Executive control development in Tourette syndrome and its role in tic reduction

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A B S T R A C T

Tourette syndrome (TS) is a childhood-onset disorder characterized by motor and vocal tics. Recent findings point to a possible role of executive functions system development in the tic reduction observed with age. The goal of the present work was to track the development of executive functions system measured by well-established cognitive tasks and its correlation with diminished tic severity over time in order to understand the role of executive functions in the remission process observed in most adults. The first study followed 25 young TS patients, measuring their executive functions and clinical condition at three time-points. In the second study we compared executive functions performance of 19 adult TS patients with 19 healthy controls and 12 remitted TS patients. The first study showed that tic reduction is related to the development of the executive functions components associated with response inhibition. The second study similarly showed impaired inhibition ability in TS patients but not in controls or the remitted TS patients. The remitted group performed at normal or even higher levels on certain measures. We conclude that inhibition, an important executive function, is impaired in subjects suffering from TS and that intact executive function development is related to remission processes.

1. Introduction

Tourette syndrome (TS) is a developmental neuropsychiatric childhood-onset disorder characterized by involuntary and premonitory urge-driven motor and vocal tics (Leckman, 2002). Generally, tics are considered involuntary. However, they can be partially controlled and suppressed for brief periods of time (Leckman et al., 2014). Older children, young and adult individuals who are able to suppress the tics for a certain amount of time, report an increased intensity of premonitory urges and in some cases increased anxiety (Specht et al., 2013).

The course of TS includes a fluctuating pattern of severity, intensity and frequency of tics (Leckman et al., 1998; Robertson, 2000). This waxing and waning pattern has been found to be quite unpredictable (Peterson and Leckman, 1998) but among other factors, related to stress, excitement, boredom, fatigue, and exposure to heat (Jankovic, 2001). The onset of tics usually begins at a mean age of approximately 6–7 years (Leckman et al., 1998). The severity, intensity and frequency of tics usually reach their peak at ages 12–14, with a significant reduction at 20–25 years of age (Leckman et al., 1998; Bloch et al., 2006). At the third decade of life, motor and vocal tics usually decline or even disappear (Walkup et al., 2010). The rate of remission in adults is controversial. Several studies have demonstrated a slight rate of remission (approximately 10%, Pappert et al., 2003), however, the majority of research studies have reported that only 20% of cases will continue throughout adulthood (Leckman et al., 1998; Bloch et al., 2006). Unfortunately, these cases tend to be more dramatic and encompass more severe symptoms such as self-injurious motor tics or socially stigmatizing coprolalic utterances or gestures (Swain et al., 2007). Coffey et al. (2004) strove to resolve this debate by dissociating relatively high tic persistence (82%) with tic-associated dysfunction (14%) found in adulthood.

It is still unclear which reliable clinical measures can predict the persistence of tics throughout adulthood. However, some studies have pointed to a few possible predictors. Increased tic severity in childhood and fine motor skill deficits were found to be associated with increased tic severity later in life (Bloch et al., 2006). Another predictor, the caudate volumes in childhood, were found inversely correlated to tic...
severity in adulthood (Bloch et al., 2005). The presence of a comorbid condition especially at disease onset was likewise found to be related to TS severity in adulthood (Rizzo et al., 2012) as was the presence of Obsessive-Compulsive Disorder (OCD) in late adolescence (Peterson et al., 2001a). Nevertheless, it is still unclear as to which exact processes are related to the persistence of TS symptoms in adulthood.

The involvement of cognitive performance in TS is unclear, especially with regard to executive functions (EF). Recent evidence has led researchers to view executive functions as a mechanism comprised of several discrete processes, related to the ability to inhibit responses, to shift between mental sets and monitor, and to update working memory (Miyake et al., 2000; Stuss, 2011). Executive functions abilities start to develop in early childhood and usually only reach their peak about early adulthood (Luna et al., 2004). Moreover, studies have shown separate developmental trajectories for working memory, shifting and inhibition (Luna et al., 2004; Huizinga et al., 2006).

Theoretically, it was unclear as to whether TS patients would exhibit diminished or hyper control of executive functions. The neural systems affected in TS are directly linked to executive functions (Wang et al., 2011) or indirectly via the high prevalence of comorbidity with OCD and Attention Deficit Hyperactivity Disorder (ADHD, Apter et al., 1992). It has been demonstrated that a deficit in cognitive flexibility, a major part of EF, has been acknowledged as a cognitive trait for OCD (Gu et al., 2008) and deficits in a cognitive control are marked in ADHD (Jacobson et al., 2011).

While some earlier studies reported no differences between TS and normally developing subjects in executive functions (Bornstein, 1991), other studies have reported significant executive functions impairments in TS patients (i.e., Ozonoff and Jensen, 1999; Müller et al., 2003). Eddy et al. (2012) reported executive dysfunction in adults with TS while Mueller et al. (2006) reported increased levels of cognitive control in a group of young TS patients compared to an age-matched control group. These findings led Jackson et al. (2011) to speculate that some young TS patients show reorganization of prefrontal areas with consequent increased executive functions ability enabling remission of symptoms. In addition, it has been shown that adults with TS show enhanced shifting ability compared to controls (Jung et al., 2014).

One of the most plausible explanations for these conflicting results regarding executive functions abilities in TS is the participant’s stage of development. Thus while executive functions enhancements were found mostly in children (Mueller et al., 2006; Jackson et al., 2007; Debes et al., 2011; Jackson et al., 2011; Jung et al., 2014), most adult studies reported executive functions impairments (Watkins, 2005; Goudriaan et al., 2006; Channon et al., 2009). In the current work, we measured executive functions at different ages and also incorporated comorbid conditions, medications and various executive functions measures in order to better understand their involvement in the disease’s course.

The main question of the current research was how the development of the executive functions system in TS affects tic reduction. To do so, we conducted two studies. The first study followed executive functions development of children and teenagers with TS using a rich executive functions task battery, investigating the possible correlations between executive functions and TS symptom severity changes. The second study focused on adult TS patients by comparing their executive functions abilities with a group of adults in TS remission and healthy control subjects. We hypothesized that the development of executive functions in TS is related to symptom severity changes. Furthermore, we hypothesized that the remission process is related to normal or even hyper performance in executive functions tasks.

2. Study 1

2.1. Method

2.1.1. Participants

Twenty-five subjects (3 females, mean age 12.7 years, SD 1.9) previously diagnosed with TS by a psychiatrist or neurologist participated in the study. Subjects were recruited from the Neuropsychiatric Tourette Syndrome and Tic Disorders Clinic, Schneider Children’s Medical Center of Israel (SCMC). Additional relevant medical information such as comorbid condition, medication, medical history and other non-related medical or psychological conditions were obtained from the subject’s medical file. In addition, a comprehensive family history was taken by the interviewing psychologist to exclude family psychopathology.

The severity of current phonic and motor tics was assessed by the YGTSS (Leckman et al., 1989). The mean YGTSS total score at the first time point (T1) was 18.92 (SD 8.69). Ten of the subjects were diagnosed by a psychiatrist or neurologist with comorbid ADHD, 4 with comorbid OCD and another 4 with both OCD and ADHD. Four patients were treated with Clonidine, 7 with Methylphenidate, 3 with Risperidone and 1 with mixed amphetamine salts. Overall, 13 patients received medications between T1 and T3. Medication was not consumed during the 24 h prior to the experimental meetings. Four patients received behavioral interventions; 2 patients were treated with Habit Reversal Therapy (HRT), and 2 more were treated with Exposure and Response Prevention (ERP, Wetterneck and Woods, 2006).

Approval for the experiment was obtained from the SCMC Helsinki Committee and informed written consent was obtained from all subjects and their parents prior to participation. The sample characteristics are presented in Table 1.

2.1.2. Materials

2.1.2.1. Wisconsin Card Sorting Task. The Wisconsin Card Sorting Test (WCST) is a well-established task used for exploring cognitive flexibility in contemporary neuropsychological practice and research. In the current experiment, we used a brief computerized version of this test, the Psychology Experiment Building Language (PEBL) test. The Berg Card Sorting Task (BCST), which is available for downloading from http://pebl.sourceforge.net/battery.html has been previously validated (Piper et al., 2012). Dependent measures from this task included the percentage of total errors and the percentage of perseverative responses.

2.1.2.2. Stop signal task. The stop signal task (SST) is a popular paradigm for measuring response inhibition (Aron et al., 2003). Herein, we used the STOP-IT program by Verbruggen et al. (2008). In this experiment, the indices for response inhibition were go reaction times (RTs) and the stop signal reaction time (SSRT) was calculated as the difference between mean RT over go trials and the mean stop signal delay (SSD) over stop trials This reflects the time duration needed to stop the response, when considering the general response speed as well

<table>
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<tr>
<th>Variable</th>
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<th>SD</th>
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<tr>
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<tr>
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<tr>
<td>T1 YGTSS total</td>
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<td>9.16</td>
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</tbody>
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M = mean SD = standard deviation, T1 YGTSS total – Yale Global Tic Severity Scale, total score (0-50, at T1).

** ** p < 0.01.
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