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Research Report

Electrophysiological signatures of inhibitory control in children with Tourette syndrome and attention-deficit/hyperactivity disorder

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ABSTRACT

Tourette syndrome (TS) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur, especially in children. Reduced inhibitory control abilities have been suggested as a shared phenotype across both conditions but its neural underpinnings remain unclear. Here, we tested the behavioral and electrophysiological correlates of inhibitory control in children with TS, ADHD, TS+ADHD, and typically developing controls (TDC). One hundred and thirty-eight children, aged 7–14 years, performed a Go/NoGo task during dense-array EEG recording. The sample included four groups: children with TS only (n = 47), TS+ADHD (n = 32), ADHD only (n = 22), and matched TDC (n = 35). Brain activity was assessed with the means of frontal midline theta oscillations, as well as the N200 and P300 components of the event-related potentials. Our analyses revealed that both groups with TS did not differ from other groups in terms of behavioral performance, frontal midline theta oscillations, and event-related potentials. Children with ADHD-only had worse Go/NoGo task performance, decreased NoGo frontal midline theta power, and delayed N200 and P300 latencies, compared to typically developing controls. In the current study, we found that children with TS or TS+ADHD do not show differences in EEG during a Go/NoGo task compared to typically developing children. Our findings however suggest that children with ADHD-only have a distinct electrophysiological profile during the Go/NoGo task as indexed by reduced frontal midline theta power and delayed N200 and P300 latencies.

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1. Introduction

In addition to chronic motor and phonic tics, children with Tourette syndrome (TS) often present with co-occurring disorders, including attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and depression (Robertson et al., 2017). ADHD is the most frequent co-occurring condition in children with TS (Bitsko et al., 2014; Freeman, 2007; Hirschtritt et al., 2015) and is associated with significant difficulties in adaptive functioning and quality of life (Conte, Valente, Fioriello, & Cardona, 2020; Ghanizadeh & Mosallaei, 2009; Sukhodolsky et al., 2003; Vermilion et al., 2020). Co-occurring ADHD also impacts neurocognitive functioning of children with TS (Eddy, Rizzo, & Cavanna, 2009; Morand-Beaulieu, Leclerc, et al., 2017; Sukhodolsky, Landeros-Weisenberger, Scahill, Leckman, & Schultz, 2010), most notably cognitive control, broadly defined as the ability to adjust behavior according to changing goals and withhold unwanted behavior (Nigg, 2017). Cognitive control includes various subtypes of functions associated with this capacity to adjust behavior. One of these subtypes is response inhibition or inhibitory control, which can be measured during a Go/No-Go task (Diamond, 2013). Historically, it was assumed that involuntary tics in TS were associated with reduced inhibitory control, which in turn led to difficulty suppressing tics. This view has been challenged by some reports of unimpaired voluntary control in children with uncomplicated TS (i.e., without co-occurring disorders) and even enhanced inhibitory control in TS, which was hypothesized to result from constant efforts to suppress tics (Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006). However, a recent meta-analysis of neuropsychological studies of TS demonstrated reduced inhibitory control in children with TS (Morand-Beaulieu, Grot, et al., 2017). That study also revealed that inhibitory control abilities were reduced in children with TS+ADHD compared to those with TS only. However, the effects of co-occurring ADHD on brain correlates of inhibitory control in children with TS have not been well-characterized due to small sample sizes in electrophysiological and neuroimaging studies. In addition, cognitive control has been proposed as one of the potential mechanisms of behavioral therapy for tics (Essoe, Ramsey, Singer, Grados, & McGuire, 2021), which is considered the first line of treatment in TS, necessitating the need to develop biomarkers that can be used to study brain mechanisms of this treatment.

Event-related potentials (ERP), which index time-locked brain responses to specific events, allow investigation of the brain correlates of inhibitory control in individuals with TS or ADHD. There exists a depth of ERP research on inhibitory control in individuals with ADHD, as documented in a recently published meta-analytical study (Kaiser et al., 2020). This study showed that in Go/NoGo tasks, compared to healthy controls, children and adults with ADHD showed delayed P300 latency for both Go and NoGo trials, as well as reduced P300 amplitude for NoGo trials. That study also noted the heterogeneity of N200 alterations in ADHD; these alterations are notably influenced by the presence of co-occurring disorders. Compared with ADHD, there has been less research documenting N200 and P300 alterations during inhibitory control tasks in children with TS (Morand-Beaulieu & Lavoie, 2019). No difference between children with TS and typically developing controls has been reported in terms of N200 or P300 amplitude during a visual-auditory Go/NoGo task (Petruo et al., 2018). Additionally, another study reported no difference in P300 amplitude during a Flanker task between children with TS or ADHD and typically developing controls. However, it remains unclear how co-occurring ADHD in some children may impact brain correlates of inhibitory control indexed by ERPs. To the best of our knowledge, only one study has assessed the EEG correlates of inhibitory control in children with TS with and without ADHD and included control groups of unaffected children and children with ADHD without tics (Shephard, Jackson, & Groom, 2016). This type of 2-by-2 experimental design enables the disentanglement of effects associated with TS, ADHD, and their co-occurrence. In this study, the ADHD diagnosis, regardless of TS diagnosis, was associated with decreased P300 amplitude for both Go and NoGo trials, suggesting that the P300 decrease in children with TS+ADHD was due to co-occurring ADHD and not tic symptoms. These findings support an additive model of TS and ADHD, which suggests that TS and ADHD are separate diagnostic entities and that their effects are additive in children with both TS and ADHD (Rothenberger & Heinrich, 2021). Nevertheless, like most ERP studies of TS, the study of Shephard et al. (2016) included a small sample size (17 children with TS-only and 17 children TS+ADHD), thus warranting replication in a larger sample. In the current study, we aimed to examine ERP correlates of inhibitory control in a large and well-characterized sample that included four groups of children with TS-only ($n = 47$), TS+ADHD ($n = 32$), ADHD-only ($n = 22$), and matched typically developing controls ($n = 35$).

Event-related spectral perturbations (ERSP), a measure that represents the change in the power of neural oscillations related to a specific event (Makeig, 1993), have also been used as an electrophysiological index of inhibitory control. The study of neural oscillations is particularly relevant in TS and ADHD (Sukhodolsky, Leckman, Rothenberger, & Scahill, 2007), but remains less investigated compared with ERPs. Frontal midline theta (FMT) oscillations, a form of ERSP assessed at medial frontal EEG electrodes, reflect the detection of the need for inhibitory control as well as its implementation (Cavanagh & Frank, 2014). Prior studies using Go/NoGo paradigms among healthy participants consistently report increased FMT during NoGo compared to Go trials (Brier et al., 2010; Harper, Malone, Bachman, & Bernat, 2016; Harper, Malone, & Bernat, 2014; Nigbur, Ivanova, & Stürmer, 2011). Source localization studies have localized FMT mainly to the anterior cingulate cortex (Holroyd & Umemoto, 2016) and the medial prefrontal cortex (Domic-Siede, Irani, Valdés, Perrone-Bertolotti, & Ossandón, 2019; Ishii et al., 2014). There is also increasing application of FMT in electrophysiological studies of inhibitory control in children with ADHD. Thus, ADHD has been associated with reduced difference in frontal theta power between the congruent and incongruent conditions of a Flanker task (McLoughlin, Palmer, Rijsdijk, & Makeig, 2014). FMT was also found to be decreased in children with ADHD following the presentation of NoGo stimuli (Baijot et al., 2017) or after committing an error (Groom et al., 2010) during a Go/NoGo

task. To date, only one study of children with TS has examined event-related brain oscillations in the context of an inhibitory control task (i.e., Flanker task) and reported reduced theta band power in children with TS relative to unaffected controls (Jurgiel et al., 2021). Our study extends this important work by testing the effects of co-occurring ADHD on theta-band power in children with TS during a Go/NoGo task of inhibitory control.

The aim of the current study was to investigate the impact of TS, ADHD, and their co-occurrence on behavioral performance, ERPs, and FMT in four groups of children: TS-only, TS+ADHD, ADHD-only and TD controls. Based on previous work supporting an additive model of TS and ADHD (Greimel et al., 2011; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008; Roessner, Becker, Banaschewski, & Rothenberger, 2007), we hypothesized that differences in behavioral performance and EEG measures would be associated with ADHD rather than TS. Therefore, we expected decreased behavioral performance (reaction time and accuracy during the Go/NoGo task), delayed N200 and P300 latency, reduced N200 and P300 amplitude, and reduced FMT power for NoGo trials in children with ADHD and those with TS+ADHD. Consistent with previous studies using Go/NoGo tasks, we predicted no differences between TS-only and typically developing control groups in terms of behavioral performance and electrophysiological activity.

2. Methods

2.1. Research transparency

The experimental procedures and analyses in this study were not preregistered prior to the research being conducted. We reported how we determined our sample size, all inclusion/exclusion criteria, all data exclusions, all manipulations, and all measures in the study. Inclusion/exclusion criteria were established prior to data analysis.

2.2. Participants

Data in the current study were collected under the context of different projects. All valid data were aggregated here for analysis. One hundred and thirty-eight children completed the experimental procedures involved in this study. Inclusion criteria were: (1) aged between 7 and 14 years old and (2) primary diagnoses of TS and/or ADHD for children in the clinical groups and no psychiatric disorders in typically developing controls. Criteria for exclusion were a history of (i) neurological illness, seizures, or head trauma with loss of consciousness, (ii) intellectual disability (IQ < 70), (iii) diagnosis of autism spectrum disorder, and/or (iv) severe psychiatric disorder that would interfere with participation in the study. Following clinical assessment (see below), children were assigned to one of the four groups according to their diagnoses. One child was excluded from the typically developing control group because they presented with symptoms of autism spectrum disorder during study evaluation. One child with TS was excluded from data analyses because no button-press responses were recorded in the Go condition of the Go/NoGo task. Thus, 136 children were included in the final sample of this study. Socio-demographic and clinical characteristics for each group are presented in Table 1. This study was approved by the Yale University Institutional Review Board. Informed consent and assent were respectively obtained from parents and children.

2.3. Procedures

2.3.1. Clinical assessment

A semi-structured clinical interview (K-SADS; Kaufman et al., 1997) was conducted by a clinician in order to assess the diagnoses of TS and ADHD and co-occurring disorders. The symptom severity of ADHD, anxiety, and disruptive behaviors were assessed using parent-rated symptom checklists. Specifically, the 18-item Swanson, Nolan, and Pelham Questionnaire (SNAP-IV; Swanson et al., 2001) assessed ADHD symptoms, the 41-item Screen for Child Anxiety Related Disorders (SCARED; Birmaher et al., 1999) assessed anxiety symptoms, and the 8-item Disruptive Behavior Rating Scale (DBRS; Barkley, 1997) assessed disruptive behaviors.

In children with TS, tic severity was assessed with the total tic score of the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). The YGTSS administration was performed by licensed clinicians with expertise in TS. The YGTSS total tic score ranges from 0 to 50 and consists of the motor and phonic tic severity subscales. In all children, best estimate DSM-IV-TR diagnoses of TS and concomitant disorders were determined from information gathered by clinical interviews and parent ratings of symptom severity (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982).

The Edinburgh Handedness Inventory (Oldfield, 1971) was used to assess handedness. IQ was assessed with the Weschler Abbreviated Scale of Intelligence – 2nd version (Wechsler, 2011).

2.3.2. Go/NoGo task

The Go/NoGo task was adapted from Serrien, Orth, Evans, Lees, and Brown (2005). Throughout the task, a fixation cross was displayed in the middle of the computer screen. Each trial began by the presentation of a left- or right-pointing arrow, which served as the cue (or warning stimulus) and was displayed on either side of the fixation cross for 500 msec. After the arrow disappeared, there was a 2,500 msec interval before the target stimulus appeared. The target (or imperative stimulus) appeared on the same side as the cue for 500 msec. There were two possible target stimuli: the figure "0" served as the Go stimulus and the letter "S" served as the NoGo stimulus. Participants were instructed to press the keyboard key corresponding to the target stimulus' location as fast as possible when the Go stimulus appeared and to refrain from responding when the NoGo stimulus appeared. The inter-stimulus interval ranged between 5,000 and 7,000 msec (mean: 6,000 msec). The task was separated in four blocks of 40 trials (30 Go and 10 NoGo), for a total of 160 trials (see Fig. 1). Twenty-five of the 136 participants included in the sample performed an earlier version of the task that contained 80 trials. These participants were included in analyses of behavioral data, but

Table 1 – Demographic and clinical characteristics of study participants.

	TS (n = 47)	ADHD (n = 22)	TS+ADHD (n = 32)	TDC (n = 35)	TS main effect	ADHD main effect	TS by ADHD interaction	Group comparison
Age in years, mean (SD)	11.0 (1.7)	10.2 (2.0)	11.4 (1.6)	11.4 (1.6)	n.s.	n.s.	$F(1,132) = 5.95$*	TDC > ADHD
Sex (% male)	89.1%	77.3%	84.4%	71.4%	Wald $\chi^2(1) = 3.87$*	n.s.	n.s.[1]	–
Handedness (% right-handed) [a]	80.4%	86.4%	91.4%	81.3%	–	–	n.s.[1]	–
Race, number (%) [b]					Wald $\chi^2(1) = 5.00$*	n.s.	n.s.	–
White	39 (83.0%)	13 (59.1%)	27 (84.4%)	31 (88.6%)	–	–	–	–
Black	4 (8.5%)	3 (13.6%)	2 (6.3%)	1 (2.9%)	–	–	–	–
American Indian	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	–	–	–	–
Asian	3 (6.4%)	0 (0%)	1 (3.1%)	3 (8.6%)	–	–	–	–
Biracial	0 (0%)	4 (18.2%)	0 (0%)	0 (0%)	–	–	–	–
Not reported	1 (2.1%)	1 (4.5%)	2 (6.3%)	0 (0%)	–	–	–	–
Ethnicity (% Hispanic) [c]	2.2%	13.6%	12.9%	2.9%	–	–	n.s.	–
Full Scale IQ, mean (SD) [d]	114.4 (14.1)	107.5 (15.3)	108.0 (17.4)	114.5 (10.8)	n.s.	$F(1,122) = 6.46$*	n.s.	–
Clinical scores, mean (SD)								
YGTSS total tic score[e]	23.8 (7.0)	–	24.9 (8.4)	–	–	n.s.	–	–
SNAP-IV[f]	9.5 (7.2)	27.8 (11.9)	26.7 (11.0)	4.5 (4.4)	n.s.	$F(1,128) = 172.75$***	$F(1,128) = 3.93$*	ADHD/TS+ADHD > TS > TDC
DBRS[g]	4.5 (4.6)	9.3 (6.0)	9.5 (5.4)	2.9 (3.3)	n.s.	$F(1,127) = 44.11$***	n.s.	–
Co-occurring diagnoses, number (%)								
Any condition (other than ADHD)	12 (25.5%)	11 (50%)	16 (50%)	0 (0%)	n.s	Wald $\chi^2(1) = 4.84$*	n.s.	–
OCD	5 (10.6%)	0 (0%)	6 (18.8%)	–	–	–	–	–
ODD	2 (4.3%)	5 (22.7%)	9 (28.1%)	–	–	–	–	–
Conduct disorder	0 (0%)	6 (27.3%)	0 (0%)	–	–	–	–	–
Any anxiety disorder	8 (17.0%)	1 (4.5%)	6 (18.8%)	–	–	–	–	–
Medication status, number (%) [h]								
On psychotropic medication	15 (32.6%)	6 (27.3%)	20 (62.5%)	1 (2.9%)	–	–	*** (Fisher's test)	TS/ADHD/TS+ADHD > TDC
Stimulants[i]	0 (0%)	6 (27.3%)	6 (18.8%)	0 (0%)	–	–	–	–
α-Agonists[j]	10 (21.7%)	1 (4.5%)	11 (34.4%)	0 (0%)	–	–	–	–
Atomoxetine	0 (0%)	0 (0%)	3 (9.4%)	0 (0%)	–	–	–	–
Antipsychotics[k]	3 (6.5%)	1 (4.5%)	8 (25.0%)	0 (0%)	–	–	–	–
SSRIs[l]	3 (6.5%)	0 (0%)	6 (18.8%)	1 (2.9%)	–	–	–	–
Other[m]	0 (0%)	0 (0%)	2 (6.3%)	0 (0%)	–	–	–	–

Note: ADHD: attention-deficit/hyperactivity disorder, DBRS: Disruptive Behavior Rating Scale, OCD: obsessive-compulsive disorder, ODD: oppositional defiant disorder, SCARED: Screen for Child Anxiety Related Disorders, SD: standard deviation, SNAP-IV: Swanson, Nolan and Pelham Questionnaire for ADHD, SSRI: selective serotonin reuptake inhibitors, TDC: typically developing controls, TS: Tourette syndrome, YGTSS: Yale Global Tic Severity Scale, *: $p < .05$, **: $p < .01$, ***: $p < .001$.

[1] Denotes when Fisher's exact test was used (comparing the four subgroups) instead of a logistic binary regression because more than 20% of cells had an expected count below 5.

[a] One TS and 1 TS+ADHD participants with missing data.

[b] Data were binarized as white/other because more than 20% of cells had an expected count below 5.

[c] Two TS and 1 TS+ADHD participants with missing data.

[d] Seven TS, 1 ADHD, and 2 TS+ADHD participants with missing data.

[e] Four TS [participants] with missing data.

[f] Three TS and 1 TS+ADHD participants with missing data.

[g] Three TS and 2 TS+ADHD participants with missing data.

[h] One TS participant with missing data.

[I] Stimulant medications included methylphenidate (n = 7), lisdexamfetamine (n = 3), dexmethylphenidate (n = 1), and dextroamphetamine (n = 1).

[j] α-Agonists included guanfacine (n = 19) and clonidine (n = 3).

[k] Antipsychotics included risperidone (n = 8), haloperidol (n = 2), aripiprazole (n = 2), and quetiapine (n = 1).

[l] SSRIs included citalopram (n = 3), fluvoxamine (n = 2), sertraline (n = 2), fluoxetine (n = 2), and escitalopram (n = 1).

[m] Other medications included benztropine (n = 1) and gabapentin (n = 1).

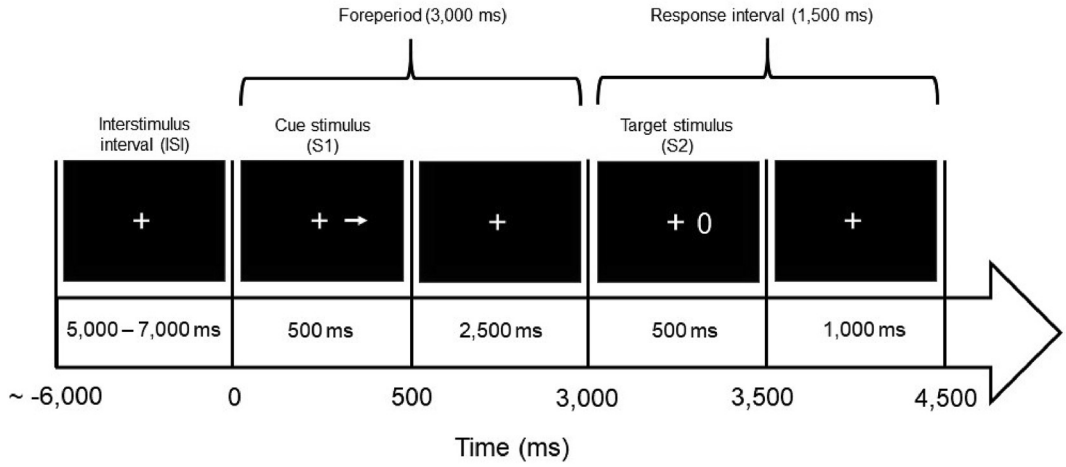

Fig. 1 – Example of a trial of the Go/NoGo task. At the beginning of each trial, an arrow appeared on either side of the fixation cross and was displayed for 500 msec. Three seconds after the onset of the arrow, the figure "0" (Go stimulus) or the letter "S" (NoGo stimulus) appeared on the same side as the arrow, prompting a response (or not) from the participant.

their EEG data was included only if they had a minimum of 15 correct epochs in each condition.

Variables related to behavioral performance [reaction times (RT), Hit rate, False alarm rate] were extracted for statistical analyses. To analyze Go/NoGo task performance, we computed the D-prime using the following formula: D-prime = $_z$Hit rate − $_z$False 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 (Macmillan & Kaplan, 1985).

2.4. *EEG recordings and signal processing*

2.4.1. *EEG recordings*

The EEG was continuously recorded at a sampling rate of 250 Hz during the Go/NoGo task. The EEG signal was recorded with a 128-channel HydroCel Geodesic Sensor Net and was referenced to the vertex electrode (Cz) during recordings. The signal was recorded through Net Station Acquisition software version 4.2.1 (EGI, Inc.) with a Net Amps 200 amplifier. The continuous signal was online filtered with a .01 Hz high-pass filter and a 100 Hz low-pass filter.

2.4.2. *EEG preprocessing*

Continuous EEG recordings were first pre-processed in Matlab 2020a with the Maryland Analysis of Developmental EEG (MADE) pipeline (Debnath et al., 2020), which relies on EEGLAB's functions and was designed to preprocess EEG in children and adolescents. Preprocessing steps involved filtering, artifact removal through independent component analysis (ICA) and threshold-based rejection, removal and interpolation of bad channels, segmentation of continuous EEG in 2-s epochs, and re-referencing. Complete details are provided in the Supplement. In all EEG analyses, only correct responses were considered. Analyses were conducted on participants who had at least 15 artifact-free trials in each condition. The number of valid trials per group is presented in Table S1.

2.4.3. *Event-related potentials*

Of the 136 participants in our sample, 22 had less than 15 artifact-free trials in one condition for ERP analyses (11 TS-only, 1 ADHD-only, 4 TS+ADHD, 6 TDC). Therefore, ERP analyses were conducted on 114 children (36 TS-only, 21 ADHD-only, 28 TS+ADHD, 29 TDC). These 114 participants had an average of 64.8 and 25.9 valid epochs in the Go and the NoGo condition, respectively. ERP analyses were performed using ERPLAB. ERPs were assessed for Go and NoGo trials at a cluster of electrodes around Pz (electrodes 61, 62, 67, 72, 77, 78; see Fig. S1) and were baseline-corrected (−200 − 0 msec). The N200 was assessed as the most negative peak in the 150–300 msec post-stimulus interval, while the P300 was assessed as the most positive peak in the 300–700 msec post-stimulus interval. Both peak amplitude and peak latency measures were extracted for statistical analyses.

2.4.4. *Event-related spectral perturbations*

Event-related spectral perturbations analysis was used to assess frontal midline theta power (FMT) time-locked to Go and NoGo stimuli. Time frequency analyses were conducted on participants who had at least 15 valid trials in each condition. Of the 136 included participants, 26 had less than 15 artifact-free trials in one condition (14 TS-only, 2 ADHD-only, 5 TS+ADHD, 5 TDC). Therefore, time-frequency analyses were conducted on 110 children (33 TS-only, 20 ADHD-only, 27 TS+ADHD, 30 TDC).[1] These 110 participants had an average of 61.3 and 27.1 valid epochs in the Go and the NoGo condition, respectively. To match the number of epochs across conditions, 27 Go epochs were randomly selected.

Time-frequency transforms were performed with EEGLAB's *newtimef* function using the -200-0 msec interval as a baseline (details are provided in the Supplement). FMT was computed between 4 and 8 Hz and was assessed at a cluster of

[1] These analyses included 107 of the 110 children who were included in time-frequency analyses. Therefore, 33 TS-only, 20 ADHD-only, 26 TS+ADHD, and 28 TDC were included in both analyses.

frontal midline electrodes surrounding FCz (electrodes 5, 6, 7, 12, 13, 106, 112), in a 200–600 msec post-stimulus interval (see Fig. S1).

2.5. Statistical analyses

Demographic and clinical data were analyzed with factorial ANOVAs (with the two factors TS and ADHD coded as 1 = present or 0 = absent) and logistic regression (with the factors TS, ADHD, and TSxADHD interaction term) where appropriate. An assumption of logistic regression is that no more than 20% of cells should have an expected count below 5 (Josephat & Ame, 2018). For variables that violated this assumption, a Fisher's exact test was performed. When more than 20% of cells had an expected count below 5, we conducted Fisher's exact test comparing the four subgroups (TS, ADHD, TS+ADHD, TDC). Following Shephard et al. (2016), behavioral data were analyzed with a MANOVA, with D-prime and reaction times serving as dependent variables, and TS (yes/no) and ADHD (yes/no) as between-subjects factors. To investigate possible interactions involving within-subjects and between-subjects factors, we decided to use factorial ANOVAs for ERP and FMT data. For ERP data, peak amplitude and latency were respectively analyzed with 2X2X2X2 ANOVAs, with the within-subject factors Condition (Go/NoGo) and Component (N200/P300), and the between-subjects factors TS (yes/no) and ADHD (yes/no). FMT was analyzed with a 2 × 2 × 2 ANOVA, with the within-subjects factor Condition (Go/NoGo) and the between-subjects factors TS (yes/no) and ADHD (yes/no). Analyses were repeated with age as a covariate, but overall results did not differ (see Supplement).

Pearson correlations were used for exploratory analyses to assess how the severity of tics in TS (YGTSS total tic score) and ADHD symptoms (SNAP-IV total score) were associated with task performance (D-prime, RT) and electrophysiological measures (N200, P300, and FMT). A Bonferroni correction was applied to correct for the number of correlations (44) that were performed. Correlations between task performance and electrophysiogical measures are presented in the Supplement (see Figs. S2-S4). Effect sizes were computed as partial eta squared (ηp^2) for interactions and variables with more than two levels and with Cohen's d for pairwise comparisons. By convention, partial eta squared of .01, .06, and .14 as well as Cohen's d of .2, .5, and .8 are considered small, medium, and large effects, respectively (Cohen, 1988).

3. Results

3.1. Behavioral results

The global MANOVA performed on D-prime and RT revealed a main effect of ADHD [$F(2,131) = 8.46$, $p < .001$, $\eta p^2 = .147$] as well as a TS by ADHD interaction [$F(2,131) = 3.79$, $p = .025$, $\eta p^2 = .055$]. A follow-up MANOVA conducted only among children without TS (ADHD-only and TDC) revealed a main effect of ADHD [$F(2,54) = 9.38$, $p = .00032$, $\eta p^2 = .258$], suggesting worse task performance in children with ADHD-only compared to typically developing controls (Fig. 2). There was no main effect of ADHD in children with TS [$F(2,76) = .60$, $p = .55$, $\eta p^2 = .016$].

3.2. Event-related potentials

Our analysis of N200 and P300 peak amplitude revealed no main effect or interaction involving either the ADHD or TS factor. However, the ANOVA performed on ERP peak latency revealed an ADHD by TS interaction [$F(1,110) = 8.76$, $p = .004$, $\eta p^2 = .074$]. A follow-up ANOVA performed among children without TS revealed a main effect of ADHD [$F(1,48) = 8.21$, $p = .006$, $d = .84$], suggesting that children with ADHD-only had delayed N200 and P300 peak latency compared to the typically developing controls (Fig. 3). In children with TS, there was no main effect of ADHD [$F(1,62) = 1.03$, $p = .31$, $d = .26$]. Interactions between Condition and Component for amplitude and latency measures are presented in the Supplement.

3.3. Frontal midline theta

The ANOVA conducted on FMT revealed a significant task condition main effect [$F(1,106) = 8.55$, $p = .004$, $d = .33$], indicating increased theta power in the NoGo condition relative to the Go condition. There was also a condition by TS by ADHD interaction [$F(1,106) = 6.95$, $p = .010$, $\eta p^2 = .062$]. In the NoGo condition, there was a significant TS by ADHD interaction [$F(1,106) = 9.07$, $p = .003$, $\eta p^2 = .079$]. A follow-up ANOVA in children without TS revealed a significantly decreased NoGo FMT in children with ADHD relative to typically developing controls [$F(1,48) = 8.28$, $p = .006$, $d = .82$] (Fig. 4). In children with TS, however, there was no main effect of ADHD [$F(1,58) = 1.55$, $p = .22$, $d = .33$]. Mean values for behavioral and EEG measures for each group are presented in Table S3.

3.4. Correlational analyses

Correlational analyses revealed that SNAP-IV total scores were associated with delayed RT [$r(130) = .24$, $p_{uncorrected} = .005$, $p_{Bonferroni\text{-}corrected} = .23$] and Go N200 latency [$r(109) = .23$, $p_{uncorrected} = .017$, $p_{Bonferroni\text{-}corrected} = .75$] (Fig. S4). However, both correlations did not survive Bonferroni correction for multiple comparisons. Also, there was no correlation between any behavioral or EEG measures and tic severity as assessed with the YGTSS total tic score.

4. Discussion

This study examined the EEG correlates of inhibitory control in children with TS and ADHD during a Go/NoGo task. Consistent with previous work (Shephard et al., 2016), our results revealed no differences in children with TS-only on either behavioral or EEG indices of inhibitory control. Contrary to our hypotheses, children with TS and co-occurring ADHD also did not evidence reduced performance on the Go/NoGo task or differences in EEG activity during this task. Only children with ADHD without tics had reduced NoGo FMT and delayed N200 and P300 latency in both Go and NoGo trials, compared to typically developing controls.

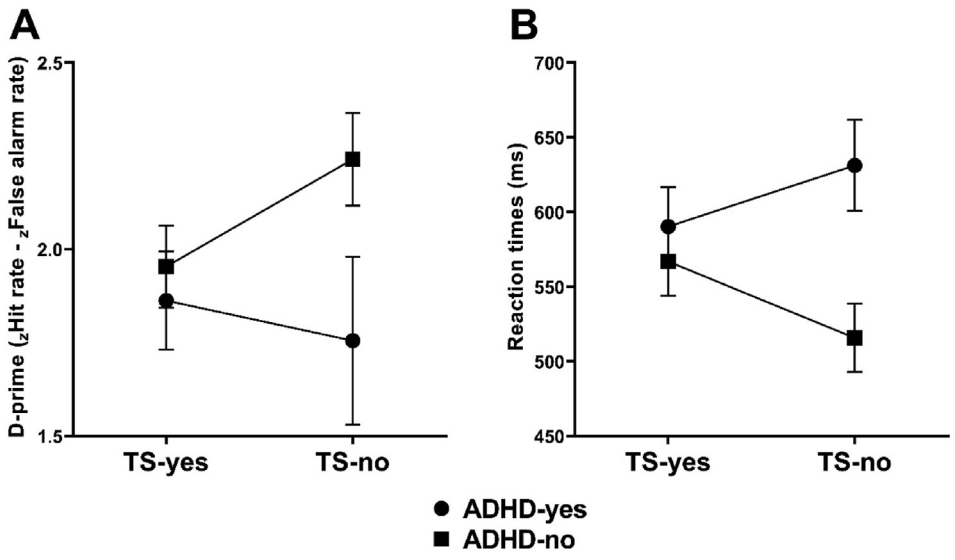

Fig. 2 – Go/NoGo task performance. The MANOVA performed on behavioral data (D-prime & RT) revealed a main effect of ADHD as well as a TS by ADHD interaction. A follow-up MANOVA conducted among children without TS suggests significantly impaired task performance in children with ADHD-only, compared to typically developing controls.

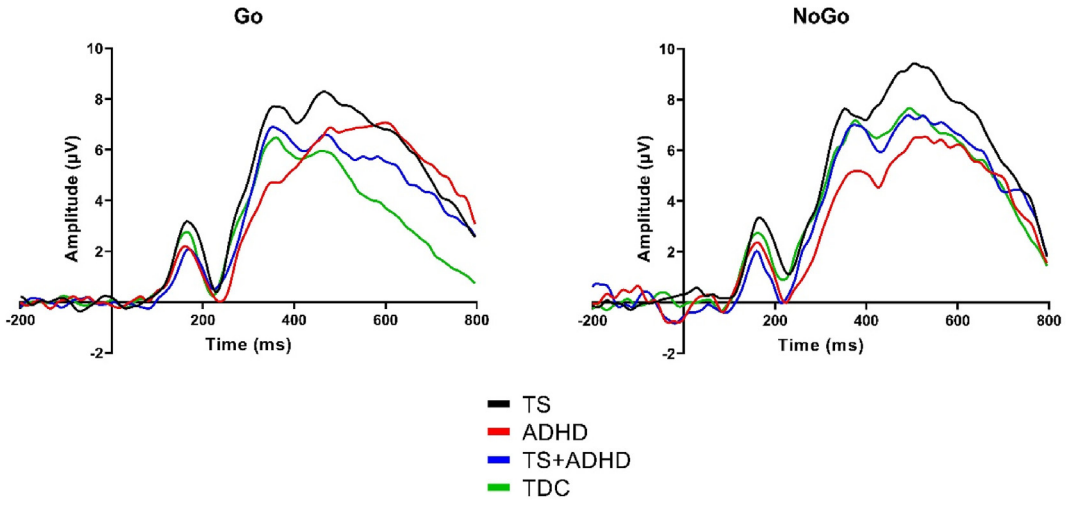

Fig. 3 – Event-related potentials. At a cluster of electrodes around Pz, the N200 for Go and NoGo stimuli respectively peaked at 223 msec and 224 msec after the target stimulus presentation. The P300 peak latency was delayed in the NoGo condition, peaking at 490 msec (*vs* 464 msec in the Go condition). The P300 peak amplitude was also larger in the NoGo than in the Go condition. Our analyses revealed no between-group difference for peak amplitude measures, but we found that the ADHD-only group showed delayed N200 and P300 peak latency, compared to typically developing controls.

First, our hypotheses regarding children with TS-only were confirmed. We did not find significant differences in behavioral or electrophysiological measures. In the prior meta-analysis of cognitive control in TS, only small effect sizes were reported for group differences between individuals with TS-only and unaffected controls (Morand-Beaulieu, Grot, et al., 2017). That meta-analysis included several tasks requiring inhibitory and interference control. Among those, the Go/NoGo task showed the least differentiation between individuals with TS and unaffected controls. Thus, our behavioral results are consistent with the literature, especially that of a Go/No-Go task, in which individuals with TS uncomplicated by co-occurring ADHD do not demonstrate large reductions in inhibitory control, but rather are similar to typically developing individuals. Our results regarding ERPs were consistent with those of Shephard et al. (2016), who did not report differences on N200 or P300 amplitude for children with TS-only during a Go/NoGo task, compared with typically developing controls. However, our results pertaining to FMT in children with TS differs from those of Jurgiel et al. (2021), who reported decreased FMT during a Flanker task – a neuro-cognitive measure of cognitive control different from the Go/NoGo task used in our study. The Go/NoGo task involves the inhibition of a prepotent motor response while the Flanker

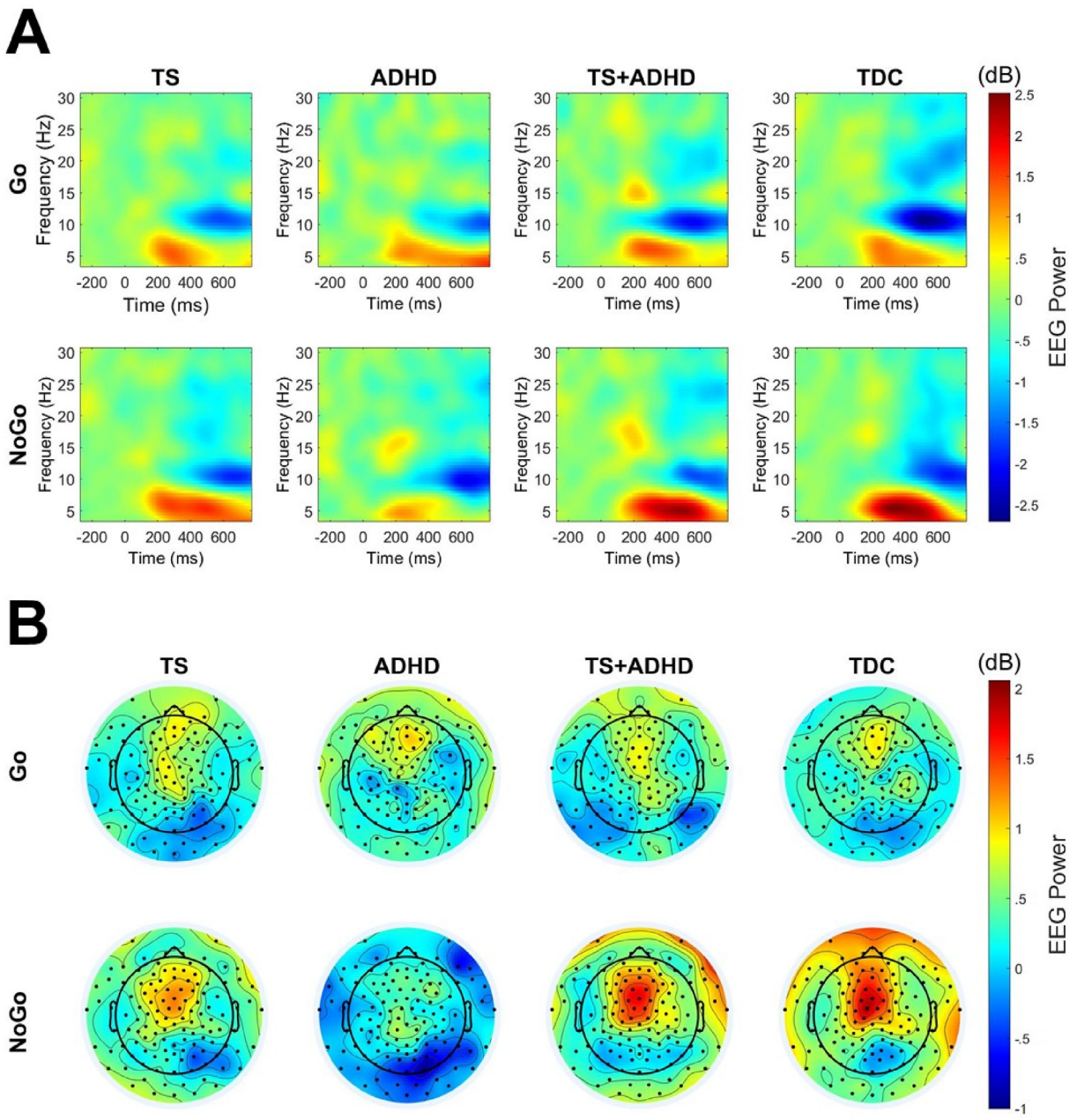

Fig. 4 – Frontal midline theta. (A) This panel shows brain oscillations in the theta band (4–8 Hz) in response to Go and NoGo stimuli at a cluster of electrodes surrounding FCz. Our analyses revealed a Condition by TS by ADHD interaction, suggesting decreased FMT in children with ADHD-only. (B) Topoplots display the average theta power distribution in the 200–600 msec interval.

task reflects interference control (Friedman & Miyake, 2004; Lindqvist & Thorell, 2008). It is thus possible that EEG markers elicited by a Go/NoGo task are less sensitive to subtle nuances of cognitive control in children with TS compared with EEG markers elicited by a Flanker task. Along these lines, Rawji et al. (2020) reported that adults with TS showed reduced automatic inhibition, assessed with a masked priming task, but not in volition inhibition, which was assessed with the Stop-signal task. This suggests that some aspects of cognitive control could be impaired in TS while others could be preserved.

In contrast, reduced behavioral performance and alterations in electrophysiological markers were found in children with ADHD without tics. Findings of diminished indices of behavioral performance on the Go/NoGo task, reflected by reduced D-prime and delayed reaction times, are consistent with the literature on Go/NoGo performance in ADHD (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Pievsky & McGrath, 2018). Additionally, delayed reaction times were associated with increased severity of ADHD symptoms, as indexed by SNAP-IV scores. Analyses of ERP data revealed that the latency of the N200 and the P300 was delayed in

children with ADHD without tics, relative to typically developing controls. The result for P300 latency is consistent with the meta-analysis of Kaiser et al. (2020), who reported medium effect sizes of d = .52 and d = .35 in favor of delayed Go and NoGo P300 latency in individuals with ADHD, respectively. In our study, the Go P300 latency was positively correlated with reaction times among all participants. This is consistent with our finding that latency measures were delayed in children with ADHD without tics, the group that showed the poorest behavioral performance during the Go/NoGo task. We also found reduced frontal midline theta power during the NoGo condition of the Go/NoGo task in children with ADHD without tics. This finding is consistent with prior work in children with ADHD showing decreased error-related FMT (Groom et al., 2010; Keute, Stenner, Mueller, Zaehle, & Krauel, 2019) and reduced difference in frontal theta power between the congruent and incongruent conditions of a Flanker task (McLoughlin et al., 2014). Importantly, our results confirm and extend the previous findings of decreased NoGo FMT in 7 children with ADHD during a Go/NoGo task (Baijot et al., 2017). These EEG studies also align well with the neuroimaging studies that link reduced inhibitory control in children with ADHD to functional differences in the anterior cingulate cortex and medial prefrontal cortex, the main generators of FMT (Domic-Siede et al., 2019; Holroyd & Umemoto, 2016; Ishii et al., 2014).

In contrast with our expectations, we found no significant differences in either behavioral or electrophysiological measures between children with TS+ADHD and the other groups. At the behavioral level, this result is not in line with the meta-analysis showing worse inhibitory control in individuals with TS+ADHD than those with TS-only (Morand-Beaulieu, Grot, et al., 2017). However, as we noted earlier, that same meta-analysis revealed that the Go/NoGo task has shown little differentiation between individuals with TS and unaffected controls in terms of behavioral performance. Thus, the Go/NoGo task may not be the best tool to investigate the expected difference in inhibitory control between children with TS-only and those with TS+ADHD. There were also no differences in the amplitude of the N200 and P300 event-related potentials components. This result is inconsistent with a prior study that reported reduced amplitudes of N200 and P300 evoked potential in children with TS+ADHD relative to children with TS-only and typically developing controls (Shephard et al., 2016). It is possible that this difference could be explained by the severity of tic symptoms across studies. In the latter study, children with TS+ADHD had more severe tics than children with TS-only, whereas in our study, both groups had the same level of tic severity (in terms of YGTSS total tic score). In contrast with children with ADHD without tics, children with TS+ADHD did not show a reduction in NoGo FMT or a delayed N200 and P300 latency. At the electrophysiological level, children with TS+ADHD were quite similar to those with TS-only and typically developing controls and did not show the distinct electrophysiological pattern observed in children with ADHD-only. This is somewhat puzzling and contrary to our expectations. It seems possible that some ADHD symptoms in children with TS could emerge from TS-associated factors, such as being distracted by one's own tics or by efforts to suppress them (Erenberg, 2005). Even though children with TS+ADHD did not differ from TDC on task performance and EEG measures, exploratory correlations showed that severity of ADHD symptoms correlated with reaction times and N200 latency during Go trials among the whole sample (although these correlations did not survive Bonferroni correction for multiple comparisons). Thus, RT and N200 latency during Go trials might be more sensitive to detecting dimensionally measured severity of ADHD symptoms than the presence of categorical ADHD as a diagnosis. Yet, results pertaining to children with TS+ADHD are not consistent with prior neuropsychological (Greimel et al., 2011; Roessner et al., 2007, 2008) or electrophysiological (Shephard et al., 2016) findings supporting the additive model of TS and ADHD. We encourage researchers to continue this line of work to understand the factors influencing the additive model.

The findings of this study must be interpreted in the light of some limitations. While the total sample size was considerable, our group of children with ADHD-only was the smallest of our 4 subgroups. Having now identified the relevance of studying FMT in an inhibitory control task among children with ADHD, future studies should aim to study this neurophysiological marker of ADHD in larger samples. Even though our study included one of the largest EEG datasets in children with TS, our analyses were underpowered to detect small differences between the groups. We reported the means and standard deviations for all behavioral and EEG measures in Table S3 for illustrative purposes and to enable effect size computations for researchers who might be interested in designing future studies aimed at testing specific differences between groups.

In conclusion, our study of children with TS and ADHD revealed that behavioral task performance, latency of N200 and P300 event-related potentials, and magnitude of frontal midline theta power oscillations during the NoGo condition only differed in children with ADHD without tics. Despite similar levels of ADHD symptoms severity, these differences in EEG markers of inhibitory control were not present in the TS+ADHD subgroup, highlighting the need for more research on the additive model of TS and ADHD.

CRediT authorship contribution statement

Simon Morand-Beaulieu: Conceptualization, Data curation, Formal analysis, Software, Validation, Visualization, Writing – original draft, Visualization. **Stephanie D. Smith:** Investigation, Writing – review & editing. **Karim Ibrahim:** Investigation, Writing – review & editing. **Jia Wu:** Data curation, Investigation, Methodology, Writing – review & editing. **James F. Leckman:** Conceptualization, Funding acquisition, Resources, Writing – review & editing. **Michael J. Crowley:** Conceptualization, Resources, Methodology, Writing – review & editing. **Denis G. Sukhodolsky:** Conceptualization, Funding acquisition, Methodology, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

Materials availability

The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact one of the corresponding authors. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data sharing agreement. Legal copyright restrictions prevent public archiving of the various tests and clinical assessments used in this study (see Section 2.3.1). These materials can be obtained from the copyright holders in the cited references. The Go/NoGo task used in this study as well as Matlab scripts used for preprocessing and analyzing EEG data is available at https://osf.io/jyzdr/.

Declaration of competing interest

The authors have no biomedical financial interests or potential conflicts of interest to declare related to this present study.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2021.12.006.

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