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Time processing in children with Tourette's syndrome

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ABSTRACT

Background: Tourette syndrome (TS) is characterized by dysfunctional connectivity between prefrontal cortex and sub-cortical structures, and altered meso-cortical and/or meso-striatal dopamine release. Since time processing is also regulated by fronto-striatal circuits and modulated by dopaminergic transmission, we hypothesized that time processing is abnormal in TS.
Methods: We compared time processing abilities between nine children with TS-only (i.e. without major psychiatric comorbidities) and 10 age-matched healthy children, employing a time reproduction task in which subjects actively reproduce different temporal intervals, and a time comparison task in which subjects judge whether a test interval is longer or shorter than a reference interval. IQ, sustained and divided attention, and working memory were assessed in both groups using the Leiter International Performance Scale-Revised, and the Digit Span sub-test of the WISC-R.
Results: Children with TS-only reproduced in an overestimated fashion over-second, but not sub-second, time intervals. The precision of over-second intervals reproduction correlated with tic severity, in that the lower the tic severity, the closer the reproduction of over-second time intervals to their real duration. Time reproduction performance did not significantly correlate with IQ, attention and working memory measures in both groups. No differences between groups were documented in the time comparison task.
Conclusions: The improvement of time processing in children with TS-only seems specific for the over-second range of intervals, consistent with an enhancement in the 'cognitively controlled' timing system, which mainly processes longer duration intervals, and depends upon dysfunctional connectivity between the basal ganglia and the dorso-lateral prefrontal cortex. The absence of between-group differences on time comparison, moreover, suggests that TS patients manifest a selective improvement of 'motor' timing abilities, rather than of perceptual time abilities. Our data also support an enhancement of cognitive control processes in TS children, probably facilitated by effortful tic suppression.

1. Introduction

Tourette syndrome (TS) is a childhood-onset disorder characterized by the presence of tics, which are rapid, stereotyped movements and vocalizations, virtually involving all body segments. Several genetic and non-genetic factors may contribute to the generation of tics through impairment of neural circuits linking the cerebral cortex to the striatum and other sub-cortical regions (Swain, Scahill, Lombroso, King, & Leckman, 2007). Dopaminergic pathways ascending from the midbrain to striatal and cortical neurons likely play a role in the causation of tics (Swain et al., 2007). Meso-cortical and meso-striatal dopaminergic pathways are also known to modulate interval timing, which is of major importance for action planning and decision making (Meck, 1996).

The processing of temporal information is a complex and distributed cognitive domain, engaging multiple brain regions, including basal ganglia, the frontal cortex, and the cerebellum (Lewis & Miall, 2006). Temporal processing is hypothesized to be functionally and anatomically distributed according to the duration range of processed time intervals, as well as according to whether the time processing activity is more associated with the perception of sensory stimuli (visual, auditory, etc.), e.g. in time discrimination or time comparison tasks, or rather with the production of motor responses, e.g. in time production or time

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reproduction tasks. The continuous processing of sub-second time intervals (automatic timing), crucial for motor control, seems functionally related to connections between the cerebellum and cortical areas such as the supplementary motor area (SMA) (Ivry & Spencer, 2004; Lewis & Miall, 2006; Macar et al., 2002). On the other hand, the right dorso-lateral prefrontal cortex (DLPFC) seems mostly involved in timing abilities influenced by other cognitive functions, such as attention and working memory, and may be crucial for encoding, storage and retrieval of temporal information, particularly in the supra-second duration range (Ivry & Spencer, 2004). Both timing systems seem to be modulated by dopaminergic projections to the basal ganglia and the cerebral cortex. In classical timing models (e.g. pacemaker–accumulator models) dopamine is hypothesized to set the firing speed of a subjective, 'internal clock' or pacemaker, based on which temporal intervals are subjectively experienced (Lewis & Miall, 2006). In other timing models meso-cortical dopamine release is thought to modulate the coupling of activity between striatal medium spiny neurons and neurons of the prefrontal cortex, which subserves accurate processing of relevant temporal intervals (Meck, Penney, & Pouthas, 2008).

A few conditions associated with dysfunctional cortico-striatal circuits and abnormal meso-striatal or meso-cortical dopamine transmission (Parkinson's disease, Huntington's disease, schizophrenia) may affect the accuracy of interval timing (e.g. in Davalos, Kisley, & Ross, 2003; Koch et al., 2008; Paulsen et al., 2004), although the extent and type of timing abnormalities in these illnesses has not been conclusively defined. There is growing evidence in favour of a major contribution of abnormalities in meso-striatal and meso-cortical dopamine transmission, and of their contribution to dysfunctional connectivity between the prefrontal cortex and the basal ganglia, also in patients suffering from TS. In addition, event-related functional imaging studies support the presence of activity changes of cerebellar structures during tic release (Bohlhalter et al., 2006; Lerner et al., 2007), although the exact role of the cerebellum in the generation of tics remains unclear. Despite the fact that the same structures which are relevant to TS are crucial also for the modulation of time processing, currently available data on timing abilities in patients with TS are surprisingly very limited (Goldstone & Lhamon, 1976; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006).

Recent works support the existence of changes in cognitive domains in subjects with isolated TS, i.e. in the absence of major psychiatric comorbidities such as attention deficit hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD). Although these cognitive abnormalities appear to be mild, their spectrum is relatively broad, involving executive functions (particularly inhibitory control), fine motor skills and visuo-motor integration ability (Como, 2001; Osmon & Smerz, 2005). The processing of temporal information in the range of milliseconds is a cognitive domain which seems related to control and execution of motor responses as well as to mechanisms of cognitive control. Exploring time processing in children with TS-only might expand current knowledge on the profile of cognitive dysfunction specifically associated with the presence of tics.

In order to explore the different functional categories of temporal processing in TS, we used two tasks engaging explicit time processing activity (Coull & Nobre, 2008), either in the form of perceptual discrimination, in which subjects state whether one stimulus duration is shorter or longer than another (*time comparison task*), or in the form of a motor response, in which subjects represent the timed duration within a sustained motor act (*time reproduction task*). Both tests allowed us to evaluate timing abilities within both the sub-second range (predominantly pertinent to automatic timing) and the supra-second range (predominantly pertinent to cognitively controlled timing). On the basis of the proposed dysfunction in prefronto-striatal connectivity in TS patients, we hypothesized to detect specific time processing abnormalities pertinent to cognitive timing (i.e. within supra-second durations), in the presence of relatively preserved time processing abilities within the sub-second range of intervals. In addition, given the recent observation in TS patients of a thinning of the sensorimotor cortex associated with tic severity (Sowell et al., 2008) which suggests an altered pattern of sensorimotor activation, we also hypothesized abnormal timing in our patients to be more evident on the time reproduction task than on time comparison.

2. Methods and materials

2.1. Subjects

Nine children with TS (five males and four females) diagnosed according to DSM-IV criteria (Diagnostic and statistic manual, 1994) were recruited from an outpatient population of the tertiary referral centre for Tourette's syndrome and related disorders at the Department of Child and Adolescent Neuropsychiatry, University of Rome "La Sapienza", Rome, Italy. Ten age-matched healthy children (five males and five females) were also recruited into the study among friends of patients and relatives of the hospital staff. In order to study only patients with the 'pure' tic disorder, subjects with a DSM-IV-R diagnosis of ADHD, OCD, anxiety, depressive and conduct disorders were excluded (American Psychiatric Association, 1994). All TS patients had never been treated before with psychotropic medications. Current tic severity was assessed by the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1998). Subjects were monitored by a single examiner in the experimental session room during all sessions; tics forcing the patient to interrupt the ongoing task were not observed in TS subjects throughout all the experiments.

Case and control subjects did not significantly differ either by age (mean age + SD: TS group 11.44 + 1.01 years, control group 12.11 + 0.78 years; $t(17) = 1.63$, $p = .12$) or sex distribution (Fisher's exact test = 1). YGTSS score was equal to zero in each of the 10 healthy volunteers. The IQ of both groups was assessed by the Brief IQ version of the Leiter International Performance Scale-Revised (Leiter-R) (Miller & Roid, 1998). The TS group had a normal level of IQ (97.3 ± 8.15); however, this was lower than the control group, who were above the norm (107.5 ± 11.6; $t(17) = -2.19$, $p = .04$). The burden of attention difficulties was measured in both groups using the two attention sub-tests of the AM battery of the Leiter-R, sustained attention (SA) and divided attention (DA). TS patients scored lower than healthy on the SA sub-test (mean score 8.8 and 10, respectively; $t(17) = -2.41$, $p = .03$), but not on the DA sub-test (mean score 11.8 and 11, respectively; $t(17) = 1.43$, $p = .2$). Working memory was tested via the Digit Span sub-test of the Wechsler Intelligence Scale for Children Revised (WISC-R). No significant difference was observed between the two groups (TS patients 12.3, healthy 10.7; $t(17) = 1.13$, $p = .3$). The study was approved by the ethics committee of the Policlinico "Umberto I" Hospital, Rome, Italy, and written consent was obtained from all participants and their adult carers. Tables 1 and 2 present a summary of demographic and clinical data for the two groups.

2.2. Time processing analysis

2.2.1. Time comparison

We used a time comparison task previously used in other works (Oliveri et al., 2008; Vicario, Caltagirone, & Oliveri, 2007; Vicario, Rappo, Pepi, & Oliveri, 2009; Vicario et al., 2008). The task was first described to the subjects; then they underwent a brief training of practice trials to ensure they fully understood it. Subjects sat 60 cm from a P791 Dell computer monitor configured to a refresh