Neural correlates of altered sensorimotor gating in boys with Tourette Syndrome: A combined EMG/fMRI study

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ABSTRACT

Objectives: It has been hypothesised that altered sensorimotor gating might be a core problem in Tourette Syndrome (TS). However, the underlying neurophysiological mechanisms are elusive.

Methods: We applied functional magnetic resonance imaging (fMRI) to investigate the neural correlates of altered sensorimotor gating by means of prepulse inhibition (PPI) in 22 boys with TS and 22 healthy boys using tactile PPI. The electromyography of the startle response was recorded simultaneously to the acquisition of the fMRI images.

Results: As expected, PPI of the startle response was reduced in boys with TS compared to the healthy boys. We found decreased PPI-related blood oxygen level-dependent (BOLD) activity in boys with TS in the middle frontal gyrus, postcentral gyrus, superior parietal cortex, cingulate gyrus and caudate body. In boys with TS PPI of the startle response was positively correlated to PPI-related BOLD activity in the superior parietal cortex.

Conclusions: Our findings indicate that deficient sensorimotor gating in boys with TS is associated with reduced recruitment of brain regions responsible for the higher-order integration of somatosensory stimuli. Due to our strict sample selection we were able to reduce confounding by neural adaptation processes, long-term medication, gender or comorbidities.

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Introduction

Tourette Syndrome (TS) is a childhood-onset neuropsychiatric disorder characterised by multiple motor tics and at least one phonic tic. Although tics are undoubtedly the hallmark of TS, abnormal somatosensory processing and sensorimotor integration might also be a core problem of the disorder that relates to structural neuroanatomical changes like a thinning of sensory cortical areas (Sowell et al. 2008) and altered connections between somatosensory and motor cortical areas (Thomalla et al. 2009). The conceptualisation of TS as a sensorimotor disorder has been underpinned by the fact that the motor and vocal expression of tics is very often connected to internal somatosensory or psychic experiences (Bliss 1980). About 82% of the patients with TS report premonitory (tic-preceding) urges, which are often described as somatosensory sensations like a muscle tension, itching or tingling (Cohen and Leckman 1992). In addition, some patients with TS are distracted, distressed or unusually aware of particular somatosensory stimuli, which most individuals would not notice, e.g., they report hypersensitivity for care labels in clothing or body contact with a chair (Cohen and Leckman 1992; Belluscio et al. 2011). Swerdlow and Sutherland (2005), suggesting those internal experiences of premonitory urges and distraction by somatosensory stimuli are associated with deficits in inhibition or “gating” of sensory, cognitive or motor information. In other words, the close link between premonitory urges and motor tics in patients with TS is assumed to stem from a breakdown in these gating mechanisms.

There is a large body of evidence indicating that TS is associated with deficient inhibitory mechanisms. With transcranial magnetic stimulation (TMS) it has been found that patients with TS exhibit reduced short-latency afferent inhibition (Orth 2009), reduced short-interval intracortical inhibition (Ziemann et al. 1997; Orth et al. 2008), as well as a shorter cortical silent period (Ziemann et al. 1997). In a study on children and adolescents with TS, Moll et al. (2006) found the relation between a shortened cortical silent period and (distal) tics to be age-dependent.
In the current study we investigated the neurophysiological and functional neuroanatomical mechanisms underlying sensorimotor gating using combined electromyography (EMG)/functional magnetic resonance imaging (fMRI) recordings during a prepulse inhibition (PPI) task. PPI refers to the reduction of the startle blink magnitude when the startle stimulus is preceded 30–500 ms by a weaker stimulus, i.e., prepulse. It has already been shown that patients with TS exhibit reduced PPI using electric (Castellanos et al. 1996) or tactile stimuli (Swerdlow et al. 2001; Zebardast et al. 2013). In a large part PPI is regulated by subcortical circuits, but PPI-related changes in blood oxygen level-dependent (BOLD) activity have also been found in the anterior insula, the anterior cingulate, the prefrontal and parietal cortex, the primary and secondary somatosensory cortices, the thalamus, the striatum and the cerebellum (Hazlett et al. 2001; Kumari et al. 2003; Goldman et al. 2006; Campbell et al. 2007; Hazlett et al. 2008; Neuner et al. 2010; Schulz-Juergensen et al. 2013). Significant correlations between PPI and grey matter volume were obtained in the frontal, prefrontal and parietal cortex, the superior temporal gyrus, the premotor cortex and presupplementary motor area, the thalamus and the basal ganglia including parts of putamen, globus pallidus and nucleus accumbens (Kumari et al. 2008; Hammer et al. 2013; Ota et al. 2013). These findings are of importance for our study, because many of those brain regions that were found to be involved in PPI also play a crucial role in the pathophysiology of TS.

A recent study found adult patients with TS (average 33.2 years) to exhibit altered PPI-related BOLD activity in several brain structures (Zebardast et al. 2013). Compared to healthy controls, patients with TS exhibited significantly lower PPI-related BOLD activity in the middle temporal gyrus, orbitofrontal cortex, posterior cingulate cortex, ventral lateral prefrontal cortex, lateral frontal cortex, posterior cerebellum as well as in the caudate. By contrast, the PPI-related BOLD activity in the left parietal cortex was stronger in patients with TS than in healthy controls.

In adult patients with a long history of tic symptoms, compensatory brain reorganisation due to long-term tic activity, tic suppression or medication intake might have taken place (Jackson et al. 2011; Eichele and Plessen 2013). It is, therefore, difficult to determine whether the abnormalities regarding the neural correlates of PPI that have been observed in adult patients are an immanent feature of the TS pathophysiology or if they are due to any compensatory mechanism. In addition to those duration of disorder-related changes, PPI is age dependent (Ellwanger et al. 2003). Both facts highlight the necessity to apply the study protocol by Zebardast et al. (2013) to children and adolescents. Therefore, we investigated exclusively boys in the age range of 11–17 years, which is close to the age in which patients with TS usually first become aware of the premonitory urges (about 10 years) (Leckman et al. 1993). In the context of inhibitory control functions it has been shown that, besides maturation of fronto-striatal networks (Luna et al. 2010), it is especially the parietal component which is subject to strong developmental changes (Mehnert et al. 2013). We therefore suggested that differences between the previous study on adult patients with TS (Zebardast et al. 2013) and our study on children and adolescent with TS might especially occur in parietal brain regions.

In previous studies on PPI in children and adolescents with TS (Castellanos et al. 1996; Swerdlow et al. 2001), comorbid disorders have not been excluded, making it difficult to ascribe the observed deficits to TS per se. In order to reduce any confounding effects of comorbidities, we excluded patients with any axis I disorders besides TS. The comparison between children and adolescents with TS and healthy controls was done with two-factorial repeated measures analysis of variance (ANOVA) including the factors Condition (prepulse, PP, condition vs. pulse alone, PA, condition) and Group (boys with TS vs. healthy controls), whereby a significant interaction indicated group differences in PPI. The integration of the startle response data and the fMRI data was done with regression analysis.

Methods

Sample characteristics

The recruitment was restricted to boys aged between 11 and 17 years. We excluded patients with any axis I disorders comorbid to TS, except phobias as long as they were no current source of impairment. Initially, 26 boys with TS and 25 healthy controls were recruited. Four boys with TS had to be excluded because of comorbidities, braces, excessive motion artefacts or technical difficulties, resulting in a total of 22 boys with TS. One of the controls had to be excluded because of claustrophobia, one because of a large intracranial cyst and one because he exhibited motor tics during the examination, resulting in a total of 22 boys in the control group.

Nine boys with TS were currently taking medication (five tiapride, one aripiprazole, one aripiprazole and fluoxetine, one pimozide and one risperidone). Four participants were left handed.

Written informed consent was obtained from both the participants and their parents. The study was approved by the local ethics committee and was consistent with the Declaration of Helsinki. The demographics and
clinical characteristics of the sample are presented in Table I.

The Yale Global Tic Severity Scale (YGTSS; Leckman et al. 1989) was obtained from all boys with TS to determine the current symptom severity. Premonitory urges were assessed with the Premonitory Urge for Tics Scale (PUTS; Woods et al. 2005).

**Task**

A tactile version of the PPI paradigm (Swerdlow et al. 2001) was employed. The startle response was elicited by an air burst of 40 pounds per square inch (psi) delivered to the subjects neck midline above the sternum. The experiment included two conditions: in the PA condition an air burst of 40 psi was presented for 40 ms. In the PP condition, the startle stimulus was preceded by an air burst of 6 psi, presented for 20 ms with a stimulus onset asynchrony of about 140 ms. White noise of 70 db was presented via binaural headphones throughout the session to mask the sound of the air bursts.

We used an event-related fMRI design. At the beginning as well as at the end of the experiment, six PA trials were presented. Forty PA trials and 40 PP trials were presented in random order between the start and end of the experiment. All trials were separated by an inter-trial interval that was randomly jittered between 3 and 10 s.

**EMG acquisition, preprocessing and analyses**

The startle response was assessed by recording the EMG activity at the left musculus orbicularis oculi and at electrode FP1 using fMRI compatible Ag/AgCl electrodes that were part of a 64-channels electrode cap. The study focussed on the startle response and EMG activity, so the other electrode sites were not analysed with respect to event-related potentials. Yet, the different electrodes were needed also for artefact correction procedures for electrodes used to measure the startle response. The electrocardiogram (ECG) was recorded simultaneously from an electrode on the participants back. Prior to the measurement of the EMG in the scanner environment, the impedances of the EMG and the ECG electrode were kept below 18 kOhm. Amplification was done using the BrainAmp MR-amplifier run with BrainVision Recorder 1.20 software (Brainproducts GmbH, Munich). The sampling rate was set to 5 kHz.

The preprocessing was done as described by Hoffmann et al. (2014). Correction of the gradient artefact was done with the Matlab toolbox EEGLAB (Delorme and Makeig 2004) using the Bergen plug-in (Moosmann et al. 2009), provided by the fMRI group of the University of Bergen, Norway. The gradient artefact was removed by applying the algorithm proposed by Allen et al. (2000), using a baseline-corrected moving average of 20 consecutive volumes. Subsequently, data were downsampled to 250 Hz, low-pass filtered at 25 Hz and high-pass filtered at 1 Hz (nonlinear IIR-filter with a 48 dB/oct). The ballistocardiogram (BCG) artefact was removed by means of a combination of the substraction method by Allen et al. (1998) and Independent Component Analysis (Comon 1994). First, the BCG artefact was removed by the method proposed by Allen et al. (1998), then independent component analysis was conducted using extended infomax and natural gradient as implemented in EEGLAB (Jung et al. 1997; Amari 1998; Lee et al. 1999; Delorme and Makeig 2004). Subsequently, the correlation between independent component activation time course and the ECG channel was calculated, and residual BCG activity was removed by removing independent components accounting for more than 90% of the variance in the ECG channel (i.e., that showed a squared correlation 0.9). On average, five components (min = 2, max = 17) were removed.

Following the artefact correction, the data were segmented relative to the stimulus onset (–400 ms: 1200 ms) and a final automatic artefact correction procedure (removal of segments containing artefacts

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**Table I. Age, IQ, tic severity and tic duration.**

|                        | Mean (SD) | Boys with TS N=22 | Healthy control boys N=22 | t (42) | P value |
|------------------------|-----------|-------------------|---------------------------|--------|---------|
| Age (in years)         | 13.45 (1.79) | 14.14 (1.94)      | –                         | –1.21  | 0.232   |
| IQ                     | 109 (13.40) | 111 (13.35)       | –                         | –0.47  | 0.638   |
| Tic duration (in years)| 6.59 (2.84) | –                 | –                         | –      | –       |
| YGTSS                  |           |                   |                           |        |         |
| Motor Tic Score        | 12.73 (4.34) | –                 | –                         | –      | –       |
| Phonic Tic Score       | 8.00 (5.76) | –                 | –                         | –      | –       |
| Tic Severity Score     | 10.36 (11.86)| –               | –                         | –      | –       |
| Global Tic Score       | 18.32 (22.96)| –              | –                         | –      | –       |
| PUTS                   |           |                   |                           |        |         |
| Total Score            | 23.18 (7.33)| –               | –                         | –      | –       |

IQ, assessed with the short version of the Hamburg-Wechsler Test for Intelligence for children (HAWIK-IV, German version of the WISC-IV; Petermann and Petermann 2010); YGTSS, Yale Global Tic Severity Scale (Leckman et al. 1989); PUTS, Premonitory Urge for Tics Scale (Woods et al. 2005).
with activity below −400 μV or above 400 μV, as well as artefacts with activity lower than 0.5 μV over an interval length of 100 ms). Following a baseline correction (−400 ms: −140 ms), the startle response was quantified as the most positive value (peak) in the time window from 20 to 150 ms at the EMG electrodes.

The inhibition of the startle response by the prepulse (PPI_{EMG}) was calculated as the difference between the peak of the startle response in the PA condition and that in the prepulse condition (PP), i.e., PPI_{EMG} = peak of PA − peak of PP. We used this difference score instead of the standardly used percent score for two reasons: First, because the higher variance of the data acquired simultaneously to fMRI potentially enables negative values in PP trials, which in turn might lead to percentages over 100%. Second, the difference score enables a direct comparability of EMG and fMRI data, because in fMRI analyses PPI is commonly calculated as the contrast between the PP and the PA condition. A two-factorial repeated measures ANOVA was conducted in order to analyse the effects of Condition (PP vs. PA) and Group (controls vs. TS) on the peak amplitude and the latency of the startle response in ms.

**fMRI acquisition, preprocessing and analysis**

The fMRI scan was performed on a 3-T Siemens Magnetom Trio A Tim. High-resolution structural images (1.0 × 1.0 × 1.0 mm) were obtained using a magnetisation prepared rapid gradient-echo (MP-RAGE) T1-weighted sequence (TR = 1900 ms, TE = 2.26 ms, TI = 900 ms, flip angle = 9°). Functional images were acquired with a gradient echo planar T2*-weighted sequence (TR = 2600 ms, TE = 30 ms, flip angle = 80°, matrix size = 256 × 256, field of view = 200 mm, 40 transversal slices with 3 mm thickness of slices). The images were acquired in descending order.

The fMRI data were analysed using SPM8 software (Wellcome Department of Imaging Neurosciences, UCL, UK, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing steps involved slice time correction, realignment (three translation and three rotation parameters), indirect normalisation and smoothing (Gaussian Kernel, Full width at half maximum, FWHM = 8 mm). Indirect normalisation involved three steps: (1) co-registration of the subjects’ functional data sets to their structural data sets, (2) segmentation of the structural image into cerebrospinal fluid, white matter and grey matter based on Montreal Neurological Institute (MNI) templates, and (3) warping of each individual data set into the MNI standard space.

After preprocessing, the single-subject (first-level) analyses were performed. For each subject the input functions representing the timing of each event (pulses in trials of the PA and PP condition) were convolved with the canonical hemodynamic response function. Additionally, regressors of temporal and dispersion derivatives were included in the statistical model to account for slight deviations of onset time and response width in the individual BOLD response relative to its canonical form (Friston et al. 1998). Data were filtered by means of a high-pass filter with a cut-off period of 128 s. Four BOLD contrasts (planned t-contrasts) were modelled: (1) PP > baseline, (2) PA > baseline, and (3) PP > PA, 4) PP < PA. Motion parameters of the realignment step during preprocessing were included as additional covariates of no interest to control for residual movement-related variance from the time series.

Using the parameter estimates obtained by single-subject analyses, we performed a second-level random effects analysis (one-sample t-test, threshold at P < 0.001, uncorrected, extent threshold of 10 voxels) to analyse the functional BOLD activity in the two experimental conditions (PP and PA) in the control and in the TS group. Group comparison (controls vs. TS) was done with two sample t-tests (threshold at P < 0.001, uncorrected, extent threshold of 10 voxels) for the contrast PP > PA (PPI_{fmri}). Beta values of the identified regions were extracted and a two-factorial Condition by Group ANOVA was run using IBM SPSS Statistics 21 Software. A regression analysis was run to predict the PPI_{EMG} out of the PPI_{fmri} in the identified regions of interest.

**Results**

**Prepulse inhibition of the startle response (PPI_{EMG})**

Exploratory data analysis of PPI_{EMG} data revealed one outlier in the TS group with a PPI_{EMG} value higher than three standard deviations above the mean, who was excluded from the subsequent analysis of the PPI_{EMG} values.

A two-factorial repeated measures ANOVA on the startle amplitude revealed a significant interaction effect between the factors Condition and Group (F(1,41) = 9.85, P = 0.003). The main effect of Condition reached trend level (F(1,41) = 2.95, df = 1, P = 0.094), while the main effect of Group was not significant (F(1,41) = 2.09, P = 0.156). Post-hoc tests showed a significant reduction of startle amplitude in the PP condition compared to the PA condition (paired t-test, t = −3.93, df = 21, P = 0.001) in healthy controls, while in the TS group there was no significant difference between startle amplitude in the PP and the PA condition (paired t-test, t = 0.90, df = 20, P = 0.380). Hence, PPI_{EMG} was higher in healthy controls (15.55 ± 18.58) compared to boys with TS (−4.55 ± 23.27)
There was a positive correlation between PPIEMG and age ($r = 0.401$, $P = 0.008$). In the TS group there was a positive correlation between PPI EMG and tic duration ($r = 0.468$, $P = 0.032$). We did not find any correlation between the PUTS score and PPIEMG in the PA or PP condition.

The ANOVA on the startle latency revealed a significant main effect of Condition ($F_{(1,41)} = 6.23$, $P = 0.017$), indicating that startle latency in the PP condition ($85.86 \pm 21.89$ ms) was shorter than the startle latency in the PA condition ($99.16 \pm 26.37$ ms). There was no significant main effect of Group ($F_{(1,41)} = 0.23$, $P = 0.676$) or interaction between Condition and Group ($F_{(1,41)} = 0.54$, $P = 0.467$). In the boys with TS the startle latency in the PA condition was positively correlated to tic severity ($r = 0.489$, $P = 0.024$), while there was a negative correlation between tic severity and startle latency in the PP condition ($r = -0.470$, $P = 0.032$) (Figure 2). We did not find any correlation between the PUTS score in the TS group and the startle latency in the PA and PP condition.

**Neural correlates of PPI (PPI$_{fmri}$)**

A whole-brain random effect analysis in the control group revealed the following functional BOLD activity as being associated with the PP condition: the medial and inferior frontal gyrus, the premotor gyrus, the postcentral gyrus and the precuneus, the middle occipital gyrus, the insula, the cingulate gyrus and the thalamus (details including talairach coordinates can be found in the Supplemental material available online). Functional BOLD activity associated with the PA condition in the control group was found in similar brain regions, namely the medial frontal gyrus, the premotor cortex, the postcentral gyrus, the precuneus, the cuneus, the cingulate gyrus, the insula and the claustrum (see Supplemental material available online).

A two sample $t$-test (threshold at $P<0.001$, uncorrected, extent threshold of 10 voxels) revealed five brain regions, in which the healthy controls exhibited a stronger PPI$_{fmri}$ (PP > PA) than the boys with TS: the middle frontal gyrus (BA9), the postcentral gyrus (BA3), the superior parietal cortex/precuneus (BA7), the cingulate gyrus (BA32) and the caudate body (details are displayed in Table II and Figure 3). In all of those brain
regions the beta values of PPI_{fMRI} were significantly lower in boys with TS compared to healthy controls (see Figure 3). We did not find any region, in which the boys with TS exhibited increased PPI_{fMRI} compared to healthy controls. In the superior parietal cortex/precuneus the beta values of the BOLD activity in the PP condition were positively correlated to age ($r = 0.413$, $P = 0.006$). We did not find any correlation between the PUTS score and PPI_{fMRI} in any of the five regions of interest.

The integration of the EMG and fMRI data was done with regression analysis determining if PPI_{EMG} was correlated to the beta values of PPI_{fMRI} in the regions of interest listed in Table II. For each region of interest a separate regression analysis was run. PPI_{EMG} was positively correlated to the beta value of PPI_{fMRI} in the postcentral gyrus (BA3) ($\beta = 0.449$, $P = 0.003$). The beta value of PPI_{fMRI} in the superior parietal cortex/precuneus (BA7) cluster was not a significant predictor, but showed a trend towards significance ($\beta = 0.288$, $P = 0.062$). PPI_{EMG} of the startle response was not correlated to the beta values of PPI_{fMRI} in the middle frontal gyrus (BA9), the cingulate gyrus (BA32) or the caudate.

Figure 2. Correlation between startle latency and tic severity in boys with TS. Correlation between tic severity and latency of the startle response in (A) the PA condition ($r = 0.489$, $P = 0.024$) and in (B) the PP condition ($r = -0.470$, $P = 0.032$) in boys with TS ($N = 21$).

Figure 3. Differential PPI_{fMRI} BOLD activity in healthy controls vs. boys with TS. (A) Brain regions in which the healthy controls ($N = 22$) exhibited an increased PPI_{fMRI} (contrast in BOLD activity between the PP condition and the PA condition) compared to boys with TS ($N = 22$) ($P < 0.001$, uncorrected, extent threshold of 10 voxels). (B) Mean beta values of the activation in those brain regions. Error bars represent 1 standard error of the mean. Boys with TS ($N = 21$) had significant lower beta values than healthy controls ($N = 22$) in all five brain regions (**$P < 0.01$, *$P < 0.05$).
When running separate analysis for each group, PPI\textsubscript{EMG} was positively correlated to PPI\textsubscript{fmri} in the superior parietal cortex/precuneus in the TS group, but not in healthy controls (TS: $b = 0.481, P = 0.027$; Controls: $b = 0.115, P = 0.611$). This regression referred only to the beta values of the BOLD activity related to the PA condition. PPI\textsubscript{EMG} was not correlated to the beta values of the BOLD activity related to the PP condition. The described regression is illustrated in Figure 4.

### Discussion

The aim of our study was to investigate the neural correlates of tactile PPI in boys with TS in order to determine which brain regions mediate potential TS-related deficits in PPI. By investigating only boys instead of adults we were able to reduce confounding by neural adaptation processes due to long-term tic activity or tic suppression. The same holds true for the exclusion of long-term medication effects and gender effects. In addition, we minimised any confounding effects of comorbidities by including only boys without any axis-I disorders comorbid to TS.

As expected, the PPI\textsubscript{EMG} was lower in boys with TS compared to healthy controls. This finding is in line with previous studies showing that patients with TS of all ages exhibit reduced PPI using both electric (Castellanos et al. 1996) and tactile stimuli (Swerdlow et al. 2001; Zebardast et al. 2013). PPI is commonly understood as a measure of sensorimotor gating, i.e., the ability to suppress a motor response to a sensory stimulus. Thus, our findings confirm the assumption that TS is associated with deficits in sensorimotor gating. We found a positive correlation between PPI\textsubscript{EMG} and tic duration, indicating increased PPI\textsubscript{EMG} with longer duration of the disorder. However, as age was also correlated to PPI\textsubscript{EMG} and PPI is known to be age dependent (with greatest PPI at middle age) (Ellwanger et al. 2003), this finding might also reflect a developmental aspect instead of TS-specific neural adaptation.

When running separate analysis for each group, PPI\textsubscript{EMG} was positively correlated to PPI\textsubscript{fmri} in the superior parietal cortex/precuneus in the TS group, but not in healthy controls (TS: $\beta = 0.481$, $P = 0.027$; Controls: $\beta = 0.115$, $P = 0.611$). This regression referred only to the beta values of the BOLD activity related to the PA condition. PPI\textsubscript{EMG} was not correlated to the beta values of the BOLD activity related to the PP condition. The described regression is illustrated in Figure 4.

**Table II.** Differential PPI\textsubscript{fmri} in healthy controls vs. boys with TS.

| Brain region                        | Side  | Number of voxels | Talairach coordinates (mm) | Brodmann area |
|-------------------------------------|-------|-----------------|-----------------------------|---------------|
| Middle frontal gyrus                | Left  | 14              | x = -34, y = 16, z = 36     |               |
| Postcentral gyrus                   | Right | 11              | x = 18, y = -32, z = 54     |               |
| Superior parietal cortex/Precuneus  | Right | 111             | x = 24, y = -52, z = 52     |               |
| Precuneus                           | Right | 24              | x = 20, y = -76, z = 38     |               |
| Cingulate gyrus                     | Left  | 11              | x = -14, y = 14, z = 40     |               |
| Caudate body                        | Left  | 10              | x = -22, y = -20, z = 22    |               |

**Brain regions associated with significant lower PPI\textsubscript{fmri} (contrast in BOLD activity between the PP condition and the PA condition) in boys with TS ($N = 22$) compared to healthy controls ($N = 22$) (two-sample $t$-test, $P > 0.001$ noncorrected). Brain regions are listed anterior to posterior and superior to inferior. In all five brain regions boys with TS exhibited significant lower beta values than healthy controls (see also Figure 3).**

![Figure 4](image-url)
tactile stimuli in those boys with more severe tics. This finding is well in line with previous reports about a somatosensory hypersensitivity in TS (Cohen and Leckman 1992; Kane 1994; Belluscio et al. 2011).

The random effects analysis in healthy controls revealed BOLD activity during the PP condition (PP > baseline) in the medial and inferior frontal gyrus, in the postcentral and superior parietal brain regions, the middle occipital gyrus, the insula, the cingulate cortex and the thalamus. These findings largely correspond to those from earlier fMRI studies on tactile PPI. BOLD activity in the parietal regions have especially been linked to tactile (but not acoustic) PPI (Kumari et al. 2003; Neuner et al. 2010; Zebardast et al. 2013). Therefore, it can be assumed that the BOLD activity we found in the postcentral and superior parietal cortex are especially relevant for mediating PPI to tactile startle stimuli, while the other brain regions are more generally involved in PPI.

Boys with TS showed aberrant PPI BOLD activity in five brain regions: the middle frontal gyrus (BA9), the postcentral gyrus (BA3), the superior parietal cortex/precuneus (BA7), the anterior cingulate gyrus (BA32) and the caudate body. In all of those regions, boys with TS exhibited less PPI BOLD activity compared to healthy controls.

In our study, PPI of the startle response was positively correlated to PPI BOLD activity in the postcentral gyrus (BA3) and the superior parietal cortex/precuneus (BA7) (only in the TS group). The right superior parietal cortex/precuneus (BA7) was the largest cluster of PPI BOLD activity, in which boys with TS differed from healthy controls. Therefore, it can be assumed that both regions (BA3 and BA7) play an especially important role in mediating the deficient tactile PPI in TS. Both regions play a central role in the processing of somatosensory stimuli. BA3 corresponds to the primary somatosensory cortex, while BA7 belongs to the somatosensory association cortex, which is responsible for the integration of different sensory information in order to produce appropriate motor responses (Cavanna and Trimble 2006; Teixeira et al. 2014). Thus, our finding of decreased PPI BOLD activity in BA3 and BA7 in boys with TS indicates that deficient PPI in TS derives from altered higher-order integration of somatosensory stimuli.

It has been proposed that TS-related deficits in sensorimotor integration might be linked to the internal experiences of premonitory urges (Swerdlow and Sutherland 2005), which are reported by about 82% of patients with TS (Cohen and Leckman 1992). Although this suggestion seems convincing from a clinical point of view, we were unable to detect correlations between the neural correlates of PPI (PPI) and subjective ratings of premonitory urges measured with the PUTS. This negative finding argues against the proposed close link between subjective experiences of premonitory urges and deficient sensorimotor gating. But it corresponds to previous studies that also failed to demonstrate a proposed link between premonitory urges and tic inhibition (Ganos et al. 2012). According to Ganos et al. (2012), this missing correlation indicates the existence of distinct neurophysiological systems, e.g., of urge/tic generation (PUTS) and tic control (tic suppressibility assessed from videos).

However it has to be taken into consideration that premonitory urges per definition are “subjective” and therefore influenced by several confounding factors such as self-awareness, and expectancies bias. Ganos et al. (2012) thoroughly discussed the unresolved problems of quantifying “subjective” premonitory urges, e.g., by the PUTS and of linking the PUTS scores to “objective” pathophysiological findings. In this regard, the validation of the PUTS as the standard measurement of the “subjective” awareness of premonitory urges should be promoted.

Besides the parietal regions being responsible for the integration of somatosensory stimuli, the middle frontal region (BA9), the anterior cingulate and the caudate body have been activated. Those regions are part of the fronto-striatal circuit involved in the planning, organisation and regulation of movements (Botvinick et al. 2004; Rushworth et al. 2004), and previously have been reported to mediate PPI (Hazlett et al. 1998; Hazlett et al. 2008; Kumari et al. 2008; Neuner et al. 2010; Zebardast et al. 2013). Interestingly, patients with TS exhibited increased fronto-striatal activity during the voluntary inhibition of eye blinks (Mazzone et al. 2010). Furthermore, structural abnormalities and functional disorganisation of cortico-basal ganglia networks constitute the underlying neuropathology of TS (Ganos et al. 2013).

To the best of our knowledge, this is the second study applying the tactile version of the PPI paradigm inside the fMRI scanner during simultaneous measuring of the startle response in TS and the first in children and adolescents. The great advantage in investigating only boys instead of adults with TS is that compensatory brain reorganisation has taken place only to a limited extent. It has been assumed that patients with TS undergo a variety of neural reorganisation processes helping to modulate tic frequency and severity (i.e., by suppressing tics) (Eichele and Plessen 2013). This includes a reduction in caudate volumes and thinning of sensorimotor cortices (Plessen et al. 2009), structural alterations in somatosensory pathways...
(Thomalla et al. 2009) and functional changes in fronto-parietal brain networks during voluntary suppression of movements (Thomalla et al. 2014). Against the background of TS-related neural adaptation, it might be possible to explain differences between neural correlates of PPI in adult patients with TS, as found in a previous study by Zebardast et al. (2013), and neural correlates of PPI in boys with TS without comorbid conditions, as found in the present study. Interestingly, Zebardast et al. (2013) report increased PPI-related BOLD activity in the parietal cortex (supramarginal gyrus) in patients with TS, while we found reduced BOLD activity in parietal regions. In the light of neural adaptation processes, it might be hypothesised that reduced PPI-related BOLD activity of parietal regions in boys with TS is transformed into increased recruitment of those parietal regions over the course of the disorder. This hypothesis is underpinned by our finding of a positive correlation between age and the BOLD activity in the superior parietal cortex/precuneus in the PP condition. It also fits with the finding by Church et al. (2009) that both fronto-parietal networks, which grow stronger with age, and fronto-parietal networks, which diminish in strength with age, are immature in adolescents with TS. Interestingly, also in the context of response inhibition functions, the parietal component is subject to strong developmental changes (Mehnert et al. 2013).

However, also some limitations have to be taken into account. Although we excluded all patients with comorbid psychiatric disorders, it was not possible to eliminate all potential confounders. That is, our patients were not treatment-naïve, whereby effects of medication cannot completely be ruled out (even though there was no correlation between medication intake and PPI\text{EMG} or PPI\text{EMD} – data not shown). In addition, we observed significant group differences on measures of psychopathology (see Supplemental material available online), therefore an effect of dimensional (subclinical) psychopathology on the results cannot be excluded. It also has to be stated that deficits in sensorimotor gating are not a unique characteristic of TS, but have also been found in several psychiatric disorders, especially in schizophrenia (Swerdlow et al. 2006). Furthermore, the approach of eliminating possible confounds by excluding patients with comorbid psychiatric disorders has the disadvantage of focussing on a sample with less clinical relevance, since only 14% of the patients suffer from TS only, while most patients exhibit comorbid attention deficit hyperactivity disorder (ADHD) or obsessive–compulsive disorder (OCD; Freeman, 2007). However, previous studies including patients with TS plus ADHD, OCD or both also found reduced PPI in their samples. Therefore we do not expect that our findings of TS-related deficits in PPI are limited to the TS only sample. However, the TS-related hypersensitivity towards the tactile stimuli that was suggested by the negative correlation between tic severity and startle latency in the PP condition might be a specific feature of TS and that becomes blurred in a sample of patients with TS plus comorbidities. Finally, the small sample further limits the conclusiveness of our results.

In summary, our findings indicate deficient sensorimotor gating in boys with TS that is correlated to reduced recruitment of brain regions responsible for the processing and integration of somatosensory stimuli. This adds support to the assumption that deficient sensorimotor integration is a core problem in TS. Because we investigated exclusively boys with TS and no comorbid condition, in whom neural reorganisation due to long-term tic activity, suppression and medication intake have not taken place yet, it can be assumed that the alterations we found are an imminent feature of the TS pathophysiology.

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Statement of interest

None to declare.

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