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Evaluation of EEG biomarkers of Comprehensive Behavioral Intervention for Tics in children with Tourette syndrome

Simon Morand-Beaulieu [a,b,*], Michael J. Crowley [a], Heidi Grantz [a], James F. Leckman [a], Lawrence Scahill [c], Denis G. Sukhodolsky [a,*]

[a] Child Study Center, Yale University School of Medicine, USA
[b] Department of Psychology, McGill University, Canada
[c] Department of Pediatrics and Marcus Autism Center, Emory University, USA

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HIGHLIGHTS

- Comprehensive Behavioral Intervention for Tics is an efficient treatment for Tourette syndrome.
- EEG markers of response inhibition in a Go/NoGo task are not associated with treatment outcome.
- More research is needed to identify brain mechanisms of behavior therapy in Tourette syndrome.

ABSTRACT

Objective: Comprehensive Behavioral Intervention for Tics (CBIT) is a first-line treatment of Tourette syndrome (TS). However, the brain mechanisms involved in CBIT are poorly understood. Enhanced frontomesial EEG coherence during a Go/NoGo task has been suggested as a mechanism involved in voluntary tic control. In the current study, we conducted a randomized controlled trial to assess whether EEG coherence during a Go/NoGo task was associated with CBIT outcome.
Methods: Thirty-two children with TS were randomly assigned to CBIT or to treatment-as-usual (TAU). Treatment outcome was assessed by a blinded evaluator with the Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impression – Improvement Scale (CGI-I). EEG was recorded during a Go/NoGo task at baseline and endpoint. EEG coherence was computed in the alpha frequency band between a priori selected channel pairs spanning the frontal and motor areas.
Results: Tic severity decreased significantly in the CBIT group. However, CBIT did not impact EEG coherence and baseline EEG coherence did not predict treatment outcome.
Conclusions: Although CBIT was superior to TAU on blinded clinical outcomes, EEG coherence during the Go/NoGo task was not associated with change in tic severity.
Significance: The brain processes involved in the inhibition of motor responses do not appear to be involved in CBIT.

1. Introduction

Tourette syndrome (TS) is a neurodevelopment disorder characterized by multiple motor and vocal tics (American Psychiatric Association, 2013). Tic severity may be influenced by stress, anxiety, boredom, relaxation, or concentration, among others (Leckman et al., 2010). Tics can be voluntarily suppressed for short periods. The pathophysiology of tics is presumed to involve disruptions of parallel cortico-striato-thalamo-cortical circuits linking the cortical and subcortical structures (Leckman et al., 2010). Such disruptions lead to heightened cortical activity, especially over the motor cortex and the supplementary motor area, which appears to be particularly involved in tic generation (Stern et al., 2000, Bohlhalter et al., 2006, Hampson et al., 2009, Neuner et al., 2014). Deficits in inhibitory control have been reported in TS (Morand-Beaulieu et al., 2017) and it is suggested that these

* Corresponding authors at: Department of Psychology, McGill University, 2001 McGill College Ave, Montreal, Quebec H3A 1G1, Canada (S. Morand-Beaulieu). Child Study Center, Yale University School of Medicine, 230 S. Frontage Road, New Haven, CT 06520, USA (D.G. Sukhodolsky).
E-mail addresses: simon.morand-beaulieu@mcgill.ca (S. Morand-Beaulieu), denis.sukhodolsky@yale.edu (D.G. Sukhodolsky).

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deficits may partially underlie tic expression. Yet, some studies reported enhanced cognitive control in TS, suggesting paradoxically that the suppression of tics in various situations may lead to better cognitive control over motor output (Jung et al., 2013).

Although tics can be suppressed for short periods, voluntary tic suppression is not sustainable in the long-term. An efficient technique to manage tics in a long-term perspective is behavioral therapy. Habit reversal training, which constitutes the first behavioral therapy for tics, was introduced in the 1970s by Azrin and Nunn (1973). Habit reversal training was later included in Comprehensive Behavioral Intervention for Tics (CBIT). The efficacy of CBIT was demonstrated by large randomized controlled trials in children (Piacentini et al., 2010) and adults (Wilhelm et al., 2012). The American Academy of Neurology now recommends CBIT as a first-line treatment for TS (Pringsheim et al., 2019). Although effective, the neurocognitive mechanisms by which tic reduction occur during CBIT are still poorly understood. Several mechanisms, such as habituation, associative learning, and cognitive control, have been hypothesized to mediate behavioral therapy for tics (Essoe et al., 2021a). The involvement of cognitive control is supported by a study showing that better performance on a visuospatial priming response inhibition task was associated with better response to habit reversal training (Deckersbach et al., 2006). Another study reported that better performance during the inhibition/switching condition of the Stroop test predicted reductions in tic severity after CBIT in children with TS (McGuire et al., 2022). However, two large randomized controlled trials assessing cognitive control in children and adults through several neurocognitive tasks failed to find significant predictors of CBIT outcome (Abramovitch et al., 2017, Chang et al., 2018).

Despite inconclusive results in neuropsychological studies, underlying brain correlates could yield a different picture. For instance, several functional magnetic resonance imaging (fMRI) and EEG studies reported differences between individuals with TS and controls during cognitive control tasks in terms of brain functioning, while behavioral performance during the task did not differ between group (Serrien et al., 2005, Morand-Beaulieu et al., 2018, Schüller et al., 2018, Rae et al., 2020). Thus, even if neuropsychological studies did not reveal significant predictors of treatment outcome, the brain correlates of cognitive control could still reflect relevant mechanisms of CBIT. To date, however, only one study investigated the brain mechanisms of CBIT or habit reversal training (Deckersbach et al., 2014). This small study of 8 adults with TS used a response inhibition paradigm during fMRI. The authors found decreased activation of the putamen from pre to post habit reversal training. Larger decreases in tic severity following treatment were also associated with reduced activation in the pars orbitalis of the inferior frontal gyrus from pre to post treatment.

Building on the empirical and theoretical work just reviewed, we aimed to fill two gaps in the literature. First, neural correlates of CBIT have never been investigated in children with TS. Second, the prior study investigating neural correlates of CBIT was not a randomized controlled trial, which limits the conclusions that can be drawn. Consequently, we conducted a randomized controlled trial comparing CBIT to a treatment-as-usual (TAU) condition in children with TS to examine EEG markers as possible mechanisms of change in tic severity.

One biomarker of interest in TS is EEG coherence in the alpha frequency band. A previous study in adults reported that EEG alpha coherence was associated with tic suppression and motor inhibition (Serrien et al., 2005). Specifically, adults with TS showed increased coherence over frontomesial electrodes during the NoGo portion of a Go/NoGo task (compared to controls) and, in a second task, as they suppressed their tics (compared to rest). This increase in EEG coherence during motor inhibition was interpreted as a mechanism deployed to compensate for neurobiological deficits associated with tics. Because alpha coherence is increased in TS during a cognitive control task and because cognitive control is a potential mechanism of CBIT, positive response to CBIT could be associated with increased EEG alpha coherence during a cognitive control task. Thus, EEG alpha coherence served as our primary electrophysiological measure of interest in the current study.

Other potential markers of cognitive control include frontal midline theta (FMT) oscillations and the N200 and P300 event-related potentials (ERP) (Huster et al., 2013, Cavanagh and Frank, 2014). In our recent study (Morand-Beaulieu et al., 2022) we did not find significant differences in FMT or ERPs between children with TS and typically developing controls during a Go/NoGo task. Nonetheless, if CBIT relies on cognitive control, FMT and N200 and P300 ERPs could be associated with CBIT response. Thus, FMT, N200, and P300 will serve as secondary EEG measures of interest in the current study.

The first objective of this study was to assess the impact of CBIT relative to TAU on EEG alpha coherence, FMT, and ERPs (N200 and P300). We hypothesized that alpha coherence, FMT power, and N200 and P300 amplitudes would increase, and that N200 and P300 latency would decrease from baseline to endpoint in children undergoing CBIT compared to TAU. Our second objective was to assess whether baseline alpha coherence, FMT, and ERPs could predict CBIT outcome. We hypothesized that children with larger baseline alpha coherence, FMT power, and N200 and P300 amplitudes, as well as faster N200 and P300 latency, would show larger decreases in tic severity after CBIT.

2. Methods

2.1. Design

This was a 10-week randomized control trial of CBIT vs a treatment-as-usual (TAU) control condition in children with TS. Participants were randomized with a 1:1 allocation to either CBIT or TAU that was carried out by a statistician who was not involved in any other aspects of the study. Randomization was stratified by sex to assure no sex differences between CBIT and TAU conditions and blocked to preclude discernable patterns of allocation. Clinical outcomes were assessed at baseline and endpoint by an independent evaluator who was blinded to the treatment assignment. EEG was collected at baseline (before initiation of treatment) and endpoint (after completion of treatment) as children performed a Go/NoGo task.

2.2. Study settings and participants

Participants were recruited from the Yale Child Study Center Specialty Clinic for TS and obsessive compulsive-disorder. Inclusion criteria consisted of (1) ages 8–14 years old; (2) DSM-IV-TR diagnosis criteria for TS or chronic tic disorder; (3) unmedicated or on stable medication for at least one month before initiating the study and throughout the duration of the study; (4) YGTSS Total Score > 14 or Total Score > 10 if only motor tics were present; and (5) fluent English speaker.

Exclusion criteria consisted of (1) intelligence quotient < 80; (2) diagnosis of severe psychiatric disorder that could interfere with participation in the behavior therapy for tics (e.g., bipolar disorder or psychotic disorder); (3) presence of any psychiatric or psychosocial condition (e.g., depression or family discord) requiring initiation of treatment other than that provided in the current study (i.e., medication, family therapy) or change in current medication type or dose; (4) previous treatment with four or more sessions of habit reversal training/CBIT.

The study was approved by the local institutional review board. Participants provided assent and their parents provided consent prior to participation in the study. Families also received small payment for their participation in study assessment and therapy visits.

2.3. Procedures

2.3.1. Baseline assessment

The baseline assessment was conducted for characterization and confirmation of eligibility. All participants were assessed with the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS; Kaufman et al., 1997) and the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). Socio-demographic data, medical history, and information about current and past treatment for tics and co-occurring conditions were also collected. The clinical interview was conducted by an experienced clinician who was not involved in delivering CBIT and was blinded to treatment assignment. Diagnosis of TS and co-occurring conditions were based on to the best estimate method (Leckman et al., 1982) following review of all available information.

The symptom severity of attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) were assessed using parent-rated symptom checklists: the 18-item Swanson, Nolan, and Pelham Questionnaire (SNAP-IV; Swanson et al., 2001) for ADHD symptoms and the 8-item Disruptive Behavior Rating Scale (DBRS; Barkley, 1997) for ODD. Intelligence was assessed with the Weschler Abbreviated Scale of Intelligence – 2nd version (Wechsler, 2011).

2.3.2. EEG recordings

At baseline and endpoint, EEG was continuously recorded at 250 Hz during a tic suppression session, a resting-state session, and a Go/NoGo task (results from the tic suppression and resting-state sessions are not included in the current paper). Participants wore a 128-channel HydroCel Geodesic Sensor Net. The net was soaked in a potassium chloride solution (KCL) and electrode impedance was assessed at or under 40 kΩ prior to data collection. Electrodes were referenced to the vertex electrode (Cz) during recordings. EEG was recorded through Net Station Acquisition software version 4.2.1 (EGI, Inc.) with a Net Amps 200 amplifier. EEG was online filtered with a 0.01 Hz high-pass filter and a 100 Hz low-pass filter.

2.3.3. Experimental tasks

The Go/NoGo task was adapted from Serrien et al. (2005) and was used in one of our prior studies of cognitive control in children with TS and/or ADHD (Morand-Beaulieu et al., 2022). The task ran on E-Prime (Psychology Software Tools, Pittsburgh, PA). Throughout the task, a fixation cross was continuously displayed at the center of a computer screen. Each trial of the task began by the presentation of the cue stimulus (a left- or right-pointing arrow) for 500 ms on either side of the fixation cross, indicating where the target stimulus would later appear. The target stimulus appeared 2500 ms after the cue stimulus disappeared and remained on screen for 500 ms. The target stimulus always appeared on the same side as the cue stimulus and prompted to press the corresponding arrow key as fast as possible (Go stimulus, letter O) or to refrain from responding (NoGo stimulus, letter S). After the target stimulus disappeared, participants were allowed a supplemental 1000 ms to provide a response. The interstimulus interval ranged between 5000 and 7000 ms (mean: 6000 ms). The task consisted of four blocks of 40 trials, for a total of 160 trials. NoGo stimuli occurred on 25 % of the trials. Task performance was assessed with reaction times and D-prime. D-prime was computed with the following formula: D-prime = zHit rate – zFalse alarm rate. To allow for D-prime computation, extreme values for the hit rate (1) and the false alarm rate (0) were respectively replaced with 1-(1/2N) and 1/2N, where N is the number of trials (160) (Macmillan and Kaplan, 1985). Reaction times were computed as the interval between presentation of go stimuli and motor responses. Accuracy and reaction times were monitored through E-Prime.

2.3.4. Randomization

Participants who met eligibility criteria were randomly assigned to either receive CBIT or to remain in treatment-as-usual (TAU) for a period of 10 weeks. Participants who were randomized to the CBIT condition were randomly assigned to one of the therapists. Participants who were randomized to the TAU condition were offered CBIT after the endpoint assessment.

2.3.5. Interventions

2.3.5.1. Comprehensive behavioral intervention for tics. CBIT was delivered for 8 60-minute sessions over 10 weeks (Piacentini et al., 2010, Wilhelm et al., 2012). The first 6 treatment sessions were scheduled on a weekly basis and the last 2 were spaced two weeks apart. The primary treatment components of CBIT are awareness training and competing response training, which were designed to break the negative pattern maintaining tic expression. Awareness training involves describing the tic and the sensations and behaviors that precede the tic. Competing response training involves teaching the patient to engage in a behavior that is physically incompatible with the tic or makes the tic difficult to occur. For example, if the patient has a leg movement tic, the competing response might involve placing the feet flat on floor and pushing downward. Additional techniques, such as self-monitoring and relaxation training, are included in CBIT to either enhance motivation for treatment or reduce negative mood states which may be related to the premonitory tic urges/sensations themselves.

2.3.5.2. Treatment-as-usual. Participants in both treatment conditions continued to see their treating clinicians according to usual practice. Interventions were provided independently from the current study and according to the needs of children and their parents as well as the judgment of their treating clinician. Participants in both conditions were allowed to continue to receive their usual treatment and services, including but not limited to school-based services and individual child psychotherapy. Parents were asked to not alter ongoing treatment or initiate new treatments during the study period.

2.3.6. Outcome assessment

Clinical outcome measures were assessed by an independent evaluator who was unaware of the participant's treatment assignment (i.e., "blinded" rater). The EEG procedure during the Go/NoGo task was repeated at the endpoint assessment in order to evaluate electrophysiological outcome measures.

2.4. Outcome measures

The primary clinical outcome measure was the total tic score of the YGTSS and the secondary outcome measure was the Clinical Global Impression – Improvement Scale (CGI-I; Guy, 1976). The YGTSS is a clinician-rated scale of tic severity in the past week. Motor and phonic tics are rated on a 6-point scale according to 5 dimensions: number, frequency, intensity, complexity, and interference. A motor and a phonic subscale, both ranging from 0 to 25, can be combined in a total tic score ranging from 0 to 50. The CGI-I is a 7-point clinician rated scale of treatment response was a key secondary measure of clinical response. Lower scores indicate improvements following treatment while higher scores repre-

sent worsening. By standard convention (Piacentini et al., 2010, Wilhelm et al., 2012) participants with CGI-I scores of 1 (very much improved) or 2 (much improved) were classified with positive response to treatment.

Our primary electrophysiological outcome measures was alpha coherence between selected channel pairs spanning the frontal and motor areas. Our secondary electrophysiological outcome measures were FMT power as well as the latency and amplitude of the N200 and P300 ERP components. The FMT is computed over frontocentral midline electrodes and is a correlate of cognitive control (see below for coherence and FMT calculation).

2.5. Data management and analysis

2.5.1. EEG preprocessing

Continuous EEG recordings from the Go/NoGo task were preprocessed with the Maryland Analysis of Developmental EEG (MADE) pipeline (Debnath et al., 2020) running on Matlab 2020a. This pipeline, which relies on EEGLAB's functions and data structure and was designed for preprocessing EEG datasets in pediatric population, involves signal filtering, removal of artifacts using independent component analysis (ICA) and threshold-based rejection, removal and interpolation of bad channels, epoching, and rereferencing. Complete details are provided in the Supplement.

2.5.2. EEG analyses

Following Serrien et al. (2005), EEG coherence was computed in the alpha band (8–13 Hz) between 4 channel pairs (F3-C3 & FCz-C3 for right-hand responses and F4-C4 & FCz-C4 for left-hand responses; see Fig. S1A). Supplementary analyses using clusters of electrodes rather than single electrodes were also performed. These supplementary analyses included electrodes 35, 36, 41 (C3 cluster), 103, 104, 110 (C4 cluster), 23, 24, 27 (F3 cluster), 3, 123, 124 (F4 cluster), and 6, 7, 106 (FCz cluster; see the Supplement and Fig. S2). EEGLAB's *newcrossf* function was used to compute coherence. The *newcrossf* function uses a sliding-window to compute time-resolved coherence. The length of the sliding window was 512 ms. We obtained coherence data over 101 linear-spaced frequencies (1–50 Hz, 0.5 Hz resolution) and 373 linear-spaced time points (−996 to 492 ms for pre-cue epochs, −496 to 992 ms for post-target epochs, 4 ms resolution). From these data, we averaged coherence values between 8 and 13 Hz in pre-cue (−250 to 0 ms relative to cue onset) and post-target (0–250 ms relative to target onset) intervals. The *newcrossf* function yields coherence values ranging between 0 and 1, which were then transformed using the hyperbolic inverse tangent. Task-related coherence was computed as a percentage ((PT – PC)/PC) score indicating coherence increase from pre-cue to post target.

To assess FMT, time–frequency transforms were separately performed on Go and NoGo trials epoched from −750 to 1250 ms relative to target stimulus onset. Across groups, participants had an average of 72 and 28 valid epochs in the Go and the NoGo condition, respectively. To match the number of epochs across conditions, 28 Go epochs were randomly selected for each participant. Time-frequency transforms were performed using the *newtimef* function in EEGLAB. This function combines Fast Fourier Transform (FFT) at low frequencies and wavelet decomposition at high frequencies. The wavelet factor was set a 0.5. Time-frequency

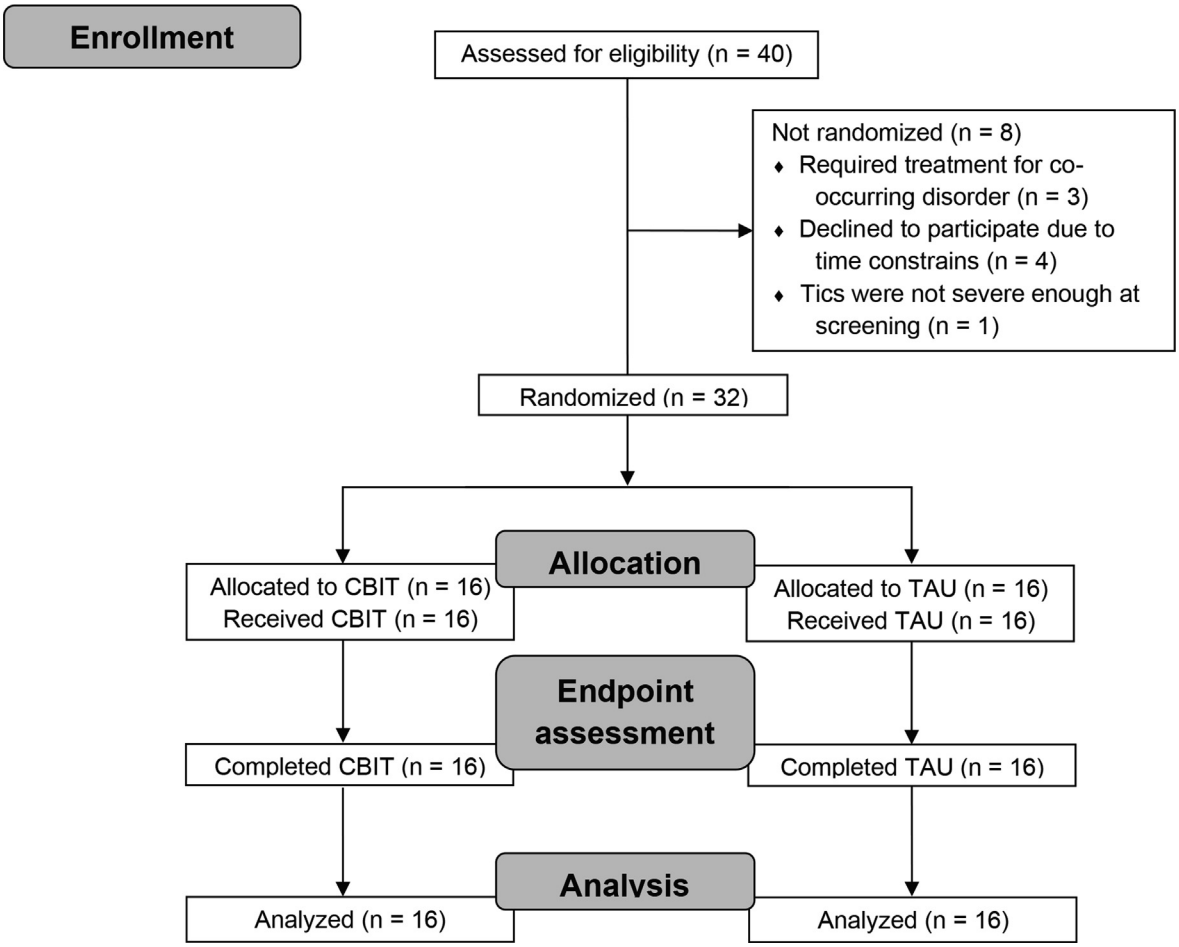

Fig. 1. Flow of participants through the study. CBIT: Comprehensive Behavioral Intervention for Tics, TAU: treatment-as-usual.

transforms were computed over 3 cycles at the lowest frequency (3.5 Hz) and 13.1 cycles at the highest frequency (30.5 Hz). The length of the sliding window was 956 ms. We obtained time–frequency data over 55 linear-spaced frequencies (3.5–30.5 Hz, 0.5 Hz resolution) and 262 linear-spaced time points (−274 to 770 ms, 4 ms resolution). The −200 ms to 0 ms interval was used as a baseline. FMT was assessed between 4 and 8 Hz at a cluster of frontal midline electrodes surrounding FCz (average of electrodes 5, 6, 7, 12, 13, 106, 112; see Fig. S1B), in a 200–600 ms post-stimulus interval.

ERP analyses were also conducted on Go and NoGo trials epoched from −750 to 1250 ms relative to target stimulus onset. ERPs were computed with the ERPLAB toolbox (Lopez-Calderon and Luck, 2014). ERPs were assessed at a cluster of electrodes surrounding Pz (electrodes 61, 62, 67, 72, 77, 78; see Fig. S1B) and were baseline-corrected (−200 ms to 0 ms relative to target stimulus). The N200 was measured as the most negative peak in the 150–300 ms post-stimulus interval and the P300 was measured as the most positive peak in the 300–700 ms post-stimulus interval.

2.5.3. Statistical analyses

Based on pilot data, we powered this study in order to detect a 25 % increase in alpha coherence from baseline to endpoint in the CBIT group (corresponding to an effect size of $\eta p^2 = 0.060$). Assuming moderate intercorrelations (r = 0.5) among repeated measures, 80 % power, and a significance threshold of $\alpha = 0.05$, a G*Power calculation suggested a total sample size of 34.

Baseline characteristics were compared with t-tests and Fisher's exact tests. YGTSS scores were analyzed with a repeated-measures ANOVA, with Time (baseline and endpoint) as a within-subjects factor and Treatment (CBIT and TAU) as a between-subjects factor. A Fisher's exact test was performed to assess whether responder status (based on CGI-I) differed between treatments. Task performance was analyzed with a MANOVA, with D-prime and reaction times as dependent variables, Time (baseline and endpoint) as a within-subjects factor, and Treatment (CBIT and TAU) as a between-subjects factor.

Task-related coherence increase, FMT, as well as N200 and P300 latency and amplitude were respectively analyzed with 2X2X2 ANOVAs, with the within-subjects factors Time (baseline and endpoint) and Task Condition (Go and NoGo), and the between-subjects factor Treatment (CBIT and TAU). Effect sizes were computed with Cohen's d, by subtracting the mean change from baseline to endpoint in the TAU group from that of the CBIT group and dividing by the baseline pooled standard deviation.

To assess whether baseline electrophysiological markers were associated with response to CBIT, we conducted separate repeated-measures ANOVAs on (i) task-related coherence increase; (ii) FMT; (iii) ERP measures. In these analyses, we assessed whether there was an interaction between task condition (Go

Table 1
Demographics and clinical characteristics by treatment group at baseline.

	CBIT (n = 16)	TAU (n = 16)	Test statistic[e]	p-value
Age in years, mean (SD)	11.4 (1.8)	11.3 (1.5)	$t_{30} = 0.23$	0.819
Sex, number of boys (%)	14 (87.5)	13 (81.3)	–	0.700
Handedness, number of right-handed (%)	13 (81.3)	14 (87.5)	–	0.633
Race, number (%)			–	0.633
White	14 (87.5)	14 (87.5)		
Black	1 (6.3)	1 (6.3)		
Asian	1 (6.3)	1 (6.3)		
Ethnicity, number of Hispanics (%)	2 (12.5)	0 (0)	–	0.242
Two-parent family, number (%)	12 (75.0)	13 (81.3)	–	1.000
School program			–	0.102
Regular, number (%)	15 (93.8)	11 (68.8)		
Regular with remedial services, number (%)	1 (6.25)	3 (18.8)		
Special education, number (%)	0 (0)	2 (12.5)		
Full Scale IQ, mean (SD)	107.6 (17.3)	118.0 (13.9)	$t_{30} = 1.85$	0.074
Clinical scores, mean (SD)				
YGTSS total tic score	23.8 (6.0)	24.4 (5.1)	$t_{30} = 0.75$	0.751
SNAP-IV	14.6 (12.5)	19.2 (14.3)	$t_{30} = 0.98$	0.337
DBRS	5.7 (4.2)	6.3 (5.2)	$t_{30} = 0.34$	0.739
Other diagnoses, number (%)				
Any co-occurring diagnosis	12 (75.0)	10 (62.5)	–	0.352
ADHD	9 (56.3)	8 (50.0)	–	0.500
OCD	3 (18.8)	2 (12.5)	–	0.500
ODD	3 (18.8)	3 (18.8)	–	0.673
Any anxiety disorder	3 (18.8)	4 (25.0)	–	0.500
Concomitant treatment status, number (%)				
Receiving psychotherapy	2 (12.5)	5 (31.3)	–	0.197
Receiving psychotropic medication	11 (68.8)	7 (43.8)	–	0.143
Stimulants[a]	2 (12.5)	2 (12.5)	–	0.700
α-Agonists[b]	5 (31.3)	6 (37.5)	–	0.500
Atomoxetine	1 (6.3)	1 (6.3)	–	0.758
Antipsychotics[c]	3 (18.8)	2 (12.5)	–	0.500
SSRIs[d]	3 (18.8)	2 (12.5)	–	0.500
Benzatropines	0 (0)	1 (6.3)	–	0.500

Note: ADHD: attention-deficit/hyperactivity disorder, CBIT: Comprehensive Behavioral Intervention for Tics, DBRS: Disruptive Behavior Rating Scale, IQ: intelligence quotient, OCD: obsessive–compulsive disorder, ODD: oppositional defiant disorder, SD: standard deviation, SNAP-IV: Swanson, Nolan and Pelham Questionnaire for ADHD, SSRI: selective serotonin reuptake inhibitors, TS: Tourette syndrome, YGTSS: Yale Global Tic Severity Scale.

[a] Stimulants included methylphenidate (CBIT: n = 2, TAU: n = 2).

[b] α-Agonists included clonidine (CBIT: n = 1) and guanfacine (CBIT: n = 4, TAU: n = 6).

[c] Antipsychotics included aripiprazole (CBIT: n = 1), haloperidol (CBIT: n = 1), and risperidone (CBIT: n = 1, TAU: n = 2).

[d] SSRIs included citalopram (CBIT: n = 1, TAU: n = 1), fluoxetine (CBIT: n = 1), fluvoxamine (TAU: n = 1), and sertraline (CBIT: n = 1).

[e] Categorical variables were analyzed with Fisher's exact tests and thus have no test statistic.

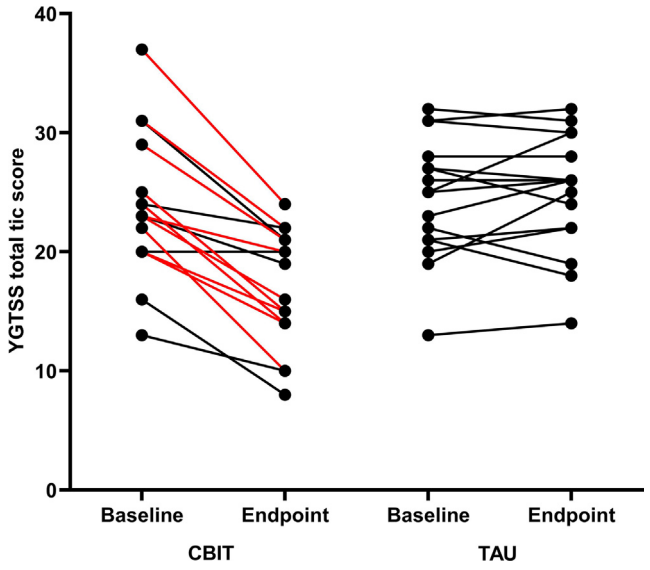

Fig. 2. Clinical outcome. Each point depicts the YGTSS total tic score at baseline and endpoint for each participant, for both the CBIT and the TAU conditions. There was a 7-point decline in mean YGTSS total tic score in the CBIT condition, while it remained constant in the TAU condition. Red lines depict children who were classified with positive response ("very much improved" or "much improved") according to the CGI-I. Ten out of 16 participants in the CBIT condition were considered as responders, while none were considered as such in the TAU condition. CBIT: Comprehensive Behavioral Intervention for Tics, TAU: treatment-as-usual, YGTSS: Yale Global Tic Severity Scale.

and NoGo), treatment (CBIT and TAU), and tic severity decrease (continuous variable calculated as baseline YGTSS total tic score minus endpoint YGTSS total tic score).

3. Results

3.1. Patient flow

Forty children with TS were recruited to participate in the current study. Eight children were not randomized for the following reasons: 3 children required treatment for co-occurring disorders, 1 child presented with low level of current tics, and 4 children declined participation due to time constrains. The remaining 32 children (27 males and 5 females, mean age 11.3 ± 1.6 years) were randomized to either the CBIT or TAU condition. There were no dropouts in this study; all patients who were randomized completed the end-point assessment (Fig. 1).

3.2. Patient characteristics

Subjects allocated to the CBIT or the TAU condition did not differ on any socio-demographic or baseline clinical characteristics (see Table 1).

3.3. Clinical outcomes

On the YGTSS total tic score there was a significant Time by Treatment interaction [$F(1,30) = 41.08$, $p < .001$, $\eta_p^2 = 0.578$]. In the CBIT group, the mean YGTSS total tic score decreased from 23.8 ± 6.0 at baseline to 16.9 ± 4.9 at endpoint, compared to 24.4 ± 5.0 at baseline to 24.9 ± 5.0 at endpoint in the TAU group ($d = 1.34$). Ten children in the CBIT group (62.5 %) and none in the TAU group (0 %) were rated "very much improved" or "much improved" on the CGI-I [Fisher's exact test, $p < .001$] (see Fig. 2).

3.4. Go/NoGo task performance

The global MANOVA performed on D-prime and reaction times revealed no significant main effect or interaction [all F's < 2.1, all p-values > 0.14], suggesting that CBIT had no impact on behavioral measures of cognitive control in the current study (Fig. 3). Mean values for behavioral and EEG measures for each group are presented in Table S1.

3.5. Electrophysiological results

3.5.1. Baseline-to-endpoint changes

The ANOVA conducted on task-related coherence increases revealed no significant time by treatment or time by condition

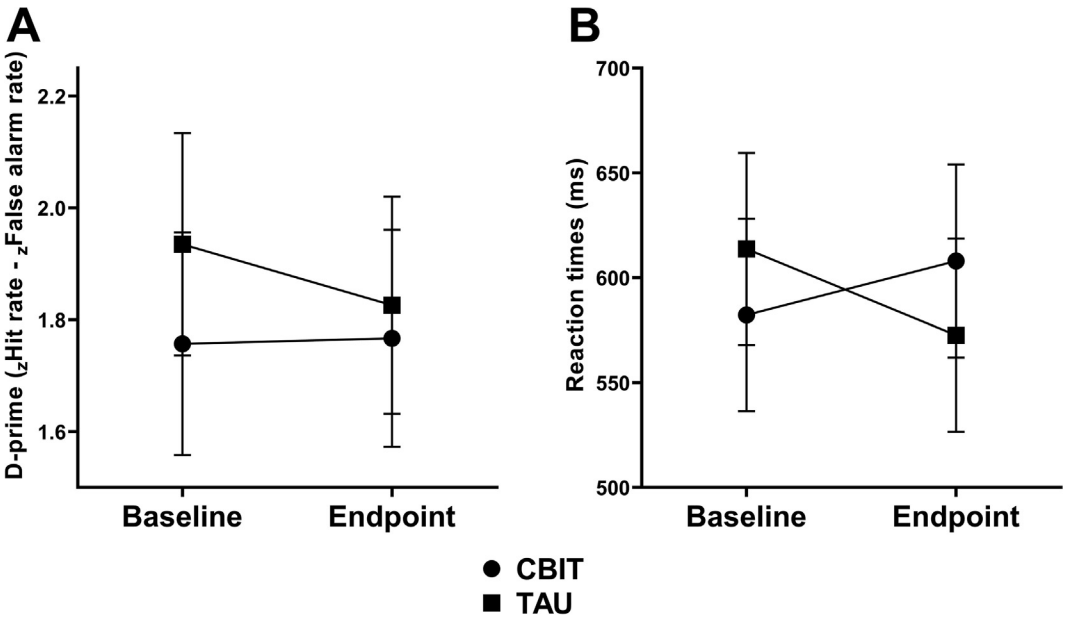

Fig. 3. Go/NoGo task performance. CBIT had no impact on the (A) task accuracy and (B) reaction times of children with TS during the Go/NoGo task. Error bars represent the standard error of the mean (SEM). CBIT: Comprehensive Behavioral Intervention for Tics, TAU: treatment-as-usual.

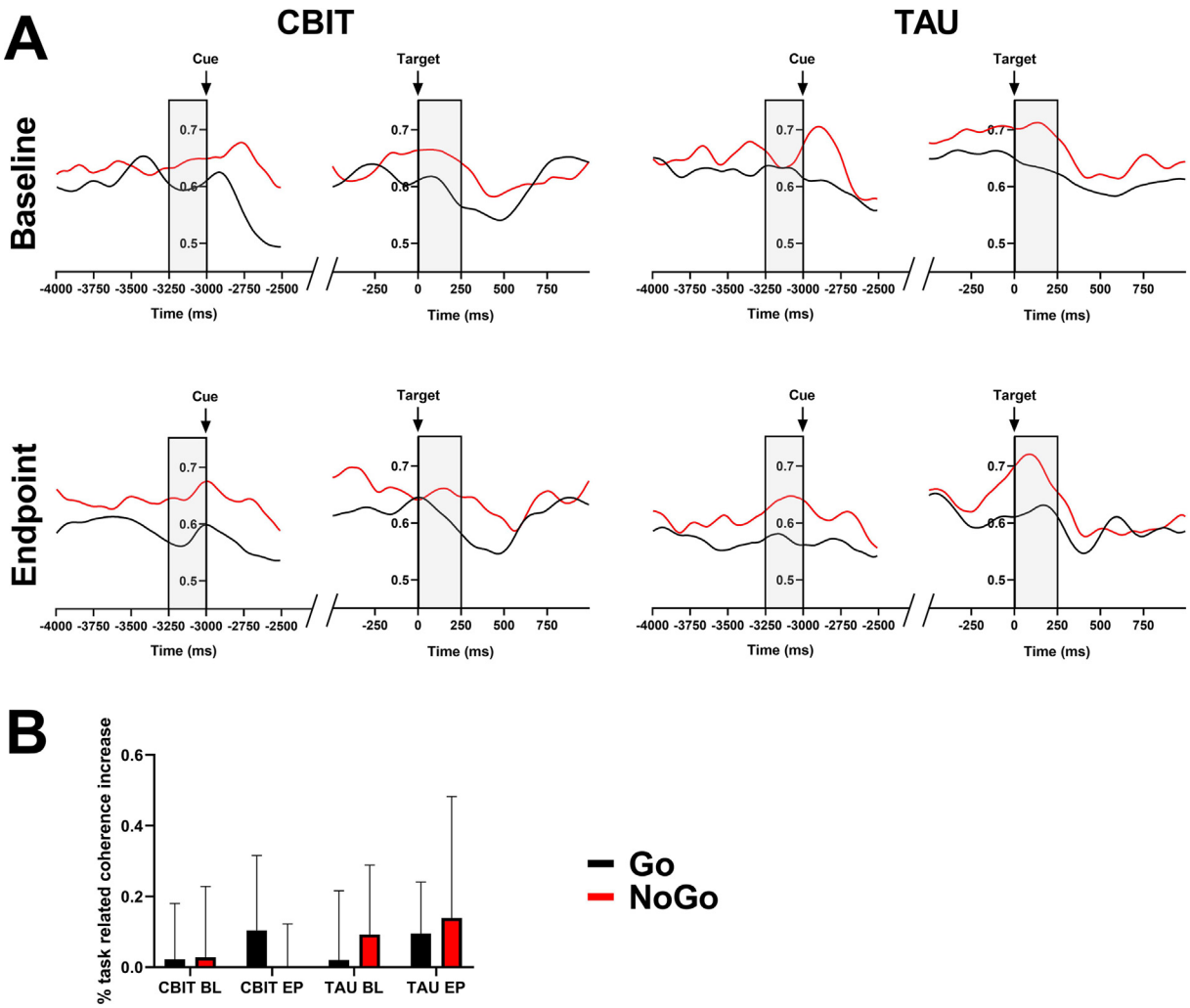

Fig. 4. Alpha-band cross-channel coherence. (A) EEG coherence for the four channel pairs was computed in the alpha band. Most of the foreperiod (interval between cue and target) was not included in this analysis so that non-neural artifact during this period would not lead to more trials being rejected. Gray boxes show the time windows used for computing alpha coherence. Black lines depict alpha-band coherence for Go trials and red lines depict alpha-band coherence for NoGo trials (B) Task-related coherence increase from pre-cue to post-target did not significantly differ across condition or group. Error bars represent the standard deviation (SD). BL: baseline, CBIT: Comprehensive Behavioral Intervention for Tics, EP: endpoint, TAU: treatment-as-usual.

by treatment interactions [all F-values < 3, all p-values > 0.09], suggesting that CBIT had no impact on the EEG coherence in the alpha frequency band during the Go/NoGo task (Fig. 4). Supplementary analyses taking advantage of high-density EEG with clusters of electrodes revealed very similar findings (see the Supplement and Fig. S3).

The analysis on the impact of CBIT on FMT revealed a Time by Treatment interaction [$F(1,30) = 4.47$, $p = .043$, $\eta p^2 = 0.130$]. However, this effect was not attributable to treatment, as there was no significant Time main effect or Time by Condition interaction within the CBIT group [all F's < 0.02, all p-values > 0.91]. Rather, FMT decreased from baseline to endpoint in the TAU group, as shown by a main effect of Time [$F(1,15) = 6.59$, $p = .021$, $\eta p^2 = 0.305$] within this group (Fig. 5).

ANOVAs conducted on ERP (N200 and P300) amplitude and latency revealed no significant time by treatment or time by condition by treatment interactions [all F-values < 3.1, all p-values > 0.88]. Thus, CBIT has no impact on ERPs either (Fig. 6).

3.5.2. Prediction of treatment outcome

The baseline task-related coherence increase, FMT, and N200 and P300 latency and amplitude measures did not significantly predict treatment outcome, given that the treatment by tic severity decrease and the treatment by condition by tic severity decrease interactions did not reach the significance threshold [all F's < 3.0, all p-values > 0.09].

4. Discussion

This study examined EEG markers potentially associated with reductions in tics in a randomized controlled trial of CBIT in children with TS. We tested whether EEG alpha coherence, FMT, and ERPs during a Go/NoGo task of response inhibition were affected by CBIT and whether these markers could predict treatment outcome.

First, participants in the CBIT condition showed a positive response, as revealed by a 7-point decrease in mean YGTSS total tic severity. These findings are consistent with the initial large randomized controlled trial of CBIT in children, which showed a similar reduction (from 24.7 to 17.1) in YGTSS total tic score (Piacentini et al., 2010). We also found a positive response rate of 62.5 % in the CBIT group, which is slightly higher than the positive response rate of 52.5 % reported by Piacentini et al. (2010). Whereas the current study had a smaller sample than other

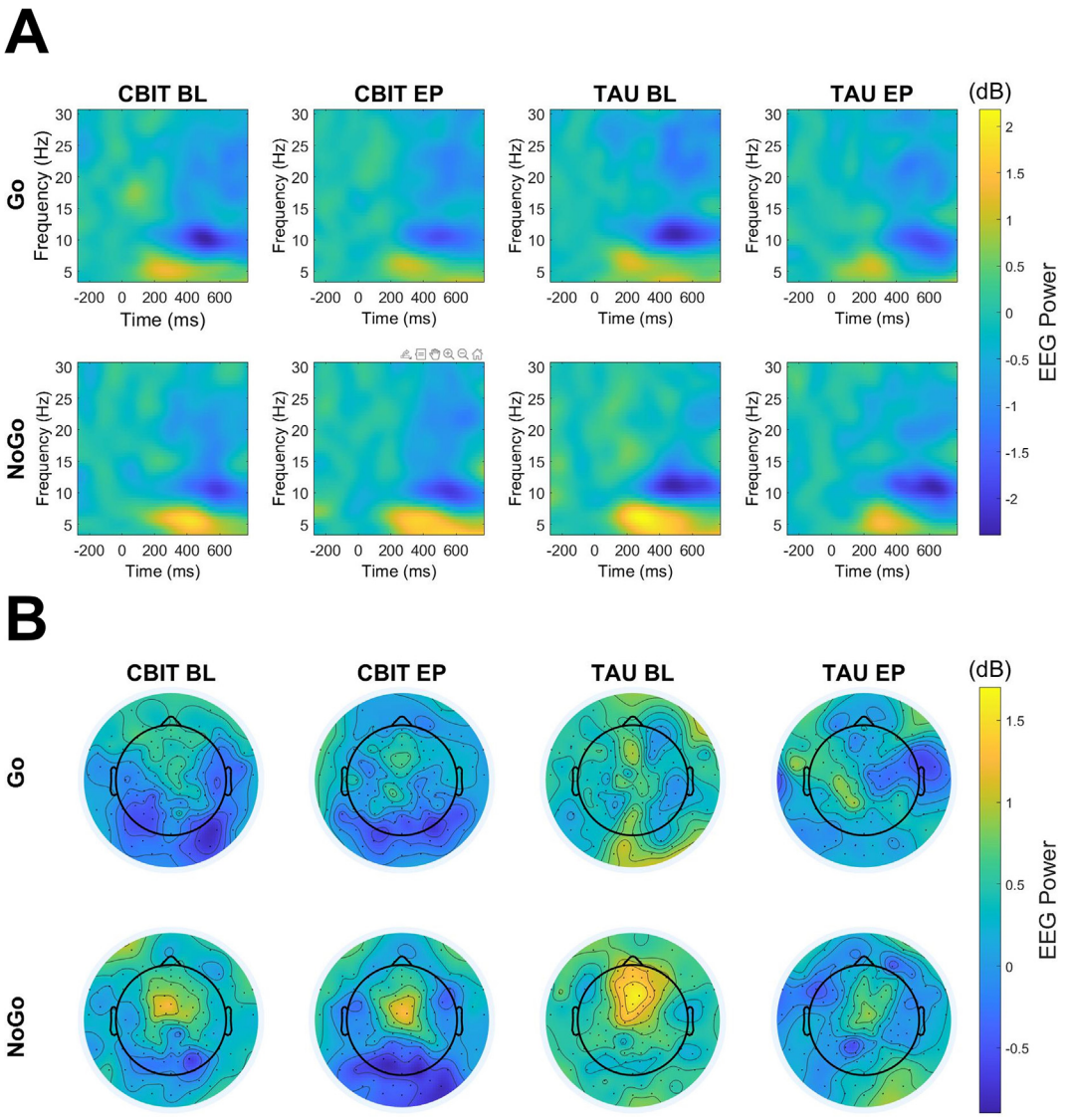

Fig. 5. Frontal midline theta. (A) Event-related spectral perturbations at a cluster of electrodes surrounding FCz. (B) Topoplots of the averaged theta (4–8 Hz) power in the 200–600 ms interval. CBIT had no impact on FMT, an electrophysiological correlate of cognitive control. BL: baseline, CBIT: Comprehensive Behavioral Intervention for Tics, EP: endpoint, TAU: treatment-as-usual.

large-scale trials, our findings can be added to the body of evidence supporting the efficacy of CBIT for reducing tics in children with TS.

Second, behavioral and electrophysiological measures of cognitive control were unrelated to behavior therapy outcome. Task-related coherence over frontomesial electrodes, which was found to be increased for NoGo stimuli in adults with TS (Serrien et al., 2005), was not associated with positive response to CBIT. We followed the methods of Serrien et al. (2005) as closely as possible, using the same electrode pairs for computing frontomesial coherence. We also took advantage of our high-density EEG system and computed coherence between 4 pairs of electrode clusters surrounding the electrodes used in the initial analyses. However, these analyses yielded very similar results. Serrien et al. (2005) observed large increases in task-related EEG alpha coherence from the pre-cue to the post-target interval. In our study, mean coherence across participants was similar in the pre-cue and the post-target interval, suggesting that the Go/NoGo task induced very little modulation of fronto-mesial alpha coherence. Increased frontomesial alpha coherence was suggested as an adaptive strategy to compensate for diminished inhibitory control mechanisms in adults with TS (Serrien et al., 2005). It is possible that children with TS have not yet developed this strategy, given that EEG coherence goes through various developmental changes during childhood and adolescence (Thatcher et al., 2008, Soroko et al., 2015).

CBIT did not affect FMT, N200, and P300, the EEG markers of cognitive control. These results are consistent with two large studies investigating whether neurocognitive measures (Stroop test and the Stop-signal task in children; Stroop test and the Go/NoGo task in adults) predicted the outcome of CBIT in children (Chang et al., 2018) and adults with TS (Abramovitch et al., 2017). In both studies, baseline behavioral performance in the cognitive control tasks was not predictive of successful treatment outcome. Additionally, the child study (Chang et al., 2018) assessed whether neuropsychological task performance changed from baseline to endpoint, but did not reveal any significant impact of CBIT on these measures.

Our results contrast with those of Deckersbach et al. (2014), who reported changes in brain function during a response inhibition task following habit reversal training in adults with TS. Other EEG studies of psychological treatments for adults with TS revealed pre-post treatment changes in ERPs associated with attentional

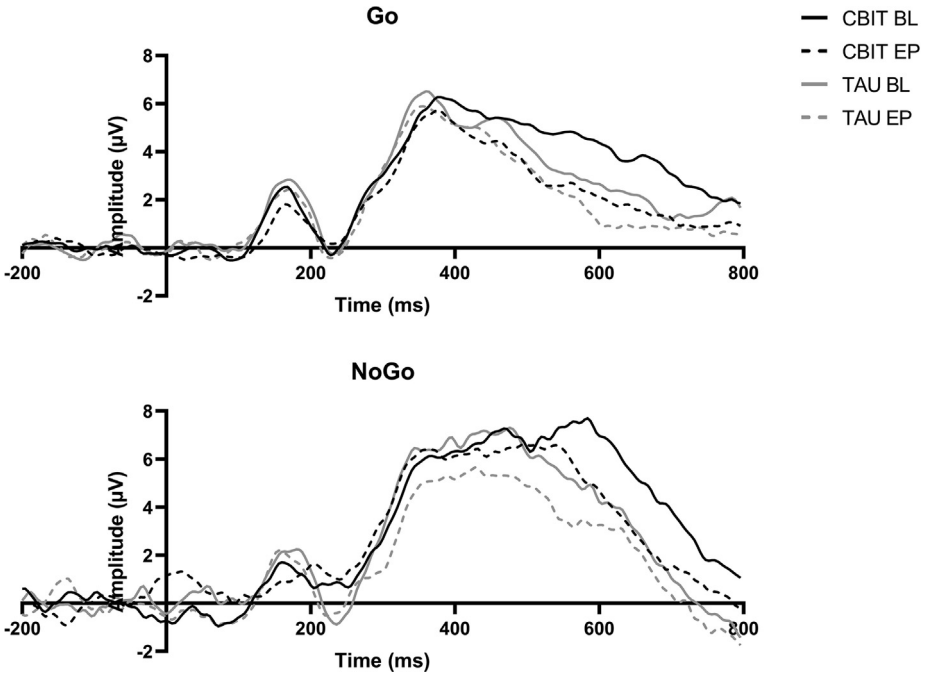

Fig. 6. Event-related potentials. This figure depicts ERPs for both the Go (upper panel) and NoGo (lower panel) conditions. CBIT had no impact on ERP measures. BL: baseline, CBIT: Comprehensive Behavioral Intervention for Tics, EP: endpoint, TAU: treatment-as-usual.

processes and movement preparation and execution (Lavoie et al., 2011, Morand-Beaulieu et al., 2015, Morand-Beaulieu et al., 2016, Morand-Beaulieu et al., 2018). However, all these studies were conducted in adults. Thus, more research on brain correlates of psychological treatment for TS in children is warranted.

In a recent review, Essoe et al. (2021a) proposed three potential mechanisms that could underlie clinical change induced by behavioral therapies for TS: cognitive control, habituation, and associative learning processes. Although our results failed to support the cognitive control hypothesis, it is possible that the Go/NoGo task used in the present study only probes some aspects of cognitive control that are not involved in the pathophysiology of TS. In a recent meta-analysis of cognitive control in TS, the Go/NoGo task was the task where differences between individuals with TS and unaffected controls were the smallest (Morand-Beaulieu et al., 2017). Therefore, the Go/NoGo task may not be sensitive or specific enough to detect impairments in cognitive control that may be associated with tics in TS. Another cognitive control task, the Flanker task, has been shown significant differences in electrophysiological measures between children with TS and typically developing controls (Jurgiel et al., 2021). The Flanker task may relate more to interference control whereas the Go/NoGo task predominantly involves the inhibition of a prepotent motor response (Friedman and Miyake, 2004, Lindqvist and Thorell, 2008). We speculate that interference control, rather than inhibition of a motor response, may be required during the awareness training and performance of competing responses in CBIT. Given that tics are often automatic and associated with premonitory urges, 'selection and deployment of a competing response' may be construed as cognitive inhibition of interference from the sensation of the premonitory urge, rather than 'motor response inhibition of an impending tic'. Thus, future work could test whether EEG measures of interference control more aptly target a neurophysiological correlate of tic reduction following CBIT.

Alternatively, pursuing other potential mechanisms of CBIT could be worthwhile. Although the available evidence does not support habituation as a mechanism of CBIT (Houghton et al., 2017), associative learning processes may play a role in the behavioral treatment of TS (Essoe et al., 2021a). For instance, homework adherence in CBIT can be increased by implementing a behavioral reward system, which highlights positive reinforcement learning. Increased homework adherence predicted better CBIT outcome (Essoe et al., 2021b). It could also be interesting to assess the role of reversal learning, given that CBIT aims to reverse the contingencies maintaining the association between premonitory urges and tics (Essoe et al., 2021a).

Another avenue for testing possible neural mechanisms of CBIT is via better understanding of how voluntary tic suppression may be associated with decreased tic severity following CBIT. For example, in a recent study, we examined resting EEG in children with TS during periods of voluntary tic suppression relative to periods when children were allowed to tic freely (Morand-Beaulieu et al., 2021). Functional connectivity analyses revealed that midline parietal and frontal brain areas were core regions in brain networks of tic suppression, suggesting a possible involvement of the default mode network in tic suppression. Given that voluntary tic suppression and CBIT may share some characteristics, notably in terms of self-awareness, it would be worthwhile to assess whether this network could constitute one of the mechanisms of CBIT.

This study has some limitations worth noting. Although our sample size was able to detect clinically significant effects of CBIT, it may have been too small to detect changes in electrophysiological measures. We encourage researchers to look for brain mechanisms of CBIT in larger samples. Additionally, we used a single task (the Go/NoGo task) to assess a motor response inhibition dimension of cognitive control. Using multiple other experimental paradigms would allow a better coverage of the different aspects of cognitive control. Finally, our study aimed to assess the relevance of alpha coherence in the context of CBIT and we thus followed closely the methodology of the study that first identified alpha coherence as a relevant biomarker in TS (Serrien et al., 2005). However, this comes with some limitations, such as focusing on a single frequency band and computing coherence measures from single electrodes spanning the frontal and motor areas. Assessing EEG coherence at the scalp level increases the risk of spurious connectivity due to volume conduction and limits the capacity for

consideration of the brain regions involved. Such limitations should be considered when designing future EEG studies to assess the mechanisms of CBIT.

In conclusion, our findings lend additional support to the clinical efficacy of CBIT as a treatment for tics in TS. We also demonstrated that electrophysiological responses to the Go/NoGo task of motor response inhibition were not associated with tic reductions after CBIT, at least in this sample. Although cognitive control may be a relevant construct to investigate in context of behavioral interventions in TS, more sensitive neurocognitive tasks may be needed to detect these effects.

Conflict of Interests Statement

Dr. Scahill has served as a consultant to Janssen, Roche Pharmaceuticals, Impel NeuroPharma, Inc., Yamo Pharmaceuticals, Teva Pharmaceuticals, and Finch Therapeutics; and has received royalties from Roche, Yamo Pharmaceuticals, Guilford Press, Oxford University Press, and American Psychiatric Association Publishing. The other authors have no potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.07.500.

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