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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.

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

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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 ($p < 0.001$;

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

	TS	TS+ADHD	ADHD	Healthy controls	*p* value
Performance IQ (Block Design) Mean (SD)	8.8 (2.9)	11.6 (4.8)	10.4 (3.2)	14.2 (2.8)	< **0.001**
Verbal IQ (Vocabulary) Mean (SD)	9.3 (3.0)	9.3 (2.3)	10.2 (2.6)	12.1 (2.6)	< **0.001**