Neural, physiological and behavioral correlates of empathy for pain in Tourette syndrome

Ronja Weiblen[1,2], Carina Robert[1], Pauline Petereit[1], Marcus Heldmann[1,3,4], Thomas F. Münte[1,3,4], Alexander Münchau[4,5], Kirsten Müller-Vahl[6], Ulrike M. Krämer[1,3,4]

[1] Department of Neurology, University of Lübeck, Germany

[2] Department of Psychiatry and Psychotherapy, University of Lübeck, Germany

[3] Department of Psychology, University of Lübeck, Germany

[4] Center of Brain, Behavior and Metabolism, University of Lübeck, Germany

[4] Institute of Systems Motor Science, University of Lübeck, Germany

[5] Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany

* Corresponding authors:

Ronja Weiblen and Ulrike M. Krämer

Department of Neurology, University of Lübeck

Ratzeburger Allee 160

23538 Lübeck, Germany

ronja.weiblen@neuro.uni-luebeck.de and ulrike.kraemer@uni-luebeck.de

Acknowledgements:

The study was supported by the Deutsche Forschungsgemeinschaft (FOR 2698; KR3691/8-1). RW was funded with a PhD scholarship by the foundation of the German economy (SDW).

Abstract

Persons with Tourette syndrome (TS) show altered social behaviors, such as echophenomena and increased personal distress in emotional situations. These symptoms may reflect an overactive mirror neuron system (MNS), causing both increased automatic imitation and a stronger tendency to share others' emotions. To test this, we measured the individual level of echophenomena with a video protocol and experimentally induced empathy for pain in 25 participants with TS and 25 matched controls.

In the empathy for pain paradigm, pictures of hands and feet in painful or neutral situations were presented, while we measured participants' EEG and skin conductance response (SCR). Changes in somatosensory mu suppression during the observation of the pictures, as well as pain ratings and SCR were compared between groups and correlated with the occurrence of echophenomena, self-reported empathy and clinical measures.

Our TS sample showed significantly more echophenomena than controls, but the groups showed no behavioral differences in empathic abilities. However, controls, but not patients with TS, showed the predicted increased mu suppression when watching painful compared to neutral actions. While echophenomena were present in all persons with TS, the hypothesis of an overactive MNS in TS could not be substantiated. On the contrary, the TS group showed a noticeable lack of mu attenuation in response to pain stimuli, questioning the normal functioning of the MNS in empathy for pain situations. In conclusion, the MNS remains an important area of study for TS, but overactivity of the system could not explain echophenomena and social symptoms of TS.

Keywords: Tourette Syndrome, Empathy, Mirror Neuron System, Mu Suppression, Echophenomena

Introduction

Gilles de la Tourette Syndrome (TS) is a neuropsychiatric disorder defined by the presence of motor and vocal tics (DSM 5, Falkai et al., 2018). Of note however, many TS symptoms are inherently social, socially relevant and/or dependent on the social context. One example are so-called echophenomena, which are defined as the automatic imitation of actions, sounds or language without explicit awareness (Ganos et al., 2012). Together with other symptoms such as coprophenomena (Freeman et al., 2009) or non-obscene socially inappropriate behaviors (NOSI, Kurlan et al., 1996), echophenomena indicate that social aspects are central to TS, and that individuals with TS are very sensitive to their social environment. This has led Albin (2018) to suggest his theory of TS as a disorder of the Social Decision Making network. It has also instigated research on the specific changes in social cognition in TS, but results so far are inconclusive (Baron-Cohen et al., 1997; Channon et al., 2012; Drury et al., 2012; Eddy et al., 2010b, 2010a, 2011, 2017; Sprengelmeyer et al., 1997). For example, individuals with TS reported increased personal distress but decreased perspective taking in the Interpersonal Reactivity Index, a measure of trait empathy (Eddy et al., 2015). Based on this and other findings, Eddy (2018) suggested that TS is characterized by increased automatic sharing of others‘ actions and emotions and at the same time reduced mentalizing, possibly reflecting an overactive mirror neuron system (MNS). Similarly, it has been speculated that an overactive MNS might be the cause of echophenomena in TS, as it is critically involved in movement imitation (Ganos et al., 2012; Heyes & Catmur, 2022; Jonas et al., 2010). The MNS has been implied in many higher order social processes such as action understanding, imitation, perspective taking and empathy (Bonini et al., 2022), thus providing a framework to explain echophenomena as well as irregularities in social behavior in TS. First neural evidence supports this theory. The temporal parietal junction, which is supposedly part of a top-down control network modulating the MNS (Brass et al., 2009), shows irregular activity in TS during social cognition tasks (Eddy et al., 2016, 2017). This supports the idea that control of the MNS might be impaired in TS, leading to its increased activation. Even though the neural basis of changes in social cognition as well as echophenomena might be the same, to our knowledge there are currently no studies investigating social cognition and echophenomena in the same sample. Here, we set out to test the hypothesis that the shared neural basis of those social symptoms of TS is an overactive MNS. We measured behavioral and neural correlates of empathy for pain in TS and related these to the patients’ level of experimentally induced echophenomena.

A well-established neural signature of the human MNS, which is measurable with EEG, is somatosensory mu suppression. Decrease of mu frequency amplitude has been shown in both action observation as well as action execution (for a meta-analysis, see Fox et al., 2016), confirming the mirroring property. Furthermore, increased mu suppression has been linked with empathic abilities in several studies looking at empathy for pain (Cheng et al., 2008; Gallo et al., 2018; Peled-Avron et al., 2018; Perry et al., 2010). To test, whether an overactive MNS is the basis of echophenomena as well as altered social behaviors in TS, we thus administered an established empathy for pain paradigm (Hoenen et al., 2015) in a group of TS patients and age-, sex- and education matched controls. Our obtained measures were somatosensory mu suppression as a putative marker for the MNS, the skin conductance response (SCR) as an autonomous response to other's pain, and behavioral evaluations of the experienced pain as a marker of empathic abilities. To pull apart empathy and perspective taking, we manipulated not only the observed pain-level (painful vs. neutral situation), but also the pain sensitivity of the observed actor (normal vs. enhanced pain sensitivity). In TS, we expected an increase in behavioral empathy, associated with stronger mu suppression and increased SCR to painful stimuli as neurophysiological markers of increased personal distress. We predicted that deficits in downregulating the automatic sharing of the actors´ pain should result in impaired differentiation between one´s own and the other's pain sensitivity in TS. Finally, we investigated the relation between experimentally induced echophenomena and behavioral and neurophysiological measures of empathy. We expected that the hypothesized overactive MNS in individuals with TS would lead to increased mirroring of others' actions, evident in echophenomena, as well as automatic sharing of emotional states and less distinction between own and other's perspective, observable as an increase in empathy and decreased perspective taking.

Methods

Participants

Data of N = 50 participants were collected from February 2020 to August 2021. Of those, n = 25 had been diagnosed with TS. They were recruited from the specialized TS outpatient clinic in the Center for Integrative Psychiatry at the University Medical Center Schleswig- Holstein, Campus Lübeck and from the Dept. of Psychiatry, Hannover Medical School, where they received a clinical diagnosis by experienced neurologists (A.M., K. M.-V.). Patients were diagnosed according to DSM-5 criteria

(American Psychiatric Association, 2013). Based on the collected clinical measures, four TS participants were excluded from all data analyses due to severe depression (n = 2), ongoing substance use disorder (n = 1), and subpar IQ (n = 1). Of the remaining n = 21 participants with TS (17 male, mean age (SD) = 33.0 years (14.0), mean years of education (SD) = 15.7 years (2.7)), four were taking antipsychotics (one each was taking pimozide, olanzapine, aripiprazole and amisulpride) and three were medicated with cannabinoids. Dosages were stable in all patients. Three were left-handed.

Additionally, n = 25 healthy controls (HC) (20 male, mean age (SD) = 33.6 years (13.6), mean years of education (SD) = 15.8 years (2.2)) were individually matched to the TS participants regarding sex, age and education. They were recruited by means of poster and online advertisements as well as the university email lists. All controls were free of clinically relevant psychiatric and neurologic symptomatology at the time of testing. One control participant was left-handed. All participants gave their written informed consent to participate in the study in accordance with the Declaration of Helsinki (1964). The local ethics committee gave their approval of the overall project (17-167).

Clinical, personality and intelligence measures

For matching purposes, we measured general intelligence in all participants with four subtests of the Wechsler Adult Intelligence Scale (WAIS-IV; Hartman, 2009; subtests: similarities, picture completion, arithmetic, coding). We further assessed psychiatric symptomatology with the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Symptoms of obsessive compulsive disorder (OCD) were scored using the Yale Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989) and the Obsessive-Compulsive Inventory (OCI; Foa et al., 2002). Severity of attention deficit hyperactivity disorder (ADHD) symptoms was scored using the ADHD-Index scale of the Conners Adult ADHD Rating Scale (CAARS; Conners et al., 1999). Depressive symptoms were measured with the revised version of the Beck-Depression-Inventory (BDI-II; Beck et al., 2009).

To measure TS symptom severity, several questionnaires were administered on the day of the measurement. Tic severity was assessed using the Yale Global Tic Severity Score (YGTSS; Leckman et al., 1989) and the Adult Tic Questionnaire (ATQ; Abramovitch et al., 2015), and premonitory urges using the Premonitory Urge for Tics Scale (PUTS; Woods et al., 2005). Lifetime occurrence of TS symptoms was assessed with the Diagnostic Confidence Index (DCI) (Robertson et al., 1999). For all participants, standardized video recordings were taken and scored using the Modified Rush Video-

Based Tic Rating Scale (MRVS, Goetz et al., 1999), which provides a total tic score ranging from 0 to 20.

To assess self-reported empathy in our participants, the Interpersonal Reactivity Index (IRI; Davis, 1980) was used. This measure includes affective as well as cognitive aspects of empathy and is divided into four subscales, three measuring aspects of affective (fantasy, empathic concern and personal distress) and one measuring cognitive empathy (perspective taking).

All questionnaires were administered in their German versions. Structured interviews (YGTSS, YBOCS, M.I.N.I, DCI) were done by trained interviewers, the rest of the questionnaires were filled out by the participants either online in the week prior to the measurement or in paper and pencil format on the day of the measurement. TS symptom questionnaires were always administered on the day of the measurement.

Procedure

Each participant was asked not to take any drugs or alcohol 24 hours prior to the appointment, but exemptions were made for necessary medications. Testing started with the IQ test, followed by two short video recordings for the MRVS (10 min) and the “Echometer” (5 min, explained below). Participants were then prepared for the EEG and SCR measurement and underwent two paradigms, a paradigm investigating provoked speech errors (50 min, unrelated to the present topic of investigation and not included in this paper) and the empathy for pain paradigm (25 min, explained below). The order of the two paradigms was counterbalanced across participants. After the EEG measurement, participants took a short break. Finally, we administered the structured interviews (M.I.N.I, Y-BOCS), all participants filled out the empathy questionnaire (IRI) and TS participants filled out the aforementioned TS symptom questionnaires. Before leaving, participants were debriefed by the experimenters. The whole appointment lasted around five to six hours. Participants were compensated with 15 Euros per hour.

Echometer

To assess participants’ tendency for echophenomena, we used a similar paradigm as Finis and colleagues (2012). In the paradigm, the participants observe short video clips while they are simultaneously videotaped, to capture any imitation of movements in the videos. Six different video clips with a duration of three seconds (1 s fixed-image, 1 s tic of a person with TS or spontaneous movement of an actor, 1 s fixed-image) were presented. The video clips showed head and shoulder

view segments of one of three individuals with TS (2 male) or one of three actors (2 male). Video clips of the individuals with TS stemmed from previous ten-minute recordings of another study and showed naturally occurring tics. Video clips of the actors were created to match those of the patients and showed spontaneous movements. Each clip included one movement; for spontaneous movements: eyes widening, one eyebrow up and tongue protrusion; for tics: mouth opening, eyebrows up and eyes rolling. Each video was presented five times in a fixed order with a fixation cross (5 s) in between each clip. Thus, each of the 30 trials lasted eight seconds.

Participants were knowingly videotaped using a camera placed on top of the screen. They were instructed to watch the video clips and to fixate on the fixation cross shown in between the video clips. To assure attention, participants were asked to remember which person performed which movement. After the last video clip, the question “Which movement was performed by this person?” was posed, and participants were requested to perform the correct movement. Participants were not instructed to imitate any movements during the task and thus were blinded to the aim of the paradigm.

Empathy for pain paradigm

Our empathy for pain paradigm was similar to that of Hoenen and colleagues (2015). Participants were seated in front of a computer screen and asked to watch 160 pictures. Each picture was presented for 2.5 s followed by a 2.5 s fixation cross (Fig.1). The stimulus set consisted of 80 pictures depicting painful

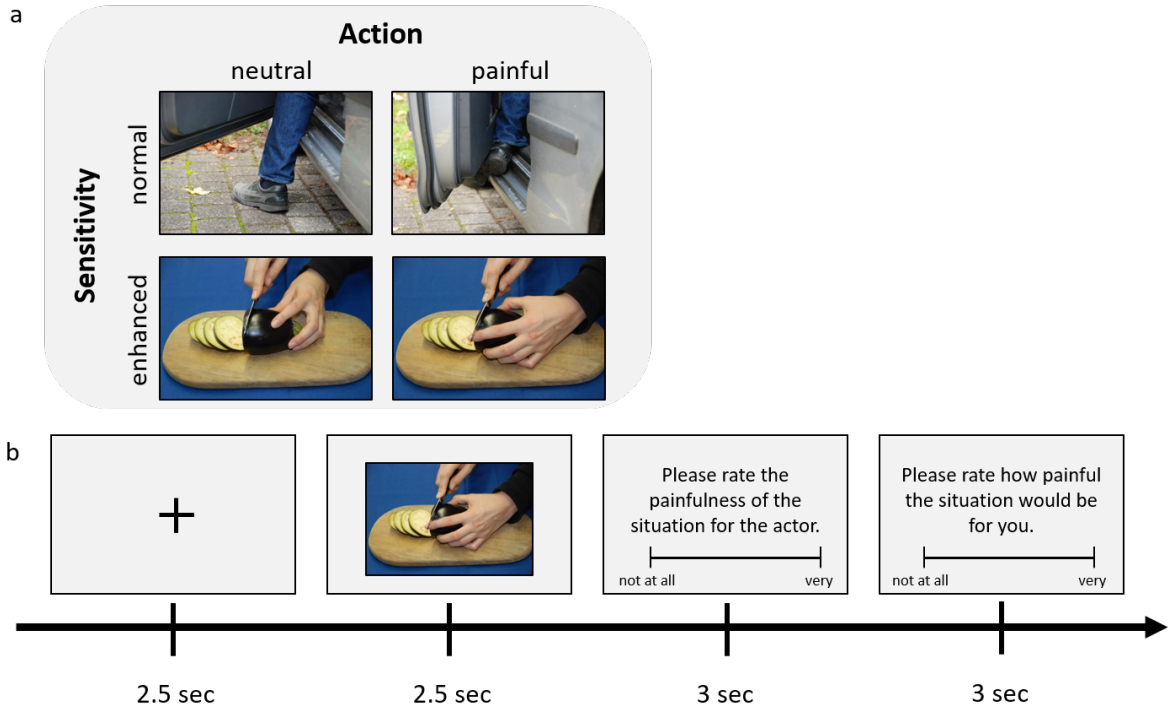


Figure 1. Empathy for pain paradigm **a:** Condition matrix with examples of stimuli. **b:** Trial sequence. Only 25% of the trials were rated.

or neutral situations, taken from the Visually induced pain empathy repository (VIPER; Paulus et al., 2017). The pictures were presented in four blocks, each consisting of 40 pictures (20/20 painful/neutral). Before each block, information about the pain sensitivity of the actors in the pictures was provided. In two blocks, participants were told that the actors have a normal pain sensitivity. In the other two blocks, participants were told that the actors have enhanced pain sensitivity, resulting in pain experience even after mild tactile stimulation. The blocks were presented in counterbalanced order and pictures in the blocks were randomized per participant. In 25% of the trials, participants were asked to rate the painfulness of the situation for the actor and for themselves if they were in that situation. All participants rated the same stimuli. Overall, participants watched 80 pictures twice, once in each pain sensitivity condition, resulting in 160 trials. Overall duration of the paradigm was 25 minutes.

Electrophysiological recordings

Electroencephalographic data (EEG) were recorded with 59 Ag/AgCl electrodes placed on an elastic cap according to the international 10–20 system using BrainVision Recorder (BrainProducts GmbH) with the Brainamp MR plus amplifier. An online reference was placed on the left earlobe, and an off-line reference electrode was placed on the right earlobe. Horizontal and vertical EOG was recorded with four electrodes placed next to the outer corners of the eyes and above and below the left eye. Sampling rate was 500 Hz, and data were recorded with an online high-pass filter of 0.016 Hz and a notch filter at 50 Hz. Impedances were kept below 10 kΩ.

Skin conductance response (SCR) was recorded using two electrodes attached to the medial phalanges of the index and middle fingers of the left hand. The online reference was placed on the left forearm and recorded with the same amplifier (BrainAmp ExG, BrainProdcts GmbH). As SCR data were measured simultaneously with EEG data, the sampling rate was 500 Hz, and an online high-pass filter of 0.016 Hz as well as a notch filter of 50 Hz were applied.

Behavioral data analysis

Videotapes of the participants during the Echometer were rated by two independent raters, who were blinded to the observed videos. We calculated echophenomena frequency for exact repetitions of the observed action (i.e., eye rolling when observing eye rolling) as well as movements in the same body part (i.e., eye movements when observing eye rolling) in the 8 seconds after onset of the video. For group comparisons, we calculated independent t-tests for both measures.

For the pain ratings in the empathy for pain paradigm, we calculated mixed ANOVAs for both the rating of others' pain as well as the rating of one´s own supposed pain. Group was used as a between group factor (TS vs. HC) and action (painful vs. neutral) and sensitivity (normal vs. enhanced) served as within subject factors. For correlating behavioral results with other measures, we calculated the four difference values for each combination of conditions (e.g., difference of action (painful – neutral) in normal sensitivity condition or difference of sensitivity (enhanced – normal) in painful condition) to get a measure of the magnitude of the action or sensitivity effect in either condition. All described correlations are Pearson's correlations

EEG data analysis

All data preprocessing was done in MATLAB®, using the *eeglab* toolbox (Delorme & Makeig, 2004). During offline processing, data were down-sampled to 250 Hz, re-referenced to left earlobe and filtered with a high-pass filter at 0.5 Hz and a low-pass filter at 44 Hz. The signal was segmented into epochs from -500 ms to 2500 ms around the beginning of stimulus presentation. Epochs with obvious movement artifacts due to voluntary movements or tics were manually removed as well as channels with very noisy data. Eye movements and further muscle artifacts and channel noise were corrected using independent component analysis (ICA). Visual screening and the automated classifier ICLabel (Pion-Tonachini et al., 2019) were used to classify components. On average, 5.9 components were removed per participant. After the ICA, the epoch baseline (-500 0) was removed from each epoch. Then, epochs with remaining artifacts were manually rejected and previously rejected channels were interpolated. On average, 27 epochs were excluded (range: 1 – 86) and 0.7 channels interpolated (range: 0 – 6) per participant. Finally, we calculated the surface Laplacian as suggested by Perrin and colleagues (1989) and implemented in MATLAB® by Cohen (2014).

Participants with more than 50 % of rejected trials or less than 15 trials per combination of conditions were excluded from further analyses. We chose this relatively high threshold, as we had to exclude many trials in the TS group due to movement artifacts because of tics. We had already anticipated this and thus chose a high number of trials to begin with. One participant from the TS group was excluded and none of the healthy controls. Thus, analyses of EEG data are conducted on n = 20 TS patients and n = 25 healthy controls.

On the preprocessed data, we did a time-frequency analysis. We calculated trial-averaged power for each subject, channel and experimental condition for linearly spaced frequencies from 1 Hz

to 30 Hz using Morlet wavelet convolution with a variable number of wavelet cycles. Wavelet cycles increased logarithmically from 4 cycles to 15 cycles as a function of frequency. We report decibel (dB) normalized data, using -400 to -100 ms pre stimulus as a baseline.

For the statistical analysis, we took the results of the time-frequency analysis and calculated mean power in the mu frequency band (8–12 Hz) for the time window of interest, 500 to 1500ms after stimulus onset. We chose this time window based on the suggestions of Whitmarsh and colleagues (2011), who underlined the importance of not including the time directly after stimulus onset as to not confound the modulation of ongoing alpha activity and stimulus-onset evoked responses. As we were interested in sensorimotor mu suppression, we focused our analysis on a cluster of central electrodes, including C1, C2, C3, C4, Cz, CPz, CP1, CP2, CP3 and CP4. The occipital cluster, including O1, O2 and Oz, served as a control. Power changes were then compared using a mixed ANOVA with group (TS vs. HC) as a between subject factor and action (painful vs. neutral), sensitivity (normal vs. enhanced), region (central vs. occipital) and laterality (right vs. middle vs. left) as within subject factors. Additionally, we calculated Bayesian statistics for the time frequency data, which enabled us to make statements for the null hypothesis. Calculations were done using JASP (Version 0.16.4). We report the results of the Bayesian model averaging (BFincl) implemented as analysis of effects across matched models. We interpret the Bayes factors according to common guidelines, suggesting values > 3 to provide moderate and values > 10 to provide strong support for the alternative hypothesis. Values < 0.33 provide moderate and values < 0.1 strong support for the null hypothesis (van Doorn et al., 2021).

For correlating EEG results with other measures, we used the same approach as with the behavioral data and calculated the four difference values for each combination of conditions.

To check, whether there are group differences in mu power independent of our task manipulations, we looked at absolute and relative mu power in all central clusters, separately for the time of stimulus presentation and the baseline. Absolute power spectral density of the mu band (8-12Hz) was obtained by applying a fast Fourier transform and averaging mu power per cluster and participant. Relative mu power was calculated by dividing mu power spectral density by the absolute power of all frequencies within 1 and 30 Hz. Group differences were tested by a mixed ANOVA with group (TS vs. HC) as a between subject factor and region (central right vs. central middle vs. central left) as a within subject factor.

SCR data analysis

Analysis of skin conductance was performed using the MATLAB® toolbox *Ledalab* (Benedek & Kaernbach, 2010). The signal was downsampled to 25 Hz and then smoothed with a Gaussian low-pass filter. Obvious artifacts were removed manually. Then, the signal was deconvolved using a continuous decomposition analysis (CDA) with four optimizations. This separates the signal into continuous traces of tonic and phasic activity. We proceeded to analyze the phasic driver component, by extracting averaged event-related responses via area under the curve, between 1 to 4 seconds after stimulus onset. Event-related phasic SCR were range normalized and log transformed across all trials within each subject. This ensured that individual variability in the signal magnitude would not bias further analyses. SCR per trial were then averaged within conditions. One participant from each group was excluded, as the data quality did not allow measurements of any SCR. Thus, analyses of SCR data were conducted on n = 20 TS patients and n = 24 healthy controls. SCR were analyzed similarly to the EEG data with a mixed ANOVA with the factors group, action and sensitivity. For correlation analyses, difference scores were calculated analogous to the behavioral and EEG data.

Results

Demographics, clinical and questionnaire results

Sex, age, and IQ did not differ between TS patients and healthy controls (Table 1), demonstrating successful matching procedures. TS patients showed significantly more obsessive-compulsive symptoms, depressive symptoms and symptoms of ADHD. Severity of TS symptoms in our TS group was comparable to similar studies (i.e.: Brandt et al., 2016; Eddy et al., 2011, 2013; Jonas et al., 2010). Regarding empathic abilities, TS participants reported significantly lower fantasy abilities in the IRI. The two groups did not differ regarding their trait empathic concern, personal distress and perspective taking (Fig. 2a). Additionally, we had hypothesized a correlation between tic severity and trait empathy. Indeed, the YGTSS total tic score correlated with self-reported personal distress in the empathy questionnaire (IRI; $r = 0.57$, $p = .009$), with higher tic severity relating to more reported personal distress (Fig. 2b). Other subscales of the IRI did not significantly correlate with the YGTSS total tic score.

Table 1:

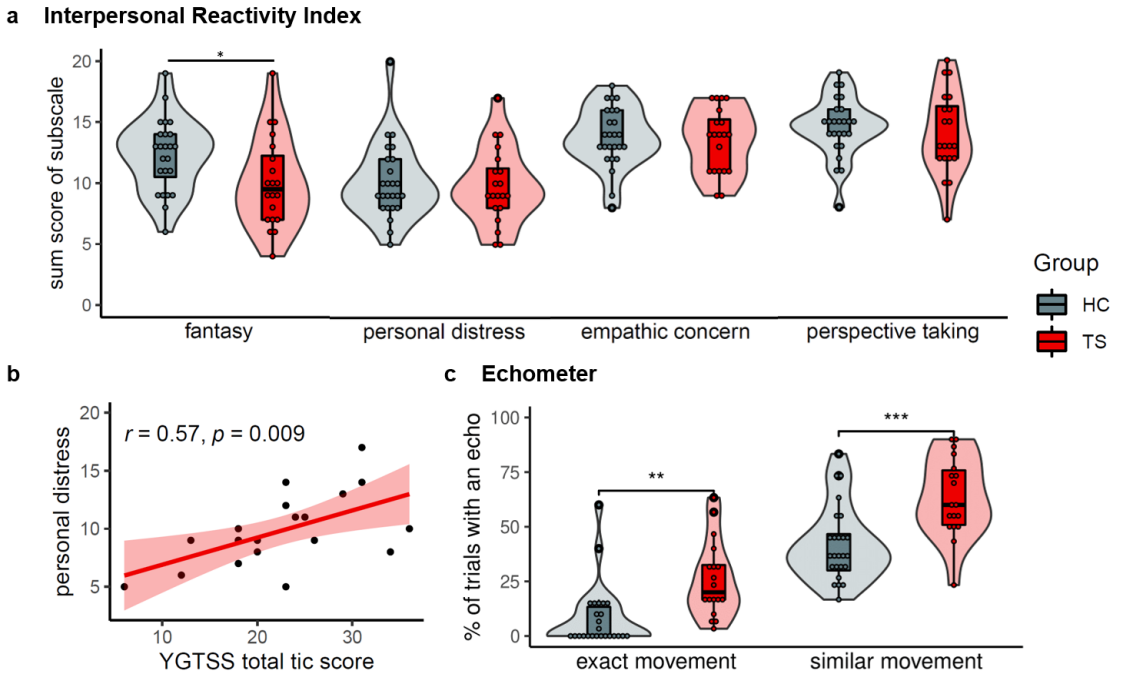
Overview of personality and clinical measures

Questionnaire	TS	HC	*t*	*df*	*p*	Cohen's *d*
Sex	17 m, 4 f	20 m, 5 f				
Age	33.00(14.04)	33.56(13.61)	0.14	42.16	.892	0.04
IQ	106.20(9.06)	104.38(10.97)	0.62	43.99	.541	0.18
Obsessive-compulsive behavior						
YBOCS thoughts	3.48(4.13)	0.20(1.00)	-3.55	21.97	.002	-1.14
YBOCS actions	4.24(4.00)	0.20(1.00)	-4.51	22.11	< .001	-1.44
YBOCS total	7.71(7.18)	0.40(2.00)	-4.52	22.61	< .001	-1.45
OCI	19.71(14.69)	8.88(7.24)	-3.08	28.02	.005	-0.96
Depression	11.14(10.69)	5.00(4.84)	-2.44	26.89	.021	-0.77
ADHD	11.29(6.82)	6.64(4.70)	-2.64	34.55	.012	-0.81
Empathy (IRI)						
Fantasy	10.05(3.72)	12.29(3.00)	2.17	36.35	.037	0.67
Empathic Concern	13.5(2.65)	13.8(2.45)	0.39	39.35	.698	0.12
Personal Distress	9.80(3.11)	10.12(3.10)	0.34	40.83	.733	0.10
Perspective Taking	14.05(3.36)	14.56(2.43)	0.57	33.59	.573	0.18
TS Symptomatology						
MRVS total score	11.90(4.20)	2.44(2.29)	-9.25	29.74	< .001	-2.87
YGTSS Total motor tic score	13.81(3.39)					
YGTSS Total vocal tic score	8.38(6.06)					
YGTSS Total tic score	22.19(7.44)					
YGTSS Global severity score	43.00(15.65)					
ATQ	37.71(25.50)					
PUTS	21.14(4.98)					
DCI	60.86(18.02)					

Note. Questionnaire data separated by group. Average scores plus standard deviations in brackets. m = male, f = female. IQ, Intelligence Quotient as measured by subtests of the Wechsler Adult Intelligence Scale (WAIS-IV). YBOCS, Yale Obsessive Compulsive Inventory. OCI, Obsessive Compulsive Inventory. ADHD, Attention Deficit Hyperactivity Disorder as measured by the Conners Adult ADHD Rating Scale. IRI, Interpersonal Reactivity Index. MRVS, Modified Rush Video-Based Tic Rating Scale. YGTSS, Yale Global Tic Severity Scale. ATQ, Adult Tic Questionnaire. PUTS, Premonitory Urges for Tics Scale. DCI, Diagnostic Confidence Index. TS, Tourette Syndrome. HC, Healthy Controls.

315 **Behavioral Task Results**

316 The analysis of echophenomena yielded clear group differences for both exact imitations ($t(1,32.58)$ =
317 -3.49, p = .001, d = -1.11) as well as movements in the same body part ($t(1,35.58)$ = -3.98, p < .001, d
318 = -1.24). As expected, participants of the TS group showed a higher tendency to echo what they observe
319 than the healthy controls (Fig. 2c).



320 **Figure 2.** Clinical and behavioral results. **a:** Group comparisons in the Interpersonal Reactivity Index
321 (IRI). **b:** Correlation in the TS group of the subscale personal distress in the IRI and total tic score as
322 measured by the Yale Global Tic Severity Scale (YGTSS). **c:** Number of echoes in Echometer. Both
323 exact replications of the observed movement and movements in the same body part were considered
324 for the analyses
325
326 In the empathy for pain paradigm, we compared the pain ratings per condition and found an
327 interaction of action and sensitivity on ratings of others' pain ($F(1,44)$ = 21.69, p < .001, η^2 = .02), with
328 all four pairwise comparisons being significant. When looking at the ratings of the pain that participants
329 themselves would feel in the observed situation, we again found an interaction of action and sensitivity
330 ($F(1,44)$ = 4.16, p = .047, η^2 < .01). However, pairwise comparisons revealed no differences between
331 sensitivity conditions in both painful and neutral stimuli. This shows that both HC and TS performed as
332 expected: They rated the other's pain higher in the painful condition compared to the neutral condition;
333 and they rated the other's pain higher in the enhanced pain sensitivity condition compared to the normal
334 pain sensitivity condition. When rating their own imagined pain, participants made no difference
335 between sensitivity conditions but rated painful stimuli as more painful than neutral ones. However, we
336 did not find any group effects in the ratings. The three-way interaction of group, action and sensitivity

on the rating of others' pain was not significant ($F(1,44) = 0.13$, $p = .72$, $\eta^2 < .01$, Fig. 3), although the differences between sensitivity conditions in the TS group were nominally smaller. On the behavioral level, the experimental manipulations were thus successful, but none of the hypothesized group differences were confirmed.

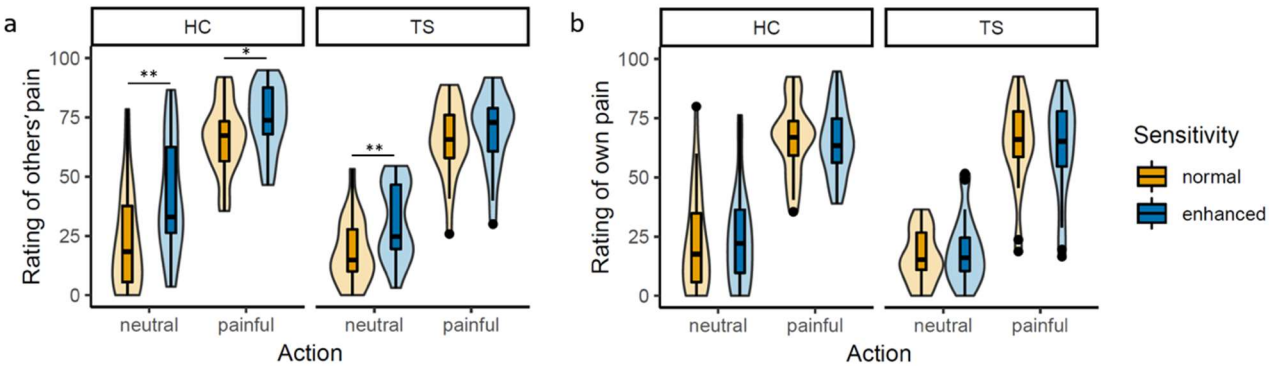


Figure 3. Pain ratings in empathy for pain paradigm. **a:** Rating of painfulness for the actor in the picture from „not at all" to „very" under the normal (yellow) and enhanced (blue) sensitivity condition for both healthy controls (HC, left side) and Tourette patients (TS, right side). **b:** Rating of own imagined pain in the depicted situation on same scale.

Electrophysiological results

The mu suppression in the empathy for pain paradigm showed an interaction of all factors (group, action, sensitivity, region & laterality): $F(2,82) = 3.37$, $p = .039$, $\eta^2 < .01$ (Fig. 4). To understand this interaction, we calculated ANOVAs separately for central and occipital sites. At occipital electrodes, we found a main effect of action ($F(1,43) = 13.80$, $p = .001$, $\eta^2 = .01$), indicating more pronounced alpha suppression after observing painful compared to neutral actions. At the central electrodes, we found a significant interaction of group, action and sensitivity ($F(1,41) = 6.52$, $p = .014$, $\eta^2 < .01$, BF = 4.58). Following ANOVAs for each of the groups revealed no significant interaction of action and sensitivity in the TS group ($F(1,17) = 2.24$, $p = .153$, $\eta^2 < .01$, BF = 2.62), nor any other effects. In HC we found an interaction of action and sensitivity ($F(1,24) = 5.11$, $p = .033$, $\eta^2 < .01$, BF = 2.26). HC showed a simple main effect of action in the normal sensitivity condition ($F(1) = 5.34$, $p = .03$) but not in the enhanced sensitivity condition ($F(1) = 0.03$, $p = .86$). Finally, there were no group differences in absolute or relative mu power, neither during the baseline period (absolute: $F(1,43) = 0.07$, $p = .790$, $\eta^2 < .01$; relative: $F(1,43) = 0.14$, $p = .707$, $\eta^2 < .01$) nor during the stimulus presentation (absolute: $F(1,43) = 1.98$, $p = .166$, $\eta^2 = .03$; relative: $F(1,43) = 0.76$, $p = .387$, $\eta^2 = .02$).

Summarizing, we found the expected increase of mu suppression after observing painful compared to neutral pictures in our control group but only in the normal pain sensitivity condition. TS

participants did not show any significant modulation of mu suppression by the experimental manipulations. Note however that the results of the Bayesian analyses show that the evidence for the interaction effect (action and sensitivity) within the HC and TS groups were similarly equivocal though. This speaks for an overall weak effect of the pain manipulation, and no clear evidence for a lacking pain-related mu modulation in TS. However, the moderate evidence for the interaction of experimental conditions with group speaks for a reduced mu-effect in TS compared to the controls. Finally, the groups had the same level of absolute and relative mu power during the baseline, making it unlikely that differences in baseline mu activity account for the different results in the groups.

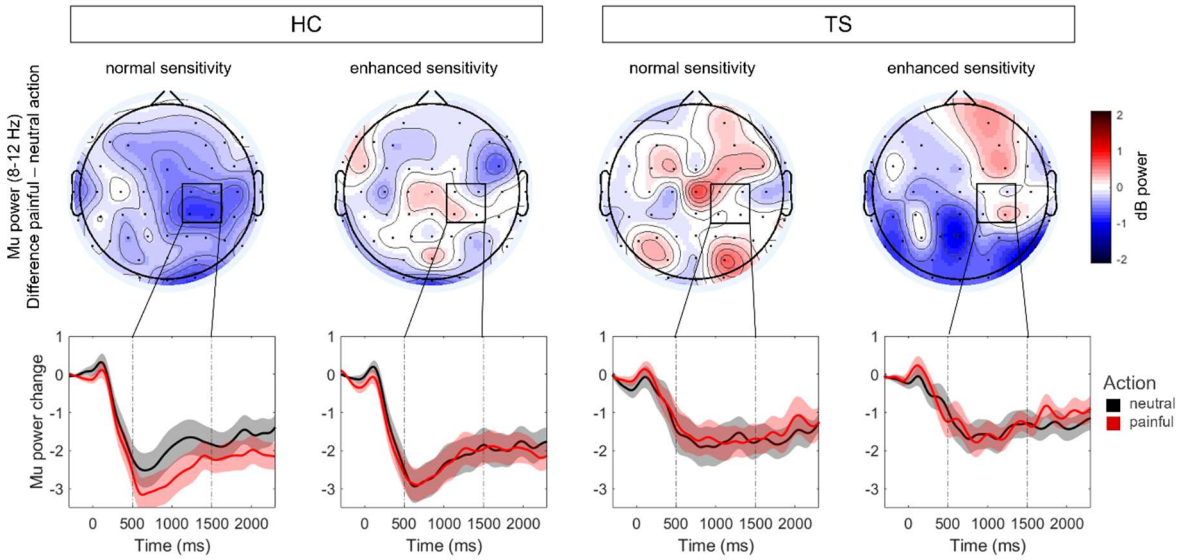


Figure 4. Baseline corrected mu power (8 – 12 Hz) in empathy for pain paradigm. *Top row:* Spatial distribution of mu power differences (painful-neutral) in time-window of interest (500 – 1500 ms). *Bottom row:* Time course of mu power in right central cluster for the painful (red) and neutral (black) condition, separately for the controls (HC, left columns) and Tourette patients (TS, right columns) and for normal and enhanced sensitivity. Time-point 0 refers to the picture onset.

Analysis of the skin conductance response revealed a significant interaction of group, action and sensitivity ($F(1,42) = 5.40$, $p = .025$, $\eta^2 = .01$; Fig. 5). ANOVAs per group revealed a main effect of action in the TS group ($F(1,19) = 4.39$, $p = .050$, $\eta^2 = .01$), with participants showing an enhanced skin conductance response after watching painful actions. For the healthy controls we found an interaction of action and sensitivity ($F(1,23) = 6.24$, $p = .020$, $\eta^2 = .01$), with nominally stronger responses after painful pictures in the enhanced sensitivity condition. Pairwise comparisons were not significant.

Correlations of echophenomena with empathy measures

Based on our hypothesis on a shared mechanism behind echophenomena and empathy, we expected the number of echophenomena to correlate with our behavioral, physiological and neural indices of empathic abilities. To test this, we focused on the difference of action (painful – neutral) in the normal

sensitivity condition. However, echophenomena did not correlate with trait personal distress (r = 0.22, p = .15), behavioral (r = 0.27, p = .08), physiological (SCR: r = 0.11, p = .50) or neural empathy measures (mu: r = 0.15, p = .35). Additionally, we hypothesized a correlation between tic severity and empathy. However, no correlations could be found between tic severity measures of the YGTSS or the MRVS video protocol with behavioral, neural or physiological empathy measures.

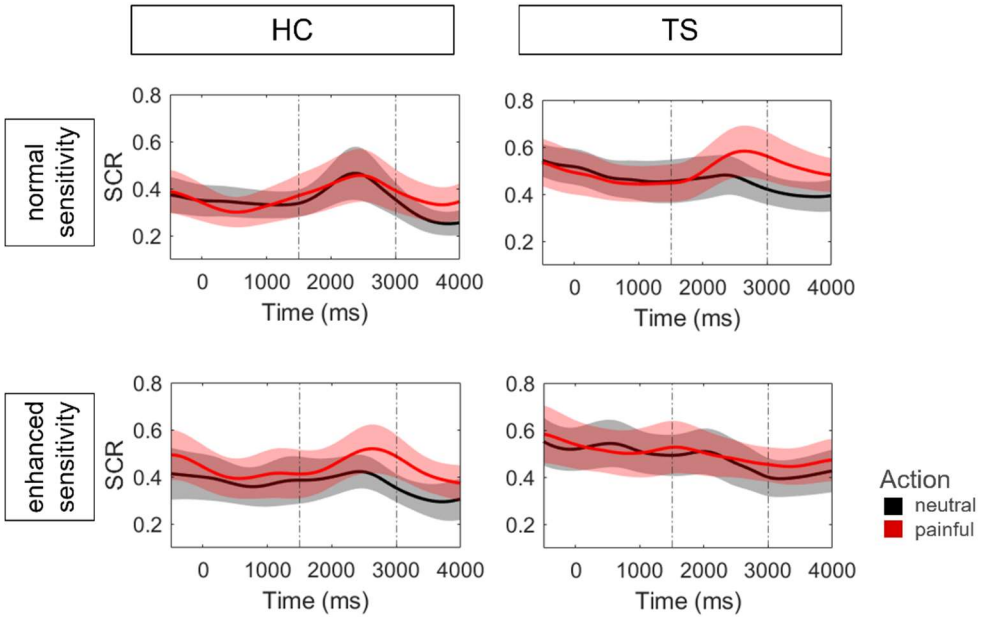


Figure 5. Skin conductance response in empathy for pain paradigm. Plotted are the time courses of the adjusted phasic driver for the painful (red) and neutral (black) pictures, separately for the controls (HC, left columns) and Tourette patients (TS, right columns) and for normal and enhanced sensitivity. Time-point 0 refers to the picture onset. Statistical analysis is based on our window of interest (1500 - 3000 ms).

Discussion

In this study, we tested the hypothesis that echophenomena in TS are related to increased mirror neuron system activity and increased automatic sharing of others' emotional states. As expected, we found that participants with TS showed more echophenomena than controls. However, we did not find any empathy related behavioral differences between TS and HC and no differences in trait empathy or skin conductance between our groups. Interestingly, the TS group showed reduced pain-related mu suppression, indicating, contrary to our hypothesis, decreased mirror neuron system activity in response to others' emotional states.

Echophenomena and trait empathy in TS

In line with a previous study (Finis et al., 2012), we found a strong difference between TS and controls in the frequency of echophenomena induced by our Echometer paradigm. This was true for both exact replications of the observed movement as well as movements with the same body part. Furthermore,

all participants with TS showed echoes, which stresses the high prevalence of echophenomena in this patient group. This is in contrast to previous, lower estimates of its prevalence, usually ranging below fifty percent (Cavanna et al., 2011; Lees et al., 1984). The difference is most likely due to the mode of measurement, as prevalence estimates in these studies were based on self-report or clinicians' observations. It is thus important for future explorations of the neural basis of echophenomena to experimentally measure their occurrence. Additionally, echoes were not only seen in the TS patient group but also, with much lower frequency, in the healthy controls, underlining that imitating others is a normal process and not per se pathological (Ganos et al., 2012). In conclusion, our TS sample exhibited the expected increased tendency for echophenomena compared to controls and should thus, according to our hypothesis, show further symptoms of altered social behaviors and an overactive MNS.

One of the previous findings which had prompted our hypothesis was the report of increased self-reported personal distress, combined with reduced perspective-taking in the Interpersonal Reactivity Index (IRI) in a relatively large TS sample (Eddy et al., 2015). The IRI personal distress subscale measures unease and anxiety in negative emotional settings and is related to poor social functioning, whereas the perspective taking subscale measures the tendency to think about the other´s point of view and is correlated with higher social functioning (Davis, 1983). We utilized the same questionnaire but could not replicate the results in our sample. TS participants in our study did not report increased personal distress or reduced perspective taking compared to the controls. We did find an increase of reported personal distress with higher tic severity, but this was also contrary to what Eddy and colleagues reported (2015), as they found a *negative* correlation between tics and personal distress. Although our sample was smaller compared to theirs, our effect sizes were also considerably smaller, which makes it unlikely that we missed the effect only because of a smaller sample. Furthermore, our sample included far less medicated participants, but comorbidities were comparable across both samples. TS participants in our study did report lower fantasy scores compared to controls, indicating a decreased tendency to imaginatively transpose themselves into fictional situations. Overall, we found group differences in self-reported empathy but those were not consistent with the previous report of Eddy and colleagues (2015). Additionally, the results of the empathy self-report did not correlate with the tendency for echophenomena.

Empathy for pain in TS

In the empathy for pain paradigm, both groups performed similarly and in line with the task manipulation, showing that task instructions were understood by both groups. We had hypothesized increased painfulness ratings after painful stimuli for our TS group, which we could not confirm. However, one could argue that the pain ratings in our paradigm did not reflect only automatic sharing of the experience of the actor but also cognitive understanding of the situation. Furthermore, the pain stimuli were not overly graphic and did not show obvious signs of extreme pain, like blood, broken limbs, painful facial expressions or body language, and might thus not elicit strong discomfort in the viewer. Hence, our paradigm might not have been sensitive enough to detect subtle behavioral differences between the groups. Moreover, TS might still show altered neural processing even in the absence of obvious behavioral differences.

Physiologically, increased distress due to increased sharing should have been visible in a stronger skin conductance response in the TS group. However, we found no such group differences. If anything, results suggested a slightly reduced modulation of skin conductance response by the sensitivity manipulation in the TS group. Previously, the magnitude of SCR to observing other's in pain has been linked to prosocial behavior (Hein et al., 2011) and implicit race bias (Forgiarini et al., 2011), with higher SCRs corresponding to increased empathy and prosocial behavior. In conclusion, our results could indicate slightly reduced empathy in TS compared to controls.

In terms of the neural data, several studies have probed mu suppression under different conditions or in different groups with an almost identical setup as ours: participants observing pictures of body parts in painful or neutral situations (Arnett et al., 2019; Hoenen et al., 2015; Li et al., 2017; Yang et al., 2009). Those studies consistently find increased mu suppression during the observation of painful compared to neutral pictures. The magnitude of mu suppression is interpreted as a measure of empathy and is modulated by several factors, with less mu suppression being observed in men than women (Yang et al., 2009), during negative mood compared to positive or neutral mood (Li et al., 2017) and after reported parental emotional invalidation (Arnett et al., 2019). In line with those findings, our healthy controls showed the expected pain-related mu suppression over the right sensorimotor cortex. This was modulated by our additional manipulation of the actors' pain sensitivity. Suppression only differed between painful versus neutral stimuli when the pain sensitivity of the actor was normal. This effect vanished under the enhanced pain sensitivity condition, indicating that controls processed both

471 kinds of stimuli as painful in this condition. Our results thus mirror those of Hoenen and colleagues
472 (2015), who originally developed this paradigm and found increased mu suppression in trials where
473 participants were informed that the actors have an increased pain sensitivity. In a similar setup,
474 participants observed hands either being pricked by a needle or being touched by a Q-tip (Perry et al.,
475 2010). Participants were asked to assume either normal pain reactions or switched pain reactions,
476 where needle pricks were not painful, but Q-tip touches were. When participants assumed normal pain
477 reactions, the classic increase of mu suppression in painful over neutral situations was observed.
478 However, when participants assumed switched pain reactions, mu suppression was equally large in
479 painful and neutral situations. Those results combined with what we observed in the healthy controls
480 indicate that mu suppression is not only elicited by automatic empathic reactions to the observed stimuli
481 but can be modulated by top-down processes, making it possible to feel empathy for pain even in
482 situations that would not be painful for the participants themselves. Interestingly, TS participants did not
483 show any significant pain-related attenuation of mu power, although Bayesian analyses indicated
484 equivocal evidence for and against this effect. However, this group difference in pain-related mu
485 suppression speaks against our hypothesis of increased automatic sharing in TS, but rather points in
486 the opposite direction. One might argue that a generally overactive MNS in TS could lead to less
487 pronounced mu attenuation during our paradigm. However, the TS group showed similar absolute and
488 relative mu power during the baseline as well as averaged across all stimulus presentations. This
489 questions that the group differences can be attributed to baseline differences and a generally overactive
490 MNS.

491 **Is an overactive MNS in TS causing echophenomena and changes in empathy?**

492 What are the implications for our hypothesis that an overactive MNS is the basis of both altered social
493 behaviors and echophenomena? First of all, we did not find any alterations in empathic behavior in the
494 TS group and can thus not draw any conclusion on possible causes of altered social behavior in TS.
495 Second, we did not find evidence that an overactive MNS is at the core of the clearly increased tendency
496 for echophenomena in our TS sample. On the contrary, we found less MNS activity in the TS group
497 during the empathy for pain task.

498 Our results might thus support an alternative hypothesis about the basis of echophenomena.
499 Rather than echophenomena being indicative of a generally increased tendency to imitate, they might
500 reflect the failure to inhibit imitation in contexts where it is not useful (Ganos et al., 2012). Thus, in

501 situations where imitation has a social function and can be found in healthy adults, we find no increase
502 of imitation in TS compared to controls. It is in situations where imitation serves no purpose, such as
503 our Echometer paradigm, that we find increased imitation in TS. This also fits with previous results in
504 an automatic imitation paradigm (Jonas et al., 2010). Both TS and HC showed a comparable modulation
505 of reaction times by incongruent movements compared to congruent movements, indicating similar
506 automatic imitation tendencies. In conclusion, in social contexts where it is beneficial, such as an
507 empathy paradigm, imitation or automatic sharing of the other´s state does not seem to be increased
508 in TS compared to controls. This interpretation is further supported by the fact that we found no
509 relationship between the extent of echophenomena or tic severity and the behavioral and neural results
510 in the empathy for pain paradigm.

511 However, not only did we not find an increase in automatic sharing in our empathy paradigm,
512 our results even pointed in the opposite direction, with TS participants showing less pain-related mu
513 suppression than controls. This fits to an additional hypothesis brought forward by Ganos and
514 colleagues (2012). They propose that people with TS compensate the deficient inhibition in motor
515 networks with increased activity in inhibitory circuits outside the motor network, presumably prefrontal
516 areas. They thus assume that compensatory activity in the TS brain leads to less responsiveness to
517 experimental manipulations. It is feasible that due to the failure to inhibit tics or echophenomena in
518 inappropriate contexts, the TS brain overcompensates by generally decreasing the responsiveness to
519 stimuli. This fits to recent Go/No-Go studies in TS, which found reduced task-related activations
520 compared to healthy controls (Niccolai et al., 2016; Thomalla et al., 2014). In one study, task-related
521 BOLD signal change was decreased in cortical motor areas but not in other areas in people with TS.
522 This was accompanied by poorer task performance compared to healthy controls (Thomalla et al.,
523 2014). In another Go/No-Go task, participants with TS showed less beta suppression in the
524 sensorimotor area but enhanced beta power in parieto-occipital brain regions compared to healthy
525 controls, but task performance was the same in both groups (Niccolai et al., 2016). Similarly, in the
526 aforementioned automatic imitation task (Jonas et al., 2010), where TS and HC showed no differences
527 in the interference effect, people with TS exhibited less movement facilitation by observing congruent
528 biological movements than healthy controls. However, they showed more interference than healthy
529 controls when observing incongruent biological movements compared to the observation of non-
530 biological movement, hinting to an overactive imitation inhibition system that is active during the task.

To conclude, our findings of decreased mu modulation in TS compared to the controls might be explained by increased inhibition. However, it is important to note, that none of these studies or our study provided direct neural evidence for increased inhibitory activity.

Limitations

Our groups were of moderate size, which might have led us to miss small group differences. The results of Bayes statistics underlined this problem, as we found moderate evidence for group differences in pain-related mu suppression in the interaction, but overall weak effects of the pain modulation in both groups. The small magnitude of pain-related mu suppression might be partly due to our sample being predominantly male, as male participants were found to exhibit less mu suppression than females in previous research (Yang et al., 2009). Another caveat regarding our results is the heterogeneity of our TS sample. TS is often accompanied by several comorbidities, and this was the same in our group. Compared to the controls, the TS group showed more symptoms of depression, anxiety, ADHD and OCD, all of which could have influenced our results. However, as most individuals with TS suffer from symptoms of one or more of these comorbidities, we considered it best to include them to create a representative sample for this clinical group. Finally, our empathy paradigm was relatively easy and might thus not be suitable to measure subtle group differences in behavioral empathy.

Conclusions

Together, our results speak against an overactive MNS and against increased levels of empathy in TS. In contrast, our findings indicate reduced pain-related neural processing in TS, although this had no behavioral impact in the current task. As our TS sample evinced high levels of echophenomena, the underlying neurocognitive processes of this symptom remain to be established. Overall, as our study, as well as previous studies (Eddy et al., 2016, 2017; Neuner et al., 2010), imply altered processing of stimuli in social contexts, future research should continue to explore the neural basis of social symptoms and echophenomena in TS.

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