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Electrophysiological predictors of cognitive-behavioral therapy outcome in tic disorders

Simon Morand-Beaulieu[a,b,*], Kieron P. O'Connor[a,c], Pierre J. Blanchet[a,d], Marc E. Lavoie[a,b,c,*]

[a] Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montreal, Qc, Canada
[b] Département de Neurosciences, Université de Montréal, Montreal, Qc, Canada
[c] Département de Psychiatrie, Université de Montréal, Montreal, Qc, Canada
[d] Département de Stomatologie, Université de Montréal, Montreal, Qc, Canada

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ABSTRACT

Cognitive-behavioral therapy (CBT) constitutes an empirically based treatment for tic disorders (TD), but much remains to be learned about its impact at the neural level. Therefore, we examined the electrophysiological correlates of CBT in TD patients, and we evaluated the utility of event-related potentials (ERP) as predictors of CBT outcome. ERPs were recorded during a stimulus-response compatibility (SRC) task in 26 TD patients and 26 healthy controls. Recordings were performed twice, before and after CBT in TD patients, and with a similar time interval in healthy controls. The stimulus- and response-locked lateralized readiness potentials (sLRP & rLRP) were assessed, as well as the N200 and the P300. The results revealed that before CBT, TD patients showed a delayed sLRP onset and larger amplitude of both the sLRP and rLRP peaks, in comparison with healthy controls. The CBT induced an acceleration of the sLRP onset and a reduction of the rLRP peak amplitude. Compared to healthy controls, TD patients showed a more frontal distribution of the No-Go P300, which was however not affected by CBT. Finally, a multiple linear regression analysis including the N200 and the incompatible sLRP onset corroborated a predictive model of therapeutic outcome, which explained 43% of the variance in tic reduction following CBT. The current study provided evidence that CBT can selectively normalize motor processes relative to stimulus-response compatibility in TD patients. Also, ERPs can predict the amount of tic symptoms improvement induced by the CBT and might therefore improve treatment modality allocation among TD patients.

1. Introduction

Tic disorders (TD) constitute a group of neurodevelopmental psychiatric disorders characterized by involuntary, rhythmic, and stereotyped motor and/or phonic tics (American Psychiatric Association, 2013). TD patients often face various comorbid conditions, such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) (Freeman, 2007). Definite causes of TD have not been established yet, but impairments in cortico-striatal-thalamo-cortical (CSTC) circuits are known to be linked with TD (Mink, 2006; Worbe et al., 2012). For instance, excitatory activity within the striatum is thought to cause greater inhibition of the internal globus pallidus, which would lead to disinhibition of cortical neurons (Felling and Singer, 2011; Mink, 2006). Such overactivation in areas such as the primary and supplementary motor areas (Biswal et al., 1998; Fattapposta et al., 2005; Morand-Beaulieu et al., 2015) causes the presence of involuntary movements (Ganos et al., 2018).

For decades, pharmacotherapy was the only efficient treatment option for TD. However, it is often accompanied by undesirable side effects. For instance, first-generation neuroleptics are among the most effective treatments for TD (Scahill et al., 2006). Yet, their long-term use may result in tardive dyskinesia (Carbon et al., 2017; Correll and Schenk, 2008), which is highly undesirable for patients already struggling with involuntary movements. Nowadays, non-pharmacological treatments are often considered first-line treatments for TD. These approaches, which include cognitive-behavioral therapy (CBT), exposure and response prevention, habit reversal therapy have similar efficiency to medication (McGuire et al., 2014b; Rizzo et al., 2018) and present the major advantage of limited side effects (Whittington et al., 2016). However, some patients only partially respond to cognitive-behavioral therapy (O'Connor et al., 2016). Identifying accurate markers before treatment would allow optimal treatment modality allocation. To date,

* Corresponding authors. Centre de recherche de l'Institut universitaire en santé mentale de Montréal, 7331 Hochelaga Street, Montreal, Qc, H1N 3V2, Canada.
E-mail addresses: simon.morand-beaulieu@umontreal.ca (S. Morand-Beaulieu), marc.lavoie@umontreal.ca (M.E. Lavoie).

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only few studies reported CBT outcome predictors. Relative to clinical symptoms, more severe tics and greater expectancy of treatment benefits predicted better therapeutic outcome, while greater premonitory urge severity and the presence of non-OCD anxiety disorders predicted lesser tic reduction (Sukhodolsky et al., 2017). Adults with TD who showed greater inhibitory impairments in a visuospatial priming task were found to respond less well to habit reversal therapy (Deckersbach et al., 2006). However, a more recent study with a larger sample reported that the Go/No-Go task was not predictive of behavioral treatment response in adults with TD (Abramovitch et al., 2017). Neuropsychological tests measuring inhibitory functions, working memory, and habit learning did not predict behavioral treatment outcomes in children with TD either (Chang et al., 2018). Therefore, the potential of neuropsychological batteries as treatment outcome predictors seems relatively limited. The current study proposes to use cognitive electrophysiology to predict therapeutic outcome in TD patients. Electrophysiology offers high temporal precision to follow the stream of fast cognitive and motor processes. This technique was useful to predict CBT outcome in other psychiatric disorders, such as anxiety disorders (Burkhouse et al., 2016; Hum et al., 2013), depression (Burkhouse et al., 2016), and OCD (Krause et al., 2015), but has yet to be tested in TD.

Very few studies investigated the impact of CBT on brain functioning in TD. The first investigation on this matter reported a normalization of electro-cortical activity related to the inhibition of automatic motor responses (Lavoie et al., 2011). A functional magnetic resonance imaging study also found decreased putamen activation in a motor inhibition task following behavioral treatment (Deckersbach et al., 2014). Recently, we reported event-related potentials (ERP) changes during an oddball task (Morand-Beaulieu et al., 2016) and an alteration of motor processing (Morand-Beaulieu et al., 2015) following CBT. In the latter study, the delayed stimulus-locked lateralized readiness potentials (sLRP) onset and the larger response-locked LRP (rLRP) peak found in TD patients before treatment were both normalized following CBT. LRPs, which are obtained through a double subtraction of ERPs recorded bilaterally over the motor cortex, constitute electrophysiological measures sensitive to motor response selection and activation (Coles, 1989). They mainly involve the primary (Coles, 1989; Miller and Hackley, 1992; Praamstra et al., 1999; Requin and Riehle, 1995) and supplementary (Rektor, 2002) motor areas, which represent brain areas of particular interest in TD (Polyanska et al., 2017). However, we cautiously interpreted our findings, given the absence of a comparable repeated measure for our control group.

By comparing TD patients with healthy controls at both pre- and post-treatment assessments, this study aimed to ascertain that treatment effects on motor processes previously identified (Morand-Beaulieu et al., 2015) are attributable to the CBT and not to a repetition or practice effect. Therefore, we hypothesized that there would be no change in sLRP onset and rLRP peak in healthy controls over a four-month period. We also wished to expand our previous findings and to explore the relationship between ERP components and tic severity. Given that our experimental task relies on motor skills, we expected ERP components to be linked to motor rather than phonic tic severity. Most importantly, we aimed to use ERPs to identify a prediction model of CBT outcome in TD patients. Given the novelty of electrophysiological prediction of CBT outcome in TD, our analyses were exploratory and no specific hypotheses were formulated.

2. Methods

2.1. Participants

Twenty-six TD patients were included in the current study.[1] They constituted a subset of a larger project on cognitive-psychophysiological treatment of TD (O'Connor et al., 2016). Criteria for inclusion were to (i) fulfill DSM-IV-TR criteria for Tourette syndrome or chronic TD (confirmed by a neurologist (PJB)) and to (ii) be aged between 18 and 65 years old. Criteria for exclusion were: (i) history of other neurological disorders; (ii) head injury in the last year; (iii) IQ < 75; (iv) psychiatric disorders that are not common comorbidities of TD (e.g. schizophrenia or dissociative disorders); (v) currently receiving treatment for TD (other than medication); and (vi) misuse of alcohol or drugs. Common comorbidities of TD, such as ADHD, OCD, depression, anxiety, etc., were not excluded. Psychiatric medication for TD or associated symptoms was permitted if it remained constant over the course of the therapy and if the symptoms were stable since at least 3 months. Among the 26 TD patients, nine were under medication and eight had comorbid disorders (see Table S1 for individual characteristics). TD patients were matched on age and sex with a group of 26 healthy controls (see Table 1 for socio-demographic characteristics of all participants). Age range of inclusion for the healthy controls was between 18 and 65 years old, whereas the exclusion criteria were: (i) the history of neurological or psychiatric disorder; (ii) presence of head injury in the last year; (iii) psychiatric medication uptake; and (iv) misuse of alcohol or drugs. This study was approved by the local institutional ethics board and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants prior to their participation in the study.

2.2. Procedures

2.2.1. Clinical assessment

In both groups, anxiety and depression symptoms were assessed with the Beck Anxiety Inventory (BAI; Beck et al., 1988) and the Beck Depression Inventory (BDI; Beck et al., 1961), respectively. In TD patients, tic severity, impulsivity, and obsessive-compulsive symptoms were assessed with the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989), Barratt Impulsiveness Scale (BIS-10; Bayle et al., 2000), and the Vancouver Obsessional Compulsive Inventory (VOCI; Thordarson et al., 2004), respectively.

2.2.2. Cognitive-behavioral therapy

The CBT used in the current study (the cognitive-psychophysiological therapy; CoPs) aims at changing the underlying physiological process leading to tic behavior, rather than modifying the tic itself (O'Connor et al., 2016; O'Connor, 2002; O'Connor et al., 2017). It is divided into 10 stages and administered over 14 one-hour sessions by licensed psychologists (supervised by KPO). It mainly consists of awareness training, muscle discrimination, muscular relaxation, reduction of sensorimotor activation, modification of style of action planning, cognitive and behavioral restructuration, generalization, and relapse prevention. After the 14th session, there is a four-week home practice where patients implement the strategies themselves (see O'Connor et al. (2017) for further details). Therefore, post-treatment assessment was performed approximately 18 weeks after the beginning of the therapy.

2.2.3. Stimulus-response compatibility (SRC) task

The SRC task offers valuable insight regarding response selection processes as well as motor preparation and execution in TD patients.

[1] The same 26 patients were included in an earlier study (Morand-Beaulieu et al., 2016), which involved a different experimental paradigm (oddball task). The study that demonstrated CBT effects on motor processes (Morand-Beaulieu et al., 2015) also included 20 of the 26 patients included in the current study with the same protocol. Here, they were compared to a newly recruited group of 26 healthy controls in which ERP/LRP measures were assessed twice to control for a possible practice effect.

Table 1
Socio-demographic and clinical characteristics at first assessment.

	TD patients		Healthy controls		*t*	p	*d*
	Mean	SD	Mean	SD			
Age	38	*11.9*	37	*11.3*	.28	.785	.08
Sex (M:W)	17:9	*N/A*	16:10	*N/A*	2.17[a]	.141[a]	N/A
Intelligence (RPM)	88	*13.8*	78	*22.1*	1.90	.064	.53
Handedness (R:L)	24:2	*N/A*	26:0	*N/A*	N/A	1.00[b]	N/A
Anxiety (BAI)	8	*5.9*	3	*3.9*	3.26	.002	.90
Depression (BDI)	11	*10.2*	3	*4.0*	3.45	.002	.96

SD, Standard deviation; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; RPM, Raven's Progressive Matrices.
[a] Chi-squared test.
[b] Fisher's exact test.

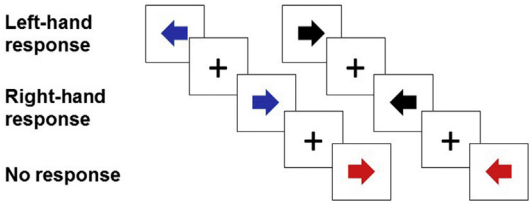

Fig. 1. Stimulus-response compatibility task. Participants had to press a key or withhold their response according to the color and direction of arrows. Blue arrows: same direction (compatible condition), black arrows: opposite direction (incompatible condition), red arrows: withhold response (No-Go condition). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

During this task, left- and right-pointing colored arrows were presented over a white background for 200 ms, with an interstimulus interval ranging from 1500 to 1800 ms. Responses were determined by the color of the arrows and delivered on a computer keyboard, by pressing either the left arrow with the left index finger or the right arrow with the right index finger (see Fig. 1). In the compatible condition (100 blue arrows), participants pressed the keyboard key corresponding to the direction of the arrow. In the incompatible condition (100 black arrows), participants pressed the key opposed to the direction of the arrow. In the No-Go condition (50 red arrows), participants were asked to halt any response. Left- and right-pointing arrows were equally distributed in each condition, and presented in a pseudo-random order during a single block. To ensure correct performance during the SRC task, visual acuity (Snellen) and color perception (Ishihara) were assessed prior to testing. Since tic suppression would likely impact the results during the task (Serrien et al., 2005), no particular instruction was given to TD patients regarding their tics.

2.3. EEG recordings and signal extraction

The electroencephalogram (EEG) was recorded during the SRC task, pre- and post-CBT in TD patients, and before and after a similar four-month interval in healthy controls. The EEG signal was recorded from 62 Ag/AgCl electrodes mounted in a lycra cap (Electrode Arrays, El Paso, TX, USA), placed according to standard EEG guidelines (American EEG Society, 1994), and referenced to the nose. The signal was recorded through IWave (InstEP Systems, Montreal, QC, Canada) coupled with a digital amplifier (Sensorium Inc., Charlotte, VT, USA). The raw EEG was sampled continuously at 500 Hz and recorded with a 0.01 Hz high-pass filter and a 100 Hz low-pass filter. Impedance was kept below 5 KΩ with an electrolyte gel (JNetDirect Biosciences, Herndon, VA). Additional electrodes were placed at the outer canthus of each eye and below and above the left eye to correct ocular artifacts with the Gratton algorithm (Gratton et al., 1983). Stimuli presentation was monitored by Presentation (Neurobehavioral Systems, Albany, CA, USA). Raw EEG signals were averaged offline and time-locked to stimulus and response onset. Averaged data were filtered with a 0.3 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 were removed. All participants had at least 40 valid trials without artifact in each condition (see Supplementary material for further details).

The following electrodes were used in ERP analyses: AF1, AF2, AF3, AF4, F1, F2, F3, F4, F5, F6 (frontal); FC1, FC2, FC3, FC4, C1, C2, C3, C4, C5, C6 (central); CP1, CP2, CP5, CP6, P1, P2, P3, P4, P5, P6 (parietal). The N200 was measured as the most negative peak in the 150–300 ms interval, while the P300 was scored as the most positive peak in the 300–700 ms interval. The LRP were computed through a double subtraction as proposed by Coles (1989): $LRP = \frac{[Mean(C4-C3)^{left\ hand} + Mean(C3-C4)^{right\ hand}]}{2}$. LRP peaks and onsets were measured in a 150–900 ms interval after stimulus onset for stimulus-locked LRP (sLRP) and in a −500 to 0 ms before response onset for response-locked LRP (rLRP). The onset of sLRP and rLRP was calculated with the relative criterion method (Mordkoff and Gianaros, 2000), which was set at 20%. Five TD patients and three healthy controls were excluded from LRP analyses since they did not show any measurable LRP.

2.4. Statistical analysis

Between-group comparisons of socio-demographic and clinical data were performed with independent-samples t-tests, chi-square tests and Fisher's exact test. CBT impact on TD symptoms and associated features was assessed with paired-samples t-tests. Electrophysiological and behavioral data were analyzed with mixed ANOVAs, all involving the between-subjects factor Group (TD/HC). Within-subjects factor differed between components. The N200 and P300 analyses involved the within-subjects factors Time (pre/post), Compatibility (compatible/incompatible/No-Go) and Region (frontal/central/parietal). Response accuracy, reaction times (RT), and LRP data were analyzed with the within-subjects factors Time (pre/post) and Compatibility (compatible/incompatible (and No-Go for response accuracy)). Pearson correlations between electrophysiological components and tic severity were performed for pre-CBT measures (Table S2). Greenhouse-Geisser corrections for sphericity violation were applied when $\varepsilon < 0.75$, while Huyhn-Feldt corrections were applied when $\varepsilon > 0.75$ (Vieira, 2017). The Bonferroni test was used for post-hoc comparisons. Effect sizes were reported with Cohen's d for pairwise comparisons and partial eta-squared (ηp^2) for interactions and variables with more than two levels. To identify potential predictors of CBT outcome, we performed correlations between electrophysiological components and the percentage of improvement in motor and phonic tics subscales following CBT. Correlations were performed between improvement measures and each region and condition for ERP components, and in compatible and incompatible conditions at electrode C3′ for LRP components.[2] Any electrophysiological components correlated to tic symptoms improvement were entered in a stepwise multiple regression analysis to identify the best prediction model.

3. Results

3.1. Assessment of clinical improvement following CBT

All but one patient had motor tics, and 19 of the 26 patients had phonic tics. The CBT had a significant impact on TD symptoms (Table 2). The mean decrease in YGTSS global scores was 36% (95% CI: 28%–44%), and the YGTSS total tic scores decreased by 26% (95% CI: 16%–36%). Tic domain analyses revealed that CBT significantly

[2] The C3′ electrode position (calculated from C3 and C4) overlaps the premotor and supplementary motor regions.

Table 2
CBT impact on TD symptoms and associated features.

			Pre		Post		*t*	p	*d*
			Mean	SD	Mean	SD			
Depression (BDI)			10.8	*10.2*	6.4	*6.5*	**2.92****	< **.01**	.51
Anxiety (BAI)			8.6	*5.9*	6.6	*6.5*	1.70	ns	.32
OCS (VOCI)[a]			28.7	*20.5*	29.8	*18.4*	-.36	ns	-.06
YGTSS	Global		40.2	*15.3*	25.6	*11.2*	**7.52*****	< **.001**	1.09
	Impairment		19.7	*10.5*	10.2	*5.0*	**5.84*****	< **.001**	1.16
	Motor tics severity		13.2	*4.3*	10.7	*4.6*	**3.66****	< **.01**	.56
	Motor domains	Number	2.5	*1.2*	2.3	*1.2*	1.77	ns	.17
		Frequency	4.1	*1.2*	3.2	*1.5*	**3.05****	< **.01**	.66
		Intensity	3.2	*1.0*	2.5	*1.1*	**3.05****	< **.01**	.67
		Complexity	1.6	*1.0*	1.6	*1.3*	-.39	ns	.00
		Interference	1.9	*1.2*	1.1	*1.0*	**3.1****	< **.01**	.64
	Phonic tics severity		7.4	*5.6*	5.6	*4.7*	**4.39*****	< **.001**	.35
	Phonic domains	Number	1.0	*0.8*	0.9	*1.0*	.77	ns	.11
		Frequency	2.4	*1.9*	1.4	*1.6*	**4.35*****	< **.001**	.57
		Intensity	2.2	*1.5*	1.4	*1.3*	**4.28*****	< **.001**	.57
		Complexity	0.5	*1.1*	0.4	*0.8*	1.69	ns	.10
		Interference	1.2	*1.3*	0.7	*0.9*	**3.38****	< **.01**	.45
Impulsivity (BIS-10)[b]			71	8.8	69	9.0	1.45	ns	.16

**: p < .01, ***: p < .001.
SD, Standard deviation; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; OCS: obsessive-compulsive symptoms; VOCI, Vancouver Obsessional Compulsive Inventory; YGTSS, Yale Global Tic Severity Scale; ns: not statistically significant.
[a] Four TD patients with missing data.
[b] One TD patient with missing data.

reduced the frequency, intensity, and interference of both motor and vocal tics, with medium to large effect sizes. For instance, motor and phonic tic frequency decreased by approximately a full point.

3.2. Behavioral results

RT were faster during compatible than incompatible trials [F(1,50) = 13.63, p = .001, d = 0.19]. Both groups responded with similar RT latency (TD: 648 ms; HC: 661 ms) and accuracy (TD: 98%; HC: 96%), and they were both slightly faster at the second assessment [F(1,50) = 14.97, p < .001, d = 0.25]. There was a compatibility effect regarding accuracy [F(1.28,64.16) = 5.82, p = .013, ηp^2 = 0.104], which revealed better accuracy for No-Go trials [p = .048, d = 0.47 vs compatible; p = .041, d = 0.49 vs incompatible].

3.3. Event-related potentials

3.3.1. Stimulus-locked lateralized readiness potentials

In both groups, the sLRP onset was faster during compatible trials [F(1,42) = 76.35, p < .001, d = 1.43] (Fig. 2A). It was also delayed in TD patients pre-CBT [F(1,42) = 6.94, p = .012, d = 0.79] and the incompatible sLRP onset was negatively correlated with motor tic severity [r = −.46, p = .036]. There was a main effect of Time [F(1,42) = 6.44, p = .015, d = 0.36], but the Time by Group interaction did not quite reach significance [F(1,42) = 2.76, p = .104, ηp^2 = 0.062]. The trend-level p-value and the medium effect size of this interaction suggested that we might have lacked the necessary statistical power to detect a significant interaction. We therefore performed pre-post comparisons in separate groups and interpreted these cautiously. These separate group comparisons suggested that the global Time effect was in fact driven by the TD group's sLRP onset acceleration [F(1,20) = 8.23, p = .010, d = 0.56], while the sLRP onset remained stable over the four-month interval in healthy controls [F(1,22) = 0.41, p = .527, d = 0.13] (Fig. 2B).

There was a Time by Group interaction regarding the sLRP peak amplitude [F(1,42) = 5.21, p = .028, ηp^2 = 0.110] (Fig. 2C). This was explained by a larger group difference before CBT which became non-significant after CBT. No other interaction or main effect reached significance.

3.3.2. Response-locked lateralized readiness potentials (rLRP)

The rLRP data (Fig. 3A) revealed a Time by Group by Compatibility interaction regarding rLRP onset [F(1,42) = 7.10, p = .011, ηp^2 = 0.145] (Fig. 3B). In TD patients, a time by compatibility interaction [F(1,20) = 4.50, p = .047, ηp^2 = 0.184] revealed an enhancement of the compatibility effect induced by the CBT. In healthy controls, this interaction was not significant, despite a non-significant reduction in the compatibility effect attributable to repetitions.

There were Time by Group [F(1,42) = 21.65, p < .001, ηp^2 = 0.340] and Time by Group by Compatibility [F(1,42) = 5.62, p = .022, ηp^2 = 0.118] interactions regarding rLRP amplitude (Fig. 3C). Before CBT, the rLRP peak amplitude was larger in TD patients than in healthy controls [F(1,42) = 8.53, p = .006, d = 0.88]. In the TD group, CBT induced a selective amplitude reduction to the incompatible condition, as revealed by a time by compatibility interaction [F(1,20) = 5.63, p = .028, ηp^2 = 0.220]. Patients with the largest incompatible rLRP peak amplitude pre-CBT were shown to have the most severe symptoms of phonic tics [r = −.52, p = .016], and patients who had the largest relative reduction in incompatible rLRP peak amplitude were the ones with the most improvement in phonic tics following treatment [r = .70, p = .004]. In healthy controls, this time by compatibility interaction was not significant, despite an increase in incompatible rLRP peak amplitude following the four-month interval [t(20) = −2.51, p = .020, d = 0.41].

3.3.3. N200

Among all participants, the N200 showed a Compatibility main effect [F(1.67,83.73) = 9.71, p < .001, ηp^2 = 0.163], with larger amplitude during No-Go trials [p = .003, d = 0.32 vs compatible, p = .001, d = 0.26 vs incompatible]. There was also a Compatibility by Region by Group interaction [F(2.54,126.76) = 5.31, p = .003, ηp^2 = 0.096], which revealed smaller compatible N200 over the frontal region in TD patients [F(1,50) = 4.83, p = .033, d = 0.61]. However, the CBT had no impact on this component (Fig. 4).

3.3.4. P300

The P300 amplitude showed a Compatibility by Region by Group interaction [F(1.60,79.96) = 4.81, p = .016, ηp^2 = 0.088]. The latter revealed a Region by Group interaction within the No-Go condition [F

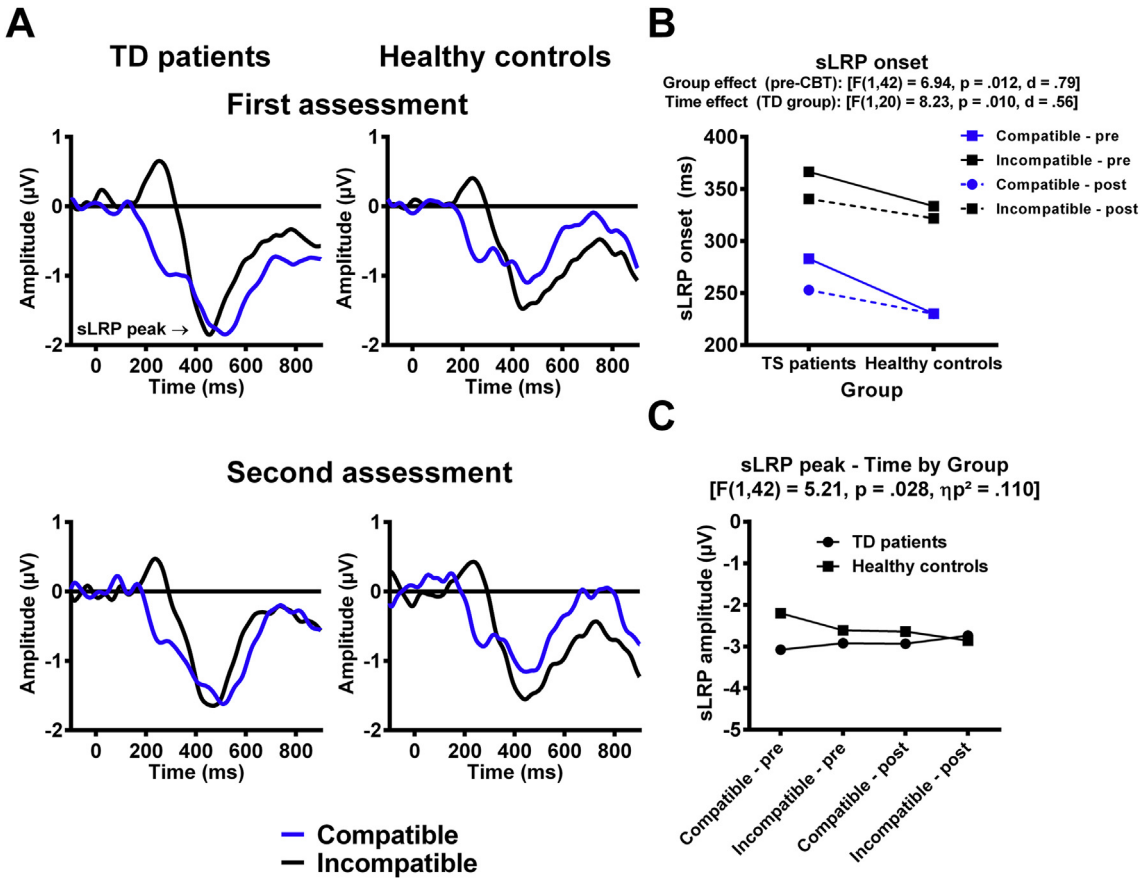

Fig. 2. Stimulus-locked LRP (sLRP). (A) Grand averages waveforms of the sLRP. (B) The sLRP onset was delayed in TD patients pre-CBT, but was earlier following CBT. In healthy controls, the sLRP onset did not change over the four-month interval. (C) A group difference regarding sLRP peak amplitude pre-CBT became non-significant post-CBT.

(1.20,60.11) = 5.10, p = .022, ηp^2 = 0.093]. While the No-Go P300 showed a central distribution in healthy controls [p = .045 vs frontal; p < .001 vs parietal], it was more prominent over frontal electrodes in TD patients [p = .132 vs central; p = .051 vs parietal]. Here again, there was no effect of CBT on this component (Fig. 5).

3.3.5. Electrophysiological predictors of treatment response

Improvements in motor tic severity were negatively correlated with the parietal compatible P300 [r = −0.43, p = .032] and positively correlated with the incompatible sLRP onset [r = 0.55, p = .012], while improvements in phonic tic severity were negatively correlated with the central [r = −0.49, p = .035] and parietal [r = −0.47, p = .042] incompatible N200, the central incompatible P300 [r = −0.49, p = .034], the frontal No-Go P300 [r = −0.46, p = .048], and the incompatible rLRP peak [r = −0.55, p = .033]. These variables were entered in a stepwise multiple linear regression analysis, which revealed that improvements in the total tic subscale were predicted by the incompatible sLRP onset and the incompatible parietal N200 [F(2,18) = 8.52, p = .002, adjusted-R^2 = 0.43] (Fig. 6). Regression coefficients are presented in Table 3. To ensure that our prediction model was not attributable to a difference in baseline tic severity between patients, we also performed a linear mixed model analysis to evaluate the ability of electrophysiological markers to predict the outcome (YGTSS/50 post-CBT). The model included the fixed effects of baseline tic severity (YGTSS/50), incompatible sLRP onset and incompatible parietal N200. Taking baseline tic severity into account had no impact on the model, as both electrophysiological markers remained significant predictors (see Table 4).

3.3.6. Assessment of the impact of medication on electrophysiological results

To ascertain that results were not attributable to the medication uptake, we reanalyzed data while excluding the 7 TD patients who were under medication (see Supplementary material). Since this affects our statistical power, some of our group differences were reduced in these analyses. However, most effect sizes were similar to our original analyses, suggesting that our results should not be attributable to patients' medication uptake.

4. Discussion

The current study aimed at ascertaining that CBT impacts on brain functioning were not attributable to a practice effect, and at identifying predictors of treatment outcome. Over the four-month interval, pre-motor and motor processes did not change substantially in healthy controls, suggesting that CBT impacts in TD patients were not related to the repetition of the task. Pre-motor and motor processes were also associated to TD symptomatology. Furthermore, a combination of specific electrophysiological markers also yielded a model of treatment prediction.

At the behavioral level, the RT during the SRC task showed a classical compatibility effect, which was similar across groups and was not affected by the treatment. Differences were however evident regarding underlying brain functioning. Before CBT, pre-motor processes (sLRP onset) were delayed in TD patients, and this effect was associated with less severe motor tics. While delayed sLRP onset has been reported in ADHD patients (Cross-Villasana et al., 2015), it is unlikely to have influenced our findings, given the low rate of comorbid ADHD in our sample (< 4%). We initially believed that the delayed sLRP onset in

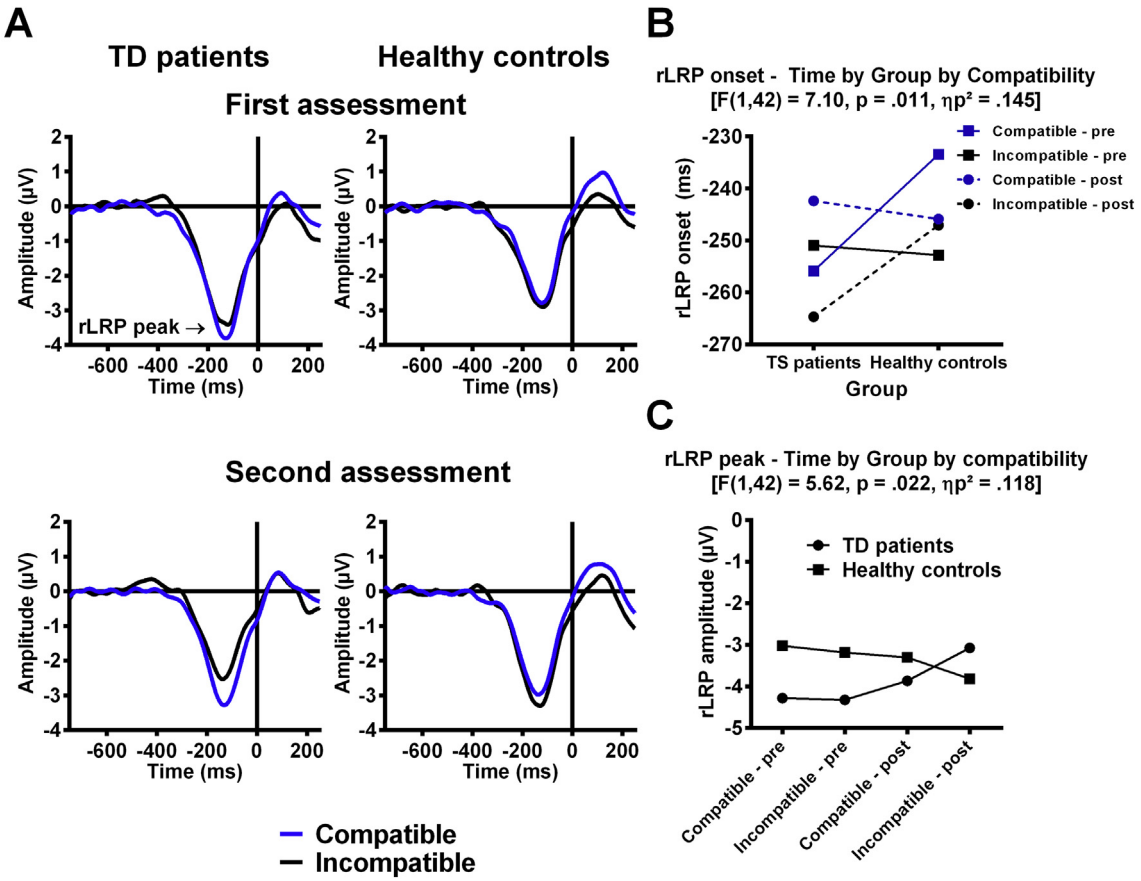

Fig. 3. Response-locked LRP (rLRP). (A) Grand averages waveforms of the rLRP. (B) In TD patients, the CBT induced a significant enhancement of the compatibility effect. (C) The CBT induced a reduction of the incompatible rLRP peak amplitude, which was associated to the decrease in phonic tic severity.

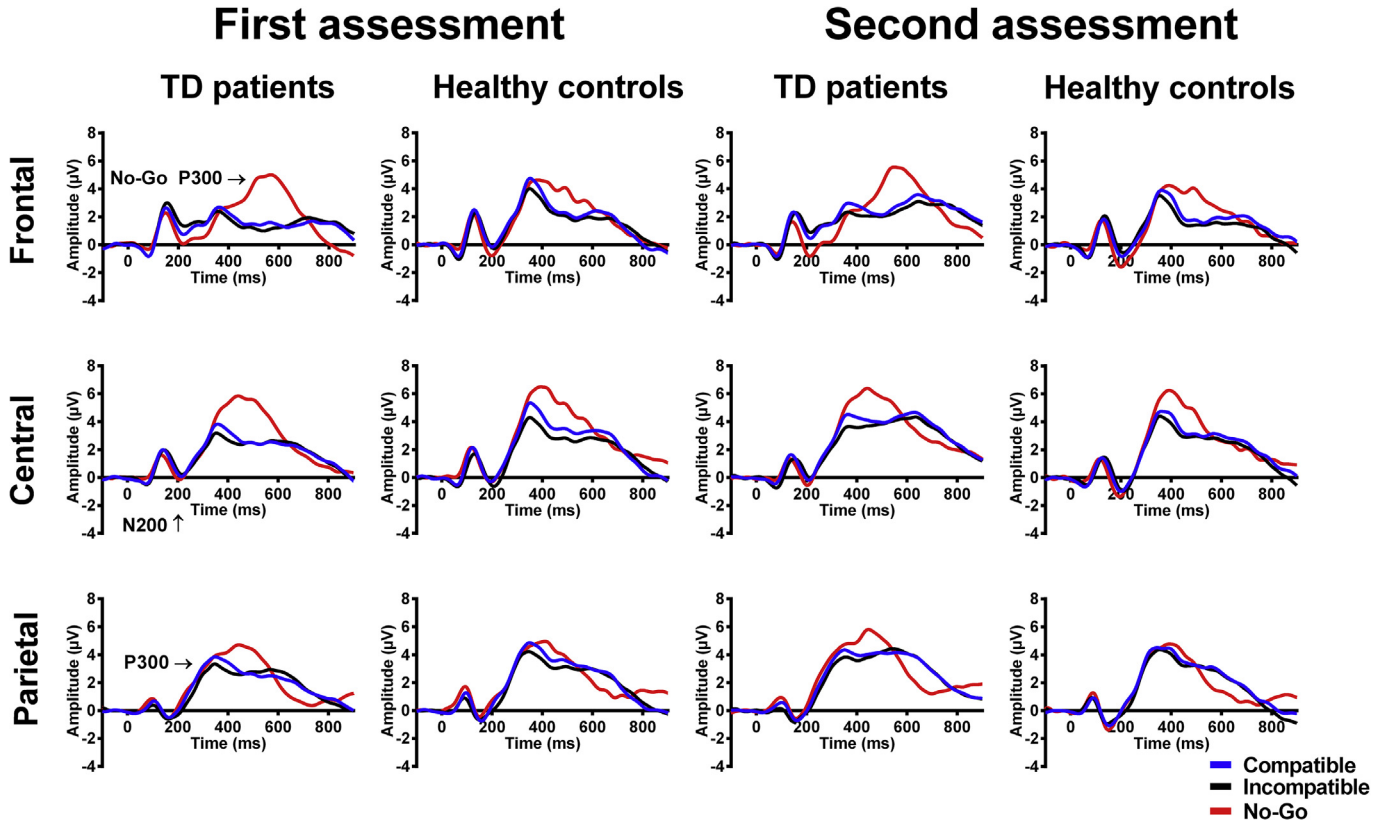

Fig. 4. Grand averages of the stimulus-locked event-related potentials (ERP).

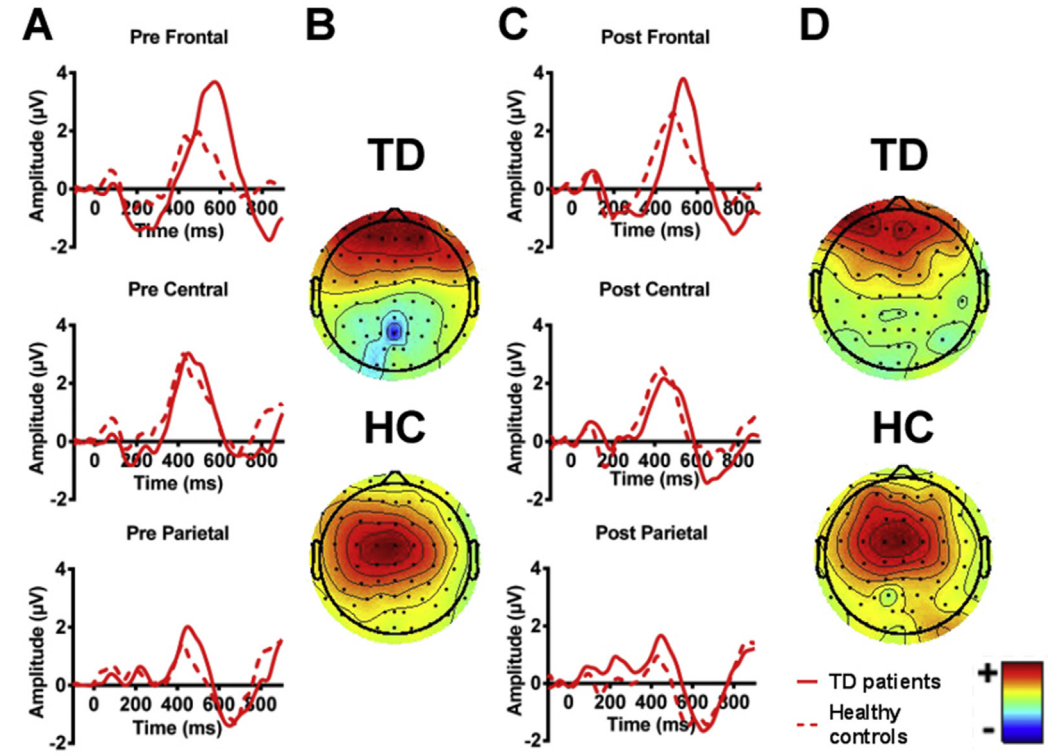

Fig. 5. Illustration of the stimulus-locked No-Go Anteriorization (NGA). To demonstrate the NGA effect, we calculated the difference wave between Go and No-Go conditions. Grand averages of the No-Go minus Go trials (A) before and (C) after CBT. Scalp topographies were obtained through EEGLAB (Delorme and Makeig, 2004), at the corresponding latency of the NGA peak. The scalp topographies show the frontal shift of the NGA observed in the TD group (B) before and (D) after CBT.

untreated TD patients represented a disruption of motor planning (Morand-Beaulieu et al., 2015). However, since a delayed sLRP onset pre-CBT was correlated to less severe motor tics and because it predicted improvement in motor tic symptoms post-CBT, it might represent an adaptive mechanism. Indeed, a better control of motor output would lead to less severe tics but would come with a delay in motor planning. The use of such mechanism could lead to a better application of some CBT principles, such as managing muscular tension and reducing sensory-motor activation (O'Connor et al., 2017). The sLRP onset latency was reduced post-CBT, inferring that patients correctly implemented therapeutic strategies in place of pre-CBT tic control mechanisms. In the meantime, the sLRP onset remained stable in healthy controls, suggesting that the acceleration seen in patients should not be attributable to a practice effect. However, since the Time by group interaction did not quite reach the significance level, it is not possible to completely rule out the practice effect at this time.

Unlike the delayed sLRP onset, the overactive motor processes (rLRP peak) reported in TD patients pre-CBT did not evolve from some adaptive mechanism, since they were associated to more severe phonic tics. The CBT allowed a selective reduction of the incompatible rLRP

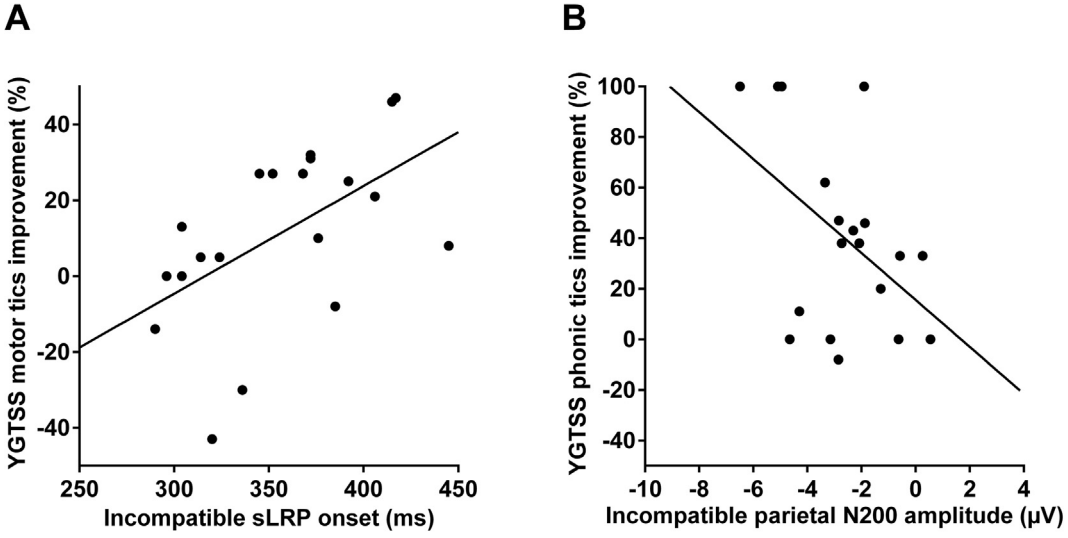

Fig. 6. Electrophysiological model of treatment outcome prediction. A multiple linear regression analysis revealed that the incompatible sLRP onset and the incompatible parietal N200 predicted decrease in tic severity following CBT. (A) Slower incompatible sLRP pre-CBT onset was associated with more improvements in motor tic severity, (B) while larger incompatible parietal N200 pre-CBT was associated greater decrease in phonic tic severity.

Table 3
Prediction model of improvement in tic severity.

	Predictor variables	B	SE B	β	t	p	Adjusted-R^2
Model 1	–	–	–	–	–	–	.24
	(Constant)	-.460	.240	–	−1.91	.072	
	Incompatible sLRP onset	.002	.001	.53	2.74	.013	
Model 2	–		–	–	–	–	.43
	(Constant)	-.689	.226	–	−3.05	.007	
	Incompatible sLRP onset	.002	.001	.62	3.60	.002	
	Parietal incompatible N200 amplitude	-.050	.019	-.46	−2.67	.016	

SE, Standard error.

Table 4
Linear mixed model predicting tic severity following CBT.

Predictor variables	B	95% CI	t	p
Baseline tic severity (YGTSS/50)	.732	0.481–0.983	6.16	< .001
Incompatible sLRP onset	−.037	−0.064–−0.010	−2.88	.010
Parietal incompatible N200 amplitude	.730	0.037–1.791	2.20	.042

CI, confidence interval.

peak. Interestingly, this reduction in incompatible rLRP peak amplitude was strongly correlated to the decrease in phonic tic severity induced by CBT.

There is some debate in the literature regarding the necessity to distinguish motor and phonic tics, since phonic tics involve laryngeal, oral, or nasal movements (Cohen et al., 2013; Robertson, 2008). Consistently, the association between rLRP peak amplitude and phonic tic symptoms confirms the involvement of the cortical motor areas in the pathophysiology of phonic tics. However, our results also showed that motor and phonic tics were specifically associated with different stages of motor processing. Such distinction is consistent with animal models of TD. In macaque monkeys, the sensorimotor CSTC and cerebellar circuits seem involved in motor tic generation (McCairn et al., 2009, 2013), while phonic tics are suggested to arise from motor and limbic circuits (McCairn et al., 2016).

CBT effects were specific to pre-motor and motor processes, as there was no change in N200 and P300 amplitude. Despite the pre-post stability of the N200, our prediction analyses revealed that patients with larger pre-CBT N200 showed more phonic tic improvement post-CBT. In SRC paradigms, the N200 is generally larger during incompatible stimuli and is thought to reflect cognitive control and conflict monitoring (Folstein and Van Petten, 2008). Comorbid ADHD was found to decrease an otherwise intact N200 amplitude among TD patients (Shephard et al., 2016). Such results are consistent with ours, given the low rate of comorbid ADHD in our sample. In a therapeutic context, it seems plausible that patients who put more effort into cognitive control have better chances to successfully apply the principles learned during CBT. In anxiety disorders, it was found that patients who improved following CBT had larger N200 amplitude increase pre-post therapy, which is attributed to more cognitive resources recruited to effectively implement CBT strategies (Hum et al., 2013). In our investigation, patients showing an enhanced N200 to incompatible stimuli pre-CBT were more likely to respond successfully to the treatment. This suggests that in TD patients, this increased allocation of cerebral resources to cognitive control should be present before CBT to maximize the chances of success.

In healthy controls, the No-Go P300 showed a typical central distribution. In TD patients, it was shifted over frontal electrodes, which replicated earlier findings regarding the No-Go-Anteriorization effect (Johannes et al., 2001; Morand-Beaulieu et al., 2015; Thibault et al., 2009). This effect is produced by an overactive frontal network during inhibition of motor responses, which is consistent with previous studies of TD patients reporting cortical motor inhibitory anomalies (Polyanska et al., 2017). In the presence of normal behavioral performance, an overactivation of this network during response inhibition was thought to be adaptive (Serrien et al., 2005). This network was also thought to be involved in the voluntary suppression of tics. However, our analyses showed that smaller No-Go P300 was correlated with larger improvement in tic symptoms following CBT. Therefore, our results might be more consistent with the findings of Jung et al. (2013), who reported that frontal cortex overactivity could lead to a long-term hyperexcitability of the sensorimotor cortex, which would in turn lead to the occurrence of tics.

Even though multiple treatment options for TD exist, finding the right treatment remains a challenge. Having reliable predictors of pharmacotherapy or CBT response would allow a better allocation of available resources. Our prediction model allowed the explanation of 43% of the variance of tic reduction following CBT. This suggests that an important factor accounting for CBT outcome is how the TD patients' brain processes the interference between stimulus and response. In our patients behavioral performance was not associated with treatment outcome, which is similar to the findings of Abramovitch et al. (2017) and Chang et al. (2018). According to our results, markers of brain activity elicited during inhibition or interference control tasks might reveal predictors of treatment outcome in these cohorts.

As it can be seen in Fig. 6, few patients showed a worsening of either motor or phonic tics. Yet, there was a decrease in YGTSS global score for all patients included in this study. Therefore, a worsening of motor tic severity could come with an improvement in phonic tic severity, or vice versa, or even a reduction in tic impairment. While we argue that CBT must be considered as a first-line treatment option for TD – just as medication – we are aware that not all patients respond significantly to CBT. Identifying patients who are unlikely to respond this specific CBT before it begins would allow patients and healthcare professionals to save time, money, and energy. It would also allow them to find alternative solutions. This study is the first to identify psychophysiological markers predicting CBT success in TD patients. In future years, these markers could be used in combination with other biomarkers to refine treatment outcome prediction. Furthermore, identifying predictors of treatment response could allow to tailor the treatment specifically to the patient's needs and in accord with his neurocognitive profile. Given the potential of cognitive enhancers to improve SRC performance and since they can boost therapeutic outcome in other psychiatric disorders (McGuire et al., 2014a), one could test if they could also improve CBT outcome in TD patients with low treatment response.

While our results are promising, future replication studies with larger samples could possibly explain a greater part of the variance of tic reduction following CBT. Also, while having a control group that was assessed twice allowed to control for possible confounds, adding a group of untreated patients in a natural wait-list would allow comparing the practice and time effects in both healthy controls and TD patients. It would also ascertain that treatment effects on brain functioning are not attributable to the “waxing and waning” nature of tics. These analyses could also be performed in a non-medicated sample, to completely rule out the possible contribution of medication. Finally, the low prevalence of comorbid ADHD in our sample limits the potential confounds induced by this disorder, but also limits the generalizability of our results to other samples.

In summary, the current study suggests that CBT impacts on motor processes that we previously observed are not attributable to a practice effect. We also extended our previous findings and identified specific relations between sLRP onset and motor tics, and rLRP peak amplitude and phonic tics. Finally, SRC processing in TD patients is predictive of their potential to benefit from CBT.

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Contributors

KPO, MEL and PJB designed the study and obtained the necessary funding to conduct the experiment. SMB contributed to the electrophysiological recordings, performed the statistical analyses, and prepared the first draft of the manuscript. PJB performed the neurological evaluation to confirm the TD diagnosis. KPO supervised the CBT administration. MEL supervised the electrophysiological recordings and the statistical analyses. All authors revised and approved the final draft of the manuscript.

Declaration of interest

KPO receives book royalties from Wiley-Blackwell, Elsevier and MultiMonde publishers. MEL receives book royalties from Wiley-Blackwell. PJB receives an honorarium from UCB Pharma Canada and speaker fees from Novartis Pharma Canada. SMB reports no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.08.020.

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