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Impact of co-morbid attention-deficit and hyperactivity disorder on cognitive function in male children with Tourette syndrome: A controlled study

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Abstract

Tourette syndrome (TS) and attention-deficit and hyperactivity disorder (ADHD) are co-morbid neurodevelopmental conditions affecting more commonly male patients. We set out to determine the impact of co-morbid ADHD on cognitive function in male children with TS by conducting a controlled study. Participants included four matched groups of unmedicated children (age range 6-15 years): TS (n=13), TS+ADHD (n=8), ADHD (n=39), healthy controls (n=66). Following clinical assessment, each participant completed a battery of tests from the Wechsler Intelligence Scale for Children-III, the Italian Battery for ADHD, the Tower of London test, the Corsi test, and the Digit Span test. All patient groups reported significantly lower scores than healthy controls across the neuropsychological tests involving executive functions. The TS+ADHD group was the most severely affected, followed by the ADHD group and the TS group, particularly in the tests assessing planning ability, inhibitory function, working memory and visual attention, but not auditory attention. Problems in executive functions are more common in patients with neurodevelopmental disorders than controls. Deficits in planning ability, inhibitory function, working memory and visual attention reported by children with TS appear to be more strongly related to the presence of co-morbid ADHD symptoms than core TS symptoms.

Keywords: Tourette syndrome; tics; attention-deficit and hyperactivity syndrome; cognition; executive functions.

1. Introduction
Tourette syndrome (TS) is a neurodevelopmental disorder characterised by the presence of both motor and phonic tics (Cavanna and Seri, 2013). Although the exact pathophysiology of TS is yet unknown, a key role seems to be played by basal ganglia dysfunction in regions involved in motor control and action inhibition, such as the striatum (Peterson et al., 2003; Makki et al., 2008).

It is estimated that around 90% of patients with TS present with behavioural co-morbidities, mainly attention-deficit and hyperactivity disorder (ADHD), obsessive-compulsive disorder, affective disorders, impulse control disorders and personality disorders (Cavanna and Rickards, 2013). ADHD is the most frequent co-morbidity in children with TS, affecting over 60% of patients (Stewart et al., 2006; Cavanna et al., 2011) and possibly resulting from alterations in prefrontal activity (Cortese et al., 2012).

Both TS and ADHD are neurodevelopmental disorders affecting predominantly male children and presenting in association with specific cognitive deficits across the domains of attention (Channon et al., 1992; Silverstein et al., 1995), memory (Stebbins et al., 1995) and executive functions (Bornstein et al., 1991; Willcutt et al., 2005; Cavanna et al., 2009; Eddy et al., 2009; Robertson and Cavanna, 2009).

However few studies were conducted in patients with uncomplicated TS or controlled for the presence of co-morbid conditions, in particular ADHD (Eddy et al., 2012), raising the possibility that at least some of the cognitive deficits reported in TS populations can be related to the presence of co-morbid ADHD. The assessment of the relative contribution of tic symptoms and ADHD symptoms to cognitive problems in patients with TS poses considerable challenges. We set out to determine the impact of co-morbid ADHD on cognitive function in male children with TS by conducting a controlled study with a comprehensive battery of neuropsychological tests. Specifically, we explored the cognitive profiles (with focus on executive functions and attention) of four matched groups of children: patients with uncomplicated or ‘pure’ TS (TS), patients with TS and co-morbid ADHD (TS+ADHD), patients with ADHD only (ADHD), and healthy controls.

2. Methods

2.1 Participants

Participants included four groups of unmedicated age- and gender-matched children (mean age 10-12 years, range 6-15 years; 85-100% male gender): TS group (n=13 children with a diagnosis of uncomplicated or ‘pure’ TS), TS+ADHD group (n=8 children with TS and co-morbid ADHD), ADHD group (n=39 children with ADHD in the absence of tics) and controls (n=66 healthy children). All patients had a DSM-validated diagnosis and were recruited from the Child Neuropsychiatry Unit, Varese, Italy, whereas healthy controls
were randomly selected from a pool of research volunteers from local schools. The distribution of DSM criteria for ADHD in patients with ‘pure’ TS only showed that this group was not close to the diagnostic threshold for ADHD. The study was approved by the ethical committee of the host institution and informed consent was obtained from the participants’ guardians.

2.2 Instruments

All participants completed a standardised neuropsychological battery to assess cognitive functions.

2.2.1 Wechsler Intelligence Scale for Children-III

The Wechsler Intelligence Scale for Children-III (Orsini and Picone, 2006) is used to study intelligence in children. In our study, two components of this scale (Block Design and Vocabulary) were administered to assess performance and verbal IQ. In the Block Design test, children are asked to move some coloured blocks to reproduce the figure shown. In the Vocabulary test, participants have to explain the meaning of words, ordered by difficulty.

2.2.2 Italian ADHD Battery

The Italian ADHD Battery (Mazzocchi et al., 2010) includes a set of cognitive tests used to explore neuropsychological functions of children. The first one (Walk-Don’t Walk test) is a typical go-no go test, in which children have to make a mark that corresponds to a go-sound and to stop it when they hear the no-go-sound. In this task motor inhibition but also visual and auditory sustained attention can be studied. In addition to sustained attention, the Sustained Auditory Attention test (SAA) assesses working memory, as participants are asked to listen to a sequence of sounds and to count them. The Italian ADHD Battery also includes a Stroop test to estimate access inhibitory processes, by asking children to count symbols while ignoring their meaning. The Sentence Completion test (SC) assesses verbal inhibition, as subjects are asked to complete sentences, alternating the right answer with a wrong one. In the Matching Familiar Figures test (MF) participants are shown a figure and are asked to find the matching one among six choices: this task requires a good control of the impulsive answer, sustained attention and visual searching strategies. Finally, the Sustained Visual Attention test (SVA) assesses visual attention in a sustained task, by asking participants to find a repeated sequence of letters within three pages filled with letters.

2.2.3 Tower of London
The Tower of London test (Sannio Fancello et al., 2006) is widely used to assess planning skills, examining planning efficiency, time to complete and comprehension of rules. Children have to move three coloured balls on three stockings to reach the goal position, given the rules and number of moves.

2.2.4 Corsi test and Digit Span test

The Corsi test (Mammarella et al., 2008), in which participants have to repeat a sequence of movements showed by the examiner (both forward and backward), assesses visual and spatial working memory. In the Digit Span test (Mammarella et al., 2008) participants are required to repeat a sequence of increasing numbers (again both forward and backward), in order to assess their working memory.

2.3 Statistical analysis

As the distribution of all non-categorical variables showed a normal distribution according to the Kolmogorov-Smirnov test, frequency distributions were compared by using the chi-square test and mean values by using the independent samples t-test and one-way ANOVA for normal variables (Scheffe’s post-hoc test). All statistical analyses were conducted with SPSS Version 17.0.

3. Results

The four groups were highly homogeneous in terms of demographic characteristics: male gender accounted for 13/13 (100%) of patients with TS (mean age 12.5±2.4 years), 8/8 (100%) of patients with TS+ADHD (mean age 11.0±2.1 years), 35/39 (90%) patients with ADHD (mean age 10.3±2.6 years) and 56/66 of healthy controls (mean age 10.7±2.9 years).

All patient groups reported significantly lower scores than healthy controls across the neuropsychological tests focusing on intelligence (Table 1), executive functions and attention (Tables 2 and 3), and working memory (Table 4).

A specific pattern in cognitive performances emerged, showing that the TS+ADHD group was the most severely affected, followed by the ADHD group and the TS group. This was particularly evident from the results of the tests assessing planning ability (Block Design test, Matching Familiar Figures test, Tower of London test), inhibitory function (Walk-Don’t Walk test, Stroop test, Matching Familiar Figures test), working memory (Sustained Auditory Attention test, Corsi test, Digit Span test) and visual attention (Walk-
Don’t Walk test, Matching Familiar Figures test, Sustained Visual Attention test), but not auditory attention (Sustained Auditory Attention test).

Post-hoc analysis (Scheffe) showed that the ADHD group performed significantly worse than the control group in each Tower of London subtest: the ADHD group reported lower T total scores (p<0.001), violating rules (p<0.001), needing a higher number of moves (p<0.001) and more time to complete the task (p<0.001; decision time p=0.021 and total time p=0.001). The TS group needed more moves than the healthy control group to reach the goal position (p<0.001), violated more rules (p<0.001) and had longer execution time (p=0.002) and total time (p=0.022). The TS+ADHD group reported lower scores than healthy controls (p=0.003), with a higher number of moves (p=0.001) and mistakes (p=0.021).

With regard to working memory function, post-hoc analysis revealed that the ADHD group performed significantly worse than the TS group (p=0.022) and control group (p<0.001) according to the Corsi forward scores. The ADHD group also reported lower scores than the control group on the backward task (p<0.001). The ADHD group also reported lower scores than the control group on both components (forward p=0.001 and backward p=0.010) of the Digit Span Test. Finally, the ADHD group reported a poorer performance than the TS group on the backward task (p=0.043).

4. Discussion

We conducted a controlled study to disentangle the contributions of tics and ADHD symptoms to cognitive function in male children with uncomplicated TS and TS+ADHD, in comparison to children with ADHD and healthy controls. Although all patients groups reported impaired scores across the neuropsychological tests involving executive functions and attention compared to controls, children with ADHD and TS+ADHD reported lower scores than children with uncomplicated TS. Specifically, deficits in planning ability, inhibitory function, working memory and visual attention reported by children with TS were confirmed to be more strongly related to the presence of co-morbid ADHD symptoms than core TS symptoms (Ozonoff et al., 1999; Channon et al., 2003; Sukhodolsky et al., 2010; Lin et al., 2012). According to the findings of a study of action inhibition in adult patients with TS (Ganos et al., 2014), motor inhibition seems to be normal across the lifespan, whereas the selective deficits in inhibitory performance reported by our ‘pure’ TS group appear to improve with age, possibly reflecting the presence of compensatory mechanisms.

The widespread executive function deficits reported in the context of ADHD did not appear to be modified by the presence of TS. This finding is in line with the results of previous studies, suggesting that co-morbid ADHD symptomatology is the main factor in determining the presence of most executive deficits in children with TS (Mahone et al., 2001; Roessner et al., 2007; Sukhodolsky et al., 2010). Taken together, these
findings suggest that the pathophysiological process leading to tic expression in children with TS does not seem to affect core aspects of neuropsychological functioning captured by standard executive function tests.

With regard to attention abilities, we found evidence of pervasive deficits in patients with ADHD, in line with their diagnosis, as well as more selective impairments in measures of auditory attention in patients with TS. This might reflect the role played by motor and phonic tics in interfering with attention skills in the auditory modality or the independent presence of selective attention deficits in the absence of full-blown ADHD, as reported in previous research (Channon et al., 2003; Eddy et al., 2015 in press). Implications might include a functional dissociation between fronto-striatal pathways involved in tic generation and prefrontal networks subserving higher cognitive functions.

This study has limitations. Firstly, referral bias needs to be taken into account when interpreting our findings, as participants were recruited from a tertiary referral centre and may therefore not be representative of the community population with TS. Secondly, all patients with TS in our study samples were of male gender: this also limits the generalizability of our study to the general population of patients with TS, which include a proportion (20-30%) of female patients. Thirdly, at the time of data collection, participants were asked to complete multiple questionnaires, which can be time-consuming and for this reason some of them might have chosen to rush their answer quickly, leading to inaccuracy. Finally, the four study groups were not homogeneous in sample size, with the TS groups having lower sample sizes. The relatively small sample sizes (especially the TS+ADHD group) might have led to selection bias, possibly explaining the finding that the ‘pure’ TS group reported the lowest IQ scores of all. It cannot be ruled out that this, in turn, could have affected some of the results of some neuropsychological tests. Future studies should be conducted to test the robustness of our findings using comprehensive neuropsychological batteries in larger samples of patients, especially children diagnosed with TS and co-morbid ADHD.

**Conflicts of interest**

None.

**References**


**TABLES**

Table 1. Wechsler Intelligence Scale for Children–III Block Design and Vocabulary test scores, assessing performance (Block Design) and verbal (Vocabulary) IQ.

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>TS+ADHD</th>
<th>ADHD</th>
<th>Healthy controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance IQ (Block Design) Mean (SD)</td>
<td>8.8 (2.9)</td>
<td>11.6 (4.8)</td>
<td>10.4 (3.2)</td>
<td>14.2 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verbal IQ (Vocabulary) Mean (SD)</td>
<td>9.3 (3.0)</td>
<td>9.3 (2.3)</td>
<td>10.2 (2.6)</td>
<td>12.1 (2.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. Italian ADHD Battery scores, assessing motor inhibition (Walk-Don’t Walk), verbal inhibition (SC test) and general inhibition processes (Stroop test), as well as impulsivity (MF test) and visual (SVA test) and auditory (SAA test) attention.

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>TS+ADHD</th>
<th>ADHD</th>
<th>Healthy controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor inhibition (Walk-Don’t Walk) n with deficit (% in case/control)</td>
<td>1 (7.7%)</td>
<td>3 (37.5%)</td>
<td>3 (7.7%)</td>
<td>1 (1.5%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Sustained Auditory Attention test (SAA test) Error n with deficit (% in case/control)</td>
<td>5 (38.5%)</td>
<td>19 (48.7%)</td>
<td>10 (25.6%)</td>
<td>7 (10.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inhibition (Stroop test) Baseline time n with deficit (% in case/control)</td>
<td>1 (7.7%)</td>
<td>3 (37.5%)</td>
<td>4 (10.3%)</td>
<td>2 (3.0%)</td>
<td>0.108</td>
</tr>
<tr>
<td>Baseline time/item n with deficit (% in case/control)</td>
<td>1 (7.7%)</td>
<td>1 (12.5%)</td>
<td>5 (12.8%)</td>
<td>2 (3.0%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Total time n with deficit (% in case/control)</td>
<td>2 (15.4%)</td>
<td>12 (30.8%)</td>
<td>1 (1.5%)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Total time/item n with deficit (% in case/control)</td>
<td>1 (7.7%)</td>
<td>1 (12.5%)</td>
<td>11 (28.2%)</td>
<td>1 (1.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verbal inhibition (SC test) Score n with deficit (% in case/control)</td>
<td>0 (0.0%)</td>
<td>3 (37.5%)</td>
<td>3 (7.7%)</td>
<td>5 (7.6%)</td>
<td>0.421</td>
</tr>
<tr>
<td>Impulsivity (MF test) Error n with deficit (% in case/control)</td>
<td>3 (23.1%)</td>
<td>7 (17.9%)</td>
<td>5 (7.6%)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>First answer mean time n with deficit (% in case/control)</td>
<td>0 (0.0%)</td>
<td>4 (10.3%)</td>
<td>2 (3.0%)</td>
<td>0.288</td>
<td></td>
</tr>
<tr>
<td>Omission n with deficit (% in case/control)</td>
<td>2 (15.4%)</td>
<td>17 (43.6%)</td>
<td>14 (21.2%)</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Sustained visual attention (SVA test) Total time n with deficit (% in case/control)</td>
<td>1 (7.7%)</td>
<td>5 (12.8%)</td>
<td>2 (3.0%)</td>
<td>0.094</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Tower of London scores, assessing planning skills (T total score) and efficiency (T moves number), time to complete (T initiation, execution and total time) and comprehension of rules (T rule violation).

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>TS+ADHD</th>
<th>ADHD</th>
<th>Healthy controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T total score)</td>
<td>Mean (SD)</td>
<td>49.0 (9.7)</td>
<td>39.7 (11.4)</td>
<td>46.0 (12.5)</td>
<td>56.7 (12.0)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>1 (7.7%)</td>
<td>3 (37.5%)</td>
<td>6 (15.4%)</td>
<td>5 (7.6%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Planning efficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T moves number)</td>
<td>Mean (SD)</td>
<td>69.3 (19.0)</td>
<td>72.2 (17.5)</td>
<td>63.9 (16.7)</td>
<td>49.3 (10.8)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>7 (53.8%)</td>
<td>5 (62.5%)</td>
<td>15 (38.5%)</td>
<td>5 (7.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comprehension of rules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T rule violation)</td>
<td>Mean (SD)</td>
<td>80.5 (20.7)</td>
<td>82.6 (21.1)</td>
<td>79.1 (24.0)</td>
<td>58.1 (18.3)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>10 (76.9%)</td>
<td>5 (62.5%)</td>
<td>24 (61.5%)</td>
<td>17 (25.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T initiation time)</td>
<td>Mean (SD)</td>
<td>50.8 (16.2)</td>
<td>47.1 (8.8)</td>
<td>50.1 (8.8)</td>
<td>43.4 (10.4)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>1 (7.7%)</td>
<td>1 (12.5%)</td>
<td>3 (7.7%)</td>
<td>6 (9.1%)</td>
<td>0.567</td>
</tr>
<tr>
<td>Time to complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T execution time)</td>
<td>Mean (SD)</td>
<td>56.5 (21.8)</td>
<td>52.1 (8.2)</td>
<td>53.4 (11.1)</td>
<td>43.1 (8.1)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>3 (23.1%)</td>
<td>0 (0%)</td>
<td>4 (10.3%)</td>
<td>0 (0%)</td>
<td>0.005</td>
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<tr>
<td>Time to complete</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(T total time)</td>
<td>Mean (SD)</td>
<td>53.7 (19.4)</td>
<td>50.0 (6.3)</td>
<td>52.5 (11.2)</td>
<td>42.6 (10.3)</td>
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<tr>
<td>n with deficit</td>
<td>3 (23.1%)</td>
<td>0 (0%)</td>
<td>5 (12.8%)</td>
<td>3 (4.5%)</td>
<td>0.076</td>
</tr>
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### Table 4. Corsi test and Digit Span test scores, assessing working memory.

<table>
<thead>
<tr>
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<th>ADHD</th>
<th>Healthy controls</th>
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<td>Corsi test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward score</td>
<td>Mean (SD)</td>
<td>0.3 (1.0)</td>
<td>-0.6 (0.9)</td>
<td>-0.6 (0.9)</td>
<td>0.2 (0.9)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>1 (7.7%)</td>
<td>2 (25.0%)</td>
<td>7 (17.9%)</td>
<td>3 (4.5%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Backward score</td>
<td>Mean (SD)</td>
<td>-0.1 (1.1)</td>
<td>-0.4 (1.2)</td>
<td>-0.6 (0.7)</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>2 (15.4%)</td>
<td>7 (87.5%)</td>
<td>4 (10.3%)</td>
<td>1 (1.5%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Digit Span test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward score</td>
<td>Mean (SD)</td>
<td>0.5 (1.6)</td>
<td>0.1 (1.1)</td>
<td>-0.3 (1.0)</td>
<td>0.8 (1.3)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.6%)</td>
<td>0 (0.0%)</td>
<td>0.472</td>
</tr>
<tr>
<td>Backward score</td>
<td>Mean (SD)</td>
<td>0.9 (1.6)</td>
<td>0.2 (1.2)</td>
<td>-0.4 (1.1)</td>
<td>0.6 (1.6)</td>
</tr>
<tr>
<td>n with deficit</td>
<td>2 (15.4%)</td>
<td>1 (12.5%)</td>
<td>4 (10.3%)</td>
<td>2 (3.0%)</td>
<td>0.052</td>
</tr>
</tbody>
</table>
Highlights

- We investigated the impact of co-morbid ADHD on cognition in male children with TS
- We recruited 4 groups of unmedicated children (TS, TS+ADHD, ADHD, healthy controls)
- All patient groups reported more problems in executive functions than controls
- Patients with both TS and ADHD group were the most severely affected
- We found specific cognitive problems to be related to co-morbid ADHD rather than TS