Neuropsychological Functioning in Children with Tourette Syndrome (TS)

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Abstract

Objective: We examined whether children with Tourette syndrome (TS) displayed a unique pattern of neuropsychological deficits on the CANTAB® relative to control children. We also looked at whether children with TS and other comorbidities had more neuropsychological impairments than those with uncomplicated TS and how age was related to the profile of neuropsychological deficits in TS. **Method:** Participants included 38 children with TS (aged 7 to 13 years) and 38 control children (aged 6 to 12 years). All children were administered 8 subtests from the CANTAB® and parents and teachers completed the BRIEF rating scale on children in the TS group. **Results:** Children with TS displayed deficits relative to control children on measures of visual memory, executive functioning, and attention from the CANTAB®. Among the TS group, age was negatively correlated with performance on measures of executive functioning, speed of response and working memory. **Conclusions:** Identifying the pattern of neuropsychological deficits in children with TS on the CANTAB® is important for highlighting areas of deficit that can be targeted for intervention and teaching strategies. With further research, the CANTAB® may prove to be a useful resource in the assessment and treatment of children with TS.

Key words: CANTAB®, Tourette Syndrome, executive function, BRIEF, child development

Résumé

Objectif: Comparer les résultats obtenus aux tests CANTAB® par des enfants atteints du syndrome de Tourette à ceux d'un groupe témoin; vérifier si le déficit neuropsychologique des premiers suit un schéma unique; établir si les enfants atteints de ce syndrome et de comorbidités ont davantage de déficits neuropsychologiques que ceux qui souffrent du syndrome de Tourette simple; déterminer si l'âge influe sur le profil des déficits neuropsychologiques de ces derniers. **Méthodologie:** Huit sous-tests CANTAB® ont été administrés à 38 enfants âgés de 7 à 13 ans souffrant du syndrome de Tourette et à 38 enfants âgés de 6 à 12 ans (groupe témoin); les parents et les enseignants ont appliqué l'échelle abrégée d'appréciation psychiatrique (BPRS) aux enfants du groupe Tourette. **Résultats:** Les enfants atteints du syndrome de Tourette affichaient des déficits de la mémoire visuelle, du fonctionnement exécutif et de l'attention. Dans ce groupe, l'âge était en corrélation négative avec les mesures de fonctionnement exécutif, de rapidité de réponse et de mémoire de travail. **Conclusion:** Il est important de comprendre le schéma des déficits neuropsychologiques révélés par les tests CANTAB® pour mettre en lumière les zones sur lesquelles les enseignants peuvent intervenir. Les tests CANTAB® peuvent aider à évaluer et à traiter les enfants souffrant du syndrome de Tourette.

Mots clés: CANTAB®, syndrome de Tourette, fonction exécutive, BPRS, développement

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Tourette Syndrome (TS) is a neurodevelopmental disorder that begins in childhood and is characterized by involuntary motor movements and vocalizations called tics (Kenney, Kuo, & Jimenez-Shahed, 2008). TS is frequently associated with difficulties in self-esteem, school performance, social acceptance, and family life. TS usually becomes apparent in children between ages 2 to 15, with approximately 50% of patients affected by age 7, and it is more frequent in males than females by a ratio of about 5 to 1 (Kenney et al.; Hirtz et al., 2007). Although prevalence estimates vary, TS is no longer considered a rare disorder, with the number of children affected estimated to be 7 in 1000 (Kenney et al.; Hirtz et al.).

In addition to tics, TS is frequently accompanied by other symptoms including speech and conduct problems, mood instability, impulsivity, distractibility, anxiety, motor hyperactivity, learning dysfunctions, and obsessive-compulsive symptoms (Leckman, Yeh, & Lombroso, 2003; Shapiro, Shapiro, Young, & Feinberg, 1988). The disorders that most commonly occur with TS are Attention Deficit Hyperactivity Disorder (ADHD) (55%) (Freeman, 2007) and Obsessive-Compulsive Disorder (OCD) (20-60%) (Apter et al., 1993; Cath et al., 2001; Pitman, Green, Jenike, & Mesulam, 1987). Children with TS and another comorbid disorder are often referred to as TS-plus (Packer, 2007). The nature of the relationship between TS and comorbid conditions is poorly understood, but in general, the more severe the tics the higher the psychiatric comorbidity. Individuals with TS also typically display a variety of neuropsychological deficits (Bornstein, King, & Carroll, 1983), but the nature of these deficits is still unclear.

TS has been linked to disruption of fronto-striatal pathways (Robertson, 2000) and the basal ganglia (Mink, 2001). There is evidence for frontal lobe abnormalities in both children and adults with TS, particularly in lateral and anterior cingulate areas (Peterson et al., 2001) and reduced volume of the prefrontal cortex (Gerard & Peterson, 2003). Executive functions are higher-order cognitive processes involved in goal-oriented behavior and are thought to be mediated by the frontal lobe (Zelazo & Mueller, 2002). Executive function includes many cognitive processes including planning, inhibition, working memory, set shifting, flexible thinking, strategy employment, abstract thinking, concept formation, and fluency. There is new emerging research indicating that executive function may be a significant area of impairment in individuals with TS (Channon, Pratt, & Robertson, 2003).

Channon, Pratt, and Robertson (2003) conducted a study on executive function and memory in 21 control children and 29 children with TS (mean age 12.33 years), 9 of whom had TS+ADHD, 6 who had TS+OCD, and 14 with TS alone. The TS alone group performed worse than controls on a measure of inhibition and strategy use, whereas the TS+ADHD group performed worse than the controls on all executive functioning measures (inhibition and strategy use, multitasking, rule following, and set shifting). However, the TS+OCD group did not differ from the control group on any of the executive functioning measures and there were no significant group differences on tests of implicit or explicit aspects of memory.

In another study, Chang, McCracken, and Piacentini (2007) found that children with TS, aged 7 to 14, had difficulties on measures of response inhibition, visual motor integration, memory, and attention relative to control children. Crawford, Channon, & Robertson (2005) studied executive functioning and other cognitive abilities in children with TS ranging in age from 11 to 18 years and found that inhibition was an area of deficit for children with TS, but found no significant group differences in working memory or gambling tasks. Executive functioning appears to be an area of deficit for children with TS, however not all researchers have documented these deficits (Mahone, Koth, Cutting, Singer, & Denckla, 2001). Ozonoff, Strayer, McMahon, and Filloux (1994) failed to find executive function impairments among children with uncomplicated TS, indicating that perhaps the cognitive impairments in TS may be related to comorbidities. Finally, attentional deficits in TS are important to consider. Georgiou and colleagues (1998) found that adults with TS were impaired on tests for which they were required to hold attention. Others have found attention deficits among adults with TS (particularly those with comorbid ADHD) (Silverstein, Como, Palumbo, West, & Osborn, 1995).

In addition to traditional neuropsychological tests, another tool used to measure executive dysfunction is the Behavioral Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000). The BRIEF is a parental and teacher rating scale of a child's executive functioning behaviors in everyday situations and settings, measured across eight domains of functioning. There are few studies on the use of the BRIEF in TS. Mahone et al. (2002) studied children with TS (aged 7 to 14) and found that those with pure TS differed significantly from controls on the BRIEF working memory subscale, indicating that this may be an area of cognitive impairment for children with TS. In addition, TS+ADHD participants were impaired on all of the BRIEF index scores and subdomains that were studied compared to both the control group and the pure TS group.

An innovative measure of neuropsychological and executive functioning is the Cambridge Neuropsychological Test Automated Battery (CANTAB®) (Cambridge Cognition, 2004). The CANTAB® is a computerized test which assesses a variety of neuropsychological functions (visual memory, verbal memory, decision making, attention, executive functioning, working memory, and planning) using a computer touch screen and visual cues. The CANTAB® has been successfully used in the assessment of many different developmental disorders including children with autism (Hughes, Russell, & Robbins, 1994), ADHD (Kempton et al., 1999; Luciana, 2003), Down's Syndrome (Visu-Petra L, Benga, Tincas, & Miclea, 2007), and Fetal Alcohol Spectrum Disorders (Green et al., 2009). However, there are very few studies on use of the CANTAB® in the assessment of TS. One study that has utilized the CANTAB® in TS is that conducted by Watkins et al. (2005). They found that adults with TS (n=20) were impaired on measures of spatial recognition memory, extra-dimensional set-shifting, and decision making. Overall, the areas of deficits seen in the TS and OCD groups were similar, although the OCD group demonstrated greater deficits with the exception of a decision making task in which the TS group was more impaired (Watkins et al. 2005).

Children with TS display deficits on some aspects executive functioning. However, there are few published studies on executive functioning in children with TS and there have been mixed results among them (Ozonoff et al., 1994). Furthermore, in these studies, typically only a few aspects of executive functioning have been examined, and because it refers to many different cognitive processes, it is important to examine executive functioning across a variety of domains within the same group of individuals. This is essential for identifying the profile of executive functioning deficits among children with TS and for identifying specific areas of weakness. There is one published study which used the CANTAB® with individuals with TS (Watkins et al., 2005), however only adults were tested, and some of the subtests from the CANTAB® were not administered.

Thus, the goal of this study was to examine whether children with TS display a unique profile of neuropsychological and executive functioning deficits on a variety of CANTAB® subtests relative to control children. We also examined how performance on the CANTAB® related to performance on a behavioral measure of executive functioning (the BRIEF) and whether children with TS and other comorbidities had more neuropsychological impairments than those with uncomplicated TS. Finally, we wanted to determine how age was related to the profile of neuropsychological deficits in TS because research indicates that some of the neuropsychological deficits in TS may become more pronounced with age (Bornstein, Carroll, & King, 1985).

Method

Participants

The sample consisted of 38 participants (36 males) aged 7 to 13 years (*M* = 10 years 9 months, *SD* = 1 year 10 months), with a confirmed diagnosis of Tourette Syndrome. Thirty-eight control participants (24 males) aged 6 to 12 years (*M* = 9 years 1 month, *SD* = 1 year 6 months) were also included. Children with TS were recruited through an outpatient Tourette clinic. The diagnosis of TS and other comorbidities was based on clinical interviews utilizing the DSM-IV-TR (American Psychiatric Association, 2001) criteria and supplemented by clinical rating scales including the Weiss Functional Impairment Rating Scale, SNAP, Dimensional Yale Brown Obsessive Compulsive Severity Scale, and the Yale Global Tic Severity Scale (YGTSS). The diagnosis was conducted by two Child Psychiatrists. Exclusion criteria for this study included brain injury, Fetal Alcohol Spectrum Disorder, psychotic disorder, mental delays, or other neurological disorders. On the YGTSS mean raw scores (which range from 0-50) on the Total tic impairment scale were 23.33 (range 0-50), and on the Total tic severity scale were 23.27 (range 7-37). The mean Total tic severity and impairment score (which ranges from 0-100) was 46.73 (range 7-86).

Control children were recruited through local schools. They were screened for neurodevelopmental disorders prior to inclusion in the study and none had TS or any other neurodevelopmental disorder. Among the control group, 81.6% of children lived with both parents, and 88.2% were of Caucasian ethnicity. Among the TS group, 73.7% of children were living in two-parent homes, and 94.6% were of Caucasian ethnicity. Furthermore, 54.0% of the children in the TS group attended a special school program or had a school aide and 84.2% were taking medication at the time of testing. Medications included: Risperdal (antipsychotic), Tenex, Clonidine (alpha 2 adrenergic agonists), and SSRI's (antidepressants). As shown in Figure 1, the most frequently occurring comorbidities among the participants with TS were ADHD (36.8%) and OCD (28.90%).

Materials and Procedure

All children were administered the same CANTAB® subtests and were compared to the same norm group, with respect to their age, to determine z-scores. Parents and teachers of children in the TS group also completed the BRIEF rating scale and parents completed various clinical rating scales mentioned above.

CANTAB® subtests. Eight subtests from the child battery of the CANTAB® were administered (see Table 1) measuring 1) Visual Memory through the PRM (Pattern Recognition Memory), and SRM (Spatial Recognition Memory) tasks, 2) Executive Function through the SSP (Spatial Span), SOC (Stockings of Cambridge), IED (Intra-Extra Dimensional Set Shift), and SWM (Spatial Working Memory) tasks, and 3) Attention through the RTI (Reaction Time), and RVP (Rapid Visual Information Processing) tasks. A Slimbook P110 Touch ICP1.3GHZ touch screen was utilized. These tests were carried out in one session unless time constraints of the child's schedule forced the remainder of the test to be conducted on a different day. The same child battery was used for all children. See Appendix A for a detail description of each CANTAB subtest.

Behavioral Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000). The BRIEF is a parent and teacher rating scale that measures executive functioning in children aged 5 to 18 years. The BRIEF consists of eight clinical scales: three scales (Inhibit, Shift, and Emotional Control) that comprise the Behavioral Regulation Index (BRI); and five scales (Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor) that comprise the Metacognition Index (MI). The BRI and MI combine to form the Global Executive Composite (GEC). Scores on the BRIEF have a mean of 50 and standard deviation of 10, with higher scores indicating more impairment. Abnormally elevated scores suggesting clinical significance are indicated by T-scores of 65 or greater which are at least 1.5 standard deviations above the mean. The BRIEF has high validity and reliability scores; the Cronbach alpha coefficient measure of internal consistency ranges from 0.80-0.98 for parent form clinical and normative samples and the test-retest reliability correlations range from .76 to .85 (Gioia, Iquith, Retzlaff, & Espy, 2002).

Table 1. Description of CANTAB® subtests

Domain	CANTAB® subtest	Function measured
Visual Memory	Pattern Recognition Memory (PRM) Spatial Recognition Memory (SRM)	Visual recognition memory Spatial recognition memory
Executive Functioning, Working Memory and Planning	Spatial Span (SSP) Stockings of Cambridge (SOC) Intra-Extra Dimensional Set Shift (IED) Spatial Working Memory (SWM)	Working memory capacity Spatial planning and motor control Rule acquisition and attentional set shifting Working memory and strategy use
Attention	Reaction Time (RTI) Rapid Visual Information Processing (RVP)	Speed of response Visual sustained attention

Figure 1. Prevalence of comorbidities among children with TS

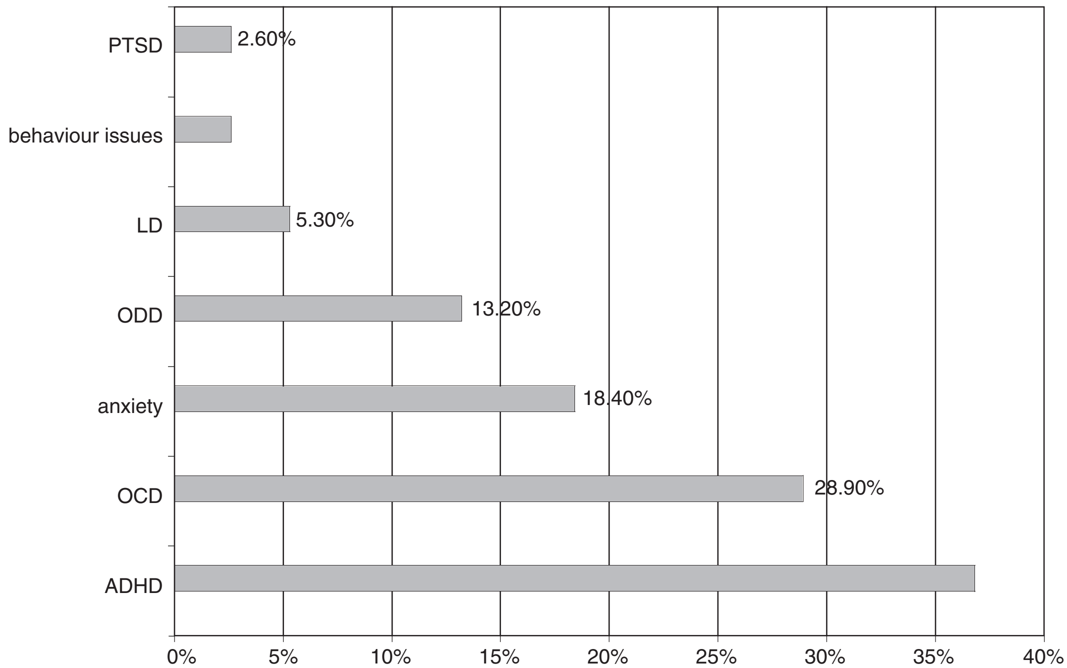
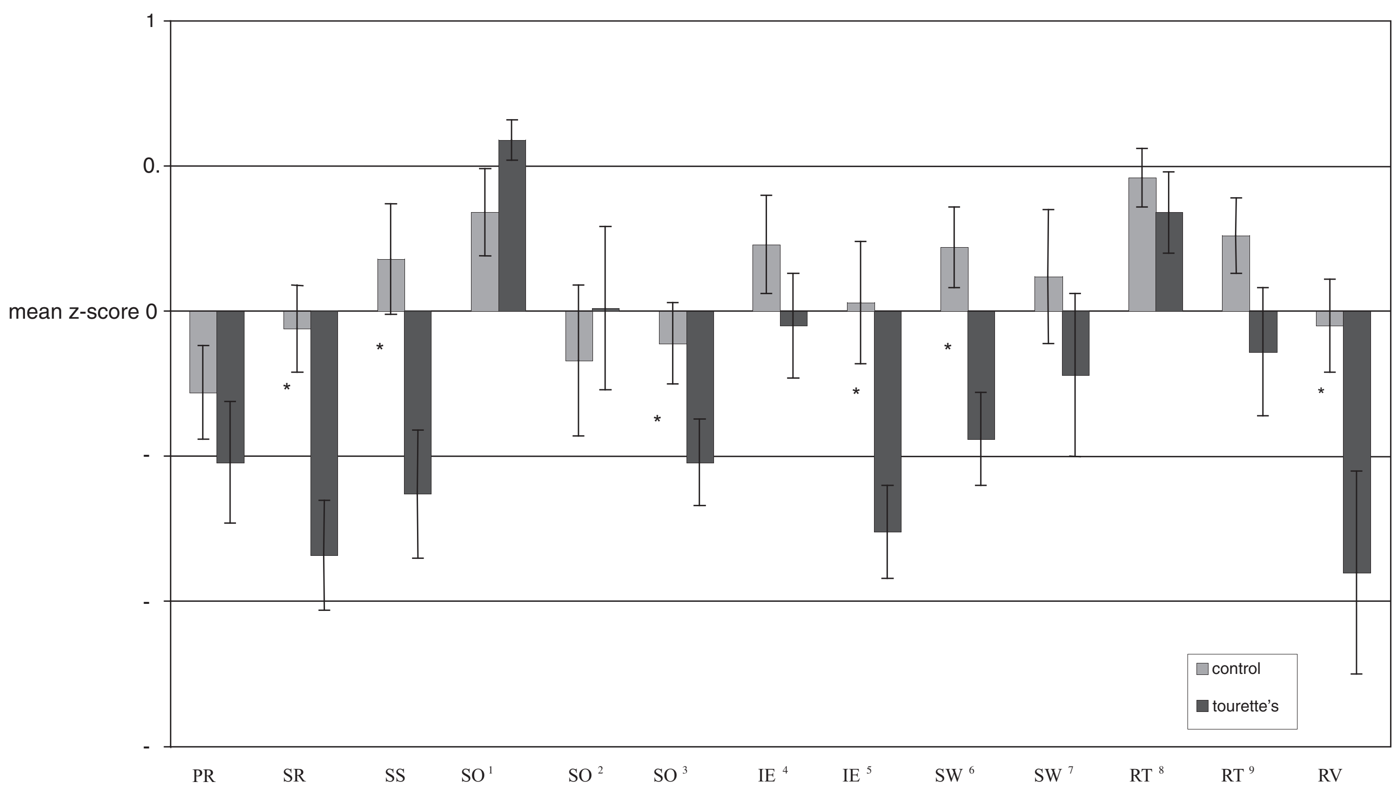


Figure 2. Comparison of CANTAB® z-scores for children with TS and control children



Note. SOC[1] initial thinking time, SOC[2] subsequent thinking time, SOC[3] problems solved, IED[4] stages completed, IED[5] total errors, SWM[6] between errors, SWM[7] strategy, RTI[8] movement time, RTI[9] reaction time.

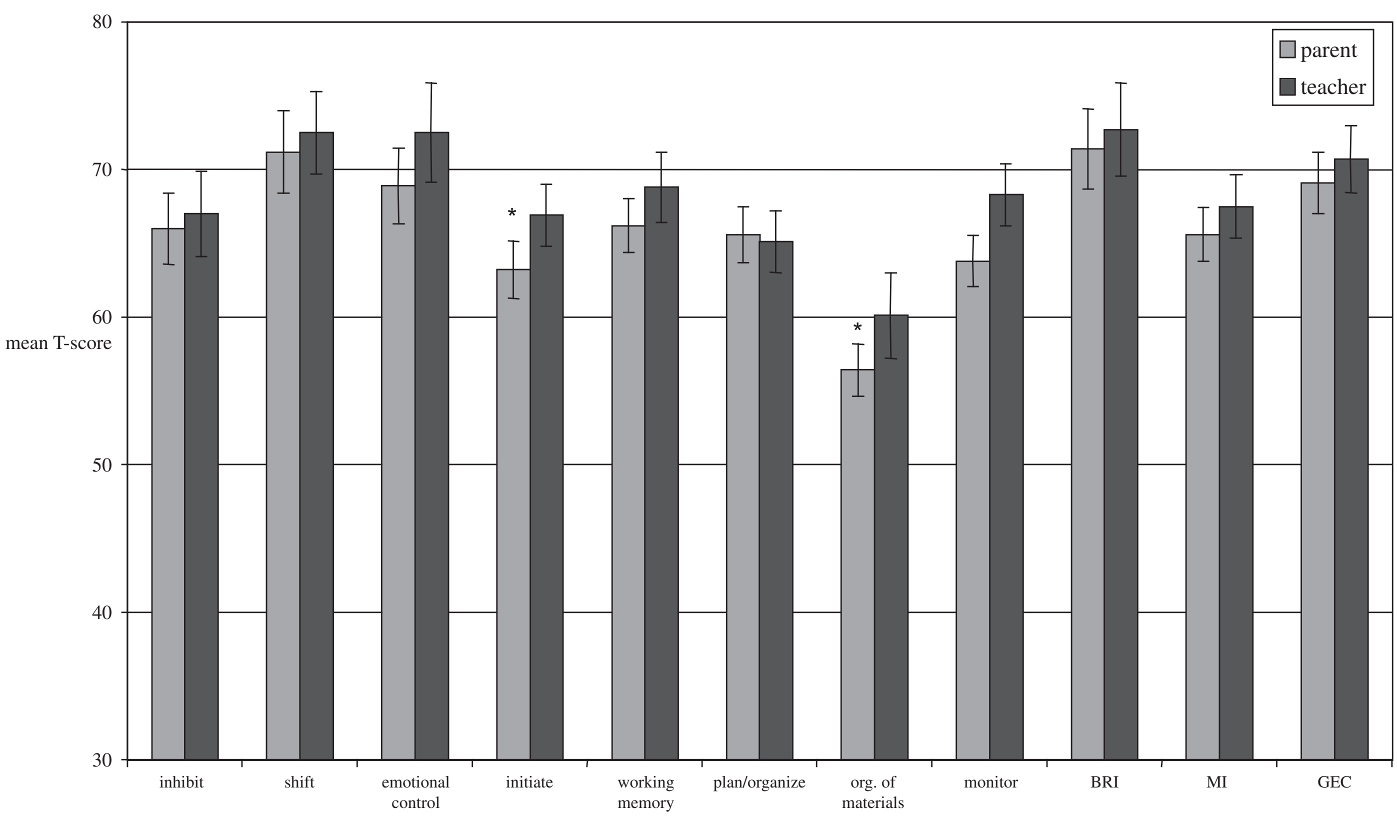
Results

Figure 2 compares standardized (z-score) performance of children with TS and control children on the CANTAB® subtests. Control and TS children were compared on the subtests of CANTAB® using separate one-way ANOVAs. The Children with TS scored significantly lower than control children on the SRM, SSP, SOC problems solved in minimum moves, IED total errors, SWM between errors, and RVP. We also looked at the rates of failing or aborting a subtest and found that within the TS group, 2.6% (1 child) failed the SOC problems solved in minimum number of moves, and mean subsequent thinking time, while 2.6% (1) aborted the SOC mean initial thinking time. The control group displayed similar failure rates: 5.3% (2) failed the SOC mean initial and subsequent thinking time while 2.6% (1) failed the SOC problems solved in minimum number of moves and 2.6% (1) aborted the IED stages completed and total errors measures.

Figure 3 displays mean t-scores on the parent and teacher BRIEF among the TS group. The majority of scores were at least one standard deviation above the mean (indicating impairment), with the exception of Organization of Materials. Separate ANOVAs were used to compare teacher and parent ratings on the subscales of the BRIEF. In general, teachers reported higher scores (indicating more difficulty) than parents, with group differences being significant on the Initiation and Organization of Materials scales. We also examined how performance on the CANTAB® correlated with the parent and teacher BRIEF among the TS group. To control for multiple comparisons we set alpha at .01 and found that the SOC problems solved in minimum number of moves correlated significantly with the parent Inhibit $r(31)=0.50$ $p<0.01$, Emotional Control $r(31)=0.50$ $p<0.01$, and Monitoring scales $r(31)=0.47$ $p<0.01$. No significant correlations were found on the teacher form.

Next we examined how children with pure TS performed compared to children with TS+ADHD and TS+OCD on the CANTAB® and the BRIEF. For these analyses the total TS group was divided into pure TS (n = 14), TS+ADHD (n = 14) and TS+OCD (n = 11). Separate one-way ANOVAs were used to compare the groups on the subtests of the CANTAB® and the index scores of the parent BRIEF. Index scores on the teacher BRIEF were not analyzed because there was not enough data (n<10 for most groups). Children with TS+OCD did not perform significantly different than the pure TS group on any of the CANTAB® subtests or index scores of the parent BRIEF (all ps > .30). Children with TS+ADHD performed significantly better (M=0.10 SD=0.86) than the pure TS group (M=-0.92 SD=1.28) on PRM percent correct, $F(1, 27) = 6.12$, $p < .05$. The TS+ADHD performed significantly worse that the pure TS group on BRIEF parent MI (M=70.25, SD=8.00; M=59.50, SD=11.00), $F(1, 23) = 7.53$, $p < .05$, and parent GEC (M=74.00, SD=9.84; M=62.17, SD=13.40), $F(1, 23) = 6.08$, $p < .05$.

Figure 3. Comparison of BRIEF parent and teacher ratings among the TS group



Finally we examined the correlations between age and CANTAB® z-scores (see Table 2). Age correlated negatively with IED stages completed, RTI movement time, and SWM between errors among the TS group. However, there were no significant correlations with age among the control group. We also looked at the correlation between age and BRIEF index scores, and none were significant, all *p*s > .31.

Discussion

We investigated whether children with TS display a unique pattern of neuropsychological deficits on the CANTAB® relative to control children. We also looked at how performance on the CANTAB® related to performance on a behavioral measure of executive functioning (the BRIEF), whether children with TS and other comorbidities had more neuropsychological impairments than those with uncomplicated TS, and whether age was related to the profile of neuropsychological deficits in TS. Children with TS scored significantly lower than the control children on measures of visual memory (SRM), executive function (SSP, SOC problems solved in minimum moves, IED total errors, SWM between errors) and attention (RVP). Our results support the findings of Watkins et al. (2005), as they found that adults with TS were also impaired on the SRM and IED, indicating that visual memory and executive function impairments occur in both children and adults with TS.

Children with TS also showed deficits on a behavioral measure of executive functioning (the BRIEF). The majority of scores on the BRIEF were in the impaired range (with the exception of Organization of Materials), indicating that children with TS display a variety of behavioral executive function deficits on the BRIEF. Teacher ratings on the BRIEF tended to be higher (indicating more impairment) than parent ratings, which suggests that the executive functioning deficits in children with TS may be more pronounced in the classroom where they are required to sit still and focus for longer periods of time. There were very few correlations between the CANTAB® and the BRIEF, but a measure of planning (SOC) correlated with parental ratings of Inhibition, Emotional Control, and Monitoring on the BRIEF.

Table 2. Correlations between performance on the CANTAB® and age for the TS and control groups

CANTAB® subtest	Tourette	Control
PRM percent correct	-.15	-.00
SRM percent correct	.13	.23
SSP span length	.07	.30
SOC mean initial thinking time	.19	-.22
SOC mean sub. thinking time	.08	-.19
SOC problems solved	.03	.27
IED stages completed	**-.34***	.04
IED total errors	-.21	-.16
SWM between errors	**-.32***	.04
SWM strategy	-.16	.25
RTI movement time	**-.37***	-.19
RTI reaction time	.14	-.28
RVP	.07	.26

*$p < 0.05$

Next we examined how children with pure TS performed compared to children with TS+ADHD and TS+OCD on the CANTAB® and BRIEF indexes. For these analyses the entire TS group was divided into one of three groups: pure TS, TS+ADHD, and TS+OCD. There were no differences between the TS+OCD and the pure TS group on the CANTAB® or the BRIEF indexes. Children with TS+ADHD performed significantly better than the pure TS group on PRM percent correct. This finding may be due to the fact that more participants in the TS+ADHD group (93%) were on medication than the pure TS group (79%) which may have allowed the TS+ADHD group to focus more effectively on the PRM task and control tics. The TS+ADHD group performed significantly worse than the pure TS group on the parent BRIEF MI and GEC indexes, indicating that parents report those with TS+ADHD as having more difficulty on metacognitive and global executive functioning behaviors. This supports the findings of Mahone et al. (2002) who found also found that individuals with TS+ADHD had more impairments on the BRIEF than pure TS and control participants.

Finally, we examined how age correlated with performance on the CANTAB® and BRIEF because research suggests that the neuropsychological deficits in TS may become more pronounced with age (Bornstein et al., 1985). Among the TS group, age correlated negatively with measures of attentional set shifting, speed of response, and working memory, indicating that older children with TS have more difficulty (relative to the norm) in these areas than younger children. Thus, our results support the findings of previous research (Bornstein et al.) indicating that some of the neuropsychological deficits may increase with age among children with TS.

Despite the importance of these findings some limitations must be noted. The number of females in the control group was greater than in the TS group. TS occurs more often in males, and it was difficult to obtain a primarily male sample for the control group. However, there is little evidence to suggest that cognitive performance differs significantly from one gender to another. Furthermore, our TS group was a clinically referred sample and thus may have been more severe than the general TS population. Many children in the TS group were on medication and/or attending a special school program which indicates that they may have been more severe. Group differences between the pure TS and TS+ADHD groups are confounded by the fact that more children TS+ADHD were currently on medication than the pure TS group. Thus it is unclear whether similar group differences would be found if the two groups were matched on medication status. It is probable that medication aided the TS+ADHD group on some tasks. Furthermore, 84% of the entire TS group was currently taking medication, which may have impacted their performance on the CANTAB®. It is possible that medication may have lessened their tics and allowed them to focus more which would likely aid performance, thus group differenced on the CANTAB® may actually be underestimated. However, we did not feel it was appropriate or ethical to ask the children to withhold from taking their medication for the purposes of this study. Furthermore, any relations with age may be confounded by when the child was referred and diagnosed.

The results of this study display different neuropsychological profiles on the CANTAB® between TS children and controls. The CANTAB® is designed to assess higher level cognition including executive function, working memory, and planning functions associated with the frontal cortex. Measures of spatial memory (spatial recognition memory, spatial span, and spatial working memory) were significantly impaired in the TS group. From a clinical perspective, this spatial memory deficit may be related to the characteristic difficulty that children with TS show in school when copying information from the board onto paper (e.g. transposing). Executive functions as measured by the spatial SSP, SOC, IED, and SWM were also significantly impaired, with children with TS+ADHD showing particular difficulty on the SOC.

Another interesting result was that the pattern of performance between the TS and control groups on the two tests of attention (RTI and RVP) was very different. Performance on a test of speed of response and reaction time (RTI) was slightly above the mean in both groups of children, however children in the TS group showed marked difficulty relative to controls on the RVP which involves more sustained attention and inhibition. Children with TS also showed strengths on the SOC mean initial thinking time. Taken together, these results indicate that children with TS are quick to respond and have adequate reaction time, but tend to show more difficulty in holding their attention and inhibiting delayed responses. On the BRIEF, nearly all teacher and parent ratings were in the impaired range with teachers rating behaviors worse than the parents. This may indicate more stress and distraction for children with TS in the classroom. Clinically, children with TS tend to do quite well in quiet and non-distractible situations, suggesting that distractibility (not only pure attention problems) is a major factor in the academic functioning of these children.

Conclusion

In conclusion, the CANTAB® may help isolate discrete cognitive functions that may have implications for theory, strategy use, and treatments of the underlying cognitive process which are important in children's learning and pathology. For example, the CANTAB® may help differentiate between pure impulsivity and inhibition of delayed responses which may respond to different strategies. Shifting set difficulties may be worsened by certain medications such as stimulant and other medication groups may be more efficacious. Clinically, stimulants help with inattention and impulsivity in TS with ADHD but may worsen tics and mental rigidity. This latter symptom can be measured by shifting set on the CANTAB®. Depending on the profile of a drug naïve patient on the CANTAB®, it could help the clinician chose a medication such as Guanfacine, over a stimulant, because Guanfacine does not increase mental rigidity and may help a broader range of executive dysfunction. Thus, the CANTAB® could be used to elucidate in an objective manner the effects of specific medications on executive function in TS plus. In addition, the unique profiles displayed by children with TS may aide in diagnosis. Identifying specific deficits that children with TS display on the CANTAB® is important for highlighting areas of weakness that can be targeted for intervention and teaching strategies. For instance, in this study children with TS had impairments on visual memory, executive functioning, and attention, and thus intervention should focus on improving these specific areas. Future research with larger and more diverse samples on the clinical utility of the CANTAB® for children with TS is important. Finally, longitudinal research on the developmental trajectory of neuropsychological deficits among children and adolescents with TS is critical.

Acknowledgements/Conflict of Interest

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Appendix A - CANTAB® Subtests

Visual Memory

Pattern Recognition Memory (PRM). The PRM test is designed to test visual memory. In this test, a series of images are shown to the participant in the centre of the screen, and then a series of images are shown in sets of two. The participant must choose the image that they think they have previously seen. The computer notifies the participant whether or not they are correct. The score that is obtained is a measure of the percent of correct responses.

Spatial Recognition Memory (SRM). The SRM test assesses spatial recognition memory. In this test, the participant is instructed to observe the movement of a square around the screen. Then, the participant is presented with a set of boxes, one of which is in the same location that the original square traveled to and the other which is not. The participant must successfully identify which of the boxes is in the same location as the original square's path. The score that is obtained is a measure of percent of correct responses.

Executive Function

Spatial Span (SSP). The SSP task is designed to test working memory capacity. In this test, a series of squares at random locations on the screen light up in a particular path. The test participant must repeat the path that was just shown to them by touching the squares in proper order. The level of difficulty increases from 2 boxes to 9 boxes. The score that is obtained is a measure of span length (the length of the pattern the participant is able to follow).

Stockings of Cambridge (SOC). The SOC test is designed to assess planning and motor skills. In this Tower test, the computer screen is divided into two halves. Both halves have identical visual setups of what appear to be three hanging stockings holding three colored balls (red, green, blue) in different arrangements. The participant is instructed to arrange the balls on the bottom half of the screen to match the arrangement on the top of the screen. On the right hand side of the screen, the participant is informed of the number of moves that the pattern can be accomplished in. If the participant exceeds a certain number of moves, the test stops and the next pattern is shown. The level of complexity and number of moves increases as the test progresses. In the second part of this test, the participant is asked to follow the pattern of movement of the balls that is seen in the top half of the screen. The scores that are obtained are a measure of the length of time taken by the participant to make the first move, the length of time taken for each subsequent move, and the number of problems solved in the minimum number of moves.

Intra-Extra Dimensional Set Shift (IED). The IED is designed to assess frontal lobe function. In this test, four large rectangles appear on the computer screen and in two of these rectangles, a set of large images appears. The participant is instructed to choose an image from the two and then make subsequent decisions based on the outcome of the first trial. If the "correct" image is chosen, the computer notifies the participant by lighting up green. Then the participant chooses from the next set of images based on information gathered from the previous trials. At a certain point, the pattern changes (i.e. a secondary shape appears next to the larger shape) and the participant must be able to detect this. The scores that are obtained are a measure of the number of stages of the task completed as well as the number of errors made.

Spatial Working Memory (SWM). The SWM task is designed to test spatial working memory. A series of colored boxes appear at random locations on the computer screen. By touching the boxes, the participant may or may not uncover a blue chip. Upon finding the blue chip, the participant must drag it to a meter on the right hand side of the screen until the meter is filled. The participant is told that once a blue chip has been uncovered, the colored box will never again be covering a blue chip. In this way, the test assesses working memory by determining whether the participant remembers which boxes have already been chosen. The level of difficulty increases as the number of boxes increases. The scores that are obtained are a measure of between errors (where the participant chooses a box under which they have already discovered a chip) and strategy (the number of boxes used for each new search).

Attention

Reaction Time Index (RTI). The RTI test measures the speed of response and movement. During this test, a hand-controlled device is attached to the computer for use by the participant. A large circle appears in the centre of the screen. A small yellow circle appears in the centre of this circle when the participant pushes a button on the handheld device. The participant must then quickly touch the yellow circle on the screen. In this way, the test measures how quickly the participant is able to touch the yellow circle once it appears. In the second part of the test, the same task is performed, except now there are five circles in which the yellow circle may appear, and the participant has no way of determining which of these larger circles will contain the yellow one. The scores that are obtained are a measure of movement time and reaction time.

Rapid Visual Information Processing (RVP). In the RVP test, visual attention is assessed. In this test, the participant is presented with a number sequence (3, 5, 7) on the screen next to a large box in which numbers appear in random order. Whenever the participant sees the 3, 5, 7 sequence, he/she must press a button on the handheld device (the same that is used in the RTI subtest). The participant must wait until the last number of the sequence is shown (i.e. the seven) before pushing the button. Initially, the participant is given visual cues such as underlined sequences or colored numbers. As the test progresses, these visual cues are removed. The score that is obtained is a measure of the number of times the participant correctly detects the pattern.