials of which 36 (10 percent) are the nontargets. Thus, the motor system is primed to respond, and the subject must inhibit that prepotent response in the nontarget trials. The 360 trials are presented in 6 blocks, with three 20-trial sub-blocks which have different inter-stimulus intervals (1, 2, or 4 seconds). Each letter is displayed for 250 milliseconds. Average administration time is 14 minutes. Percent of omission and commission errors, the mean reaction time (RT) for hits, and between block RT variability were used as dependent variables. [39]

The Stroop Color-Word Interference Test [40] is a widely used test of cognitive inhibition. It consists of three conditions: A) color naming, B) word reading, and C) color-word interference. In the color naming condition subjects were asked to name, as quickly as possible, the color (red, green, or blue) of 126 dots, arrayed randomly in nine columns and 14 rows on a sheet of white paper (8.5×11 inches) and scanned left to right and then top to bottom. In the word reading condition subjects were asked to read, as quickly as possible, an equal number of similarly arrayed words ("red," "green," or "blue") printed in black ink. In the color-word reading condition, subjects were asked to name a similar array of words written in incongruent colors as quickly as possible. The time to completion of each task was recorded in seconds. Stroop interference score was calculated as $C-[(A×B)/(A+C)]$. [41]

Purdue Pegboard Task [42] is a measure of fine motor control which was previously shown to be impaired in children with TS and to predict tic persistence from childhood to adulthood. [43] This instrument includes a 12×18-inch board and 50 one-inch pins that are located in two cups at the top of the board. [44] The subject must place pins in one of the two columns each of which have 25 slots. The dependent variables from this test were the number of correctly placed pins for the dominant hand, nondominant hand, and bimanual hand conditions averaged across two 30 second trials for each condition.

Developmental Test of Visual Motor Integration (VMI; 4th Edition) [45] is a paper-and-pencil test in which the child copies 24 geometric designs, arranged in order of increasing difficulty. It assesses visual-graphic ability or the degree to which visual perception and finger–hand movements are coordinated. Previous studies suggested that children with TS experience difficulty on this task. [17] The Beery standard score was used as the dependent variable.

Data Analysis

Separate MANCOVAs with age, gender and a diagnosis of OCD as covariates were used to examine the differences among the four diagnostic groups on the Conners' Continuous Performance Test and Purdue Pegboard Task. ANCOVAs with the same covariates were used for Stroop Color-Word Interference Test and Developmental Test of Visual Motor Integration. SPSS was used for all data analyses and employed an alpha level of $p<.05$ (two-tailed). The multivariate and univariate tests were followed by the post hoc multiple comparisons with the Bonferroni adjustment for each dependent variable. Pearson's correlations were used to examine the associations among normally distributed continuous variables, and Chi-square statistics were used to test the differences between categorical variables. Diagnostic status was coded as a categorical variable with four values (1=TS, 2=TS+ADHD, 3=ADHD, and 4=unaffected controls) for the analyses of variance. List-wise deletion of missing values was used in MANCOVA and pair-wise deletion of missing values was used in univariate comparisons, Chi-square tests, and Pearson correlations. The data for each dependent measure were checked for normality of distribution and for outliers, defined as scores deviating by 3 or more SD from the group means. Nine outliers on the Conners' CPT and one outlier on Purdue were identified. Because outliers were few in number and outside the range of acceptable

performance, they were excluded form corresponding analysis of these measures. [46] Cases with missing values or outliers coded as dummy variables were not associated with any study variables. In a preliminary analysis, the differences on demographic and clinical characteristics as well as all dependent measures between the groups of subjects with and without the diagnosis of OCD were examined using independent sample t-tests and Chi-square tests. Subjects with OCD were more likely to have an additional diagnosis of another anxiety disorder than subjects without OCD ($Chi^2_1 = 14.34$, $p<0.001$), and no significant differences were found on other variables (data not shown). Consequently, all individuals with TS were considered together in the primary analyses, and a diagnosis of OCD (0=absent and 1=present) was used as a statistical covariate. Because younger age was associated with lower Conners' CPT and Stroop scores and older age was associated with higher VMI and Purdue scores, age was also included as a covariate in all subsequent analyses. All analyses were re-run for children under 14 years of age to control for the possible ceiling effects on neuropsychological measures and the results remained nearly identical.

RESULTS

Demographic and clinical characteristics of the four diagnostic groups are reported in Table 1. Significant difference was found in gender distributions across four diagnostic groups, which was controlled statistically in the subsequent analyses. No significant differences were detected among the diagnostic groups on age, race, or socioeconomic status. Table 1 also presents the scores on the Yale Global Tic Severity Scale and the Conners' Hyperactivity Index. The TS-only and TS+ADHD groups did not differ significantly in the current severity of tic symptoms. Likewise, the TS+ADHD and ADHD groups were similar on scores for the Conners' Hyperactivity Index. When entered in analysis of covariance, the Conners' Hyperactivity Index was not a significant covariate of the effects of diagnostic group on neuropsychological variables. There were no differences among the diagnostic groups on the measures of intelligence, percentage of subjects with co-occurring psychiatric disorders, and percentage of subjects receiving medication. Among the patients, there were no differences on any of the dependent variables between children receiving psychotropic medication and children not receiving psychotropic medication. The number of children receiving alpha$_2$ agonists differed among the groups (30, 40, and 16 percent in the TS-only, TS-plus-ADHD, and ADHD groups, respectively, $Chi^2_2 = 8.32$, $p<0.05$). However, when entered as a covariate in the analysis of variance, the effects of being on alpha$_2$ agonist medication on neuropsychological variables were not significant. The number of children receiving two or more medications did not differ across the three diagnostic groups or between the TS-plus-ADHD versus ADHD groups.

To minimize the number of comparisons, MANCOVAs (with a diagnosis of OCD, age, and gender as covariates) were performed with the Connors' CPT and Purdue variables and ANCOVAs (also with a diagnosis of OCD, age and gender as covariates) were performed with the Stroop and VMI variables. Multivariate effects of diagnostic status were significant for the Conners' CPT variables (Pillai trace=0.16; $F_{3, 202}$=2.90; $p<.001$) and the Purdue variables (Pillai trace=0.09; $F_{3, 226}$=2.34; $p<.01$). Post hoc univariate analyses and significant pair-wise comparisons are reported in Table 2.

Response inhibition

Univariate ANCOVAs revealed significant effects of diagnostic status on the Conners' CPT errors of omission and reaction time variability. Age emerged as significant covariate of these effects (an older age was associated with better performance) and was retained in the further runs of this analysis. Gender and OCD were not significant covariates and were excluded from consecutive analysis without affecting the results. Bonferroni corrected pair-wise comparisons revealed significant effects of ADHD on the Conners' CPT errors of omission and reaction

time variability. ADHD and TS+ADHD groups scored below the unaffected controls. Similarly, age (but not gender or OCD) emerged as a significant covariate in the ANCOVA of the effect of diagnostic status on the Stroop Golden Interference Score. Bonferroni corrected pair-wise comparisons revealed that subjects with ADHD had higher interference scores than unaffected controls.

Visual motor integration and fine motor control

Univariate ANCOVAs revealed significant effects of diagnostic status on the VMI. The covariate effects of age, gender and OCD diagnosis were not significant and these covariates were excluded. In the Bonferroni corrected pair-wise comparisons subjects with ADHD showed poorer performance on the VMI than unaffected control and TS-only groups. Given the mean standard score of 100, the TS-only group does not appear to be impaired on the VMI. Multivariate ANCOVA also revealed significant effect of diagnostic status on the Purdue Pegboard Task variables. Age and gender were significant covariates on all three Purdue Pegboard Task variables and OCD status was a significant covariate on the dominant hand performance, but not on the nondominant hand and bimanual performance variables. Bonferroni corrected pair-wise comparisons revealed that, compared to unaffected controls, subjects with ADHD had significantly lower scores on all three Purdue Pegboard Task variables.

To understand the effect of gender on the dominant hand Purdue performance in children with TS, we compared children with TS-only (n=56) to healthy controls using univariate ANCOVA with age and OCD diagnosis as covariates. Significant diagnosis by gender interaction effect $F_{(1, 120)}=4.12$, $p<0.05$ revealed that boys but not girls with TS were impaired in their dominant hand Purdue performance. We then compared boys (n=46) and girls (n=10) in the TS-only sample using independent samples t-test which revealed poorer performance in boys on dominant hand $t_{54}=2.67$, $p<0.01$ and bimanual performance $t_{54}=2.05$, $p<0.05$. Boys with TS-only did not differ from girls with TS-only on the clinical or demographic measures.

DISCUSSION

We examined neuropsychological functioning of children with TS with and without ADHD in a well-characterized and, to our knowledge, largest to-date sample. There were no differences between children with TS-only and unaffected controls on the measures of response inhibition. This finding is in agreement with the earlier neuropsychological studies [23, 47, 48] and with reports of normal behavioral performance in neuroimaging studies of response inhibition in TS. [12, 49] Using the Stroop task in an event-related functional MRI study, Marsh and colleagues reported that compared to unaffected controls, 51 children and adults with TS had normal behavioral performance but increased activation in the frontostriatal circuitry of response inhibition including right inferolateral prefrontal cortex, left mesial frontal gyrus, left dorsolateral prefrontal cortex, lenticular nucleus, and thalamus. Similar results of increased activation in prefrontal cortex during a cognitive control task were reported in 18 children with TS. [49] It was hypothesized that the lack of impairment in response inhibition represents a manifestation of a neural compensatory mechanism that develops in children with TS as a result of ongoing efforts to inhibit involuntary tics. [12, 13] Our study lends support to the neural compensation hypothesis by demonstrating the lack of impairment in response inhibition in a large sample of children with uncomplicated TS.

Similarly to children with ADHD, children with TS-plus-ADHD revealed deficits in sustained attention as evidenced by lower scores on the Conners' CPT errors of omission and reaction time variability. However, no significant differences between TS-plus-ADHD and unaffected controls were detected on the Stroop, VMI and Purdue tests suggesting that children with TS plus ADHD are less impaired than children with ADHD alone. Similar findings of greater

impairment in children with ADHD without tics compared to children with ADHD-plus-TS on the measures of sustain attention and response inhibition were reported by others. [26, 29, 50] It is possible that greater levels of impairment in children with ADHD alone were caused by an ascertainment bias, that is, children recruited for ADHD were more impaired than children recruited for TS and later diagnosed with both TS and ADHD. However, similar scores on the parent rated severity of ADHD symptoms between these two groups make this interpretation unlikely. There was also no difference in the mean age of ADHD onset between the TS-plus-ADHD group (4.81±1.5 years) and the ADHD-only group (5.14±1.6 years). An alternative explanation of the lack of difference between children with TS-plus-ADHD and healthy controls, by contrast to the difference between the ADHD and healthy controls groups, is that children with TS-plus-ADHD may represent a different neuropsychological endophenotype than children with ADHD without tics. Longitudinal studies can elucidate the utility of this endophenotype for discerning the developmental course of ADHD symptoms in children with TS.

Moderate size reduction in Purdue Test scores can be noted in direct comparison of children with TS-only to unaffected controls (Cohen's d = 0.50; 0.42 and 0.53 for dominant, nondominant and bimanual performance, respectively). However, these differences fell short of statistical significance when sex was entered as a covariate in the analysis. Significant diagnosis by gender interaction revealed that boys but not girls with TS-only were impaired in their dominant hand Purdue performance. Because impaired Purdue performance in childhood was shown to predict tic severity in adulthood, [43] our finding of the gender difference in Purdue performance in children with TS suggests that tics may have different developmental trajectories in boys and in girls. Performance on the Purdue Pegboard Test, a task of motor speed and dexterity, is associated with activation of frontal, sensorimotor and premotor cortices in both hemispheres. [51] Diminished sex differences in the frontoparietal regions were reported in TS [52] and a recent study reported thinning of the frontoparietal cortex in boys relative to girls with TS [53] suggesting that cortical morphology in girls may be associated with better tic control. Our result highlights the importance of investigating the effects of gender on the pathophysiology of TS.

The finding of unimpaired functioning on the VMI test is at odds with the previously published results. [17] It is possible that the small sample size of the TS without ADHD group (n=16) and elevated VMI scores in the control group (Mean Standard Score=105.3; SD=12.4) may be responsible for the significant difference between these groups in our previous study. It is also possible that the recognition of visuoperceptual deficits in TS in the early studies led to educational services, [54] which may be reflected in normalized VMI performance in this study.

Children with ADHD without tics differed from healthy controls on all dependent variables measures except Connors CPT errors of commission and reaction time. This is consistent with report of impaired interference control, [55] visual-motor integration [56] and fine-motor coordination, [57] and small magnitude of effect size on the Conners' CPT in children with ADHD. [58] Because TS co-occurs with OCD in 20 to 60 percent of clinically referred cases and both disorders are etiologically related, [59] children with co-occurring OCD were included in the study and the diagnosis was entered in analysis as covariate. In agreement with earlier studies, the presence of co-occurring OCD was not associated with neurocognitive impairment. [21]

Several limitations should be noted. The first limitation pertains to sample composition. Subjects with TS were ascertained from a specialty clinic, which may not reflect the full breath of TS phenomenology. Similarly, the ADHD sample was ascertained in part from the CHADD organization. Children in families who participate in voluntary organizations may represent a biased sample. In addition, the sample included mostly middle class Caucasian subjects and

the results may not be generalizable to other populations. The second limitation concerns the composition of the neuropsychological battery. It is possible that tasks with greater inhibitory demands than traditional Stroop and CPT may be more sensitive to performance deficits. To this end, task complexity was shown to increase response inhibition deficits in children with ADHD. [60] Recent studies in TS also suggested that inhibitory deficits emerge under increasingly complex conditions of the Hayling task. [61, 62] Other areas of executive functioning such as extra-dimensional set shifting may be impaired in TS and merit investigation. [63] However, the goal of this study was to examine neuropsychological performance on well-established tasks in a large sample in order to enhance compatibility with previous neurocognitive and recent neuroimaging studies. The third limitation includes lack of observational measures of tics, particularly during performance of the neuropsychological tasks. It has long been assumed that the occurrence of tics such as blinking and head jerks during testing may interfere with the performance on tasks of attention, speed and coordination. Indeed, it is plausible that a subject experiencing a bout of tics during a timed task may evidence decreased performance. Direct tic counts during neuropsychological testing would make it possible to investigate the association of the number of tics during performance of the task with the results. Our findings of unimpaired performance on the Conners' CPT, Stroop and VMI suggest that even if the tics were present during these tests, it did not significantly affect the results. This finding is also congruent with reports of lower likelihood of involuntary tics when individuals with TS are engaged in activities that require focused attention and purposeful movement. [64] Finally, the cross-sectional design makes it impossible to determine the directionality of associations between the variables.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographic and Clinical Characteristics by Diagnostic Group

	TS		TS+ADHD		ADHD		Normal Controls		Test	P
N	56		45		64		71			
Mean Age (SD)	10.94	(2.23)	11.29	(2.69)	11.66	(2.87)	11.49	(2.51)	$F_{3,232} = 0.85$	.467
Gender (% male)	46	(82.1%)	40	(88.9%)	45	(70.3%)	41	(57.7%)	$Chi^2_3 = 16.71$	.001
Race (% Caucasian)	48	(85.7%)	43	(95.6%)	60	(93.8%)	66	(93.0%)	$Chi^2_3 = 4.11$	.250
Socioeconomic status[a]	1.19	(0.86)	1.93	(0.84)	2.02	(0.88)	2.13	(0.91)	$F_{3,232} = 0.77$	.509
Mean Full Scale IQ (SD)	112.10	(15.18)	115.45	(17.11)	111.05	(19.70)	116.69	(17.66)	$F_{3,223} = 1.42$	.238
YGTSS[b] Total Tic Current	20.40	(9.45)	18.27	(7.54)					$t_{82} = 1.14$	.259
YGTSS Total Tic Worst Ever	27.70	(7.22)	29.48	(7.19)					$t_{82} = -1.12$	.265
Conners' hyperactivity index[c]	53.7	(12.8)	69.4	(13.9)	71.0	(12.3)	42.2	(8.8)	$F_{3,218} = 78.24$	.001
Medication Status (N, %)										
On medication[d]	35	(64.8%)	32	(71.1%)	49	(80.3%)		--		
No medication	19	(35.2%)	13	(28.9%)	12	(19.7%)		--	$Chi^2_2 = 3.52$	.172
Other diagnoses[e] (N,%)										
OCD	18	(32.1%)	16	(35.6%)	14	(21.9%)			$Chi^2_2 = 2.78$	.249
Oppositional Defiant	8	(17.0%)	14	(33.3%)	15	(26.3%)		--	$Chi^2_2 = 3.17$	.205
Conduct Disorder	0	(0%)	0	(0%)	3	(5.3%)		--	$Chi^2_2 = 4.78$	.092
Depression	9	(19.1%)	11	(26.2%)	21	(37.5%)		--	$Chi^2_2 = 4.37$	.112
Anxiety (except OCD)	11	(23.4%)	5	(12.2%)	13	(23.2%)		--	$Chi^2_2 = 2.25$	.325

Note: OCD = Obsessive-Compulsive Disorder; TS = Tourette Syndrome; YGTSS = Yale Global Tic Severity Scale.

[a] Measured with the Hollingshead Index of Social Status.[30] Distribution of educational attainment by study group is provided in Table S1, available online.

[b] Total tic score (range 0–50) does not include Impairment score.

[c] Post hoc pairwise test showed that all diagnostic groups scored higher than controls and TS+ADHD did not differ from Attention-Deficit/Hyperactivity Disorder (ADHD)

[d] Included stimulants (N=49), alpha2 agonists (N=45), selective serotonin reuptake inhibitors (N=32), antipsychotics (N=32), anxiolytics (N=5), mood stabilizers (N=4), and tricyclic antidepressants (N=2); 47 subjects were receiving more than one type of medication).

[e] Lifetime diagnosis based on structured interview and available data.

Table 2

Neuropsychological performance of children with Tourette Syndrome (TS), children with TS plus Attention-Deficit/Hyperactivity Disorder (ADHD), children with ADHD, and Unaffected Control Subjects

	TS		TS+ADHD		ADHD		Controls		Analysis		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	Significant Post Hoc Bonferroni Comparisons
Conners' CPT											
Errors of omission (%)	4.55	3.70	6.78	6.28	5.79	6.32	3.15	3.82	$F_{(3, 208)}=5.08$	.002	TS+ADHD = ADHD < NC
Errors of commission (%)	53.35	22.65	55.90	22.46	58.38	18.73	49.74	18.57	$F_{(3, 208)}=1.90$	.131	
Reaction time (ms)	414.55	76.61	423.12	88.45	429.50	102.58	405.68	83.58	$F_{(3, 208)}=0.80$	.497	
RT variability (SE)	11.76	5.90	13.81	6.50	15.02	8.57	10.13	5.92	$F_{(3, 208)}=5.80$	.001	TS+ADHD = ADHD < NC
Stroop											
Golden Interference Score	168.57	77.25	171.63	75.57	180.41	77.11	140.91	62.34	$F_{(3, 221)}=3.90$	.01	ADHD < NC
Purdue											
Dominant raw score[a]	13.55	2.21	13.47	1.90	13.10	1.97	14.54	1.67	$F_{(3, 231)}=6.73$	.000	ADHD<NC
Nondominant raw score	12.53	1.89	12.64	1.97	12.19	2.24	13.27	1.64	$F_{(3, 231)}=3.62$	.014	ADHD<NC
Bimanual raw score	10.35	1.69	10.37	1.75	10.09	1.61	11.20	1.51	$F_{(3, 231)}=5.88$	.001	ADHD<NC
VMI											
Beery Standard Score	100.44	15.59	92.89	14.26	88.65	14.21	98.63	14.81	$F_{(3, 224)}=7.96$	.000	ADHD < NC = TS

Note: ADHD =Attention-Deficit/Hyperactivity Disorder; CPT=Continuous Performance Test; NC=Normal Controls; RT=reaction time; SE=standard error; TS=Tourette Syndrome; VMI=Beery Visual Motor Integration Test;

[a] Significant diagnosis by gender interaction effect $F_{(1,120)}=4.12$, $p<0.05$ revealed that boys but not girls with TS-only were impaired in their dominant hand Purdue performance.