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Neuroscience Letters 403 (2006) 96–99
Neuroscience Letters
www.elsevier.com/locate/neulet

Tic distribution and inhibitory processes in the sensorimotor circuit during adolescence: A cross-sectional TMS study

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Received 4 January 2006; received in revised form 9 April 2006; accepted 18 April 2006

Abstract

Deficient inhibitory processes within the sensorimotor circuit, reflected by a shortened cortical silent period (CSP), have previously been described in both children and adults with tic disorders (TD) using transcranial magnetic stimulation (TMS). In contrast to adults, tic distribution (presence or absence of distal tics) did not affect CSP duration in children. The aim of this developmental TMS study was to clarify this striking difference. 127 children with TD were stratified into three age-groups (8–11.5, 11.5–15, 15–19 years) with and without distal tics. CSP was recorded from the abductor digiti minimi. Statistics revealed a significant tic distribution × age interaction effect. Only in the 15–19 years subgroup, CSP was shorter in patients with distal tics in comparison to patients without distal tics (94.1 ± 54.1 ms versus 135.2 ± 36.8 ms at a stimulus intensity of active motor threshold plus 30%). Inhibitory processes in the sensorimotor circuit could reflect developmental aspects of tic phenomenology, particularly tic distribution during adolescence.

Keywords: Tic disorders; Development; Inhibition; Transcranial magnetic stimulation (TMS); Cortical silent period

Tics begin during childhood (median onset: at ages 6–7), wax and wane but worsen to a maximum severity that occurs on average during adolescence (at ages 10–15), and are mostly followed by a steady decline in frequency and severity. During the first years, an unfolding of symptoms can often be observed, e.g., the original simple motor tics (most often of the eyes and face) may then be accompanied by vocal tics and motor tics of limbs and body. A patient's repertoire of tics usually stabilizes after adolescence [8,9,13]. This developmental picture implicates that TD pathophysiology also shows an age-dependent time course. However, only little attention has been paid to developmental aspects of TD pathophysiology as yet, particularly concerning inhibitory processes in the sensorimotor system.

Excitability of the cortico-striato-thalamo-cortical circuit can be investigated in vivo by means of transcranial magnetic stimulation [2,4]. In previous studies, a significantly reduced cortical silent period (CSP), which was recorded from the right abductor digiti minimi, was found in adults with TD [15] as well as in children with TD [11,12] indicating deficient inhibitory processes within the sensorimotor circuit. However, these TMS studies showed a striking difference between adults and children which emphasizes the significance of developmental processes concerning the pathophysiological background of TD. In adults, the shortened CSP was mainly seen when patients had distal tics. In contrast to adults, tic distribution (i.e., presence or absence of distal tics) did not affect the duration of the cortical silent period in the group of children with TD.

In order to study this age-dependent difference in more detail, the development of the CSP was investigated in patients with TD aged 8–19 years with or without distal tics using a cross-sectional design.

127 patients with TD (103 boys and 24 girls) aged 8–19 years were included in the study. They were divided into two groups, namely patients with distal tics (i.e., tics in the arm–hand area at the time of evaluation) and patients without distal tics.

Both TD groups were further divided into three age groups (8–11.5 years, 11.5–15 years, 15–19 years, see Table 1).

All patients (outpatients and inpatients of the Department of Child & Adolescent Psychiatry, University of Göttingen)

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doi:10.1016/j.neulet.2006.04.021

Table 1
Sample characteristics

	TD patients without distal tics			TD patients with distal tics		
	8–11.5 years ($N=18$)	11.5–15 years ($N=30$)	15–19 years ($N=10$)	8–11.5 years ($N=22$)	11.5–15 years ($N=31$)	15–19 years ($N=16$)
Boys/girls	16/2	23/7	7/3	17/5	27/4	13/3
Tourette syndrome	16	20	8	19	25	11
Tic severity ($\mu \pm \sigma$)	1.33 ± 0.62	1.61 ± 0.88	1.80 ± 0.79	1.82 ± 0.82	1.82 ± 0.81	1.83 ± 0.92
Neuroleptic medication	8	11	3	12	14	9
ADHD	7	5	1	6	7	4
OCD	0	5	1	2	6	5

TD, tic disorders; ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder.

fulfilled the diagnostic criteria for either Tourette syndrome (307.23) or chronic motor tic disorder (307.22) according to DSM IV criteria [1]. Since attention-deficit hyperactivity disorder (ADHD) and comorbid obsessive-compulsive disorder (OCD) do not seem to affect CSP duration [5,6,11,15] TD children with these comorbid disorders (according to DSM-IV criteria) were allowed to participate.

Diagnoses were assigned by a board certified child and adolescent psychiatrist based on a clinical interview with parents and patients, a physical investigation and, for TD diagnosis, the Yale Tourette Syndrome Symptom List [3] and the Tourette Syndrome Severity Scale [14]. An overall clinical rating of tic severity (1 = low, 2 = moderate, 3 = high) was determined.

Nearly half of the patients received a D2 receptor antagonist medication (mainly tiapride). Two of the seven patients with comorbid OCD receiving medication were co-medicated with a serotonin reuptake inhibitor. Patients with comorbid ADHD stopped taking their stimulant medication 48 h before TMS investigation ($N=4$). All children were at least of normal intelligence. Any neurological disorder was considered as an exclusionary criterion.

After a complete description of the study to the children and their parents, assent was obtained from the children and written informed consent from their parents. The study was approved by the local ethics committee and conducted according to the declaration of Helsinki.

During investigation, the children were seated in a comfortable chair. Focal TMS was applied to the hand area of the left motor cortex by using a figure-eight magnetic coil (diameter of one wing: 70 mm) and a Magstim 200 magnetic stimulator (Magstim Co., Whitland, UK) as described in detail in [15]. The resulting motor evoked potential (MEP) was recorded from the right abductor digiti minimi. For data recording, a Neuroscan system (Neuroscan, Sterling, VA, USA) was used (filter bandwith: 10–1000 Hz; sampling frequency: 5 kHz).

Motor threshold, expressed as a percentage of the maximum stimulator output, was approached from a slightly suprathreshold intensity by reducing stimulus intensity in 1% steps. It was defined as the first stimulus intensity that did not elicit a MEP of more than 50 μV in five consecutive trials. Motor thresholds were determined in the resting and moderately tonically active target muscle. The degree of pre-innervation (ca. 1/3 of maximum voluntary contraction) was controlled visually on the screen.

In a tonically active muscle, the MEP initiated by a magnetic stimulus is followed by a silent period in the EMG, the so-called cortical silent period [7]. In this study, the duration of the CSP was measured at stimulus intensities of active motor threshold (AMT) plus 30% and 40% of maximum stimulator output. Ten trials were conducted for each stimulus intensity. CSP onset and offset were identified visually by a person blinded to a subject's clinical status. The mean value of the trials with adequate activation was computed.

To analyze age-related effects of TMS parameters with respect to the presence or absence of distal tics, an ANOVA with the between-subject factors DISTAL TICS (yes, no) and AGE (8–11.5, 11.5–15, 15–19) and TIC SEVERITY as covariate was computed for resting and active motor threshold. For the cortical silent period, a within-subject factor INTENSITY for the two stimulus intensities (AMT + 30%, AMT + 40%) was introduced. In case of a significant DISTAL TICS × AGE interaction, specific contrasts were calculated comparing patients with and without distal tics for each age-subgroup separately. Post hoc-analyses were intended to control for possibly confounding factors (comorbidity, medication). The level of significance was set to 0.05.

For resting and active motor threshold, a significant AGE effect was obtained (resting motor threshold: $F(2,121) = 19.1$, $p < 0.001$; active motor threshold: $F(2,121) = 5.2$, $p < 0.01$) indicating a decrease of motor thresholds with increasing age (see Table 2 for a summary of results).

The cortical silent period showed a significant prolongation with age (AGE effect: $F(2,121) = 3.4$, $p < 0.05$) mainly due to the increase in patients without distal tics in comparison to patients with distal tics. In the statistics, this effect was reflected in a significant DISTAL TICS × AGE interaction effect ($F(2,121) = 3.8$, $p = 0.02$, see also Fig. 1).

Repeating the ANOVA without the children with comorbid ADHD, without the children with comorbid OCD and without the children on medication, the DISTAL TICS × AGE interaction effect could be confirmed ($F(2,91) = 3.54$, $p = 0.03$, $F(2,102) = 2.85$, $p = 0.06$ and $F(2,64) = 3.17$, $p = 0.05$, respectively).

Presence or absence of distal tics did not have a significant effect on the duration of the CSP in the 8–11.5