Archival Report

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Distinct Brain-Oscillatory Neuroanatomical Architecture of Perception-Action Integration in Adolescents With Tourette Syndrome

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ABSTRACT

BACKGROUND: Gilles de la Tourette Syndrome (GTS) is a neurodevelopmental disorder with a peak of symptom severity around late childhood and early adolescence. Previous findings in adult GTS suggest that changes in perception-action integration, as conceptualized in the theory of event coding framework, are central for the understanding of GTS. However, the neural mechanisms underlying these processes in adolescence are elusive.

METHODS: A total of 59 children/adolescents aged 9 to 18 years (n = 32 with GTS, n = 27 typically developing youths) were examined using a perception-action integration task (event file task) derived from the theory of event coding. Event-related electroencephalogram recordings (theta and beta band activity) were analyzed using electroencephalogram–beamforming methods.

RESULTS: Behavioral data showed robust event file binding effects in both groups without group differences. Neurophysiological data showed that theta and beta band activity were involved in event file integration in both groups. However, the functional neuroanatomical organization was markedly different for theta band activity between the groups. The typically developing group mainly relied on superior frontal regions, whereas the GTS group engaged parietal and inferior frontal regions. A more consistent functional neuroanatomical activation pattern was observed for the beta band, engaging inferior parietal and temporal regions in both groups.

CONCLUSIONS: Perception-action integration processes lag behind in persisting GTS but not in the GTS population as a whole, underscoring differences in developmental trajectories and the importance of longitudinal investigations for the understanding of GTS. The findings corroborate known differences in the functional/structural brain organization in GTS and suggest an important role of theta band activity in these patients.

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Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder characterized by multiple motor and vocal tics commencing in childhood/adolescence and lasting for at least 1 year. Recently, there has been a shift in perspective on this disorder in that cognitive functions and not only motor symptoms have been subject to intense research. Together, findings showing strong relations between perceptual and motor processes in GTS (1), abnormalities of sensorimotor integration (2) and the planning/execution of movements in these patients (3,4), strong modulatory effects of attention on tics (5,6), increased perception-action association (7), and an increased tendency for habit formation (8) have led to the hypothesis that GTS might be conceptualized in a framework integrating perceptual, motor, and cognitive aspects of action (9–12). Indeed, data in adult GTS (13) support the notion that an abnormally strong coupling between perception and action may be the key to understand GTS. Kleimaker *et al.* (13) have shown this using an approach derived from the theory of event coding (TEC) (14,15). TEC states that whenever actions are triggered by perceptual information, the specific action becomes associated (bound) with the particular features defining the perceptual input. This binding occurs in event files (15) and can facilitate action execution when the same stimulus is reencountered and the same motor response is required (16,17). However, binding can compromise performance either when the same action has to be performed in response to an altered stimulus input or when a different action has to be performed using identical stimulus input (16,17). Such behavioral effects are referred to as partial-repetition costs/benefits and are a marker of event file binding processes. Previous data in adult patients with GTS have shown higher behavioral partial-repetition costs (13). A similar behavioral pattern may also be evident in children/adolescents with GTS.

If event file binding processes are central for the understanding of GTS (9,13), it is important to examine this in adolescents with GTS for a number of reasons: tics as the defining feature of GTS are most pronounced in childhood/adolescence, with first tics appearing between 5 and 7 years (18). In

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most patients, symptom severity is strongly pronounced in late childhood and early adolescence, which is then followed by an amelioration or even complete remission toward the end of the second decade (19). Between 60% and 85% of children/adolescent patients are tic free or only have mild tics as adults (20). Whereas all patients with a diagnosis of GTS are affected in childhood/adolescence, only a minority is affected in adulthood. Thus, children/adolescents but not adults with GTS are most representative for the GTS population. Moreover, tics are generally common in childhood with a prevalence of tic disorders in childhood/adolescence in the range of 3.4%–24.4% (21). Thus, a better understanding of the pathophysiology of GTS in childhood/adolescence is relevant for the much larger population of children/adolescents with tics not fulfilling criteria of GTS. Because of the neurodevelopmental character of GTS (19), the functional brain organization differs between GTS and typically developing (TD) children/adolescents (22). This is central, because event files are not represented in discrete neural assemblies but by widely distributed networks (17,23,24) and require information integration across the frontal and parietal cortex (23–27). Differences in the functional brain organization between children/adolescents with GTS and those with TD (22) thus make it likely that the functional neuroanatomical structures involved in event file processing may differ substantially between youths with GTS and those in a TD group. Biophysical considerations (28–30) and electroencephalogram (EEG) findings (27) suggest that particularly low-frequency high-amplitude oscillations (e.g., theta band) are central for cognitive control and perception-action integration (i.e., event file processes). Intriguingly, activity in the theta frequency band is particularly implicated in the pathophysiology of GTS (31,32). Therefore, we hypothesize that children/adolescents with GTS and TD youths would differ in the functional neuroanatomy associated with theta frequency band activity during event file binding, which can be examined using whole-brain EEG-beamforming methods (33,34).

A whole-brain approach is necessary because neurophysiological evidence shows that event file coding reflects processes in a distributed network of activity (23,24,27), with medial anterior cingulate and medial superior frontal areas playing a prominent role (25,27,35,36) and the inferior as well as superior parietal cortex also being relevant (13,25–27). These areas, particularly medial/superior frontal areas, have also frequently been associated with theta band activity during cognitive control (30). Therefore, and because of evidence that parietal areas may underlie event file binding processes in GTS (13,26), it is likely that event file coding processes in patients with GTS and healthy controls show a qualitative different pattern of activity in these areas. In addition to theta activity, we also investigated beta frequency activity, because both are jointly involved in sensorimotor control (37,38). Furthermore, beta band activity is important for rule-guided processing (39) and reactivation/retrieval of (working) memory traces (40). Because event files are episodic memory traces (17,35) and the retrieval of event file information contributes to binding effects (41), an evaluation of whether and how beta band activity may differ between the GTS and TD groups is necessary. Because particularly lateral prefrontal, temporal, and/or (para) hippocampal regions are important for such visually guided short-term memory-related processes (42) and because these structures are involved in event file processing (35,43), these regions may be associated with beta band activity processes during event file coding in patients with GTS and healthy controls. Taken together, the goal of this study was to investigate distinct features in the brain-oscillatory architecture of perception-action integration in adolescents with GTS.

METHODS AND MATERIALS

Participants

Detailed patient characteristics can be found in the Supplement. We investigated 32 GTS patients (27 males, 5 females; mean [SD] age 13.97 [± 2.87] years, range 9–18 years) and 27 healthy TD individuals (20 males, 7 females; mean [SD] age 13.41 [± 2.68] years, range 9–18 years). Each participant underwent clinical assessment including a semi-structured clinical neuropsychiatric interview, IQ testing, and scoring of tic severity and obsessive-compulsive symptoms. Psychiatric comorbidities were assessed using the Mini International Neuropsychiatric Interview Kid (44) or the Mini International Neuropsychiatric Interview (45), depending on participant's age. Tic severity was assessed by the Yale Global Tic Severity Scale (46). Lifetime tics were assessed by the Diagnostic Confidence Index (47). Premonitory urges were inquired using the Premonitory Urge for Tic Scale (48). Obsessive-compulsive disorder was examined using the Yale Brown Obsessive Compulsive Scale (49) or the Children's Yale Brown Obsessive Compulsive Scale (50), depending on participant's age. For IQ testing, we used the short version of the Hamburg-Wechsler Intelligence Test-IV (51) or the Wechsler Adult Intelligence Scale (52), depending on participant's age. Handedness was evaluated by the Edinburgh Handedness Inventory (53). Based on the interview, four healthy control participants had comorbidities. One had a hypomanic episode in the past, one had an agoraphobia with mild symptoms at the time of participation the study, and two had depression in the past. None of the TD participants had clinically relevant psychiatric symptomatology at the time of study participation. Written informed consent was obtained from every participant or their legal guardians. The study had been approved by the Ethics Committee of the TU Dresden (EK350902017).

Task

A detailed task description can be found in the Supplement. The task is identical to a study in adult patients with GTS (13) using the TEC framework (14) (Figure 1).

The experiment started with a presentation of three centrally located boxes, which were vertically aligned. First, a left- or right-pointing arrowhead was presented in the middle box and served as a cue. Participants had to remember the direction of the cue for the later execution of the first response (R1). After a blank screen was shown, the first stimulus (S1) appeared, which was either a vertical or horizontal line, located in the top or the bottom box, and was either green or red. When S1 was presented, participants had to execute R1; i.e., the response to the cue. Thus, R1 was independent of S1, but associations/bindings between features of R1 and S1 were nevertheless established. After S1, the screen turned blank again, followed

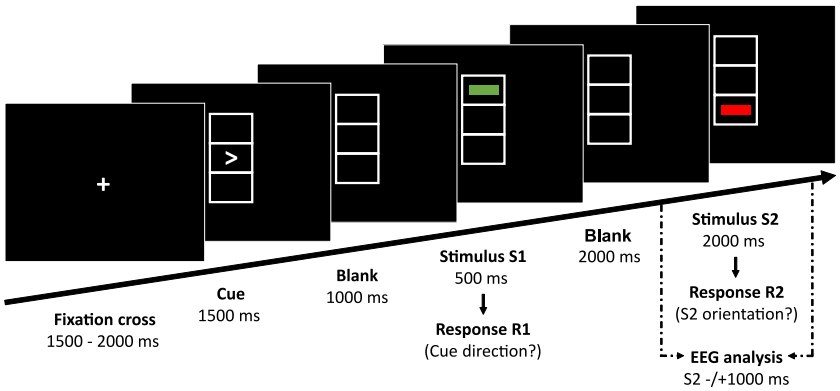


Figure 1. Schematic illustration of the event file coding paradigm used in the present study. For further details, see the text. EEG, electroececphalogram.

by a second stimulus (S2), which, as S1, randomly differed with respect to orientation (vertical or horizontal), location (top or the bottom box), and color (green or red). For each trial, it was therefore possible that S1 and S2 were identical by sharing all features (full feature overlap), shared one or two features (partial feature overlap), or did not share any feature (no feature overlap). Neither S1 and S2, nor S1 and R1 were systematically related to each other. S2 required a second response (R2), which was a left keypress in response to a horizontal line or a right keypress in response to a vertical line. Therefore, within a trial, R1 and R2 were either identical (response repetition) or different (response alternation). In the behavioral data (i.e., response accuracy, reaction time data of the R2-response), event file binding is indicated by an interaction of feature overlap (between S1 and S2) and response (alternation vs. repetition between R1 and R2) (16,27). The whole experiment consisted of at least 384 trials, which were divided into three blocks of 128 trials.

EEG Recording and Analysis

A detailed description of EEG analysis procedures is given in the Supplement. The procedures were based on previously established protocols (54,55). The EEG was recorded from 60 Ag/AgCl electrodes. After preprocessing the data (filtering, independent component analysis decomposition to correct blink and eye-movement artifact), the EEG was segmented on the presentation of the S2. Separate segments were created according to the different feature overlap levels in response repetition and response alternation trials. Only trials with correct responses were included, and an artifact rejection procedure was applied to discard trials with residual artifacts. After applying average reference, a time-frequency (TF) decomposition was run to examine theta band activity (between 4 and 7 Hz) and beta band activity (between 13 and 30 Hz). Using the TF-decomposed data in the theta and beta bands, a dynamic imaging of coherent sources (33) beamformer was run to estimate which functional neuroanatomical structures were associated with binding effects in the theta and beta frequency bands. The source reconstruction was computed separately for the TD group and the GTS group. Because of methodological limitations of the beamformer approach used for source reconstruction (as outlined in detail in the Supplemental Methods and Materials), the source activity of TD group and GTS group cannot be directly contrasted and interpreted in a statistically valid way.

RESULTS

Behavioral Data

The behavioral data were analyzed using SPSS, version 25 (IBM Corp., Armonk, NY). We also provide the probability of the null hypothesis (H0) given the data (p(H0ID)), known as Bayes factor (BF), by conducting a Bayesian analysis using the toolbox by Masson (56). Binding effects are reflected in the interaction between feature overlap and response (16,27). Individual level behavioral data are shown in Figure 2 for the full feature overlap condition and the condition with no feature overlap, because these are the conditions between which binding effects are largest. An analysis with all possible feature overlap levels is presented in the Supplement.

Results in Figure 2 suggest that, in line with previous findings (15,16), the reaction time and accuracy data revealed binding effects, with performance becoming worse with increasing feature overlap in response alternation trials and becoming better with increasing feature overlap in response repetition trials. This is also reflected in the data analysis. The mixed effects omnibus analysis of variance using the reaction times revealed an interaction "feature overlap × response" ($F_{3,171}$ = 22.18; $p < .001$; η_p^2 = 0.280; p(H0ID) = .02). Further post hoc analyses showed that there was a main effect feature overlap for the response repetition condition ($F_{3,174}$ = 9.70; $p < .001$; η_p^2 = 0.280; p(H0ID) = .99) and the response alternation condition ($F_{3,174}$ = 8.63; $p < .001$; η_p^2 = 0.130; p(H0ID) = .99). Clear performance differences ($p < .001$) were always evident between the full feature overlap condition compared with the no feature overlap condition. No further modulation of the interaction "feature overlap × response" by the factor "group" was evident ($F_{3,171}$ = 0.62; p = .602; η_p^2 = 0.011; p(H0ID) = .99); rather, the BF showed that there is strong evidence for the null hypothesis.

In addition, for the accuracy data, the analysis of variance revealed an interaction "feature overlap × response" ($F_{3,171}$ = 74.74; $p < .001$; η_p^2 = 0.567; p(H0ID) = 8.3 × 10^{-9}), and post hoc testing showed that there was a main effect feature overlap for the response repetition condition ($F_{3,174}$ = 56.60; $p < .001$; η_p^2 = 0.494; p(H0ID) = 8.9 × 10^{-7}) and the response

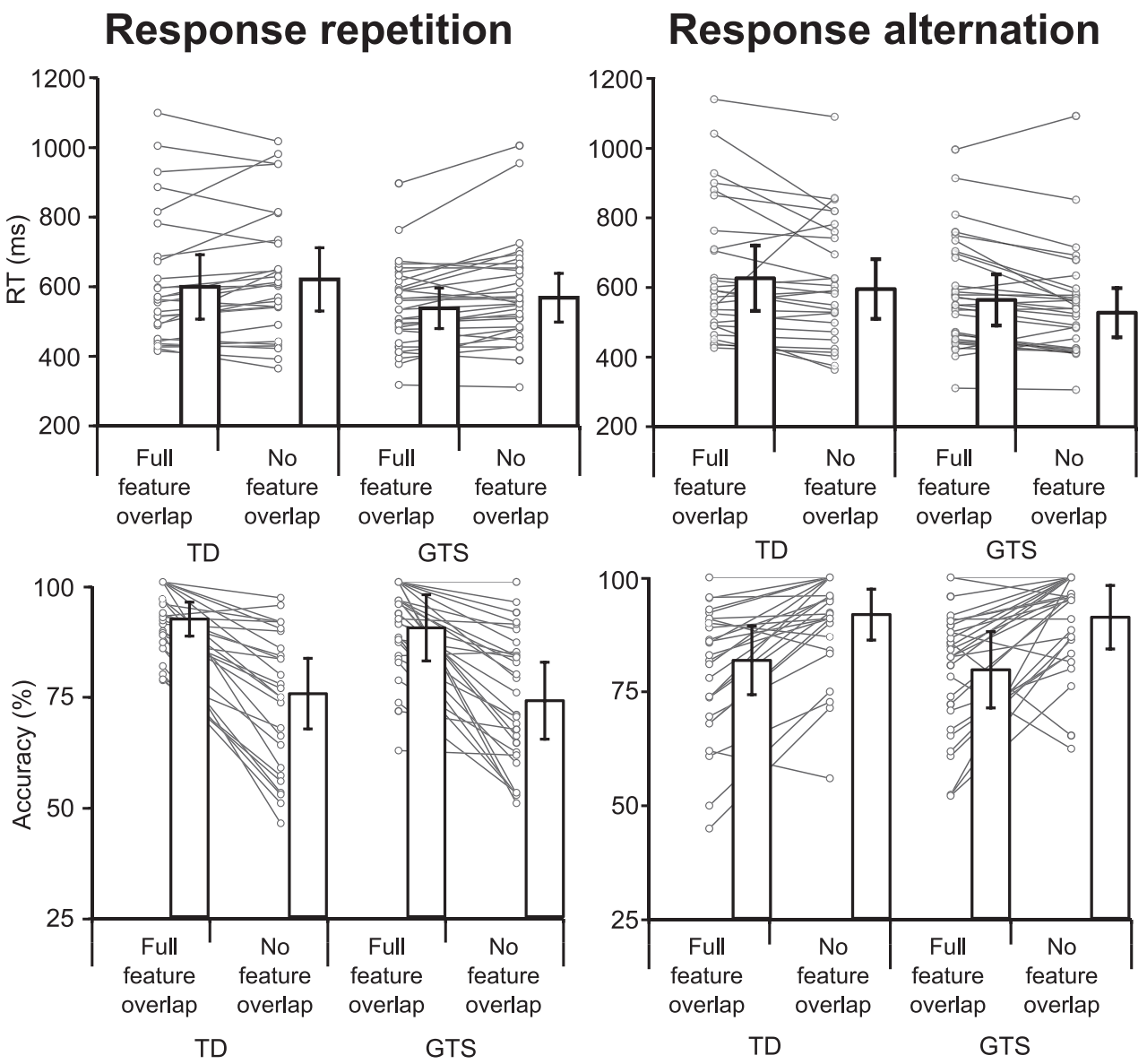


Figure 2. Behavioral results. Reaction time (RT) data (top) and accuracy (bottom) are shown in patients with Gilles de la Tourette syndrome (GTS) and typically developing (TD) youths as a function of feature overlap (full feature overlap vs. no feature overlap) and response repetition vs. response alternation. Individual data points are presented according to Weissgerber *et al.* (81). In addition, mean values and standard deviation are given in histograms.

alternation condition ($F_{3,174}$ = 32.19; $p < .001$; η_p^2 = 0.357; BF_{10} = 0.0009), with clear differences between the full feature overlap condition and the no feature overlap condition. Again, no further modulating effect of group was evident ($F_{3,171}$ = 0.09; p = .961; η_p^2 = 0.002; p(H0ID) = .99), with the BF also underlining an absence of the modulatory effects of group. Bonferroni-corrected pairwise comparisons revealed that each feature overlap level differed from the other feature overlap levels (all $p < .001$). Apart from the main effect feature overlap for the accuracy data where the Bayes analyses were not consistent ($F_{3,171}$ = 5.39; $p < .001$; η_p^2 = 0.086), there were, generally, no main effects of group, feature overlap, and response (all Fs < 0.69, $p > .40$; all p(H0ID)s < .1). Thus, unlike findings in adults with GTS (13), there was no evidence for an alteration of event file binding effects in children/adolescents with GTS. Rather, behavioral binding effects were similar in TD youths and children/adolescents with GTS.

Neurophysiological Data

Because the binding effect is maximal between the no feature overlap condition and the full feature overlap condition, we considered these feature overlap conditions in the analysis of binding effects in theta and beta band activity, as done in previous studies (13,24,27). For the statistical analysis, we calculated the binding effect between the full feature overlap

minus and the feature overlap condition separately for response repetition and alternation trials. For methodological details on this procedure, refer to the Supplement.

Data from the theta band are shown in Figures 3 and 4 for response alternation and response repetition trials, respectively.

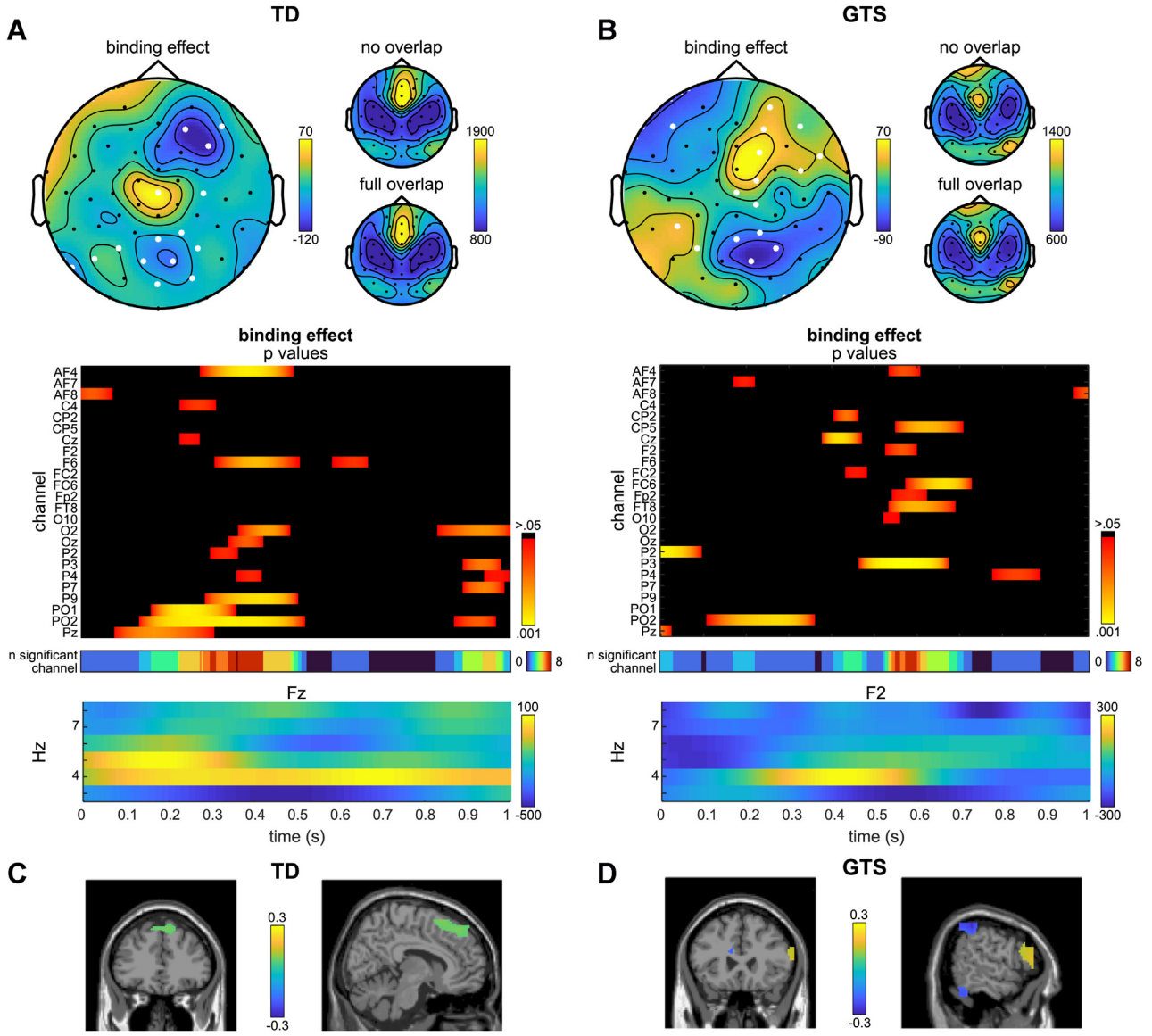


Figure 3. Alternation condition—theta band power and source activity. The data for the typically developing (TD) group are given on the left and for the Gilles de la Tourette (GTS) group on the right side. **(A)** and **(B)** show groupwise theta band topography plots for the binding effect (full overlap − no overlap condition), the no overlap, and the full overlap conditions. The averaged power of the time window of 0 to 1000 ms relative to stimulus onset is depicted. (Top) White dots indicate channels with significant power differences ($p < .05$) between the no overlap and full overlap conditions in this time window. Colors denote power, with warmer colors denoting higher power values. (Middle) p values of t tests comparing full overlap and no overlap conditions. t tests were conducted for each sample, i.e., time points in the time window of 0 to 1000 ms relative to stimulus onset. Channels are given on the y-axis, time in seconds on the x-axis. Only channels showing significant differences are depicted. The number of significant channels at each time point, denoted by color, is depicted below. (Bottom) Power plot of the binding effect for the channel showing the largest power difference. Frequency in Hz is given on the y-axis, time in seconds on the x-axis. Colors denote power, with warmer colors denoting higher power values. **(C)** and **(D)** show the results of the dynamic imaging of coherent sources beamformer contrasting full overlap and no overlap conditions. Only source activity that exceeds a threshold of 70% of the respective maximum source activity is shown. Yellow colors denote positive source activity differences; blue colors denote negative source activity differences. Assuming that the full feature overlap condition in alternation trials is cognitively more demanding, positive source activity differences (i.e., larger activity in the full feature overlap condition) are expected. For the TD group **(C)**, theta power differences are associated with positive differences in the superior frontal gyrus (Brodmann area [BA] 6, BA 8) encompassing supplementary motor area and premotor areas. For the GTS group **(D)**, theta power differences are associated with positive differences in the right inferior frontal cortex (BA 46).

For the theta band activity, significant binding effects were observed in response repetition and response alternation trials at several electrode sites, and TF plots revealed clear theta band activity in the TD group (Figures 3A, 4A) and the GTS group (Figures 3B, 4B). The beamforming analysis (contrast: full feature overlap vs. no feature overlap) revealed that in the

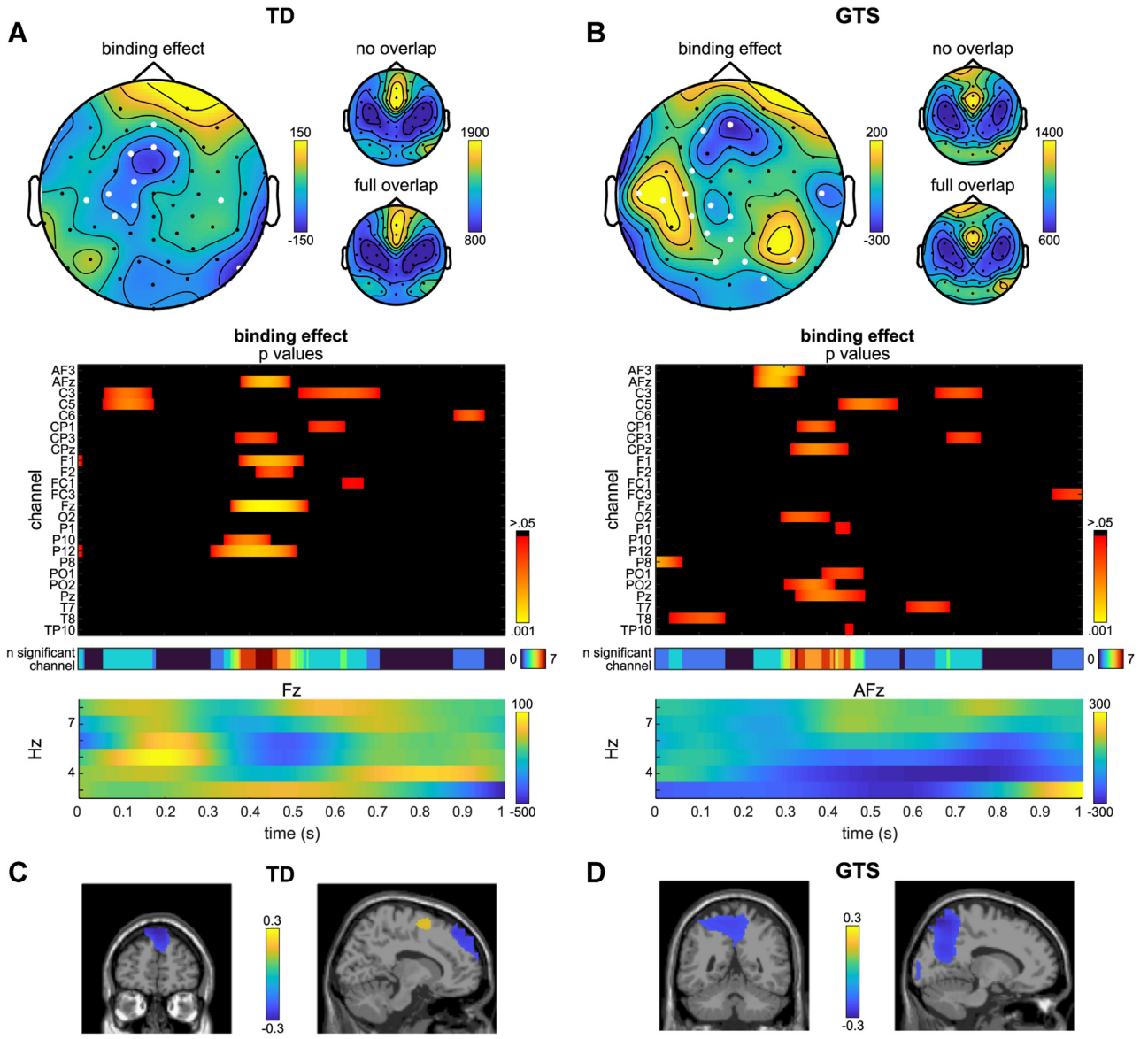
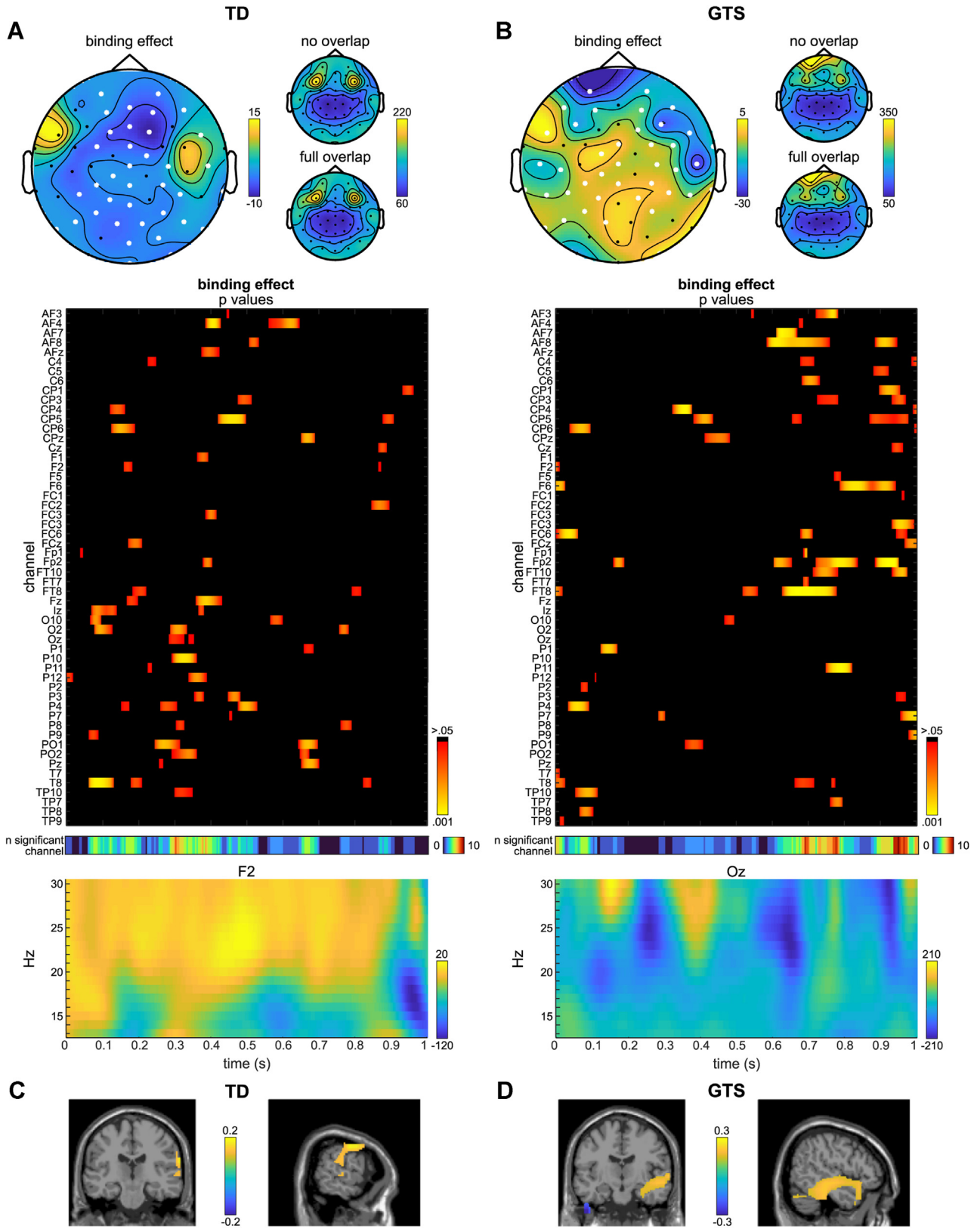


Figure 4. Repetition condition—theta band power and source activity. The data for the typically developing (TD) group are given on the left and for the Gilles de la Tourette (GTS) group on the right column. **(A)** and **(B)** show groupwise theta band topography plots for the binding effect (full overlap − no overlap condition), the no overlap, and the full overlap conditions. The averaged power of the time window of 0 to 1000 ms relative to stimulus onset is depicted. (Top) White dots indicate channels with significant power differences ($p < .05$) between the no overlap and full overlap conditions in this time window. Colors denote power, with warmer colors denoting higher power values. (Middle) p values of t tests comparing full overlap and no overlap conditions. t tests were conducted for each sample, i.e., time points in the time window of 0 to 1000 ms relative to stimulus onset. Channels are given on the y-axis, time in seconds on the x-axis. Only channels showing significant differences are depicted. The number of significant channels at each time point, denoted by color, is depicted below. (Bottom) Power plot of the binding effect for the channel showing the largest power difference. Frequency in Hz is given on the y-axis, time in seconds on the x-axis. Colors denote power, with warmer colors denoting higher power values. **(C)** and **(D)** show the results of the dynamic imaging of coherent sources beamformer contrasting full overlap and no overlap conditions. Only source activity that exceeds a threshold of 70% of the respective maximum source activity is shown. Yellow colors denote positive source activity differences; blue colors denote negative source activity differences. Assuming that the no feature overlap condition in repetition trials is cognitively more demanding, negative source activity differences (i.e., larger activity in the no feature overlap condition) are expected. For the TD group **(C)**, theta power differences are associated with negative differences in the superior frontal gyrus (Brodmann area [BA] 6, BA 8) encompassing supplementary motor area and premotor areas. For the GTS group **(D)**, theta power differences are associated with negative differences in superior and inferior parietal areas (BA 7) including the precuneus.


A
TD
binding effect
no overlap
full overlap
15
-10
220
60
B
GTS
binding effect
no overlap
full overlap
5
-30
350
50
binding effect
p values
channel
>.05
.001
n significant channel
0
10
F2
Oz
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time (s)
20
-120
210
-210
C
TD
0.2
-0.2
D
GTS
0.3
-0.3

TD group, binding effects in the theta band were associated with activation differences in the superior frontal gyrus (Brodmann area [BA] 6, BA 8) encompassing supplementary motor area (SMA) and premotor areas. This was the case for binding effects in response repetition trials and response alternation trials (Figures 3C, 4C). In the GTS group, different regions were activated, and the pattern of activation was not consistent across response repetition and response alternation trials. The GTS group revealed extended activations of superior and inferior parietal areas (BA 7) for binding effects in the response repetition trials. In response alternation trials, binding effects were associated with activity differences in the right inferior frontal cortex (BA 46) (Figures 3D, 4D). Functional neuroanatomical regions associated with binding effects in the theta band thus clearly differed between the TD group and the GTS group. Moreover, the GTS recruited different brain regions to process event file binding effects in response repetition and alternation trials. Data from the beta band are shown in Figures 5 and 6 for response alternation and response repetition trials, respectively.

For the beta band activity also, significant binding effects were observed in response repetition and response alternation trials, and TF plots revealed clear activity in the TD group and the GTS group (Figures 5A, B and 6A, B). Yet, unlike theta band activity, event file binding effects in the beta band were observed in similar brain regions in both groups: in response alternation trials, superior and middle temporal activity (BA 21, BA 22) was evident in both groups (Figures 5C, D); the TD group also revealed right inferior parietal cortex activity (BA 40). Left inferior parietal cortex activity (BA 40) was revealed during repetition trials in the TD group (Figure 6C). In the GTS group, binding effects in beta band activity were associated with activations in superior parietal and frontal regions (BA 7, BA 6) (Figure 6D).

DISCUSSION

In the current study, we examined the functional neuroanatomical organization of EEG theta and beta band activity during perception-action integration in children and adolescents with GTS. The study was motivated by clinical, neurodevelopmental, and neurophysiological considerations. The latter suggested that the functional organization, especially of theta band activity, differs between children/adolescents with GTS and those with TD.

The behavioral data show robust event file binding effects in both groups, as indicated by substantial interaction effects of the factors feature overlap and response alternation/repetition replicating the principal effects produced by the task and predicted by the TEC framework (16,24,27). Previous data, using the same experimental approach in adults, however, showed that perception-action integration is stronger in GTS (13). This was not the case in the current study examining children and adolescents with GTS. Basic research in healthy controls revealed that event file binding effects are stronger in children than in young adults (57), indicating a maturation of event file binding. The fact that binding is stronger in adults with GTS than in age-matched controls suggests less flexible event file processing in them (13). The finding that this is not the case in children/adolescents with GTS (substantiated by Bayesian analyses) at the behavioral level is in keeping with the notion that the development of certain cognitive functions lags behind in GTS (58,59). Importantly, however, this is the case only for those patients with persisting GTS who continue to be symptomatic beyond adolescence, but not for the GTS population as a whole. It has to be considered that increased event file binding has previously been shown in adolescents with GTS in a Go/NoGo task (26), indicating that the strength of binding in GTS has different developmental trajectories depending on whether response inhibition or response selection processes are involved. The lack of maturation of event file processing in adults with GTS (10,13) might be one determinant of tic persistence. However, this can only be confirmed on the basis of longitudinal data in larger GTS cohorts.

The findings of the present data set in conjuncture with previous results (13) suggest that behavioral differences in event file binding in GTS become apparent predominantly in early adulthood but not necessarily in adolescence, which underscores the view of GTS as a typically transient neurodevelopment disorder. This is not unprecedented. For instance, using a mental chronometry paradigm (60), it was shown that the experience of volition is disturbed in adults with GTS (58) but not in children with GTS (59). Moreover, a longitudinal follow-up study showed that the experience of volition developed in a cohort of GTS patients re-examined 5.5 years later (61). Yet, such learning was impaired in GTS patients with longer disease duration (61), suggesting that developmental abnormalities become apparent particularly in patients not showing symptom remission. These data along

Figure 5. Alternation condition—beta band power and source activity. The data for the typically developing (TD) group are given in the left column and for the Gilles de la Tourette (GTS) group in the right column. **(A)** and **(B)** show groupwise beta band topography plots for the binding effect (full overlap − no overlap condition), the no overlap, and the full overlap conditions. The averaged power of the time window of 0 to 1000 ms relative to stimulus onset is depicted. (Top) White dots indicate channels with significant power differences ($p < .05$) between the no overlap and full overlap conditions in this time window. Colors denote power, with warmer colors denoting higher power values. (Middle) p values of t tests comparing full overlap and no overlap conditions. t tests were conducted for each sample, i.e., time points in the time window of 0 to 1000 ms relative to stimulus onset. Channels are given on the y-axis, time in seconds on the x-axis. Only channels showing significant differences are depicted. The number of significant channels at each time point, denoted by color, is depicted below. (Bottom) Power plot of the binding effect for the channel showing the largest power difference. Frequency in Hz is given on the y-axis, time in seconds on the x-axis. Colors denote power, with warmer colors denoting higher power values. **(C)** and **(D)** show the results of the dynamic imaging of coherent sources beamformer contrasting full overlap and no overlap condition. Only source activity that exceeds a threshold of 70% of the respective maximum source activity is shown. Yellow colors denote positive source activity differences; blue colors denote negative source activity differences. Assuming that the full feature overlap condition in repetition trials is cognitively more demanding, positive source activity differences (i.e., larger activity in the full feature overlap condition) are expected. For the TD group **(C)**, beta power differences are associated with positive differences in the superior and middle temporal areas (Brodmann area [BA] 21, BA 22) and the left inferior parietal cortex (BA 40). For the GTS group **(D)**, beta power differences are associated with positive differences in superior and middle temporal activity (BA 21, BA 22).

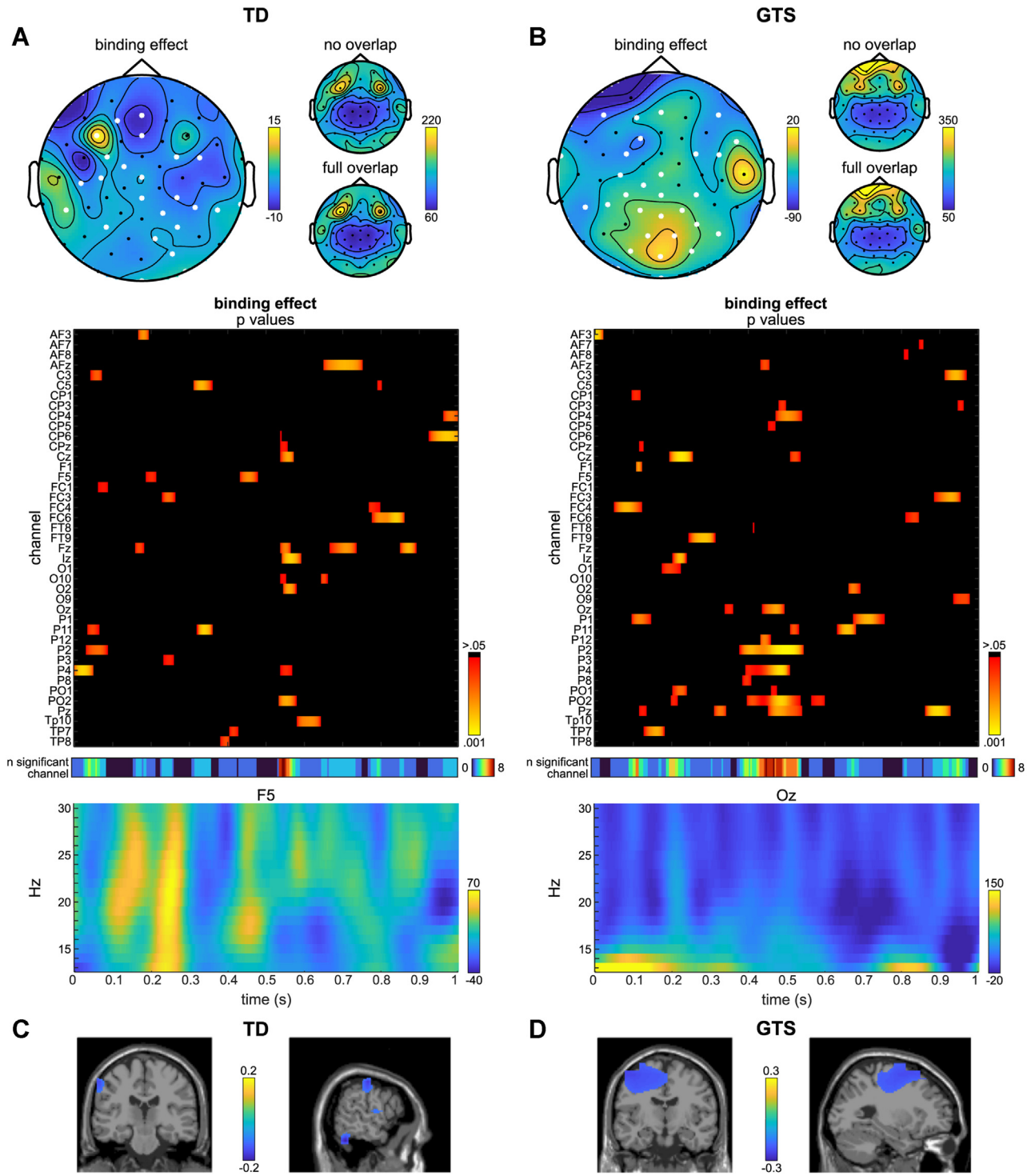

Figure 6. Repetition condition—beta band power and source activity. The data for the typically developing (TD) group are given in the left column and for the Gilles de la Tourette (GTS) group in the right column. **(A)** and **(B)** show groupwise beta band topography plots for the binding effect (full overlap − no overlap condition), the no overlap, and the full overlap conditions. The averaged power of the time window of 0 to 1000 ms relative to stimulus onset is depicted. (Top) White dots indicate channels with significant power differences ($p < .05$) between the no overlap and full overlap conditions in this time window. Colors denote power, with warmer colors denoting higher power values. (Middle) p values of t tests comparing full overlap and no overlap conditions. t tests were conducted for each sample, i.e., time points in the time window of 0 to 1000 ms relative to stimulus onset. Channels are given on the y-axis, time in seconds on the x-axis. Only channels showing significant differences are depicted. The number of significant channels at each time point, denoted by color, is depicted below.

with findings of event coding in GTS [present study and previous data (13)] underscore that developmental trajectories are crucial for the understanding of GTS and require further longitudinal investigations.

Although, at a behavioral level, event file coding in the cohort of children and adolescents with GTS studied here did not differ from that in TD, the underlying pattern of neural oscillatory activity in the theta band was profoundly different in the two groups. At the electrode level, manifold activity at different electrode sites and time points was evident in the theta and beta frequency bands. This is well in line with the concept of TEC, according to which event files processing occurs in a distributed network, which was also shown previously by our group (24,27). At the source level, binding effects in the theta band were associated with activation differences in the SMA/premotor areas in the TD group in both response repetition and response alternation trials. Superior frontal areas have previously been shown to be associated with event file coding processes in healthy controls (36). In contrast, there was activation of superior and inferior parietal areas (BA 7) in the response repetition and right inferior frontal cortex (BA 46) activity in the response alternation trials in GTS. Interestingly, in GTS, the SMA appears to play a prominent role in tic severity (62) and tic generation (63), with the SMA being active before tic onset (64–66). Such engagement of the SMA in tic-related processes probably limits this brain region's processing resources, so that alternative areas are instead recruited for event file processing, including the inferior parietal areas and the right inferior frontal cortex. The latter was activated during response alternation trials, i.e., when response switching was required and for which inhibitory control processes play an important role (67–70). The inferior frontal gyrus is implicated in response inhibition (71). In GTS, this region likely subserves voluntary tic inhibition (72). Therefore, GTS patients may also readily recruit this area in situations when inhibitory control is required in other contexts (e.g., in the response alternation condition in the event file paradigm). The finding that during theta band–related event file coding different areas were recruited in patients with GTS and controls may well reflect known differences in the functional/structural brain organization between children/adolescents with GTS and those with TD (22), likely affecting the integration of information essential during event file processing (23–27). This is reasonable, considering evidence that especially theta band activity is central for top-down cognitive control regulation and information integration across distant brain areas (28–30), which has also been shown for event file binding (27). Interestingly, the finding of a functionally different organization of brain regions involved in theta-associated processing of event files dovetails with findings that theta band activity in particular is relevant for the pathophysiology of GTS (31,32,73–80). This importance is corroborated by the data obtained from beta band activity not showing gross differences in functional brain area activation pattern during event file binding. As mentioned, beta band activity is important for the contribution of rule-guided processing (39) and reactivation/retrieval of memory traces (40) to event file binding effects (41). On the basis of the current findings, it may be speculated that the functional neuroanatomical implementation of these processes during event file coding is not strongly altered in children/adolescents with GTS. However, conceptually, binding effects might be separated into integration and retrieval processes (41). On the basis of the present study and the experimental paradigm used, it cannot be stated whether qualitative differences in functional brain organization between patients with GTS and healthy controls reflect differences in the relative contribution of integration versus retrieval. This is a limitation of the study that should be addressed in the future. Moreover, future studies should investigate how far this relates to modulations in the severity of clinical symptoms in GTS and also whether, and if so, how, the pattern changes intraindividually during the developmental course of this disorder. Another limitation is that the methods used are not suitable to capture basal ganglia activity during event file coding, which may also be relevant in the context of GTS.

To conclude, behavioral data of the present study and previous related work suggest that maturation of perception-action integration processes lags behind in persisting GTS but not the GTS population as a whole, underscoring that developmental trajectories are crucial for the understanding of GTS. This calls for longitudinal investigations of GTS cohorts. The different pattern of neural oscillatory activity in the theta band in GTS confirms known differences in the functional/structural brain organization in these patients. The results also corroborate the importance of theta band oscillations for the integration of information across distant brain areas and, likewise, the role of theta band activity for the understanding of GTS.

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ARTICLE INFORMATION

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(Bottom) Power plot of the binding effect for the channel showing the largest power difference. Frequency in Hz is given on the y-axis, time in seconds on the x-axis. Colors denote power, with warmer colors denoting higher power values. **(C)** and **(D)** show the results of the dynamic imaging of coherent sources beamformer contrasting full overlap and no overlap condition. Only source activity that exceeds a threshold of 70% of the respective maximum source activity is shown. Yellow colors denote positive source activity differences; blue colors denote negative source activity differences. Assuming that the no feature overlap condition in repetition trials is cognitively more demanding, negative source activity differences (i.e., larger activity in the no feature overlap condition) are expected. For the TD group **(C)**, beta power differences are associated with negative differences in the left inferior parietal cortex (Brodmann area [BA] 40). For the GTS group **(D)**, beta power differences are associated with negative differences in superior parietal and frontal regions (BA 7, BA 6).

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