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Cognitive-behavioral therapy induces sensorimotor and specific electrocortical changes in chronic tic and Tourette's disorder

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ABSTRACT

Background: Tic disorders, such as the Gilles de la Tourette syndrome and persistent tic disorder, are neurodevelopmental movement disorders involving impaired motor control. Hence, patients show repetitive unwanted muscular contractions in one or more parts of the body. A cognitive-behavioral therapy, with a particular emphasis on the psychophysiology of tic expression and sensorimotor activation, can reduce the frequency and intensity of tics. However, its impact on motor activation and inhibition is not fully understood.

Methods: To study the effects of a cognitive-behavioral therapy on electrocortical activation, we recorded the event-related potentials (ERP) and lateralized readiness potentials (LRP), before and after treatment, of 20 patients with tic disorders and 20 healthy control participants (matched on age, sex and intelligence), during a stimulus–response compatibility inhibition task. The cognitive-behavioral therapy included informational, awareness training, relaxation, muscle discrimination, cognitive restructuration and relapse prevention strategies.

Results: Our results revealed that prior to treatment; tic patients had delayed stimulus-locked LRP onset latency, larger response-locked LRP peak amplitude, and a frontal overactivation during stimulus inhibition processing. Both stimulus-locked LRP onset latency and response-locked LRP peak amplitude normalized after the cognitive behavioral therapy completion. However, the frontal overactivation related to inhibition remained unchanged following therapy.

Conclusions: Our results showed that P300 and reaction times are sensitive to stimulus–response compatibility, but are not related to tic symptoms. Secondly, overactivity of the frontal LPC and impulsivity in TD patients were not affected by treatment. Finally, CBT had normalizing effects on the activation of the pre-motor and motor cortex in TD patients. These results imply specific modifications of motor processes following therapy, while inhibition processes remained unchanged. Given that LRPs are partially generated within the sensorimotor and supplementary motor area, the reported reduction in tic frequency and improvements of LRPs components suggest that CBT induced a physiological change in patients' motor area.

1. Introduction

The Gilles de la Tourette syndrome (GTS) is considered as a neurodevelopmental movement disorder. Individuals with GTS have multiple motor tics and at least one phonic tic, which must be present for at least one year. In parallel, persistent tic disorder involves motor or phonic tics, but not both. In the DSM-5, these two diagnoses are included in the tic disorders (TD) category (American Psychiatric Association, 2013). Simple tics take the form of repetitive non-voluntary muscular contractions in one or multiple parts of the body, including blinking, cheek twitches, head or knee jerks, shoulder shrugs, etc. Complex tics may take the form of self-inflicted repetitive actions, such as nail biting, hair pulling, head slapping, face scratching, teeth grinding, tense-release hand

Abbreviations: CBT, cognitive-behavioral therapy; CTSC, cortico-striato-thalamo-cortical; ERP, event-related potentials; GTS, Gilles de la Tourette syndrome; SMA, supplementary motor area; SRC, stimulus–response compatibility; TD, tics disorders

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gripping cycles, or finger twiddling (Robertson, 2012; Shaw and Coffey, 2014). Tics are usually preceded by premonitory sensory urges, often reported as a feeling of discomfort or muscular tension (Bliss, 1980). They are also described as intrusive feelings or sensations, which can be focalized or generalized, driving the patient to perform a tic to relief the tension (Miguel et al., 2000). Premonitory urges could be caused by sensory gating dysfunctions, which would lead to an excessive inflow of somatosensory information and an increased activation from the supplementary motor area (SMA) (Rajagopal et al., 2013). For instance, stimulation of the SMA in healthy individuals leads to an urge to perform a movement (Fried et al., 1991). In the same vein, it was demonstrated that GTS patients show greater activation in the SMA prior to tic onset (Hampson et al., 2009). The SMA seem to play a role in sensory phenomenon happening before tics, but recent functional neuroimaging studies also identified the SMA as a key cortical region in tic generation (Bohlhalter et al., 2006; Hampson et al., 2009; Wu et al., 2014). In addition, cortical thickness in sensorimotor regions is correlated with tic symptoms (Sowell et al., 2008). Activation in sensorimotor cortex, putamen, pallidum, and substantia nigra was also found, while weaker activity in some portions of the cortico-striato-thalamo-cortical (CSTC) circuits seems to exert top-down control over the aforementioned motor pathways (Wang et al., 2011).

Despite these significant advances, the temporal dynamic of TD patients' cortical activity and the cerebral structures involved in tic generation remain poorly understood. A better grasp of these processes will open the door to refine state-of-the art treatment for tic disorders. In order to follow rapid processing of SRC mapping and motor-related brain response, we need a cognitive, behavioral and physiological integration. To achieve that integration, we utilize event-related potentials (ERPs), which index fast cortical responses associated with sensory, cognitive or motor events in real time (Luck, 2005). The high temporal resolution of ERPs allows the tracking of various stages of the information processing stream, and can serve as cognitive and physiological markers (Coles, 1989). Lateralized readiness potentials (LRP), which are a subtype of motor ERP derived from the readiness potential, can yield significant information on preparation and executions of movements (Coles, 1989). Several experiments showed that LRPs have generators located in the primary motor cortex (Coles, 1989; Miller and Hackley, 1992; Praamstra et al., 1999; Requin and Riehle, 1995) and the SMA (Rektor, 2002). This component is a good candidate as a psychophysiological marker of TD, since patients often face motor impairments thought to be related, at least partially, to SMA and the CSTC motor loop (Eddy et al., 2009). However, very few studies have used LRPs in TD patients. For instance, faster LRP onset and reaction times were found in the incompatible condition, negatively correlated with tic frequency (Thibault et al., 2009). The proposed hypothesis of a faster retrieval of motor programs is congruent with the motor cortical overactivation often observed in TD (Biswal et al., 1998; Eidelberg et al., 1997). In the context of a stimulus–response incompatibility, an overactivation of the SMA and premotor cortex, could create a higher baseline activation in these structures (Eidelberg et al., 1997), which might in turn lower the threshold for retrieval of the motor program and lead to a more rapid and ample activation of the required response (Thibault et al., 2009). The perspective that the SMA underlies LRP generation, and constitutes a key cortical region responsible for sensory urges and tic generation, strongly suggests that the SMA could be an efficient target for treatment intervention.

Efficient treatments of tic disorders first involved neuroleptics, which act mainly on dopaminergic motor networks (Scahill et al., 2006). However, a major drawback of their usage is the numerous side effects, especially for the typical neuroleptics. Additionally, insufficient data limits our understanding of the involved neural networks, which prevents the development of molecules with a higher specificity (Leckman, 2002). To complement treatment strategies, various types of treatments have emerged in the last decade, such as cognitive-behavioral therapies (CBT). Encouraging results were reported for such treatments that have been tailored to deal with specific behavioral problems associated with tic disorders (McGuire et al., 2014). Comprehensive Behavioral Intervention for Tics (CBIT), which involves elements of the habit reversal therapy, is efficient to treat tics in both children (Piacentini et al., 2010) and adults (Wilhelm et al., 2012). Two meta-analyses have shown that behavioral therapies are effective in treating tics. They even reached medium to large effect, which is comparable to pharmacological treatments (McGuire et al., 2014; Wile and Pringsheim, 2013). As mentioned earlier, previous studies consistently reported specific motor processing impairments in TD. Also, it should be noted that tic symptoms can be significantly reduced following a CBT that placed particular emphasis on motor activation/inhibition and the psychophysiology of tic expression. However, only a few studies focused on the neurocognitive impact of such therapy in TD. For instance, CBT improves fine motor dexterity of adults with TD, as shown by improved scores on the Purdue Pegboard test (O'Connor et al., 2008). This finding was replicated, and associated with an altered pattern of cerebral activation during a countermanding motor task. Interestingly, the degree of cortical normalization was correlated with the reduction of tic frequency (Lavoie et al., 2011). A better understanding of this neural mechanism could be a key component in the development of more specific pharmaceutical and psychological interventions targeting sensorimotor cortex and SMA activation, or even by individually adapted EEG and/or fMRI neurofeedback (Neuner et al., 2013). This is consistent with the bio-psycho-social model of TD, which suggests that tics are mainly caused by a heightened sensorimotor activation that could be targeted for efficient treatment (Lavoie et al., 2013).

The current study aimed to characterize the electrocortical activity, related to motor activation and motor inhibitory functions in TD, before and after the therapy, by using a stimulus–response compatibility paradigm. Moreover, we addressed the potential impact of CBT on impulsivity and frontal inhibitory function. Finally, we assessed the effect of CBT on activation of the motor cortex in TD patients. We hypothesized that (1) before CBT, TD patients would have an altered motor cortical activation and this would be reflected on some LRP components; (2) there would be a frontal overactivation relative to the inhibition (NoGo) condition in TD patients, associated to higher amplitudes of the Late-Positive Component (LPC) in frontal regions; (3) TD patients would show a delay of the P300 latency and reaction times, but no difference on P300 amplitude; (4) tics would diminish significantly, as well as depression and anxiety scores; (5) affected electrocortical activation in brain regions involved in movement control should normalize in TD patients after CBT.

2. Methods

2.1. Participants

Thirty-six adults with GTS or persistent tic disorder were selected to participate to our CBT program. *Criteria for inclusion were to* present multiple motor tics occurring daily for at least one year and to be aged between 18 and 65 years. Tic onset also had to be before 18 years old. All participants were screened by telephone for suitability in terms of geographical accessibility and absence of medical history. All patients were referred by clinician experts in evaluation and treatment from the OCD and tic study center (see

http://www.iusmm.ca/obsessive-compulsive-disorder-tic-studies-centre.html) and recruited from announcements in the media. Following the *telephone screening*, an appointment was made with a neurologist (PJB) for medical screening of other medical conditions, such as neurological problems. Assessments were also made by a clinical psychologist (supervised by KPO) and a neuropsychologist (supervised by MEL). *Criteria for exclusion* were the presence of any of these diagnoses: schizophrenia, bipolar disorder, somatoform disorders, dissociative disorders and substance related disorders. The presence of personality disorders was screened with the personality diagnostic questionnaire-4th Ed (Hyler, 1994; Rodgers et al., 2004; Wilberg et al., 2000).

From the 36 participants enrolled in the CBT program, 11 dropped out before its completion (30%). Also, two patients were not included in the present study because of comorbid habit disorder ($n=1$) and narcolepsy ($n=1$). From the 23 remaining participants, three did not show any measurable LRP, and were not included in the present study. Therefore, our final sample includes a total of 20 *patients* (aged between 19 and 61 years old) who meet DSM-IV-TR criteria for GTS or persistent tic disorder (American Psychiatric Association, 2000). Some of the patients included in our sample had a comorbid diagnostic, such as major depressive disorder ($n=1$), ADHD ($n=1$), social anxiety disorder ($n=5$) and panic disorder ($n=1$). Also, six of our 20 patients were taking medication, such as antidepressant ($n=4$), benzodiazepine ($n=2$), atypical neuroleptic ($n=1$) and clonidine ($n=1$). Their medication uptake remained the same throughout the therapy. Our sample size compares to most of past ERP research published earlier, which used comparable TD patients samples at $n=6$ (van de Wetering et al., 1985), $n=10$ (Johannes et al., 2001a, b, 2003), $n=12$ (Johannes et al., 1997), $n=15$ (Thibault et al., 2009) and $n=24$ (van Woerkom et al., 1994).

Our clinical group was matched to 20 healthy control participants on age (20–60 years old), sex, and intelligence (Raven, 1938). Handedness was assessed (Oldfield, 1971), and while the majority of participants were right handed, two patients from the TD group were left handed, one control participant was left handed, and one was ambidextrous. Because the task was visual and colored, all participants needed normal visual acuity (Snellen) and color perception (Ishiara). Socio-demographic characteristics are presented in Table 1.

The study was approved by the local ethics committee of the *Centre de recherche de l'Institut universitaire en santé mentale de Montréal* (a mental health university institute). All participants gave an informed written consent before their participation in the study. TD patients were tested before and after the therapy, but the control group was only tested once.

2.2. Clinical assessment

All participants completed tests of self-reported questionnaires. The Beck Anxiety Inventory (BAI; Beck et al., 1988) and Beck Depression Inventory (BDI; Beck et al., 1961) were used to assess anxiety and depression symptoms, respectively.

The clinical group undertook two clinician-reported tests to assess tic severity: the Tourette Syndrome Global Scale (TSGS; Harcherik et al., 1984) and the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). The Vancouver Obsessional Compulsive Inventory (VOCI; Thordarson et al., 2004) was used to assess the presence of obsessions/compulsion symptoms in our clinical group, while the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was used to assess impulsiveness.

Table 1
Socio-demographic and clinical characteristics.

	Controls ($n=20$)		TD ($n=20$)		t	p
	Mean	SD	Mean	SD		
Age	38	12.2	38	12.9	0.04	ns
Sex (M:W)	11:9	–	13:7	–	–	–
Intelligence (percentiles)	85	17.7	87	14.8	0.31	ns
Laterality (R:L:A)	18:1:1	–	18:2:0	–	–	–
Depression (BDI)	3	4.2	10	9.5	2.81**	.009
Anxiety (BAI)	4	4.3	7	4.4	1.64	ns

Note: SD: Standard deviation. Sex: M: Men, W: Women, Laterality: R: right handed, L: left handed, A: Ambidextrous. Intelligence: Raven matrice percentiles. ns: not statistically significant.

2.3. Procedures

2.3.1. Treatment program

TD patients underwent a CBT for tics, based on the cognitive-psychophysiological treatment model presented by O'Connor (2005). This treatment includes some components of the habit reversal therapy, as well as cognitive and behavioral restructuration when facing high-risk tic situations (O'Connor et al., 2009). It aims to reduce the excessive overall motor activation, by decreasing tension created by cognitive and physiological sources (Lavoie et al., 2013). The individualized treatment was carried out by two licensed psychologists (supervised by KPO). The CBT program had major cumulative steps where the person built on exercises of the previous week. The entire treatment package was administered during 14 weekly sessions, with a further one month home practice (total: 18 weeks), after what full post-treatment evaluation was made. The *information stage* consists of the presentation of the rationale of the program and information on tic disorders. Patients are informed about the basic principles of tics and inappropriate strategies of dealing with them (e.g. suppression). The *awareness stage* includes self-observation, awareness training and monitoring exercises. Patients must also complete a situational functional profile, analyze high and low risk situations for ticcing, and identify the perceptual-cognitive factors associated with situations at high risk for ticcing. The *sensorimotor and muscle discrimination stage* involves a biofeedback section to demonstrate how behavioral strategies produce a change in motor and autonomic arousal, psychophysiological exercises to increase knowledge of different muscle tension levels, and the learning relaxation techniques. The overactive style and perfectionist concerns with personal organization are addressed by relaxation strategies. The *cognitive* aspect of action restructuration and planning aims to introduce flexibility into anticipations and judgements. *Relapse prevention and generalization strategies* consist of taking account of stressful states and excitable events that are likely to occur in the future; adopting a rational approach to relapse and identifying why the relapse happened.

2.3.2. Stimulus–response compatibility inhibition task

Stimuli in the SRC task were blue, black, and red arrows (subtending a visual angle of 2°x2°), presented for a duration of 350 ms on a white background at the center of the monitor screen. The arrows pointed to the left or to the right with an inter-stimulus-interval randomly ranging between 2200 and 2800 ms. Stimulus sequence was quasi-random with less than four identical trials in a row. The SRC design required a response with the hand corresponding to the direction of the arrow to one color, with the hand opposite to the direction of the arrow to the other color, and to inhibit the response when the arrow is red (pointing left or right). Participants gave their response with the left and right arrows of a

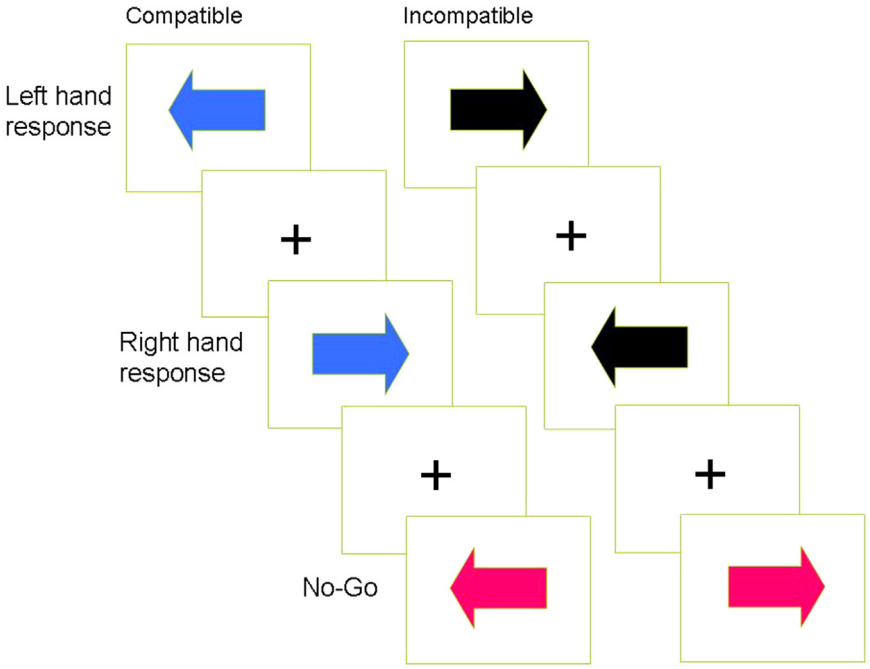

Fig. 1. Design of the stimulus–response compatibility task. Colored arrows are presented on a computer screen for a duration of 350 ms, with an inter-stimulus interval ranging between 2200 and 2800 ms.

traditional computer keyboard. Instructions were counterbalanced for hand across subjects. Two identical blocks of 150 arrows were presented (25 left-blue, right-blue, left-black, right-black, left-red arrows and right-red arrows). The task design is shown in Fig. 1.

2.4. Electrophysiological recordings

The EEG was recorded by a digital amplifier (Sensorium Inc, Charlotte, VT) during the SRC task. The signal was recorded from 60 Ag/AgCl electrodes mounted in a lycra cap (Electrode Arrays, El Paso, TX http://www.electrodearrays.com) and placed according to the standard EEG guideline (American EEG Society, 1994). EEG was recorded with high- and low-pass filter settings of 0.01 and 100 Hz respectively, sampled continuously at 500 Hz with impedance below 5 KΩ with an electrolyte gel (JNetDirect Biosciences, Herndon, VA). Bipolar electro-oculogram (EOG) was recorded to clear EEG from eye artifacts. EOGs were placed at the outer canthus of each eye (horizontal EOG) and infra-supra-orbital to the left eye (vertical EOG). All electrodes were referenced to the nose. The stimuli were monitored by *Presentation* (Neurobehavioral Systems, Albany, CA http://www.neurobs.com/), while signal acquisition was controlled by *IWave* (InstEP Systems, Montréal, QC) running on two PCs.

2.5. EEG signal extraction

Ocular artifacts were corrected offline with the Gratton algorithm (Gratton et al., 1983). Raw signals were averaged offline, time-locked to the stimuli onset, in a time window of 100 ms prior to stimulus onset until 1500 ms after stimulus onset within three separate conditions: compatible, incompatible, and NoGo. For LRP analyses purpose, EEG is also average time-locked to response onset, in a time window ranging from 500 ms before response onset to 500 ms after. ERP and LRP data were filtered with a 0.30 Hz high-pass filter, a 30 Hz low-pass filter, and a 60 Hz notch filter. Clippings due to amplifiers saturation and remaining epochs exceeding 100 μV and were removed during the averaging procedure. Epochs containing less than 20 trials for each category were excluded.

The amplitude and latency of the P300 component were calculated in a 250–450 ms interval, while the amplitude and latency of the LPC were calculated in a 450–950 ms interval. Thirty electrodes were used to analyze the P300 and LPC, and were clustered in six categories: AF1, AF3, F1, F3, F5 (left frontal), AF2, AF4, F2, F4, F6 (right frontal), FC1, FC3, C1, C3, C5 (left central), FC2, FC4, C2, C4, C6 (right frontal), CP1, CP5, P1, P3, P5 (left parietal), CP2, CP6, P2, P4, P6 (right frontal). From an anatomical perspective, both frontal and central regions are located over the frontal cortex. Our frontal region would approximately correspond to the prefrontal cortex, while our central regions have electrodes corresponding to sensorimotor areas, posterior to the prefrontal cortex.

The *LRP* were computed through a double substraction, with the formula proposed by Coles (1989):

$$\mathrm{LRP} = \frac{\left[\mathrm{Mean}(C4 - C3)^{\text{left hand}} + \mathrm{Mean}(C3 - C4)^{\text{right hand}}\right]}{2}$$

The same standard was applied for all sites (F1′, FC1′, FC3′, C1′, C3′, CP1′ & P1′), with the subtraction of the corresponding electrode on the opposite hemisphere. This LRP topography design was based on earlier work by Lavoie and Stauder (2013). LRP onsets were calculated for each participant with the proportional method (Osman and Moore, 1993), and calculated as 20% of the maximum peak. The onset was determined from 500 ms before the response for response-locked LRP (rLRP), and between 150 and 900 ms post-stimulus for stimulus-locked LRP (sLRP) (Smulders et al., 1996). The Gratton dip, which shows an activation of the incorrect response (Gratton et al., 1988), was assessed as the most positive peak in a 150–350 ms interval after incompatible stimulus presentation. rLRP peak and onset latency were analyzed in an interval going from 500 ms prior to response onset to the moment of response onset.

2.6. Statistical analyses

Since the control group was only tested once, two separate sets of analyses were performed. The first set of analyses compared the

TD and control groups at baseline, while a second set of analyses compared the TD group at baseline and after CBT. Therefore, we performed each repeated-measure ANOVA twice, first with the between-group factor Group (TD/controls), and then with the within-group factor Therapy (pre/post). Independent samples *t*-tests were performed to compare the two groups on age, intelligence, depression and anxiety scores. Paired samples *t*-tests were also performed to compare TSGS, YGTSS, BDI and BAI scores before and after the therapy.

The standard deviation and median of reaction times was analyzed with repeated-measures ANOVA, with the between-group factor Group (TD/controls), and two within-group factors: Condition (compatible/incompatible) and Hand (dominant/non-dominant). To assess the therapy effects, the between-group factor Group was replaced by the within group factor Therapy (pre/post).

To compare TD and controls on P300 and LPC peak amplitude and latency, repeated-measures ANOVAs were performed with the between-group factor Group (TD/controls), and four within-group factors: Condition (compatible/incompatible), Hand (dominant/non-dominant), Region (frontal/central/parietal), and Hemisphere (left/right). To assess the therapy effects, the between-group factor Group was replaced by the within group factor Therapy (pre/post). Since the NoGo effect only appears later in the stimulus processing stream, this condition was not included in the P300 analyses, and the NoGo level was added to the Condition factor in LPC analyses.

To compare the two groups before the therapy, sLRP and rLRP peaks, as well as incorrect activation (Gratton dip), were analyzed with repeated-measures ANOVAs with the between-group factor Group (TD/controls) and two within-group factors, Condition (compatible/incompatible) and Topography (F1′/FC1′/FC3′/C1′/C3′/CP1′/P1′). Further analyses were performed at electrode site C3', where LRP onset and peak were analyzed with repeated-measures ANOVAs, with the between-group factor Group (TD/controls) and the within-group factor Condition (compatible/incompatible). To assess the therapy effects on LRPs, the between-group factor Group was replaced with the within-group factor Therapy (pre/post) in all ANOVAs described above.

Significant interactions in all components were further analyzed with repeated-measures ANOVAs and independent samples *t*-tests. Huynh–Feldt corrections for repeated-measures analyses were performed when required.

3. Results

3.1. Clinical comparison before and after CBT

The therapy induced a significant reduction of YGTSS and TSGS scores. Furthermore, there were significant improvements in several YGTSS subscales, such as tic impairment, motor and phonic tics severity. Additionally, there was a trend toward reduced anxiety and depression evaluation. Clinical data are shown in Table 2.

3.2. Behavioral results

Before CBT, there was a significant condition main effect on median reaction times [$F(1,38)=7.36$, $p<.05$, partial $\eta^2=.162$], which showed that all participants were faster to respond to compatible than to incompatible stimuli. There was also more within-subject variance in response to the compatible than to incompatible stimuli [$F(1,38)=5.32$, $p<.05$, partial $\eta^2=.120$]. There was a hand by condition interaction [$F(1,38)=17.32$, $p<.001$, partial $\eta^2=.313$], which showed that faster responses were given with the dominant hand, to compatible trials. There was no significant difference in median reaction times or within-subject variances in reaction times between controls and patients with tic disorders, and no therapy effect.

3.3. Event-related potentials

3.3.1. P300 component

Before CBT, there was a significant compatibility effect on the P300 amplitude [$F(1,38)=4.30$, $p<.05$, partial $\eta^2=.102$], which shows slightly larger amplitude to compatible (6.3 μV) than to incompatible (6.0 μV) condition, with no difference across groups. The P300 mean peak latency was at 350 ms, with a significant condition effect on the P300 latency [$F(1,38)=9.10$, $p<.01$, partial $\eta^2=.193$] revealing earlier latency to incompatible (346 ms) than to compatible condition (353 ms), without difference across groups.

3.3.2. Late positive component (LPC) and NoGo anteriorization

The mean LPC peak amplitude was 6.2 μV and analyses revealed that before CBT, there were main effects of group [$F(1,38)=4.58$, $p<.05$, partial $\eta^2=.108$], condition [$F(2,37)=14.75$, $p<.001$, partial $\eta^2=.444$], region [$F(2,37)=17.38$, $p<.001$, partial $\eta^2=.484$] as well as a condition by region [$F(4,35)=4.54$, $p<.005$, partial $\eta^2=.342$] interaction, and a three-way group by condition by

Table 2
Pre-post comparison of clinical scales.

			TD group				*t*	*p*	*d*
			Pre		Post				
			Mean	SD	Mean	SD			
Depression (BDI)			10	9.5	7	7.1	2.05	0.055	.36
Anxiety (BAI)			7	4.4	3	3.3	1.85	0.081	1.03
Tic severity	TSGS total score		19	10.9	10	9.2	4.40**	0.000	.89
	YGTSS	Total	42	15.1	28	10.9	7.10**	0.000	1.06
		Tics impairment	21	9.8	11	5.0	6.02**	0.000	1.29
		Motor tics severity	13	4.8	11	4.2	3.03*	0.007	.44
		Phonic tics severity	8	5.8	6	4.8	3.36*	0.003	.38
Obsessive-compulsive symptoms (VOCI)			28	16.9	30	17.5	−.77	ns	.12
Impulsiveness (Barratt)			61	8.6	60	8.2	1.01	ns	.12

Note: SD: Standard deviation, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, TSGS: Tourette's Syndrome Global Scale, YGTSS: Yale Global Tic Severity Scale, *d*: Cohen's *d*.

* $p<.01$.
** $p<.001$.

region [$F(4,35)=4.34$, $p<.01$, partial $\eta^2=.331$] interaction. Further analyses were performed for each condition separately, and revealed that there was a group by region interaction only in response to the NoGo condition [$F(2,37)=9.05$, $p<.001$, partial $\eta^2=.329$], showing that the LPC was stronger in the frontal region for TD patients. This interaction remained significant after covariation with eye movements [$F(2,36)=6.06$, $p<.01$, partial $\eta^2=.252$] which partial out ocular artifacts bias. There was a correlation between the frontal LPC during the NoGo condition and depression (BDI) [$r=.49$, $p<.01$], but the group by region interaction remained significant after covariation with BDI [$F(2,36)=5.81$, $p<.05$, partial $\eta^2=.224$]. Finally, there was no significant change in the LPC amplitude following therapy.

The mean LPC latency peaked at 611 ms, and before CBT, there were main effects of condition [$F(2,37)=5.06$, $p<.05$, partial $\eta^2=.215$] and region [$F(2,37)=3.88$, $p<.05$, partial $\eta^2=.173$] on the LPC latency, revealing earlier LPC latencies in response to the NoGo condition over the frontal area. There was also a significant group by region interaction [$F(2,37)=3.48$, $p<.05$, partial $\eta^2=.158$], which showed a delayed frontal LPC latency for TD patients at baseline, but there is no significant effect in the LPC latency range following therapy (Fig. 2).

3.3.3. Lateralized readiness potentials (LRP)

3.3.3.1. Incorrect activation of the stimulus-locked LRP (Gratton dip; 150–350 ms from stimulus). Analyses on the incorrect sLRP

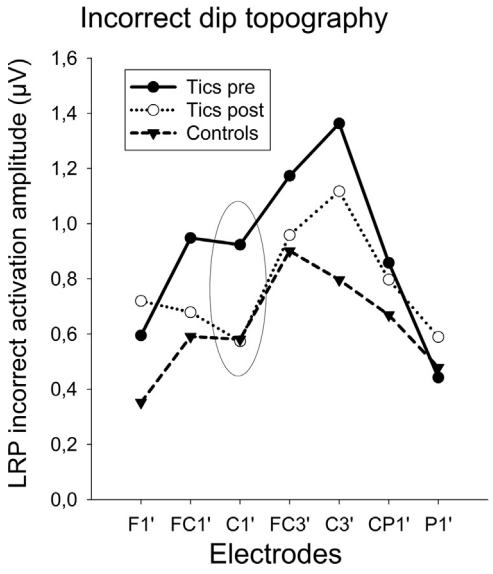

Fig. 3. *Gratton dip scalp topography of the incorrect activation.* The incorrect activation (Gratton dip) was larger over fronto-central areas. TD patients had a larger dip than control participants at most sites. The circle indicates where the reduction in amplitude was significant.

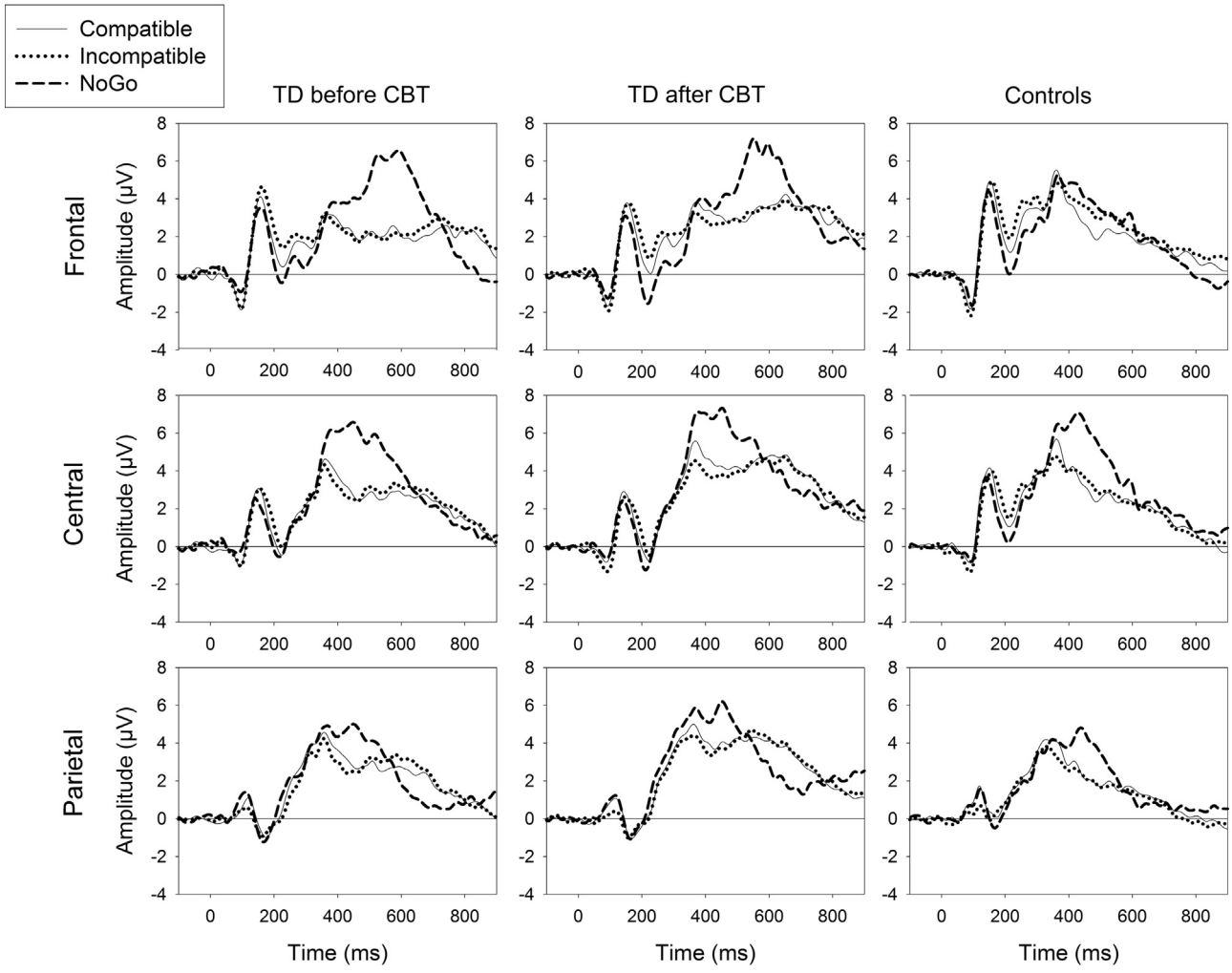

Fig. 2. *ERP waveforms.* Stimulus-locked ERP waveforms representing the topography of the amplitude in function of times in milliseconds. This figure shows that the LPC (400–800 ms) was more frontal and enhanced in TD patients during NoGo trials. That frontal activation persisted after the therapy.

activation (Gratton dip) revealed that before CBT, there were significant main effects of group [$F(1,38)=4.56$, $p<.05$, partial $\eta^2=.107$] and topography [$F(6,33)=7.75$, $p<.001$, partial $\eta^2=.585$], as well as a group by topography interaction [$F(6,33)=2.59$, $p<.05$, partial $\eta^2=.320$]. A regional analysis revealed that there was a larger group effect at the C3′ site, where the TD group showed a larger incorrect activation, in comparison with the control group ($t(38)=2.52$, $p<.05$, $d=.797$). After CBT, the topography effect remained significant [$F(6,14)=6.03$, $p<.005$, partial $\eta^2=.721$], and there was a topography by therapy interaction [$F(6,14)=3.21$, $p<.05$, partial $\eta^2=.579$]. Further analyses revealed that the CBT had a reducing effect on the incorrect activation and this CBT effect was significant over the C1′ region [$F(1,19)=8.26$, $p<.05$, partial $\eta^2=.303$] (Fig. 3).

3.3.3.2. Correct activation of the stimulus-locked LRP (150–900 ms from stimulus). Analysis on the mean peak amplitude of the sLRP, revealed that before CBT, there was a topography main effect [$F(4.43, 168.46)=40.80$, $p<.001$, partial $\eta^2=.518$], along with a group by topography by compatibility interaction [$F(4.50,171.16)=2.62$, $p<.05$, partial $\eta^2=.064$]. Regional analyses revealed that the amplitude was more prominent over C3′ and at that location, there was a group main effect [$F(1,38)=4.58$, $p<.05$, partial $\eta^2=.107$], revealing that TD patients showed a larger sLRP amplitude. However, this larger sLRP amplitude was not affected by CBT (Fig. 4).

The sLRP mean onset at electrode C′ was at 312 ms, and the analyses revealed that there was a compatibility effect [$F(1,38)=19.46$, $p<.005$, partial $\eta^2=.339$], showing faster onset latency for compatible (276 ms) than incompatible (349 ms) stimuli. Despite that the sLRP onset latency was generally delayed in the TD group, compared to the control group [$F(1,38)=4.24$, $p<.05$, partial $\eta^2=.100$], the compatibility effect was present for both patients [$F(1,19)=10.16$, $p<.01$, partial $\eta^2=.348$] and control [$F(1,19)=9.38$, $p<.01$, partial $\eta^2=.330$] groups. The CBT had a significant effect on the sLRP onset latency, where the TD group showed a significantly earlier onset of the sLRP following CBT [$F(1,19)=7.78$, $p<.05$, partial $\eta^2=.291$], and this post CBT onset was similar to the control group values. The sLRP waveforms at electrode C3′ are shown in Fig. 5.

There was a correlation between age and incompatible sLRP onset in all participants [$r=.56$, $p<.01$]. Even after covarying with age, the group difference remained significant [$F(1,37)=5.82$, $p<.05$, partial $\eta^2=.136$].

3.3.3.3. Correct activation of the response-locked LRP (−500 to 500 ms from response). The rLRP onset latency was at 245 ms before the response, without significant difference between groups. Before CBT, rLRP peak amplitude was slightly larger in the compatible (2.5 μV) than the incompatible (2.3 μV) condition [$F(1,38)=4.27$, $p<.05$, partial $\eta^2=.101$]. The amplitude of the rLRP was maximum over C3′ (lateral central) revealing a main effect of topography [$F(4.58,174.11)=69.58$, $p<.001$, partial $\eta^2=.647$] (Fig. 6). This topography effect was present in both TD and control groups, but TD patients showed a significantly larger rLRP amplitude in both conditions, as revealed by a group main effect [$F(1,38)=4.81$, $p<.05$, partial $\eta^2=.112$]. After CBT, there was a therapy by topography interaction [$F(4.32,82.02)=3.03$, $p<.05$, partial $\eta^2=.138$], which revealed that the amplitude reduction was only significant at C3′ site [$F(1,19)=11.61$, $p<.005$, partial $\eta^2=.379$]. There was also a therapy by condition interaction at C3' site [$F(1,19)=5.62$, $p<.05$, partial $\eta^2=.228$]. Supplementary analyses revealed that the amplitude reduction following CBT was only significant in the incompatible condition [$F(1,19)=12.57$, $p<.005$, partial $\eta^2=.398$], and not in the compatible one ($p=.119$, partial $\eta^2=.123$). The rLRP waveforms at electrode C3′ are shown in Fig. 7.

4. Discussion

Our main goal was to characterize the effect of CBT on motor-related and event-related electrocortical responses in TD patients.

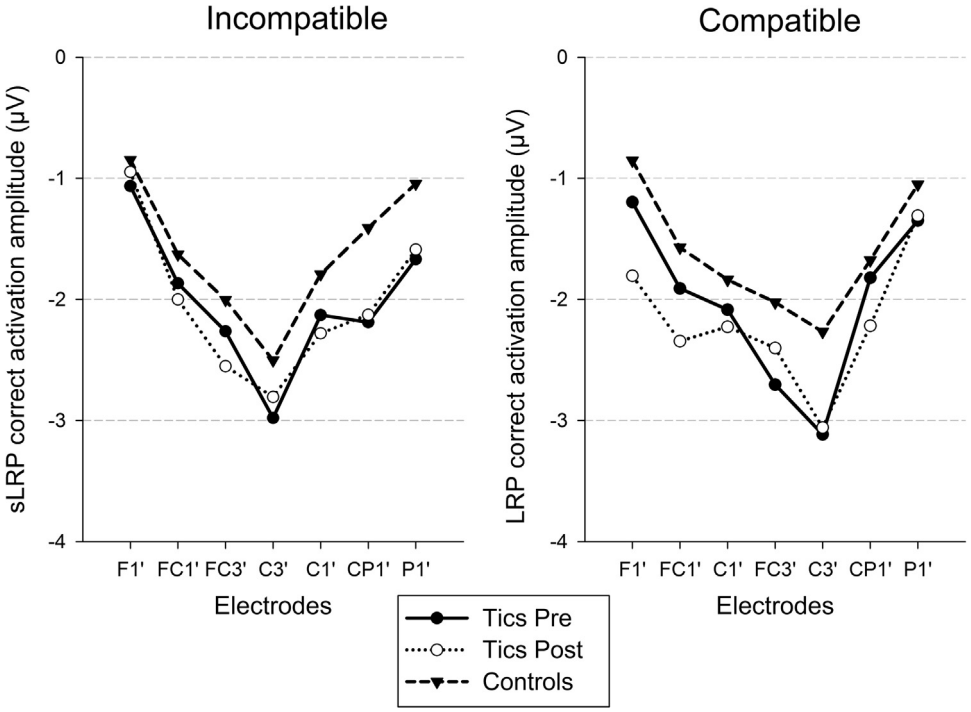

Fig. 4. *sLRP scalp topography of the correct activation for incompatible and compatible condition*. The sLRP topography was more prominent at C3′ site for all participants and both conditions. There was also a group difference at this site, where the TD patients displayed a larger sLRP amplitude than controls. However, the topography remained practically unchanged following therapy.

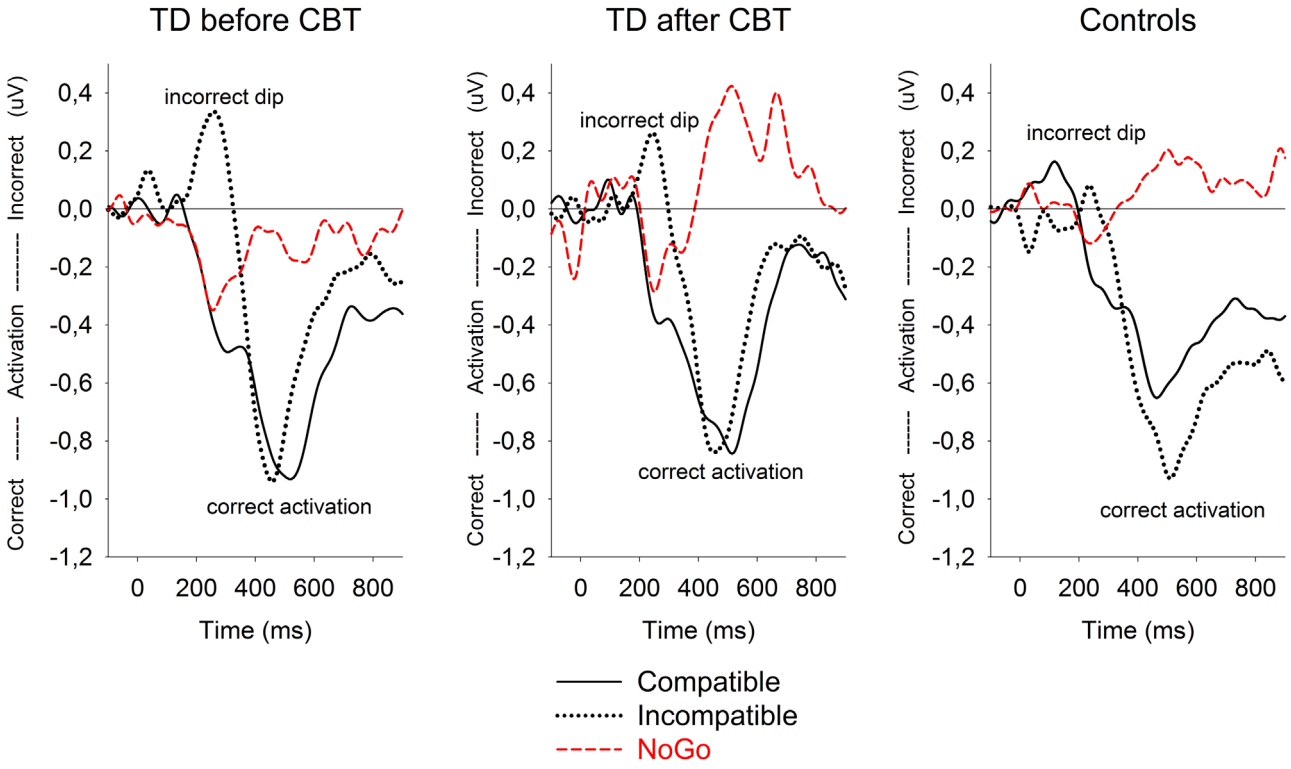

Fig. 5. *sLRP waveforms at electrode C3′*. Stimulus-locked LRP waveforms representing the pre-motor activation over C3′ (uV) in function of times (milliseconds). The positive polarity activation represents the incorrect activation and the negative polarity activation represents the correct activation of the response. At electrode C3′, TD patients had larger peak amplitude and a larger incorrect dip than controls.

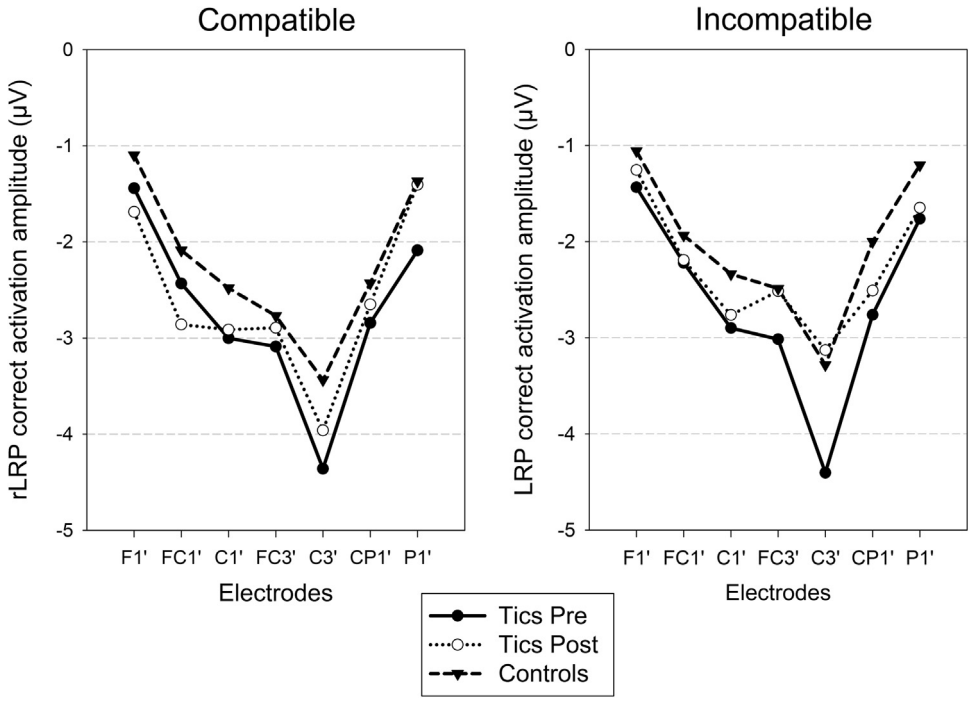

Fig. 6. rLRP scalp topography peak amplitude of the correct motor activation. The rLRP was more prominent at C3′ site. TD patients had larger rLRP amplitude (bold line) than control (dashed line) participants at that site, but this overactivation was normalized following CBT (dotted line), in response to the incompatible.

Our hypotheses predicted a delayed P300 and reaction times in TD patients. Our results confirmed that these measures are sensitive to stimulus–response compatibility, but TD patients showed typical P300 and reaction times. Moreover, we predicted that before therapy, TD patients would show electrocortical differences related to the activation of the motor cortex during SRC mapping. Our results confirmed that LRP, reflecting motor cortex activations, were generally more prominent in TD. In addition, we predicted a frontal LPC overactivation relative to condition of motor inhibition (NoGo) in TD patients. Our current finding was that overactivity of the frontal LPC was effectively present in TD patients, but that frontal activity was not affected by CBT. Finally, we predicted that

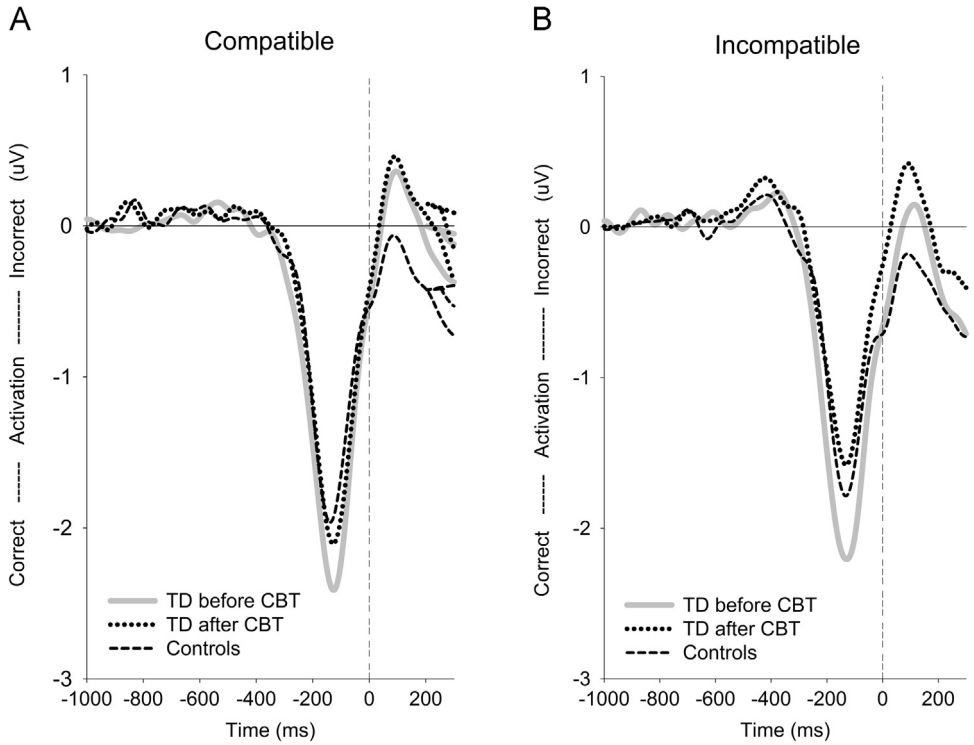

Fig. 7. rLRP waveforms at electrode C3′. Response-locked LRP waveforms representing the motor activation over C3′ (uV) in function of times (milliseconds) for the compatible (Panel A) and incompatible (Panel B) conditions. At electrode C3′, TD patients had larger rLRP peak amplitude than controls. This overactivation normalized after CBT, in response to the compatible but especially to the incompatible condition.

tics would diminish significantly following CBT, as well as clinical scores, which in turn would normalize electrocortical activation in brain regions involved in movement control. Our results showed that CBT has normalizing effects on the activation of the LRP and motor cortex in TD patients.

4.1. P300 and reaction times are sensitive to stimulus–response compatibility but not to tic symptoms

First, our results showed that the P300 and the reaction times are both sensitive to stimulus–response incompatibility with larger amplitude and delayed latency to incompatible stimulus, compared to compatible ones. Despite initial findings showing insensitivity of the P300 to compatibility effect (Magliero et al., 1984; McCarthy and Donchin, 1981), later studies reported a delayed P300 latency to incompatible stimuli (Fournier et al., 1997; Leuthold and Sommer, 1998; Masaki et al., 2000), which is consistent with our results. Also, as Ragot and Renault (1985) argued, S–R incompatibility is less influenced by semantic in comparison to spatial information, which might explain some of the differences found in the literature. Nonetheless, at that level in the stimulus processing stream, there is no difference between groups. This differs from the findings of Thibault et al. (2009), who reported a delayed P300 latency for TD patients. However, the P300 temporal window used in their study was several milliseconds larger than ours, and might have included later components that we classified under a different component (i.e. the LPC). This result suggests that, at this level of processing (300 ms after stimulus onset), TD patients are unimpaired in the processing of stimulus–response compatibility.

4.2. Overactivity of the frontal LPC and impulsivity in TD patients are not affected by treatment

Later in the stimulus processing stream, the TD group showed a delayed and overactivated frontal LPC related to the NoGo condition. This result suggests that TD patients had to mobilize more cognitive resources to correctly inhibit their motor response during NoGo trials. This frontal overactivation in our TD group is in line with the current literature, especially with the results of Johannes et al. (2001) and Thibault et al. (2009), who found that TD patients showed a larger frontal amplitude to process response inhibition. This frontal activity might also represent a compensation mechanism that would be enhanced in TD patients by years of effort to control their tics. Consistent with that hypothesis, Serrien et al. (2005) found an overactive frontomesial network during suppression of tics and voluntary movements, which is also coherent with our findings. They proposed that this sensorimotor overactivity is adaptive in patients with TD, as it acts to compensate for diminished inhibitory control. This inhibitory frontal component did not normalize following CBT and it remained overactivated. This is consistent with the unchanged score at the Barratt impulsivity scale, since the therapy does not directly address inhibitory and impulsivity functions *per se*.

It is not surprising that neural mechanisms subtending inhibitory functions remain untouched after CBT. If this frontal overactivation acts as a long-term inhibition compensation mechanism for TD patients, as suggested by Serrien et al. (2005), a reduction of this frontal activation would not be beneficial for them. In fact, this frontal pattern might reflect the amount of resources that TD patients must gather to perform at the same level as control participants. Serrien et al. (2005) also mentioned that this heightened frontal activation might be engaged in the voluntary suppression of tics. Since the therapy does not completely remove symptoms, TD patients still have tics to inhibit, and still need that inhibition mechanism.

4.3. CBT has normalizing effects on the activation of the pre-motor and motor cortex in TD patients

Concerning the LRPs, at the preliminary level of the incorrect

motor activation of the sLRP (the so-called Gratton dip), the clinical group showed a larger activation than the controls. This result may indicate that TD patients have to allocate more resources to activate the motor response to incompatible stimuli (Gratton et al., 1988). The CBT had a much localized effect on the Gratton dip at electrode site C1′, reducing its amplitude. Later in the stimulus processing stream, the sLRP onset latency was delayed in the TD group. Interestingly, the therapy had a normalizing effect on the sLRP onset, as TD patients showed a significantly earlier onset of the sLRP after CBT. Also, TD patients displayed larger sLRP amplitude in comparison to controls, but that activation was not affected by the therapy. The rLRP peak was also larger in TD patients, and it normalized after CBT.

Studies using LRP with TD patients are scarce, but several investigations with healthy controls offer certain clues to interpret these LRP effects. A first indication of automatic response activation by means of LRP has been demonstrated in noise-compatibility paradigms (Coles et al., 1985; Gratton et al., 1988). In these paradigms, when the compatible condition was presented, the sLRP showed only the activation of the correct response. However, in case of the incompatible condition, the LRP revealed an initial activation of the incorrect response, followed by a delayed activation of the correct response. Concerning the compatibility between stimulus and response, the Kornblum model (Kornblum et al., 1990) postulates that when the stimulus and response show *dimensional overlap*, the presentation of a stimulus element automatically activates its corresponding response element. Whether or not the stimulus and response sets show dimensional overlap, the *response identification* process is triggered. This process identifies the correct response according to the task. Thus, in the context of our SRC task, both the automatic activation and the response identification processes are triggered and the response identified as correct must be compared before the correct response can be executed. If the two are the same (compatible instruction), the response is immediately executed without further ado. If the two responses mapping are different (incompatible instruction), then the automatically activated response, together with its program, are lately aborted, triggering an initial dip, which corresponds to the cerebral activation of the incorrect motor response. Later, the program for the correct response is retrieved and consequently executed, giving rise to the sLRP peak, corresponding to the correct activation.

The generators of these activations were studied with single-unit recordings in the dorsal pre-motor cortex and motor cortex of monkeys performing compatible or incompatible reaching movements, relative to the color of a LED (Crammond and Kalaska, 1994). Investigating the properties and neural correlates of such task in the TD population can shed new light on the understanding of sensorimotor integration. In sensorimotor tasks, a functional facilitation or depolarization of the motor cortex may occur to promote a faster and more effective stage of response production to compatible stimuli (Chamberlain and Sahakian, 2004; Salmond et al., 2005). This mechanism is considered to be the basis of the SRC effect, and could help explain possible elements of impairment in clinical groups. Usually, sLRP reflects pre-motor processes, such as response selection and preparation, while rLRPs are thought to be related to motor execution processes (Masaki et al., 2004). As the sLRP is measured over the motor region, the start of this difference would reflect the time when sensorimotor integration/response selection is finished and the moment when the effective movement is initiated (Ho et al., 2004).

But one remaining question is to examine how the stimulus–response compatibility inhibition task addresses the features of the sensory-motor loop. Our results show deficits of these cerebral mechanisms, which could pinpoint a weakening in the capacity to select motor program and motor execution. As the TD group showed larger amplitudes of both the Gratton dip and the LRP peak, this could reveal an overactivation of the pre-motor and motor cortex in TD patients, which is consistent with our hypotheses, and also with previous findings using ERPs and brain imaging. A consistent overactivation of motor areas was often reported in brain imaging of TD (Biswal et al., 1998; Braun et al., 1993; Eidelberg et al., 1997). Braun et al. (1993) previously found that the increased synaptic load in primary, lateral and supplementary motor areas might alter TD patients' ability to regulate voluntary movements. Interestingly, in healthy participants, a stimulation of the SMA induce the urge to perform a movement (Fried et al., 1991). In TD patients, the SMA has been linked to tic generation and sensory premonitory urges (Bohlhalter et al., 2006; Hampson et al., 2009). Additionally, multiple studies showed that repetitive transcranial magnetic stimulation (rTMS) applied to the SMA was effective to reduce tic symptoms (Kwon et al., 2011; Le et al., 2013; Mantovani et al., 2006, 2007). LRPs are also generated partly by the SMA (Rektor, 2002), and since we found a reduction in tics frequency, as well as improvements of rLRP peak amplitude, we propose that our treatment induced a physiological modification in the functioning of the SMA and probably on the top down neural mechanisms involved in the control of tics.

To our knowledge, this is one of the first investigation to evaluate modifications in TD patients' brain functioning following CBT. This is congruent with the finding of improvements in fine motor skills after therapy, as measured with the Purdue Pegboard (O'Connor et al., 2008) and other motor tasks which also found a normalization of the sensorimotor cortical activity related to the inhibition of automatic motor responses (Lavoie et al. (2011), Therefore, CBT clearly seems to alter the sensorimotor loop functioning in TD, and more research will be needed to completely understand its mechanism and refine effective state-of-the-art treatment for tic disorders.

5. Limitations

The main limitation of our study is the unique recording of the control group. One might consider a different statistical approach using one mixed model with modeling of a random effect to control for the fact that controls did not repeat the experiment. But with the current data, a mixed model yielded the same results than the repeated measures ANOVAs. We agree that the mixed model could have given us an advantage with missing data or if more participants would have been included before than after therapy for instance, but it was not currently the case. Testing the control group twice, with the same interval than the patient group would certainly add strength to our design. However, good test–retest reliability of electrocortical activity was demonstrated with oddball (Debener et al., 2002; Williams et al., 2005), flanker tasks (Cassidy et al., 2012) and traffic light paradigms (O'Connor et al., 2005). This suggests that our control groups would show negligible differences in brain activity due to repetition. Another strategy would have been to record the patient group twice before the treatment (wait list control group), but in that case, a larger sample would need to be recruited and the wait list would need to be natural, not artificial.

Some of our participants were under medication, or had other comorbid diagnoses. Nevertheless, the medication remained stable over the course of CBT and the diagnosis of tic disorder always constituted the dominant one. Our two samples had a wide age range, and there were certainly differences in brain maturation within our groups. For instance, the P300 amplitude increases during childhood, reaches a peak during adolescence and slowly decreases from then on (van Dinteren et al., 2014). Concerning the LRP, the developmental curve is less well known. To partly

circumvent the problem, we carefully matched each patient to a control participant of the same age, and also looked at correlations between age and electrophysiological data.

6. Conclusion

In conclusion, we found that TD patients had an impaired electrocortical activity in relation to inhibitory and motor functions. First, P300 and reaction times are sensitive to stimulus–response compatibility but not to tic symptoms. In addition, overactivity of the frontal LPC and impulsivity in TD patients are not affected by treatment, and finally, the treatment has normalizing effects on the activation of the pre-motor and motor cortex in TD patients. The CBT allowed TD patients to selectively normalize some of these motor impairments. These modifications suggest an alteration of the sensorimotor and SMA functioning, and are in line with previous studies that points out this region as responsible for tic generation.

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