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Electrophysiological predictors of cognitive-behavioral therapy outcome in tic disorders

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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,

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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.