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Tourette syndrome as a motor disorder revisited – Evidence from action coding

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ABSTRACT

Because tics are the defining clinical feature of Tourette syndrome, it is conceptualized predominantly as a motor disorder. There is some evidence though suggesting that the neural basis of Tourette syndrome is related to perception–action processing and binding between perception and action. However, binding processes have not been examined in the motor domain in these patients. If it is particularly perception–action binding but not binding processes within the motor system, this would further corroborate that Tourette syndrome it is not predominantly, or solely, a motor disorder.

Here, we studied N = 22 Tourette patients and N = 24 healthy controls using an established action coding paradigm derived from the Theory of Event Coding framework and concomitant EEG-recording addressing binding between a planned but postponed, and an interleaved immediate reaction with different levels of overlap of action elements. Behavioral performance during interleaved action coding was normal in Tourette syndrome. Response locked lateralized readiness potentials reflecting processes related to motor execution were larger in Tourette syndrome, but only in simple conditions. However, pre-motor processes including response preparation and configuration reflected by stimulus-locked lateralized readiness potentials were normal. This was supported by a Bayesian data analysis providing evidence for the null hypothesis. The finding that processes integrating different action-related elements prior to motor execution are normal in Tourette syndrome suggests that Tourette it is not solely a motor disorder. Considering other recent evidence, the data show that changes in "binding" in Tourette syndrome are specific for perception–action integration but not for action coding.

1. Introduction

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterized by multiple motor and phonic tics (American Psychiatric Association, 2013). Since tics as motor phenomena are the defining diagnostic feature, GTS has long been considered a prototype motor or movement disorder. Importantly, treatment efficacy has been determined on the basis of scales and scores focusing on tics, i.e. motor output (Pringsheim et al., 2019). However, it has become clear that conceiving GTS as a pure motor disorder falls short of its complex nature.

Most adult GTS patients report premonitory urges preceding tics (Leckman et al., 1993), which typically become attenuated following the execution of tics (Leckman, 2002) suggesting that the interaction between perceptual and motor processes plays an important role in GTS. Other features in GTS include hypersensitivity to external stimuli (Belluscio et al., 2011) most likely reflecting alterations in perceptual processing (Biermann-Ruben et al., 2012), abnormal sensorimotor interaction (Orth, 2009; Orth et al., 2005) and changes in the structural composition of cortical sensory areas (Draper et al., 2016; Sowell et al., 2008; Worbe et al., 2010). Furthermore, tics are strongly influenced by

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attention (Brandt et al., 2015; Herrmann et al., 2019; Misirlisoy et al., 2015) and can, at least partially, be controlled (Ganos et al., 2015). Given that patients have an increased tendency to form habits (Brandt et al., 2016a, 2016b; Delorme et al., 2016; Kleimaker et al., 2020a), a relation between motor learning and tic occurrence has been suggested and is supported by observations of a high prevalence of tics in people professionally engaging in activities requiring the execution of habitual, over-learned behavior, for instance musicians (Tunc and Münchau, 2017). Taken together, these data suggest that GTS is a complex disorder where in addition to motor processes also perception–action integration and cognitive control processes play a role (Beste et al., 2016; Beste and Münchau, 2018; Buse et al., 2016, 2018; Kim et al., 2019; Kleimaker et al., 2020a, 2020b, 2020c; Petruo et al., 2019, 2020). This view has been corroborated by experimental work showing that in GTS associations between sensory and motor processes are abnormally strong and that this (partly) predicts tic frequency (Kleimaker et al., 2020b; Weissbach et al., 2020). Against this background it appears likely that abnormalities of restructuring of perception–action associations rather than action coding per se are a core feature of GTS. However, this notion would only be tenable if it was shown experimentally that action coding, i.e. the integration of different motor elements constituting an action, is indeed undisturbed in GTS.

To examine how the integration of different motor elements constituting an action is modulated in GTS, we related to the Theory of Event Coding (TEC) framework (Hommel, 2009; Hommel et al., 2001). This framework addresses how different features constituting representations of actions are integrated. Considering action, the central assumption is that different features constituting an action (e.g. which finger of what hand is to use with a specific force) are stored in so-called action files. Stoet and Hommel (1999) developed an experimental paradigm to study feature binding in action files. The experimental logic is that activating an action is more than simply activating various features defining an action. Rather, different codes belonging to an action have to be integrated, i.e. bound to each other. This integration of features entails 'code occupation' effects (Stoet and Hommel, 1999). For example, when planning to carry out a right arm movement, all features related to/defining this planned movement become activated – including the feature '*right*'. Importantly, until this movement has not been fully executed the codes (e.g. '*right*') is reserved for this specific movement. This makes it difficult to execute another action that also uses the '*right*' code, but is constituted by various other action features than the previous one. Such an overlap between a planned and a to-be-performed action impairs performance (Colzato et al., 2006a; Stoet and Hommel, 1999). Based on these theoretical considerations, the experimental approach to test the integration of different motor elements uses an ABBA design for response execution, in which an action (A) is planned, but its execution has to be postponed until another action (B) was planned and performed. In the experiment, performance is better (reaction times (RTs) are shorter and more accurate), when there is no feature overlap between the A and the B motor response. Using EEG methods, the processes outlined above can be examined using lateralized readiness potential (LRP) (Coles, 1989; Gratton et al., 1988) – an index of response activation and preparation (Coles, 1989; de Jong et al., 1988) generated in motor cortical areas (Leuthold and Jentzsch, 2001). Two forms of LRPs can be distinguished – the stimulus-locked (s-LRP) and response locked (r-LRP). The s-LRP measures processes preceding motor execution (i.e., pre-motor processes); the r-LRP reflects processes related to the subsequent motor execution (Beste et al., 2009; Coles, 1989; Masaki et al., 2004; Osman et al., 1995; van der Lubbe et al., 2001; Wild–Wall et al., 2003). Code-occupation processes reflecting the integration of different action-related features precede the overt motor response. Therefore, particularly the s-LRP will be important to examine to tests whether action binding is altered in GTS. Generally, the s-LRP will be larger and its onset earlier when there is no code-occupation between actions A and B, compared to conditions when features are shared between actions A and B, as recently shown in healthy adult populations (Takacs et al., 2020). Previous findings suggest that when pre-motor inhibition is demanding, a correct negative LRP deflection is preceded by a short-lasting positive deflection that indicates the activation of the wrong response (Beste et al., 2010; Bryce et al., 2011; Falkenstein et al., 2006; Gratton et al., 1992; Stürmer et al., 2002) – in our case the response A when there is action file feature overlap between response A and B. However, it cannot be excluded that also motor execution processes per se are modulated by the experimental variations. Therefore, we also explore, how far the r-LRP is modulated by experimental variations. If increased binding as shown to be evident for perception–action integration in GTS (Kleimaker et al., 2020b) is also evident within the motor domain, then there should be an interaction between the overlap in motor elements constituting an action and group. This is also possible since, at present, TEC draws no distinctions in binding mechanisms between action files and event files. Thus, a hyper-binding in the motor domain should be reflected by stronger differences between overlapping and non-overlapping motor feature codes in GTS patients than in controls. Yet, in the case that there is no such interaction and sufficient evidence for the null hypothesis, this would suggest that motor feature binding, unlike perception–action binding is unimpaired in GTS. If so, this might have repercussions for the conceptualization of GTS and also for clinical studies suggesting that in addition to motor readouts more sophisticated measures focusing on perception–action integration should also be used to capture the effectiveness of interventions. Along the same lines this will also have repercussion on TEC, since such a pattern of results together with previously observed hyper-binding in event files in GTS (M. Kleimaker et al., 2020b) will suggest that binding mechanism differ between action files and event files.

2. Methods

2.1. Participants

N = 22 GTS patients (13 males and 9 females, mean age 32.5 years ± 11.2 years SD, range: 18–50 years) participated in the study. They were recruited from the specialized GTS outpatient clinic in the Center for Integrative Psychiatry at the University Medical Center Schleswig-Holstein, Campus Lübeck. Clinical assessment was carried out by two experienced neurologists (A.M. and M.K.). Patients were diagnosed according to DSM-5 criteria (American Psychiatric Association, 2013). Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was used for assessing psychiatric comorbidities. Lifetime likelihood of a diagnosis of GTS was assessed with the Diagnostic Confidence Index (Robertson et al., 1999). Tic severity was assessed using the Yale Global Tic Severity Score (YGTSS) (Leckman et al., 1989), premonitory urges using the Premonitory Urge for Tics Scale (PUTS) (Woods et al., 2005). Standardized video recordings were carried out using the Modified Rush Videotape Rating (Goetz et al., 1999). All videos were scored independently by A.M. and M.K. In case of discrepancy, the video was reviewed jointly and a consensus was reached. Furthermore, motor tic frequency (motor tics/minute) was computed. Obsessive compulsive disorder (OCD) and mood disorders were tested using the respective modules of the German version of the Structured Clinical Interview for DSM-5 Axis I Disorders (Beesdo-Baum et al., 2019). Attention deficit hyperactivity disorder (ADHD) was assessed according to DSM-5-TR. OCD symptoms were scored using the Yale Brown Obsessive Compulsive Scale (YBOCS) (Goodman et al., 1989) and ADHD symptoms using the ADHD-Index and the DSM-ADHD Scale of the German version of the Conners Adult ADHD Rating Scale (Christiansen et al., 2013). IQ was determined using the German version of the fourth edition of the Wechsler Adult Intelligence Scale (Hartman, 2009). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

We also studied N = 24 healthy controls (HC) (12 males and 9 females, mean age 30.0 years ± 8.7 years SD, range: 19–49 years). Gender ($X^2(1, 46)$, = 0.38, p = .536, BF_{01} = 2.4) and age ($W(1,40)$ = 0.69, p =

.496, $d = 0.204$, $BF_{01} = 2.8$) did not differ between groups. Healthy controls were also assessed with a view to neurological and psychiatric diseases. Psychiatric co-morbidities were assessed with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). According to the interview, no HC had clinically relevant psychiatric symptomatology at the time of testing. Participants gave written informed consent to participate in the study in accordance with the Declaration of Helsinki (1964). The study was approved by the Ethics Committee of the University of Lübeck (17–156).

2.2. Task

Action coding was studied using the previously established task by Colzato (Colzato et al., 2006b; Stoet and Hommel, 1999) (Fig. 1).

Participants were seated in front of a 17 in. TFT screen and practiced the task for at least 40 trials prior to the experiment. During the task, the participants completed 256 trials and took two breaks after 80 trials, the lengths of which was self-determined. At the beginning of the task, a fixation cross (10.6 mm) was displayed for 50 ms. Then, the screen turned black for 2000 ms and stimulus 1 (S1) appeared. S1 was a right- or left-pointing arrow head combined with an asterisk either above or below it (35 mm). Participants were instructed not to respond immediately to S1, but to keep the required response (Planned Responses, see below) in store. After 2000 ms, the screen turned black again for 50 ms, followed by stimulus 2 (S2), which was either a "$" or "#" sign presented for 200 ms. As soon as S2 was presented, participants were required to respond by pressing "6" on the computer keyboard's numeric keypad with the right index finger in case a "#" was shown and by pressing 4 with the left index finger in case a "$" appeared (=Immediate Response). Next, the Planned Responses determined by S1 had to be carried out immediately following completion of the Immediate Response. Planned Responses comprised a sequence of three button presses. First, participants had to react according to the direction of the arrow head by pressing 4 with the left index finger in case S1 was a left-pointing arrow head or by pressing 6 with the right index finger in case the arrow head was right-pointing ("home keys"). Second, the button above (1 or 3) or below (7 or 9) the home key had to be pressed corresponding to the position of the asterisk. Third, the corresponding home key had to be pressed again. Thus, the Planned Responses had to be carried out as a response chain. Since the Immediate Response and the Planned Responses could either be carried out with the right or left index finger, there were variations in the overlap of motor elements constituting an action in compatible and incompatible trials. In compatible trials, the motor elements matched (left-left or right-right), whereas this was not the case in incompatible trials (left–right or right-left).

2.3. EEG processing

The equipment and the parameters of EEG measurement were identical across the participating labs in Lübeck and Dresden. EEG was recorded from 60 Ag/AgCl electrodes and processed as described previously (Kleimaker et al., 2020b). Electrodes were mounted in an elastic cap with equidistant layout (EasyCap, Wörthsee, Germany). The data recoding was conducted with a "BrainAmp" amplifier and the "Brain Vision Recorder" software (Brain Products, Gilching, Germany). Sampling rate was 500 Hz and the ground and reference electrodes were positioned at coordinates of $\theta = 58$, $\varphi = 78$ and $\theta = 90$, $\varphi = 90$ (Fpz). The collected data were pre-processed in Brain Vision Analyzer (Brain Products, Gilching, Germany); i.e. data were down-sampled to 256 Hz and band-pass filtered (IIR, 0.5–20 Hz, order of 8), before it was re-referenced to the average of all electrodes and technical artifacts were discarded by manual inspection. Remaining physiological artifacts, such as horizontal and vertical eye movements, blinks, and heartbeat artifacts, were corrected using an independent component analysis (ICA, Infomax algorithm) before data were segmented. EEG segments were created both locked to stimulus S2 (comprising a time frame from 500 ms prior to 1500 ms after stimulus S2) and locked to the Immediate Response (comprising a time frame from 500 ms prior to 1500 ms after the response to S2). In addition, different segments were created for

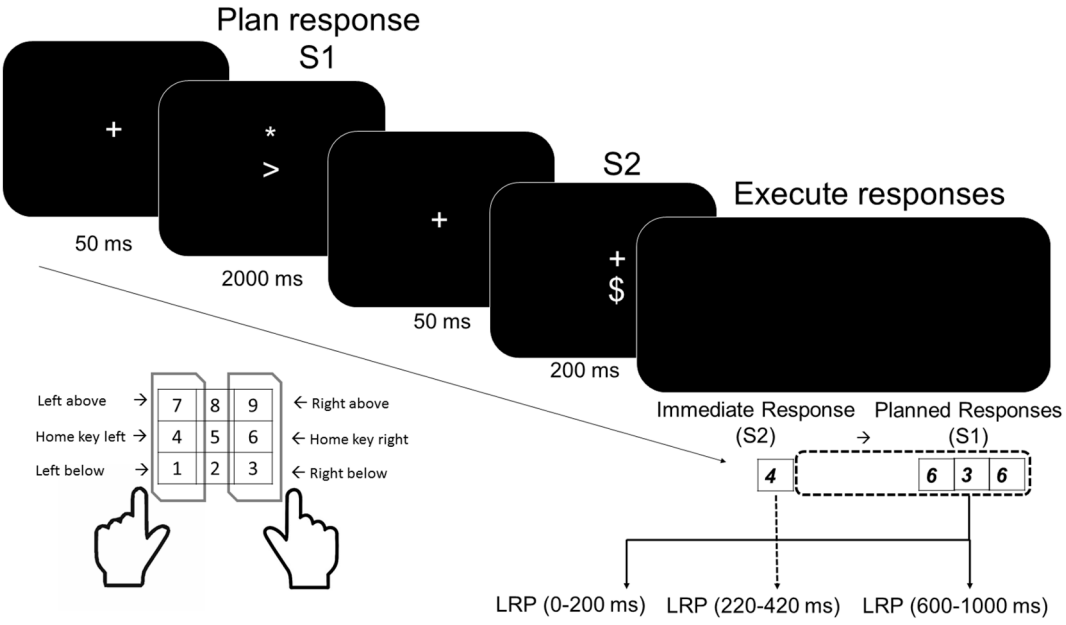

Fig. 1. Task design and data analysis plan. The figure represents the order of the stimuli during the trial including the timing of events. The timing information and the layout of the response buttons are displayed. Participants were required to use their left and right index fingers corresponding to the side of response. The example shows a trial of the no motor element overlap condition. Immediate Response has to be executed on the left side (button '4') and Planned Response on the right side (buttons '6', '3', '6'). RT of the Immediate Response to S2 was measured from the onset of S2. A rectangle with dashed lines represents the cumulated RT of the Planned Response to S1, i.e. from the release of the Immediate Response button to the release of the last button of the Planned Responses. The neurophysiological activations linked to different response windows are marked by arrows. First, the prepotent activation of the Planned Responses are represented (LRP 0–200 ms), which has to be overwritten by the Immediate Response (LRP 220–420 ms), and finally, the Planned Responses can be executed (LRP 600–1000 ms).

compatible and incompatible trials as well as for left- and right-sided responses considering possible motor lateralization effects. Only trials with correct responses (both Planned and Immediate) were included. Next, trials were discarded that showed amplitudes higher than 150 μV or lower than − 150 μV as well as activities lower than 0.5 μV for at least 100 ms within a time window of 500 prior to 1500 ms after S2. Furthermore, current source density transformation (Kayser and Tenke, 2015) was carried out to enable a reference-free evaluation of the ERP data. Then, baseline correction within a time window −300 to 0 ms before Immediate Response was applied and single-subject averages were computed for each condition. We examined the LRP that was calculated according to Coles (1989). The resulting potentials are expected to be maximal contralaterally to the responding finger. Contralateral and ipsilateral potentials were quantified above the C3 and C4 electrode channels, following the conventional analysis of LRPs (Coles, 1989). Segments locked to S2 (stimulus locked LRP; s-LRP) represent activation of the Immediate Response. According to Coles, in stimulus locked segments, a negative deviation indicates the activation of the correct response, whereas a positive deviation represents an incorrect response (Coles, 1989). The mean amplitudes of LRP signals were analyzed within time windows 0 to 200 ms, 220 to 420 and 600 to 1000 ms after S2. In the main activation window (220–420 ms), the fractional peak method (30%) was used to calculate the onset of the negative deviation.

Furthermore, after inspecting the response-locked waveform, we identified a negative deviation in the time window preceding the Immediate Response (−300 to 0 ms). This negativity represents the response-locked LRP (r-LRP), a neurophysiological marker of lateralized response execution (Coles, 1989). Within this interval, the mean amplitude was quantified for each single subject. Thus, at the neurophysiological level, action coding, i.e. response activation and preparation, represented by the s-LRP and response execution reflected by the r-LRP were studied separately.

2.4. Data analyses

Statistical analyses were performed with JASP 0.11.1. Mean accuracy (percentage of correct responses) and mean reaction time (RT) data for the correct responses were calculated for each participant and each condition. Latencies of the Immediate Responses were determined from S2 onset. Regarding RTs for the Planned Responses, the first part of the response chain was measured from the offset of the Immediate Response, i.e. the release of the button, the second part from the 1st part of the response chain of the Planned Responses, and the 3rd part was measured from the 2nd part of Planned Responses. As an overall measure of the Planned Responses, cumulative RTs were calculated between the first and the third part of the response chain, i.e. until the release of the last button. Similarly, average accuracy for the three consecutive Planned Responses was calculated.

EEG data was quantified as mean activity in the time windows of 0–220 ms, 220–420 ms, and 600–1000 ms on the s-LRP channel. The time windows were determined to match the response activations of the Immediate Response and the Planned Responses (Fig. 1). Previous research showed that a correct negative LRP deflection is often preceded by a shorter positive deflection that indicates an incorrect response activation (Beste et al., 2008; Bryce et al., 2011; Gratton et al., 1992; Takacs et al., 2020). Since participants were instructed to prepare a response after the presentation of S1, the first time window (0–200 ms) corresponds to an incorrect prepotent response activation, which then has to be overruled by the correct activation of the Immediate Response (220–420 ms). The last time window (600–1000 ms) overlaps with the execution of the Planned Responses (see Behavioral data), thus, it reflects the activations of the response chain. EEG data was quantified as mean activity in the time window of −300 ms to 0 ms preceding the onset of the Immediate Response on the r-LRP channel.

Accuracy, RT, and EEG data were analyzed in mixed design ANOVA with element overlap (no element overlap vs. element overlap) as a within-subjects factor, and group (HC vs. GTS) as a between-subject factor. Here, we report η_p^2 effect size for ANOVA main effects and interactions. The Bayes factor as BF_{01} is reported to quantify the evidence for the null hypothesis. To investigate the possible relationship between clinical characteristics of the GTS group and binding effects at the behavioral and neurophysiological levels, Pearson's correlations were conducted.

3. Results

3.1. Clinical characteristics of GTS patients

Patient characteristics are given in Table 1.

Five GTS patients had a diagnosis of a depressive disorder, two were diagnosed with ADHD, one was diagnosed with OCD and one had an anxiety disorder. During testing, 6 of 22 patients were taking medication to treat tics including aripiprazole (n = 3), tiapride (n = 1), opipramol (n = 1) and paroxetine (n = 1). None of them had changed their medication within at least 4 weeks prior to testing. In both groups, mean IQ was in the normal range. Mean IQ was 101.3 (±13.4) in GTS patients and 112.5 (±8.1) in HC. Three patients and three HC subjects were left-handed.

3.2. Behavioral data

To examine behavioral action coding effects, the levels of action element overlap (element overlap vs. no element overlap) were compared between groups with respect to accuracy (percentage of correct responses) and RTs of the Immediate Response; and average accuracy and cumulative RTs of the Planned Responses. The behavioral data on a single subject level is given in Fig. 2.

The group by action element overlap ANOVA on Immediate Response accuracy did not show significant main effects of element overlap ($F(1,44) = 2.63$, $p = .112$, $\eta_p^2 = 0.056$, $BF_{01} = 1.94$) or group ($F(1,44) = 0.17$, $p = .897$, $\eta_p^2 = 0.001$, $BF_{01} = 4.51$). Similarly, the group by element overlap interaction was not significant ($F(1,44) = 0.76$, $p = .785$, $\eta_p^2 = 0.002$, $BF_{01} = 9.12$). The group by element overlap ANOVA on Immediate Response RT showed a significant main effect of element overlap ($F(1,44) = 17.58$, $p < .001$, $\eta_p^2 = 0.286$, $BF_{01} = 0.006$). Participants performed Immediate Response faster in the no element overlap (482.5 ms ± 22.4) than in the element overlap condition (503.2 ms ± 22.2). However, the main effect of group was not significant ($F(1,44) = 1.79$, $p = .188$, $\eta_p^2 = 0.039$, $BF_{01} = 1.35$). Also, there was no significant group by element overlap interaction ($F(1,44) = 0.24$, $p = .625$, $\eta_p^2 = 0.005$, $BF_{01} = 1.41$). The group by element overlap ANOVA on the Planned Responses average accuracy showed a significant main effect of element overlap ($F(1,44) = 7.48$, $p = .009$, $\eta_p^2 = 0.145$, $BF_{01} = 0.23$). The accuracy for the response chain of Planned Responses was higher in the no element overlap (97.9% ± 0.3) than in the element overlap condition (96.8% ± 0.5). Similarly, the main effect of group was significant ($F(1,44) = 5.28$, $p = .026$, $\eta_p^2 = 0.107$, $BF_{01} = 0.49$). HC had higher overall accuracy (98.2% ± 0.5) than GTS participants (96.6% ± 0.5). However, the group by element overlap interaction was not significant ($F(1,44) = 0.14$, $p = .712$, $\eta_p^2 = 0.003$, $BF_{01} = 1.42$). The group by element overlap ANOVA on the Planned Responses' cumulative RT did not show significant main effects of element overlap ($F(1,44) = 0.02$, $p = .883$, $\eta_p^2 = 0.001$, $BF_{01} = 6.89$) or group ($F(1,44) = 1.29$, $p = .263$, $\eta_p^2 = 0.028$, $BF_{01} = 1.71$). Similarly, the group by element overlap interaction was not significant either ($F(1,44) = 0.41$, $p = .840$, $\eta_p^2 = 0.001$, $BF_{01} = 9.04$). Especially this lack of an interaction indicates that there is no differential action file binding in GTS and healthy controls and the high Bayes Factor provides moderate to strong evidence for the null hypothesis. In sum, response binding pattern did not differ between groups. Difference between no element overlap and element overlap conditions for the Immediate Response RT and Planned Responses accuracy did not

Table 1
Clinical characteristics of GTS patients.

No	Age	Sex	Yrs.	DCI	YGTSS	YGTSStics	Tics/min	Rushscore	PUTS	YBOCS	ADHD-index
1	35	F	28	44	17	7	3.9	3	15	0	0
2	18	M	8	43	17	7	4.5	10	13	10	1
3	20	M	15	56	58	28	17.3	13	27	14	20
4	38	M	32	57	34	34	72.3	14	26	15	6
5	24	M	9	63	67	27	8.7	8	22	0	12
6	50	M	43	45	30	20	76.8	15	13	0	13
7	45	F	40	52	34	14	71.9	11	26	14	15
8	18	M	11	55	50	30	42.4	10	17	0	26
9	44	M	35	92	55	25	35.8	13	19	9	7
10	29	M	15	79	48	18	29.4	13	24	16	23
11	38	F	27	42	23	13	28	11	15	2	18
12	45	M	39	55	18	18	39.7	11	23	0	10
13	22	F	18	100	46	26	30.7	13	18	0	10
14	35	F	22	76	47	27	40	14	22	13	7
15	47	M	41	35	58	18	15	10	16	0	5
16	26	F	14	39	55	15	19.8	12	19	0	14
17	54	M	44	39	43	13	35.5	10	9	0	4
18	28	F	19	57	87	37	46.0	16	26	16	9
19	22	F	17	46	20	10	10.5	4	24	0	1
20	26	M	20	55	55	25	65.0	11	16	8	12
21	23	M	16	64	31	21	62.5	14	27	11	14
22	19	F	11	35	30	10	22.3	11	13	0	9
mean	32.1		23.8	55.9	42.0	20.1	27.5	11.2	19.5	5.8	10.7

Abbreviations: ADHD = attention deficit/hyperactivity disorder; DCI = diagnostic confidence index; PUTS = premonitory urge for tic scale; YBOCS = Yale Brown obsessive compulsive scale; YGTSS = Yale global tic severity scale; Yrs. = years of disease duration.

correlate with clinical measures (Diagnostic Confidence Index, YGTSS, PUTS, motor tics/minute, Rush score, YBOCS, ADHD-Index, and Conners DSM-ADHD Scale) ($r > 0.053$, $p > .270$, $BF_{01} > 2.14$).

3.3. Lateralized readiness potentials

The s-LRP waveform is depicted in Fig. 3, and Single-subject data (mean amplitudes and onset latencies) of the s-LRP can be found in Fig. 4. The r-LRP waveform incl. single-subject data is shown in Fig. 5.

To examine the s-LRPs as a neurophysiological marker of the action coding effect, we analyzed the conditions of no element overlap and element overlap in GTS and in HC in the pre-defined time windows as outlined above. The group by element overlap ANOVA in the time window of 0–200 ms (incorrect response activation) showed a significant main effect of element overlap ($F(1,44) = 51.20$, $p < .001$, $\eta_p^2 = 0.538$, $BF_{01} = 1.00$). The mean amplitude was larger in the element overlap (2.59 $\mu V/m^2 \pm 0.27$) than in the no element overlap condition (-0.77 $\mu V/m^2 \pm 0.30$). However, the main effect of group was not significant ($F(1,44) = 0.72$, $p = .401$, $\eta_p^2 = 0.016$, $BF_{01} = 2.65$). Similarly, the group by element overlap interaction was not significant ($F(1,44) = 1.66$, $p = .204$, $\eta_p^2 = 0.036$, $BF_{01} = 3.07$). The group by element overlap ANOVA in the time window of 220–420 ms (correct response activation of the Immediate Response) showed a significant main effect of element overlap ($F(1,44) = 41.83$, $p < .001$, $\eta_p^2 = 0.487$, $BF_{01} = 1.58$). The mean amplitude was larger in the no element overlap (-7.64 $\mu V/m^2 \pm 1.09$) than in the element overlap condition (-1.93 $\mu V/m^2 \pm 0.86$). The main effect of group was also significant ($F(1,44) = 4.17$, $p = .047$, $\eta_p^2 = 0.087$, $BF_{01} = 0.58$). The negative deflection between 220 and 420 ms was larger in the HC (-6.58 $\mu V/m^2 \pm 1.22$) than in the GTS group (-2.99 $\mu V/m^2 \pm 1.27$). However, the group by element overlap interaction was not significant ($F(1,44) = 1.29$, $p = .262$, $\eta_p^2 = 0.029$, $BF_{01} = 2.14$). Moreover, we analyzed the onset latencies of the negative deflection between 220 and 420 ms after the S2 onset by a group by element overlap ANOVA. The main effect of element overlap was significant ($F(1,44) = 20.35$, $p < .001$, $\eta_p^2 = 0.316$, $BF_{01} = 0.001$). The correct response activation reflected by the LRP had an earlier onset in the no element overlap condition (266.1 ms ± 9.2) compared to the element overlap condition (312.9 ms ± 8.7). However, the main effect of group was not significant ($F(1,44) = 0.93$, $p = .340$, $\eta_p^2 = 0.021$, $BF_{01} = 2.37$). Similarly, the group by element overlap interaction was not significant either ($F(1,44) = 2.72$, $p = .106$, $\eta_p^2 = 0.058$, $BF_{01} = 1.06$). The group by element overlap ANOVA in the time window of 600–1000 ms (response activations of Planned Responses) showed a significant main effect of element overlap ($F(1,44) = 20.23$, $p < .001$, $\eta_p^2 = 0.315$, $BF_{01} = 1.00$). The mean amplitude was larger (more positive) in the no element overlap (3.88 $\mu V/m^2 \pm 1.0$) than in the element overlap condition (-4.16 $\mu V/m^2 \pm 1.0$). The main effect of group was not significant, with very strong evidence for the null hypothesis ($F(1,44) = 2.10$, $p = .158$, $\eta_p^2 = 0.045$, $BF_{01} > 100$). Similarly, the group by element overlap interaction was not significant, again with positive evidence for the null hypothesis ($F(1,44) = 1.54$, $p = .221$, $\eta_p^2 = 0.034$, $BF_{01} = 3.09$).

Furthermore, we analyzed the action file coding effect on the r-LRP by an ANOVA with the factors of group by element −300 ms prior to the Immediate Response. The main effect of element overlap was not significant ($F(1,43) = 1.43$, $p = .238$, $\eta_p^2 = 0.032$, $BF_{01} = 2.75$). Similarly, the main effect of group was not significant either ($F(1,43) = 0.57$, $p = .453$, $\eta_p^2 = 0.013$, $BF_{01} = 1.98$). However, the group by element overlap interaction was significant ($F(1,43) = 4.57$, $p = .038$, $\eta_p^2 = 0.096$, $BF_{01} = 1.65$). In the GTS group, the difference between element overlap (-6.68 $\mu V/m^2 \pm 1.7$) and no element overlap (-9.44 $\mu V/m^2 \pm 1.7$) was significant. However, in the HC group, the two conditions did not differ from each other (element overlap: -6.83 $\mu V/m^2 \pm 1.6$; no element overlap: -6.10 $\mu V/m^2 \pm 1.6$). That is, the r-LRP indicates that response execution was affected by the level of element overlap only in the GTS group. There were no correlations between mean amplitudes of s-LRP (0–200 ms, 220–420 ms, 600–1000 ms) or r-LRP (−300 to 0 ms) and clinical measures ($r > 0.015$, $p > .157$, $BF_{01} > 1.48$).

4. Discussion

Given that tics are the defining and cardinal feature in GTS it appears plausible to assume that movement related processes are disturbed in these patients. Indeed, previous studies examining movement execution in GTS using different approaches can be interpreted along these lines. For example, motor cortex activity was shown to be increased during self-paced simple finger movements using MEG (Franzkowiak et al., 2010) and transcranial magnetic stimulation revealed that corticospinal excitability is abnormally reduced in phases preceding the execution of voluntary movements (Draper et al., 2015; Heise et al., 2010), but the relation with tics depended on the population being studies (children vs.

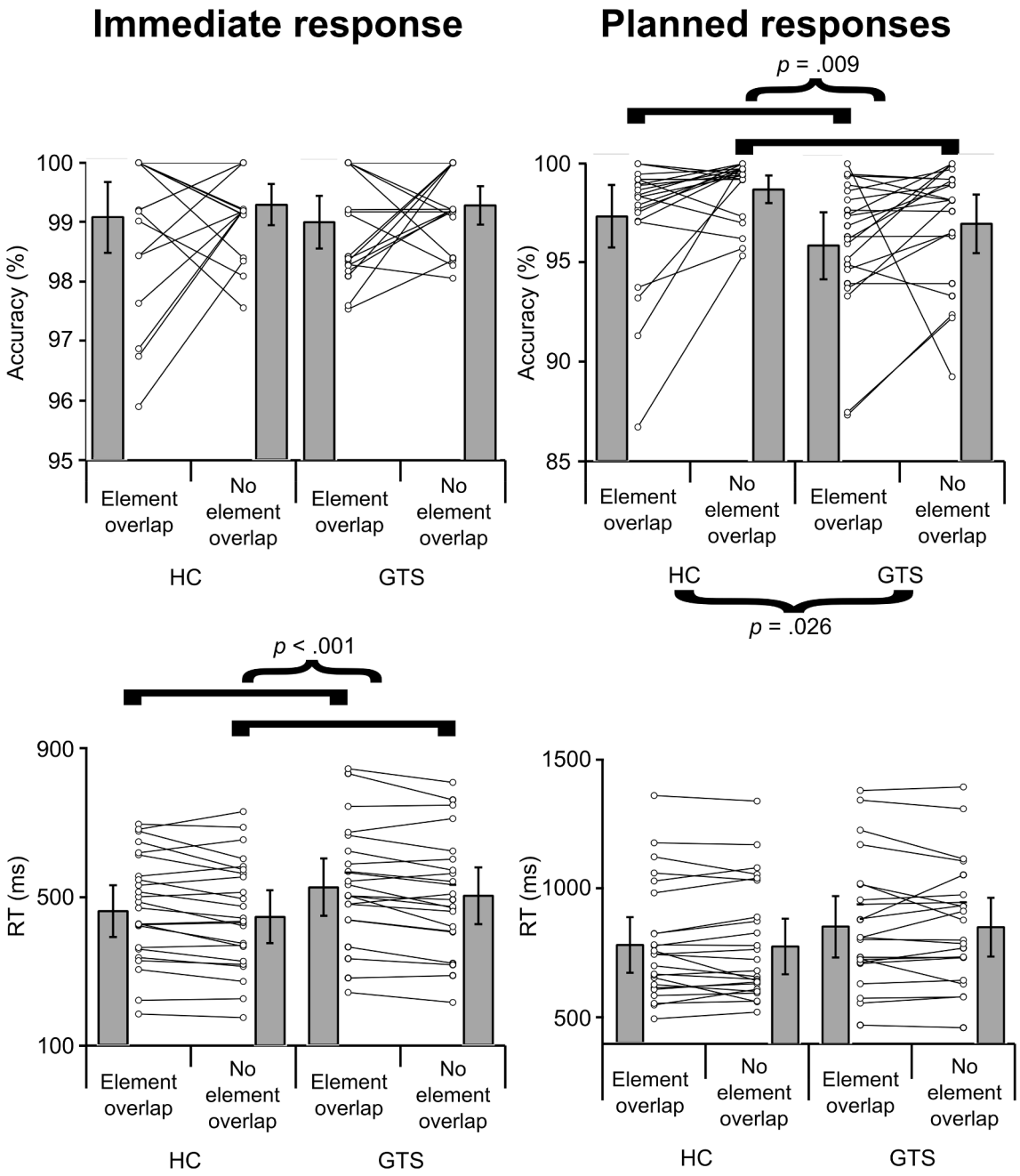

Fig. 2. Behavioral results. Accuracy and reaction time data are shown as group (Gilles de la Tourette: GTS vs. healthy controls: HC) by overlap (Element overlap vs. No element overlap) bar plots separately for the Immediate Response and Planned Responses. Individual data points are presented within the bars (Weissgerber et al., 2015). Significant effects of group and overlap are marked with curly brackets. The histogram show the mean and standard deviation (SD).

adults).

Crucially, although these studies provided valuable information, they only examined simple movements and also more in-depth neurophysiological studies on the effects of interventions targeting symptoms in GTS (Morand-Beaulieu et al., 2018, 2015) have not used more complex experiments requiring daily life relevant interleaved responding to achieve a goal. However, most goal-directed actions consist of multiple motor components requiring to integrating and interleaving different movements in a flexible way (Stoet and Hommel, 1999). This has, until now, not been studied in GTS. The present study examined how interdependencies between a planned but postponed and an interleaved immediate action are processed in GTS. We show that action coding and the binding of different motor elements comprising an action, is normal in GTS patients both at a behavioral and a neurophysiological level. We used an established task to examine action integration, allowing to test how an immediate and a planned action interfere in the motor system as a function of element overlap between the actions. We replicate that problems (i.e. behavioral costs) arise when elements of these two interdependent actions overlap compared to conditions, in which they differ. In other words, processing of two actions is less demanding when these actions are clearly distinct. These processes that have been viewed as action file processing in the framework of the theory of event coding are apparently undisturbed in GTS. The applied neurophysiological approach allowed us to separately examine processes preceding motor execution, i.e., pre-motor processes including perception, response selection and configuration (s-LRP) and processes related to the subsequent motor execution (r-LRP) (Beste et al., 2009; Coles, 1989; Masaki et al., 2004; Osman et al., 1995; van der Lubbe et al., 2001). Processes

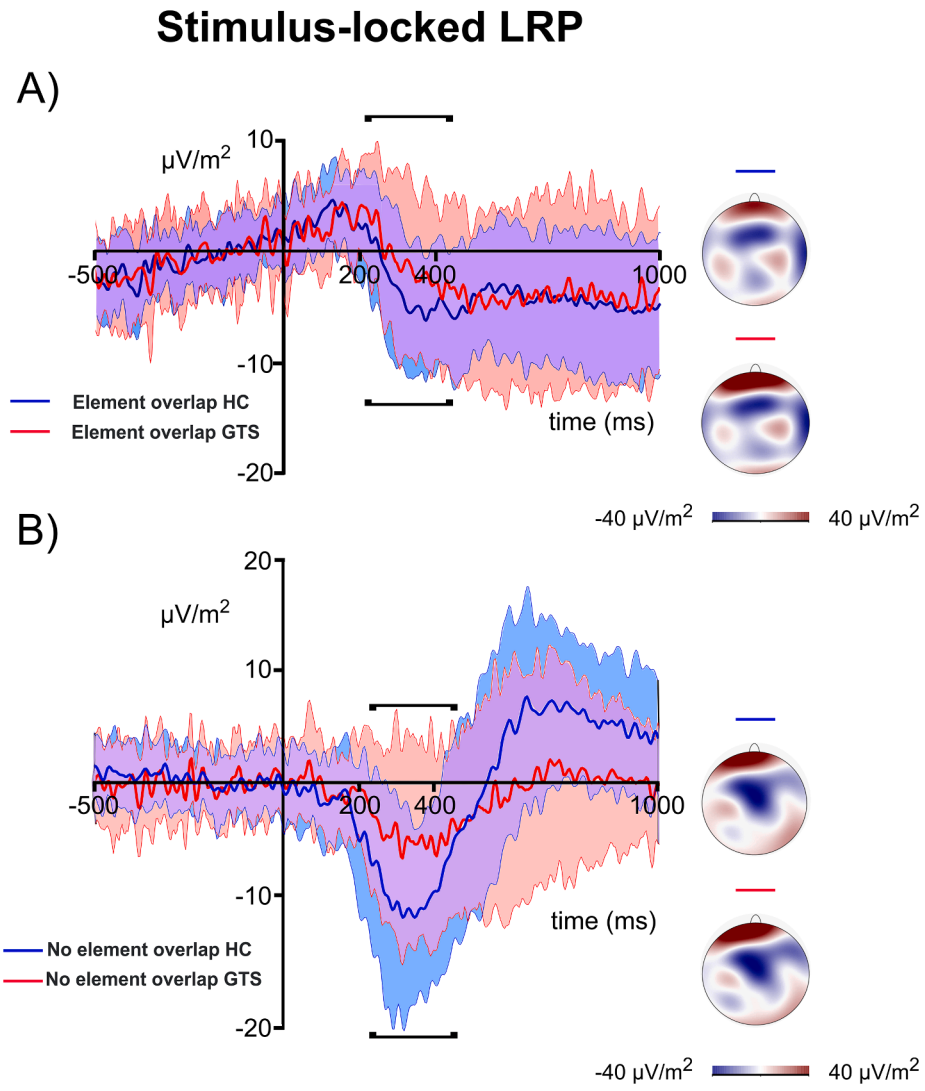

Fig. 3. Stimulus-locked lateralized readiness potential (LRP) waveforms. Time point zero denotes the stimulus presentation. Stimulus locked LRPs are shown for healthy controls in blue and for Gilles de la Tourette patients (GTS) in red. Standard deviations are represented by shaded areas in pale blue for healthy controls and pale red for GTS. Purple represents the overlap between the groups. The analyzed time window of the correct response activation (220 ms – 420 ms) is marked with horizontal brackets. For the topography plots, difference waves were created between the contralateral and ipsilateral sides in the motor element overlap and in the no motor element overlap conditions separately in the two groups. The scalp topography plots show the distribution of the mean activity of the contralateral-ipsilateral difference waves of the time window of correct response activation. Panel A presents the motor element overlap condition, panel B the no motor element overlap condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

comprising the integration of different action-related elements prior to the motor execution (s-LRP) were not different between GTS patients and HC. As with the behavioral data, this was supported by a Bayesian analysis of the data providing moderate to strong evidence for a lack of differences between groups indicating that processes integrating different action-related elements prior to the motor execution are normal in GTS. The fact that there were no correlations with clinical measures of GTS severity (supported by Bayesian statistics) suggests that tics are not related to and do not interfere with complex movement integration processes. Only during response execution cortical motor areas were overactive in GTS patients and this was also only the case under certain circumstances. Thus, r-LRP amplitudes reflecting processes related to motor execution, were only larger in the condition where no complex action integration and restructuring was required. Thus, abnormal motor activity in GTS is present only when motor processes are simple, but these changes were also not systematically related to clinical measures including YGTSS-, Rush scores or tic counts. It is known that tics are less likely to occur when patients have to concentrate on other demanding tasks (Thomalla et al., 2014). In other words, during easier tasks requiring less processing capacities as in the no element overlap condition tic activity is more likely to rise mirrored by r-LRP amplitudes compared to the more demanding element overlap condition. This interpretation, albeit speculative, is supported by previous studies on simple movement execution (Draper et al., 2015; Franzkowiak et al., 2010; Heise et al., 2010). Thus, simple motor execution shows subtle abnormalities in GTS but complex movement execution and the integration of different movements are normal in these patients suggesting that GTS is not solely a motor disorder.

There is, in fact, increasing evidence that particularly perceptual processes have to be considered with respect to pathophysiological concepts in GTS (Beste and Münchau, 2018; Kim et al., 2019). Most adult GTS patients report premonitory urges preceding tics (Leckman et al., 1993), report hypersensitivity to external stimuli (Belluscio et al., 2011) and have been shown to have alterations in perceptual processing (Biermann-Ruben et al., 2012), sensorimotor interaction (Orth, 2009; Orth et al., 2005) and also the structural composition of cortical sensory areas (Draper et al., 2016; Sowell et al., 2008; Thomalla et al., 2009; Worbe et al., 2010). Recent findings suggest that the strength of associations between perceptual and motor processes are central for the understanding of GTS, since particularly these processes correlated with tic frequency (Kleimaker et al., 2020b). Together with the findings of the present study, these data suggest that interactions between perceptual and motor processes rather than motor processing in isolation are relevant for the understanding of GTS. The validity of such a concept needs to be studied rigorously from different angles within the framework of a theoretical model with testable assumptions. This requirement is fulfilled in the approach taken in this study, which was based on the same concept that was already shown to be relevant in GTS (Kleimaker et al., 2020b). What needs to be considered is that GTS is a developmental disorder with first tics usually appearing around the age of 5-7 years

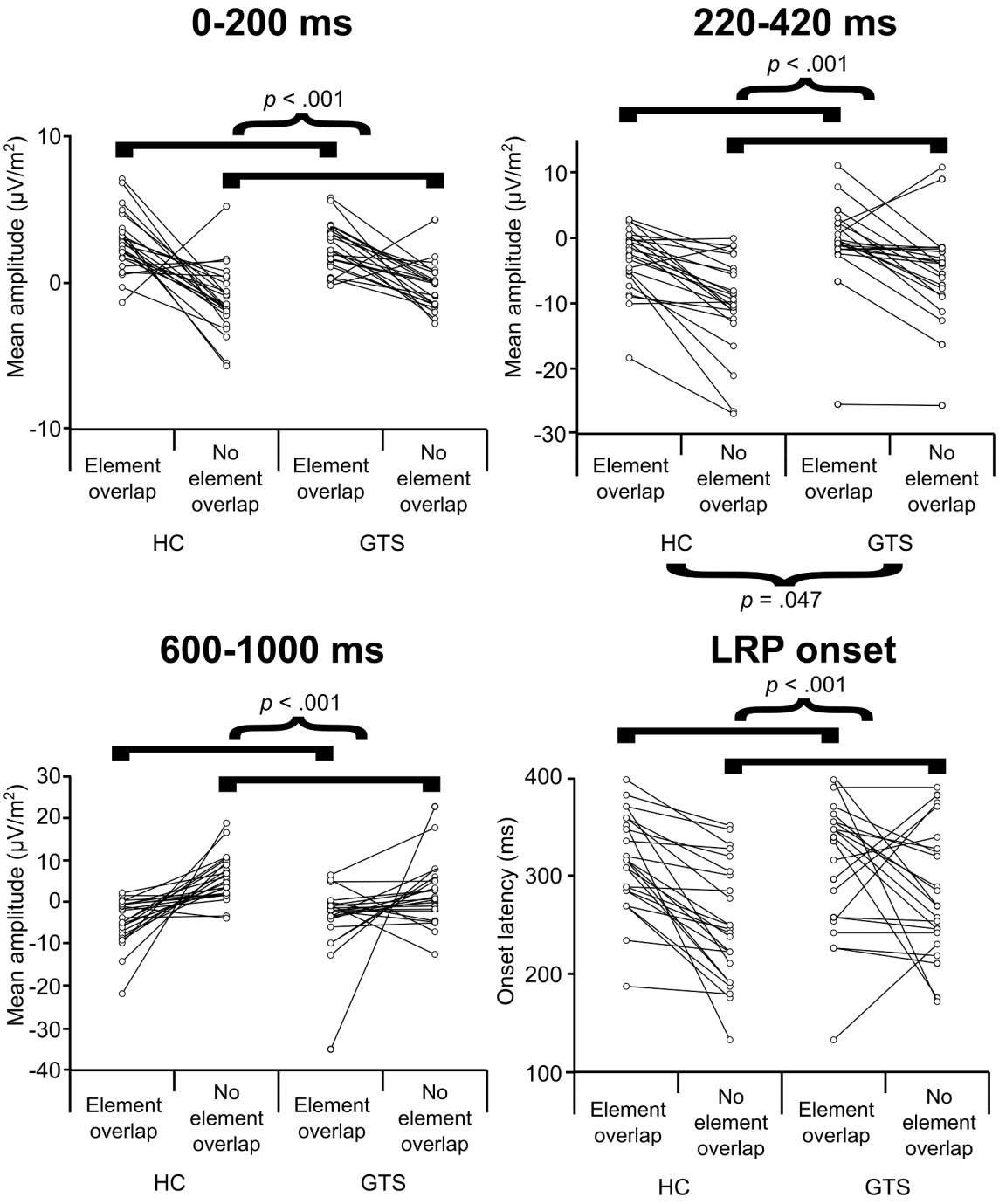

Fig. 4. Stimulus-locked lateralized readiness potential (LRP) parameters on a single-subject level. Mean amplitude and onset latency data are shown as group (Gilles de la Tourette: GTS vs. healthy controls: HC) by overlap (Element overlap vs. No element overlap) bar plots separately for the investigated time windows: early incorrect response activation of the Planned Responses (0–200 ms), main correct response activation of the Immediate Response (220–420 ms) and response window of the Planned Responses (600–1000 ms). Individual data points are presented within the bars (Weissgerber et al., 2015). Significant effects of group and overlap are marked with curly brackets.

(Robertson, 2012) and a pre-pubertal increase in tic severity, which is typically followed by a subsequent reduction or even complete remission towards the end of the second decade (Leckman et al., 1998). Therefore, a population of adults patients with GTS as studied here, is not representative for the GTS population as a whole. Nevertheless, the dissociation between a hyperbinding in event file coding (Kleimaker et al., 2020b) and no changes in action file coding (see current data) is striking and suggests that binding mechanisms are different between these file types – a finding not readily consider in TEC. However, binding between action features can also be divided into distinct functions (Mocke et al., 2020). Actions can be body-related or environment-related. Only the first one provides a sensorimotor effect, while the second one relates to a change in the environment. Although binding occurs both for body-related and environment-related action features, this is only the case if action features are task-relevant. However, task-irrelevant features only get integrated if they are body-related but not if they are environment-related (Mocke et al., 2020). Importantly, in the current paradigm, action features were always body-related (side of response) and task-relevant, thus they likely tapped on more automatic, and therefore less demanding forms of action file binding (Stoet and

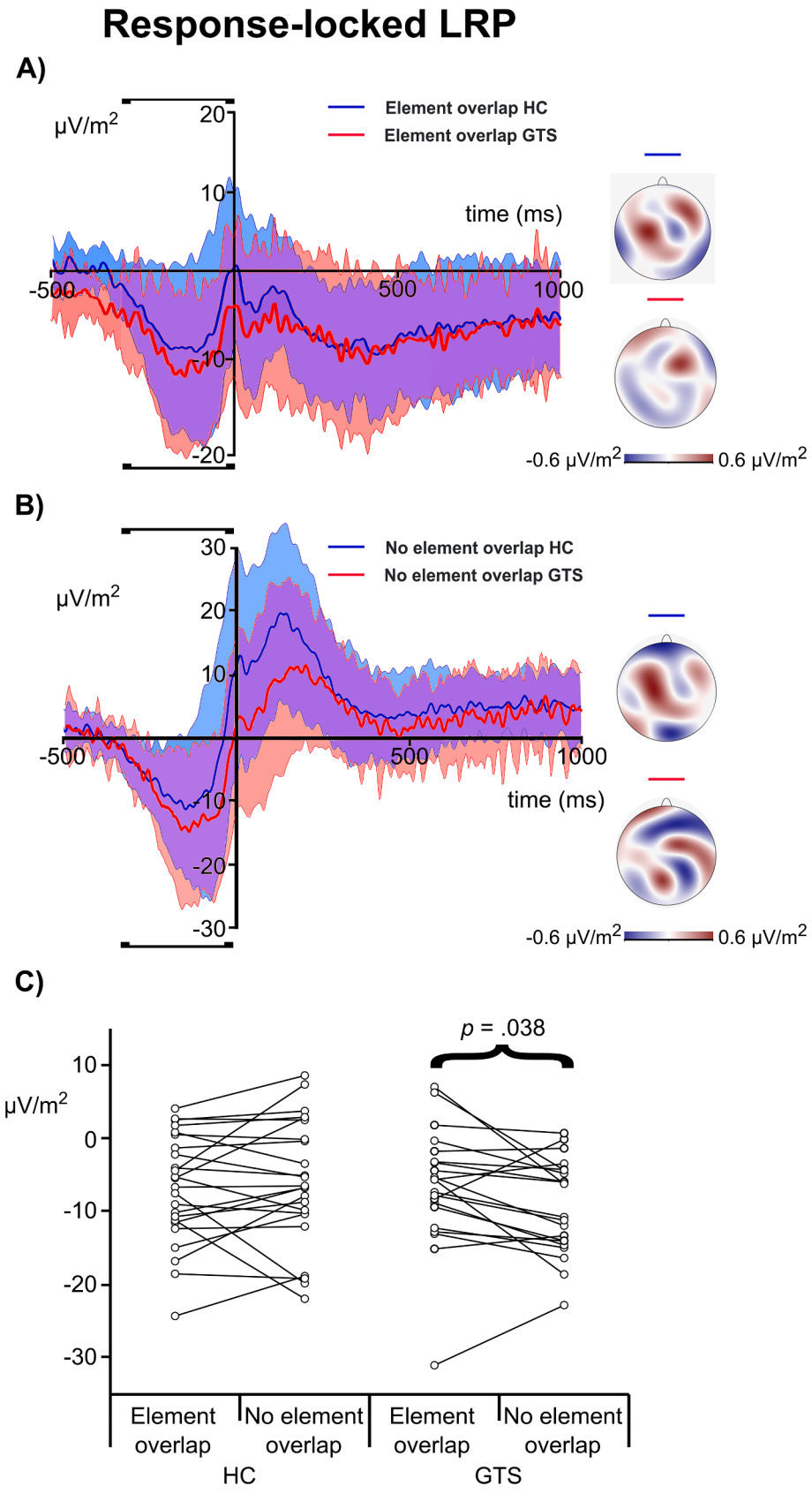

Fig. 5. Response-locked LRP waveforms. Time point zero denotes the registration of the response. Response-locked LRPs are shown across two groups. Data of healthy controls is shown in blue and that of patients with Gilles de la Tourette syndrome (GTS) in red. Standard deviations are represented by shaded areas with pale blue representing healthy controls and pale red GTS. Purple areas show the overlap between the groups. The analyzed time window of the response activation (−300 ms to 0 ms) is marked with horizontal brackets. For the topography plots, difference waves were created between the contralateral and ipsilateral sides in the motor element overlap and in the no motor element overlap conditions, separately in the two groups. The scalp topography plots show the distribution of the mean activity of the contralateral-ipsilateral difference wave of the time window of the response activation (−300 ms to 0 ms). Panel A presents the motor element overlap condition. Panel B shows the no motor element overlap condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Hommel, 1999). It remains to be seen whether action file binding processes are modulated differently in GTS when action file binding becomes more demanding. At present, there is no evidence for developmental effects in action file binding in young age since previous action file binding studies did not include children and adolescent participants (Mocke et al., 2020; Stoet and Hommel, 1999). Therefore, the argument on the possible developmental trajectories of action file binding remains tentative and future studies in health and disease need to be conducted to clarify this issue in detail. However, for the reasons mentioned above, it is conceivable that processes underlying action file binding are part of an early maturing sensory or motor processing system, stabilizing before the age of 10 (Serrien and O'Regan, 2020; Stöckel and Hughes, 2016; Stuhr et al., 2018; Thibaut and Toussaint, 2010; Whitall and Clark, 2018).

The findings of the present study also of interest for the clinical assessment of patients, for instance in clinical trials. The preferred instrument for the evaluation of tic severity and tic-related impairment is the YGTSS (Pringsheim et al., 2019), which has a very good internal consistency, interrater reliability, and convergent and divergent validity (Martino et al., 2017). Yet, it is a tic- (i.e. motor-) centered scale taking into account perceptual phenomena only marginally. The PUTS has been developed as a self-report measure to assess the severity of premonitory urges and is widely used (Woods et al., 2005). It thus often complements clinical assessment. Instruments capturing both tics and urges simultaneously as, for instance, an urge-tic monitor as a psychophysical measure (Brandt et al., 2016a, 2016b), or neurophysiological measures reflecting perception–action binding (Kleimaker et al., 2020b) might be well-suited to reflect perception–action processes on a clinical/behavioral level. However, for that the role of comorbid disorders should be investigated beforehand. In the present study this was not possible since the frequency of comorbid disorder did not allow for a reliable statistical modelling of these factors.

To summarize, complementing previous work documenting that associations between perceptual and motor processes are abnormally strong in GTS patients (Kleimaker et al., 2020aa, 2020bb, 2020cc, 2020bd), this study shows that action integration per se is normal in these patients and therefore suggests that GTS is a disorder characterized by abnormalities beyond the motor system.

CRediT authorship contribution statement

Emily Mielke: Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Adam Takacs:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Maximilian Kleimaker:** Investigation, Writing - review & editing. **Ronja Schappert:** Data curation, Investigation, Writing - review & editing. **Giulia Conte:** Investigation, Writing - review & editing. **Rebecca Onken:** Investigation, Writing - review & editing. **Till Künemund:** Investigation, Writing - review & editing. **Julius Verrel:** Investigation, Writing - review & editing. **Tobias Bäumer:** Data curation, Investigation, Writing - review & editing. **Christian Beste:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Alexander Münchau:** Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, Fifth edition. ed. American Psychiatric Association. DOI:10.1176/appi.books.9780890425596.

Beesdo-Baum, K., Zaudig, M., Wittchen, H.U., 2019. SCID-5-CV— Strukturiertes Klinisches Interview fuer DSM-5-Stoerungen Hogrefe.

Belluscio, B.A., Jin, L., Watters, V., Lee, T.H., Hallett, M., 2011. Sensory sensitivity to external stimuli in Tourette syndrome patients. Mov. Disord. 26, 2538–2543. https://doi.org/10.1002/mds.23977.

Beste, C., Saft, C., Andrich, J., Gold, R., Falkenstein, M., 2008. Stimulus-response compatibility in Huntington's disease: a cognitive-neurophysiological analysis. J. Neurophysiol. 99, 1213–1223. https://doi.org/10.1152/jn.01152.2007.

Beste, C., Konrad, C., Saft, C., Ukas, T., Andrich, J., Pfleiderer, B., Hausmann, M., Falkenstein, M., 2009. Alterations in voluntary movement execution in Huntington's disease are related to the dominant motor system: evidence from event-related potentials. Exp. Neurol. 216, 148–157. https://doi.org/10.1016/j.expneurol.2008.11.018.

Beste, C., Münchau, A., 2018. Tics and Tourette syndrome - surplus of actions rather than disorder? Mov. Disord. 33, 238–242. https://doi.org/10.1002/mds.27244.

Beste, C., Baune, B.T., Falkenstein, M., Konrad, C., 2010. Variations in the TNF-α gene (TNF-α -308G→A) affect attention and action selection mechanisms in a dissociated fashion. J. Neurophysiol. 104, 2523–2531. https://doi.org/10.1152/jn.00561.2010.

Beste, C., Tübing, J., Seeliger, H., Bäumer, T., Brandt, V., Stock, A.-K., Münchau, A., 2016. Altered perceptual binding in Gilles de la Tourette syndrome. Cortex 83, 160–166. https://doi.org/10.1016/j.cortex.2016.07.015.

Biermann-Ruben, K., Miller, A., Franzkowiak, S., Finis, J., Pollok, B., Wach, C., Südmeyer, M., Jonas, M., Thomalla, G., Müller-Vahl, K., Münchau, A., Schnitzler, A., 2012. Increased sensory feedback in Tourette syndrome. NeuroImage 63, 119–125. https://doi.org/10.1016/j.neuroimage.2012.06.059.

Brandt, V.C., Lynn, M.T., Obst, M., Brass, M., Münchau, A., 2015. Visual feedback of own tics increases tic frequency in patients with Tourette's syndrome. Cogn. Neurosci. 6, 1–7. https://doi.org/10.1080/17588928.2014.954990.

Brandt, V.C., Beck, C., Sajin, V., Baaske, M.K., Bäumer, T., Beste, C., Anders, S., Münchau, A., 2016a. Temporal relationship between premonitory urges and tics in Gilles de la Tourette syndrome. Cortex 77, 24–37. https://doi.org/10.1016/j.cortex.2016.01.008.

Brandt, V.C., Patalay, P., Bäumer, T., Brass, M., Münchau, A., 2016b. Tics as a model of over-learned behavior—imitation and inhibition of facial tics. Mov. Disord. 31, 1155–1162. https://doi.org/10.1002/mds.26607.

Bryce, D., Szűcs, D., Soltész, F., Whitebread, D., 2011. The development of inhibitory control: an averaged and single-trial Lateralized Readiness Potential study. NeuroImage 57, 671–685. https://doi.org/10.1016/j.neuroimage.2010.12.006.

Buse, J., Beste, C., Herrmann, E., Roessner, V., 2016. Neural correlates of altered sensorimotor gating in boys with Tourette Syndrome: a combined EMG/fMRI study. World J. Biol. Psychiatry 17, 187–197. https://doi.org/10.3109/15622975.2015.1112033.

Buse, J., Beste, C., Roessner, V., 2018. Neural correlates of prediction violations in boys with Tourette syndrome: evidence from harmonic expectancy. World J. Biol. Psychiatry 19, 130–141. https://doi.org/10.1080/15622975.2016.1274052.

Christiansen, H., Hirsch, O., Philipsen, A., Oades, R.D., Matthies, S., Hebebrand, J., Ueckermann, J., Abdel-Hamid, M., Kraemer, M., Wiltfang, J., Graf, E., Colla, M., Sobanski, E., Alm, B., Rösler, M., Jacob, C., Jans, T., Huss, M., Schimmelmann, B.G., Kis, B., 2013. German validation of the Conners adult ADHD rating scale-self-report: confirmation of factor structure in a large sample of participants with ADHD. J. Atten. Disord. 17, 690–698. https://doi.org/10.1177/1087054711435680.

Coles, M.G.H., 1989. Modern mind-brain reading: psychophysiology, physiology, and cognition. Psychophysiology 26, 251–269. https://doi.org/10.1111/j.1469-8986.1989.tb01916.x.

Colzato, L.S., Warrens, M.J., Hommel, B., 2006. Priming and binding in and across perception and action: a correlational analysis of the internal structure of event files. Q. J. Exp. Psychol. (Hove) 59, 1785–1804. https://doi.org/10.1080/17470210500438304.

de Jong, R., Wierda, M., Mulder, G., Mulder, L.J., 1988. Use of partial stimulus information in response processing. J. Exp. Psychol. Hum. Percept. Perform. 14, 682–692. https://doi.org/10.1037//0096-1523.14.4.682.

Delorme, C., Salvador, A., Valabrègue, R., Roze, E., Palminteri, S., Vidailhet, M., de Wit, S., Robbins, T., Hartmann, A., Worbe, Y., 2016. Enhanced habit formation in Gilles de la Tourette syndrome. Brain 139, 605–615. https://doi.org/10.1093/brain/awv307.

Draper, A., Jude, L., Jackson, G.M., Jackson, S.R., 2015. Motor excitability during movement preparation in Tourette syndrome. J. Neuropsychol. 9, 33–44. https://doi.org/10.1111/jnp.12033.

Draper, A., Jackson, G.M., Morgan, P.S., Jackson, S.R., 2016. Premonitory urges are associated with decreased grey matter thickness within the insula and sensorimotor cortex in young people with Tourette syndrome. J. Neuropsychol. 10, 143–153. https://doi.org/10.1111/jnp.12089.

Falkenstein, M., Willemssen, R., Hohnsbein, J., Hielscher, H., 2006. Effects of stimulus-response compatibility in Parkinson's disease: a psychophysiological analysis. J. Neural Transm. 113, 1449–1462. https://doi.org/10.1007/s00702-005-0430-1.

Franzkowiak, S., Pollok, B., Biermann-Ruben, K., Südmeyer, M., Paszek, J., Jonas, M., Thomalla, G., Bäumer, T., Orth, M., Münchau, A., Schnitzler, A., 2010. Altered pattern of motor cortical activation-inhibition during voluntary movements in Tourette syndrome. Mov. Disord. 25, 1960–1966. https://doi.org/10.1002/mds.23186.

Ganos, C., Bongert, J., Asmuss, L., Martino, D., Haggard, P., Münchau, A., 2015. The somatotopy of tic inhibition: where and how much? Mov. Disord. 30, 1184–1189. https://doi.org/10.1002/mds.26188.

Goetz, C.G., Pappert, E.J., Louis, E.D., Raman, R., Leurgans, S., 1999. Advantages of a modified scoring method for the rush video-based tic rating scale. Mov. Disord. 14, 502–506. https://doi.org/10.1002/1531-8257(199905)14:3<502::aid-mds1020>3.0.co;2-g.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46, 1006–1011. https://doi.org/10.1001/archpsyc.1989.01810110048007.

Gratton, G., Coles, M.G., Sirevaag, E.J., Eriksen, C.W., Donchin, E., 1988. Pre- and poststimulus activation of response channels: a psychophysiological analysis. J. Exp. Psychol. Hum. Percept. Perform. 14, 331–344. https://doi.org/10.1037//0096-1523.14.3.331.

Gratton, G., Coles, M.G., Donchin, E., 1992. Optimizing the use of information: strategic control of activation of responses. J. Exp. Psychol. Gen. 121, 480–506. https://doi.org/10.1037//0096-3445.121.4.480.

Hartman, D.E., 2009. Wechsler Adult Intelligence Scale IV (WAIS IV): return of the gold standard. Appl. Neuropsychol. 16 (1), 85–87. https://doi.org/10.1080/09084280802644466.

Heise, K.-F., Steven, B., Liuzzi, G., Thomalla, G., Jonas, M., Muller-Vahl, K., Sauseng, P., Munchau, A., Gerloff, C., Hummel, F.C., 2010. Altered modulation of intracortical excitability during movement preparation in Gilles de la Tourette syndrome. Brain 133, 580–590. https://doi.org/10.1093/brain/awp299.

Herrmann, K., Sprenger, A., Baumung, L., Alvarez-Fischer, D., Münchau, A., Brandt, V., 2019. Help or hurt? How attention modulates tics under different conditions. Cortex 120, 471–482. https://doi.org/10.1016/j.cortex.2019.06.016.

Hommel, B., 2009. Action control according to TEC (theory of event coding). Psychol. Res. 73, 512–526. https://doi.org/10.1007/s00426-009-0234-2.

Hommel, B., Müsseler, J., Aschersleben, G., Prinz, W., 2001. The Theory of Event Coding (TEC): a framework for perception and action planning. Behav. Brain Sci. 24, 849–878.

Kayser, J., Tenke, C.E., 2015. On the benefits of using surface Laplacian (current source density) methodology in electrophysiology. Int. J. Psychophysiol. 97, 171–173. https://doi.org/10.1016/j.ijpsycho.2015.06.001.

Kim, S., Jackson, G.M., Dyke, K., Jackson, S.R., 2019. Impaired forward model updating in young adults with Tourette syndrome. Brain 142, 209–219. https://doi.org/10.1093/brain/awy306.

Kleimaker, A., Kleimaker, M., Bäumer, T., Beste, C., Münchau, A., 2020aa. Gilles de la Tourette syndrome-a disorder of action-perception integration. Front. Neurol. 11, 597898 https://doi.org/10.3389/fneur.2020.597898.

Kleimaker, M., Kleimaker, A., Weissbach, A., Colzato, L.S., Beste, C., Bäumer, T., Münchau, A., 2020bbd. Non-invasive brain stimulation for the treatment of Gilles de la Tourette Syndrome. Front. Neurol. 11, 592258 https://doi.org/10.3389/fneur.2020.592258.

Kleimaker, M., Takacs, A., Conte, G., Onken, R., Verrel, J., Bäumer, T., Münchau, A., Beste, C., 2020cc. Increased perception-action binding in Tourette syndrome. Brain 143, 1934–1945. https://doi.org/10.1093/brain/awaa111.

Leckman, J.F., 2002. Tourette's syndrome. Lancet 360, 1577–1586. https://doi.org/10.1016/S0140-6736(02)11526-1.

Leckman, J.F., Riddle, M.A., Hardin, M.T., Ort, S.I., Swartz, K.L., Stevenson, J., Cohen, D. J., 1989. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J. Am. Acad. Child. Adolesc. Psychiatry 28, 566–573. https://doi.org/10.1097/00004583-198907000-00015.

Leckman, J.F., Walker, D.E., Cohen, D.J., 1993. Premonitory urges in Tourette's syndrome. Am. J. Psychiatry 150, 98–102. https://doi.org/10.1176/ajp.150.1.98.

Leckman, J.F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., Kim, Y.-S., Peterson, B.S., 1998. Course of tic severity in Tourette syndrome: the first two decades. Pediatrics 102, 14–19. https://doi.org/10.1542/peds.102.1.14.

Leuthold, H., Jentzsch, I., 2001. Neural correlates of advance movement preparation: a dipole source analysis approach. Cognit. Brain Res. 12, 207–224. https://doi.org/10.1016/S0926-6410(01)00052-0.

Martino, D., Pringsheim, T.M., Cavanna, A.E., Colosimo, C., Hartmann, A., Leckman, J.F., Luo, S., Munchau, A., Goetz, C.G., Stebbins, G.T., Martinez-Martin, P., 2017. Systematic review of severity scales and screening instruments for tics: critique and recommendations. Mov. Disord. 32 (3), 467–473. https://doi.org/10.1002/mds.26891.

Masaki, H., Wild-wall, N., Sangals, J., Sommer, W., 2004. The functional locus of the lateralized readiness potential. Psychophysiology 41, 220–230. https://doi.org/10.1111/j.1469-8986.2004.00150.x.

Misirlisoy, E., Brandt, V., Ganos, C., Tübing, J., Münchau, A., Haggard, P., 2015. The relation between attention and tic generation in Tourette syndrome. Neuropsychology 29, 658–665. https://doi.org/10.1037/neu0000161.

Mocke, V., Weller, L., Frings, C., Rothermund, K., Kunde, W., 2020. Task relevance determines binding of effect features in action planning. Atten. Percept. Psychophys. https://doi.org/10.3758/s13414-020-02123-x.

Morand-Beaulieu, S., O'Connor, K.P., Sauvé, G., Blanchet, P.J., Lavoie, M.E., 2015. Cognitive-behavioral therapy induces sensorimotor and specific electrocortical changes in chronic tic and Tourette's disorder. Neuropsychologia 79, 310–321. https://doi.org/10.1016/j.neuropsychologia.2015.05.024.

Morand-Beaulieu, S., O'Connor, K.P., Blanchet, P.J., Lavoie, M.E., 2018. Electrophysiological predictors of cognitive-behavioral therapy outcome in tic disorders. J. Psychiatr. Res. 105, 113–122. https://doi.org/10.1016/j.jpsychires.2018.08.020.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.

Orth, M., 2009. Transcranial magnetic stimulation in Gilles de la Tourette syndrome. J. Psychosom. Res. 67, 591–598. https://doi.org/10.1016/j.jpsychores.2009.07.014.

Orth, M., Amann, B., Robertson, M.M., Rothwell, J.C., 2005. Excitability of motor cortex inhibitory circuits in Tourette syndrome before and after single dose nicotine. Brain 128, 1292–1300. https://doi.org/10.1093/brain/awh473.

Osman, A., Moore, C.M., Ulrich, R., 1995. Bisecting RT with lateralized readiness potentials: Precue effects after LRP onset. Acta Psychol. 90, 111–127. https://doi.org/10.1016/0001-6918(95)00029-T.

Petruo, V., Bodmer, B., Brandt, V.C., Baumung, L., Roessner, V., Münchau, A., Beste, C., 2019. Altered perception-action binding modulates inhibitory control in Gilles de la Tourette syndrome. J. Child. Psychol. Psychiatry 60, 953–962. https://doi.org/10.1111/jcpp.v60.910.1111/jcpp.12938.

Petruo, V., Bodmer, B., Bluschke, A., Münchau, A., Roessner, V., Beste, C., 2020. Comprehensive Behavioral Intervention for Tics reduces perception-action binding during inhibitory control in Gilles de la Tourette syndrome. Sci. Rep. 10, 1174. https://doi.org/10.1038/s41598-020-58269-z.

Pringsheim, T., Holler-Managan, Y., Okun, M.S., Jankovic, J., Piacentini, J., Cavanna, A. E., Martino, D., Müller-Vahl, K., Woods, D.W., Robinson, M., Jarvie, E., Roessner, V., Oskoui, M., 2019. Comprehensive systematic review summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology 92, 907–915. https://doi.org/10.1212/WNL.0000000000007467.

Robertson, M.M., 2012. The Gilles de la Tourette syndrome: the current status. Arch. Dis. Child. Educ. Pract. Ed. 97, 166–175. https://doi.org/10.1136/archdischild-2011-300585.

Robertson, M.M., Banerjee, S., Kurlan, R., Cohen, D.J., Leckman, J.F., McMahon, W., Pauls, D.L., Sandor, P., van de Wetering, B.J.M., 1999. The Tourette syndrome diagnostic confidence index: development and clinical associations. Neurology 53, 2108–2112. https://doi.org/10.1212/WNL.53.9.2108.

Serrien, D.J., O'Regan, L., 2020. The development of motor planning strategies in children. Eur. J. Dev. Psychol. 18, 1–17. https://doi.org/10.1080/17405629.2020.1736029.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 Suppl 20, 22–33.

Sowell, E.R., Kan, E., Yoshii, J., Thompson, P.M., Bansal, R., Xu, D., Toga, A.W., Peterson, B.S., 2008. Thinning of sensorimotor cortices in children with Tourette syndrome. Nat. Neurosci. 11, 637–639. https://doi.org/10.1038/nn.2121.

Stöckel, T., Hughes, C.M.L., 2016. The relation between measures of cognitive and motor functioning in 5- to 6-year-old children. Psychol. Res. 80, 543–554. https://doi.org/10.1007/s00426-015-0662-0.

Stoet, G., Hommel, B., 1999. Action planning and the temporal binding of response codes. J. Exp. Psychol.: Hum. Perception Performance 25, 1625–1640. https://doi.org/10.1037/0096-1523.25.6.1625.

Stuhr, C., Hughes, C.M.L., Stöckel, T., 2018. Task-specific and variability-driven activation of cognitive control processes during motor performance. Sci. Rep. 8, 10811. https://doi.org/10.1038/s41598-018-29007-3.

Stürmer, B., Leuthold, H., Soetens, E., Schröter, H., Sommer, W., 2002. Control over location-based response activation in the Simon task: behavioral and electrophysiological evidence. J. Exp. Psychol. Hum. Percept. Perform 28, 1345–1363. https://doi.org/10.1037//0096-1523.28.6.1345.

Takacs, A., Bluschke, A., Kleimaker, M., Münchau, A., Beste, C., 2020. Neurophysiological mechanisms underlying motor feature binding processes and representations. Hum. Brain Mapp. 42, 1313–1327. https://doi.org/10.1002/hbm.v42.510.1002/hbm.25295.

Thibaut, J.-P., Toussaint, L., 2010. Developing motor planning over ages. J. Exp. Child Psychol. 105, 116–129. https://doi.org/10.1016/j.jecp.2009.10.003.

Thomalla, G., Siebner, H.R., Jonas, M., Bäumer, T., Biermann-Ruben, K., Hummel, F., Gerloff, C., Müller-Vahl, K., Schnitzler, A., Orth, M., Münchau, A., 2009. Structural changes in the somatosensory system correlate with tic severity in Gilles de la Tourette syndrome. Brain 132, 765–777. https://doi.org/10.1093/brain/awn339.

Thomalla, G., Jonas, M., Bäumer, T., Siebner, H.R., Biermann-Ruben, K., Ganos, C., Orth, M., Hummel, F.C., Gerloff, C., Müller-Vahl, K., Schnitzler, A., Münchau, A., 2014. Costs of control: decreased motor cortex engagement during a Go/NoGo task in Tourette's syndrome. Brain 137, 122–136. https://doi.org/10.1093/brain/awt288.

Tunc, S., Münchau, A., 2017. Boys in a famous choir: Singing and ticcing. Ann. Neurol. 82, 1029–1031. https://doi.org/10.1002/ana.25112.

van der Lubbe, R.H.J., Jaśkowski, P., Wauschkuhn, B., Verleger, R., 2001. Influence of time pressure in a simple response task, a choice-by-location task, and the Simon task. J. Psychophysiol. 15, 241–255. https://doi.org/10.1027//0269-8803.15.4.241.

Weissbach, A., Kleimaker, M., Bäumer, T., Beste, C., Münchau, A., 2020. Electro-Myo-Stimulation Induced Tic Exacerbation - Increased Tendencies for the formation of

perception-action links in Tourette syndrome. Tremor. Other Hyperkinet. Mov. (N Y) 10, 41. https://doi.org/10.5334/tohm.547.

Weissgerber, T., Milic, N., Winham, S., Garovic, V., 2015. Beyond bar graphs: time for a new data presentation paradigm. PLoS Biol. 13, e1002128 https://doi.org/10.1371/journal.pbio.1002128.

Whitall, J., Clark, J.E., 2018. A Perception–Action Approach to Understanding Typical and Atypical Motor Development, in: Advances in Child Development and Behavior. Elsevier, pp. 245–272. DOI:10.1016/bs.acdb.2018.04.004.

Wild–Wall, N., Sangals, J., Sommer, W., Leuthold, H., 2003. Are fingers special? Evidence about movement preparation from event-related brain potentials. Psychophysiology 40, 7–16. https://doi.org/10.1111/1469-8986.00002.

Woods, D.W., Piacentini, J., Himle, M.B., Chang, S., 2005. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. J. Dev. Behav. Pediatr. 26, 397–403. https://doi.org/10.1097/00004703-200512000-00001.

Worbe, Y., Gerardin, E., Hartmann, A., Valabrégue, R., Chupin, M., Tremblay, L., Vidailhet, M., Colliot, O., Lehéricy, S., 2010. Distinct structural changes underpin clinical phenotypes in patients with Gilles de la Tourette syndrome. Brain 133, 3649–3660. https://doi.org/10.1093/brain/awq293.