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Temporo-parietal dysfunction in Tourette syndrome:

Insights from an fMRI study of Theory of Mind

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ABSTRACT

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by tics, repetitive movements and vocalizations which are prompted by a sensory-cognitive premonitory urge. Complex tics can include environmentally dependent social behaviours such as echoing of other people's speech and actions. Recent studies have suggested that adults with TS can show differences to controls in Theory of Mind (ToM): reasoning about mental states (e.g. beliefs, emotions). Twenty-five adults with uncomplicated TS (no co-morbid disorders but moderate tic severity), and twenty-five healthy age and gender matched controls were scanned with fMRI during an established ToM task. Neural activation was contrasted across ToM trials involving reasoning about false-belief, and matched trials requiring judgments about physical states rather than mental states. Contrasting task conditions uncovered differential fMRI activation in TS during ToM involving the right temporo-parietal junction (TPJ), right amygdala and posterior cingulate. Further analysis revealed that activity within the right TPJ as localized by this task co-varied with the severity of symptoms including echoing tics, impulse control problems and premonitory urges in TS. Amygdala activation was also linked to premonitory urges, while activity in the left TPJ during ToM was linked to ratings of non-obscene socially inappropriate symptoms. These findings indicate that patients with TS exhibit atypical functional activation within key neural substrates involved in ToM. More generally, our data could highlight an important role for TPJ dysfunction in driving compulsive behaviors.

INTRODUCTION

Tourette syndrome (TS) is a neurodevelopmental disorder found in up to 1% of school-age children (Robertson, 2011) featuring chronic repetitive movements (e.g. blinking, grimacing) and vocalisations (e.g. grunting). These tics are commonly preceded by premonitory urges: sensations like itching or pressure (Cohen and Leckman, 1992). The neural mechanisms underlying tics involve motor regions including the basal ganglia (Orth and Münchau, 2003; Albin and Mink, 2006; Singer et al., 1993; Peterson et al., 2003). However, wider cortical dysfunction may underpin environment-dependent complex tics (Eddy and Cavanna, 2014a), such as echophenomena (imitation of other people's speech and actions).

Socially inappropriate complex tics not only include coprolalia (swearing tics), but also context-related socially inappropriate remarks (e.g. insults) and actions (e.g. setting off fire alarms unnecessarily). The prevalence of these latter non-obscene socially inappropriate symptoms (NOSIS) was found to be between 22-30% in one study (Kurlan et al., 1996), although a more recent study reported urges in up to 60% of patients attending a specialist clinic for TS (Eddy and Cavanna, 2013a). These urges are usually ironic, as the patient is aware of the possible negative consequences of acting on their urge and has no desire to create social tension, but has a conflicting need to release the behavior in order to arrest the urge. The neural mechanisms underlying these complex symptoms are currently unknown.

The observation of socially inappropriate behaviors in TS prompted the study of patients' Theory of Mind (ToM: the understanding of mental states such as beliefs and emotions). Although previous studies have not revealed any direct links between socially inappropriate symptoms and ToM in TS, performance on tests involving mental state reasoning can differ between these patients and healthy controls. Eddy et al. (2010a) showed that reasoning about socially inappropriate acts on the faux pas task (Stone et al., 1998; Gregory et al., 2002) was unusual in TS. Specifically, these patients were more likely to conclude that the offensive remarks made by story characters were intentional rather than accidental. A number of studies thereafter revealed other subtle differences in ToM between patients with TS and controls (Eddy et al., 2010b; Eddy et al., 2011; Channon et al., 2012). Everyday social problem solving may also be more challenging in TS (Channon et al., 2003). Importantly, people with TS do not exhibit an inability to comprehend mental states, and can show evidence of hyper-mentalizing (Eddy and Cavanna, 2015).

Unconventional social reasoning in TS may be reflected in neural differences to controls. Medial pre-frontal cortex, bilateral temporal parietal junction (TPJ) and temporal poles (Frith and Frith, 2003; Amodio and Frith, 2006; Saxe and Kanwisher, 2003; Saxe and Wexler, 2005) are active during ToM. More specifically, dysfunction of orbitofrontal cortex and amygdala can impair performance on the faux pas task (Stone et al., 1998), and reasoning about transgressions of social norms can additionally recruit anterior cingulate, temporal poles, and precuneus (den Ouden et al., 2005). To date, no published fMRI studies specifically investigated ToM in TS, although a few studies have explored neural activation in response to emotional facial expressions. Neuner et al. (2010) reported that when viewing such stimuli, patients with TS showed greater activation than controls in regions including medial and dorsolateral superior frontal gyrus, inferior frontal gyrus, middle temporal gyrus and posterior cingulate. These authors concluded that TS is associated with deficient inhibition of the amygdala in response to certain kinds of emotional stimuli. Another study (Mermillod et al., 2013) found that rapid serial visual presentation of emotional facial expressions suggested temporal cortex dysfunction in TS.

This study compared the neural correlates of ToM in patients with TS and healthy controls, using a standard ToM paradigm that reliably reveals core structures within the mentalizing network (Saxe and Kanwisher, 2003). The paradigm consisted of multiple conditions including "false-belief" (FB), where the participant was required to reason about an incorrect belief, and "false-photo" (FP) where the participant was required to reason about an outdated physical representation. In healthy participants, the contrast between FB and FP typically reveals activity within right and left temporo-parietal junction, medial prefrontal cortex and posterior cingulate (Saxe & Kanwisher, 2003; Saxe et al., 2006). We aimed to help explain why previous studies have reported unusual performance on ToM tasks in TS, and offer insight into how social cognition may be linked to patients' symptoms. More specifically, we hypothesised that patients with TS would show neural activation differences to controls on this false belief task during ToM related reasoning.

MATERIALS AND METHODS

Participants

Participants were 25 outpatients with uncomplicated Tourette syndrome and 25 healthy controls matched for gender (6 females, 19 males) and age (TS: mean=31.48 years, SD=11.50, median=29, range=17-59; Controls: mean=29.88, SD=10.12, median=26, range=18-59) and of similar education (TS: mean=14.68 years, SD=2.06, median=15, range=11-19; controls: mean=15.84, SD=2.39, median=15, range=11-19). Controls were individually matched one-to-one with patients. All participants were native English first language speakers with no history of head injury, seizure, substance abuse, or contraindications to MRI scanning. Patients were recruited through the specialist TS Outpatient Clinic at the Department of Neuropsychiatry, National Centre for Mental Health, Birmingham and Solihull Mental Health NHS Foundation Trust, and the UK-based charity Tourette's Action. Healthy controls were recruited through the Queen Elizabeth Hospital, Birmingham and the University of Birmingham. Controls had no psychiatric or neurological diagnoses and were not on psychoactive medication. Patients had TS diagnosed using Diagnostic and Statistical Manual for Mental Disorders version 4 text-revision (American Psychiatric Association, 2000) criteria, but no co-morbid psychiatric or neurological disorders (e.g. autistic spectrum disorder) as screened for using the National Hospital Interview Schedule for TS (Robertson and Eapen, 1996). Ten patients were taking medications (3=clonidine, 2=risperidone, 1=haloperidol, 1=sulpiride, 1=risperidone+aripiprazole, 1=risperidone+clonidine, 1=aripiprazole+clonidine). Most patients reported complex tic-related behaviors (non-obscene socially inappropriate symptoms: NOSIS=15; palilalia=16; palipraxia=16; echolalia=13; impulse control disorders=12; self-injurious behaviors=10; echopraxia=10; coprolalia=6; copropraxia=5). Mean Yale Global Tic Severity Scale (Leckman et al., 1989) lifetime total score was 53.60 (SD 13.57; median 52; range 31-90/100) with a mean tic score of 28.40 (SD 5.78; median 28; range 21-40/50), indicating moderate tic severity. Mean duration of TS was 23.76 years (SD 11.24; median 22; range 8-49) and mean Premonitory Urge for Tics Scale (Woods et al., 2005) score was 20.48 (SD 2.97; median 21; range 15-29 out of possible 9-36).

Protocol

The study was conducted in accordance with the Declaration of Helsinki and received regional and institutional ethical approvals. All participants gave written informed consent. Cognitive profiles were assessed using phonological and semantic verbal fluency tasks

(Lezak, 1995), the Digit Ordering Test-Adapted (Werheid et al., 2002; Cooper et al., 1991), the Trail Making Test (Reitan & Wolfson, 1984), the Stroop test (Stroop, 1935), the Hayling task (Burgess & Shallice, 1996), the Wisconsin card sorting test (Greve, 2001), tests of regular and irregular word reading (Torgeson et al.,1999; Reynolds & Kamphaus, 2007), and Weschsler Adult Intelligence Scale subtests assessing coding, similarities, picture sequencing and matrix reasoning (Wechsler, 1997). Scales were also administered to assess obsessive-compulsive symptoms (Yale-Brown Obsessive-Compulsive Scale: Storch et al., 2007), attention deficit hyperactivity disorder symptoms (Adult Self Report Scale for ADHD: Storch et al., 2007), anxiety and depression (Hospital Anxiety and Depression Scale: Zigmond & Snaith, 1983). Patients with TS completed additional rating scales for tics and premonitory urges (listed under participants) and the Minnesota Impulsive Disorders Interview (MIDI: Christenson et al., 1994), which screens for behaviors such as compulsive gambling, shopping and kleptomania. This assessment was completed in full by all patients and 19 controls (Supplementary Table 1). Patients with TS showed very few differences to controls, with very mild deficits in attention and inhibition, and a greater difference in set-shifting performance. The only group differences that survived multiple-comparison correction indicated significantly more obsessive-compulsive symptoms and attention problems in TS.

Participants' fMRI data was acquired using a 3T Philips Achieva scanner. Participants were shown task instructions and example stimuli, and how to use the MRI compatible button box to respond. Patients were not told to suppress tics, but that the best time to tic would be in between scanning phases and question trials, to reduce head movement.

Theory of Mind task

The ToM task was as used by Hartwright et al., (2013) and based on the experimental procedure devised by Saxe and Kanwisher (2003), after Fletcher et al., (1995). Stimuli were a set of stories (see Saxe and Andrews- Hanna, n.d.), some of which had been anglicised. There were 24 vignettes describing events resulting in either a protagonist's "false-belief" (FB) or an outdated physical representation involving a "false-photo" (FP) scenario. Each vignette was displayed for 10 s, and then followed for 4 s by a short probe question about the preceding vignette requiring a true or false response. For example:

FB vignette:

"Jenny put her chocolate away in the cupboard. Then she went outside. Alan moved the chocolate from the cupboard into the fridge. Half an hour later, Jenny came back inside."

FB probe question:

"Jenny expects to find her chocolate in the cupboard. True/False?"

FP vignette:

"A volcano erupted on a Caribbean island three months ago. Barren lava rock is all that remains today. Satellite photographs show the island as it was before the eruption."

FP probe question:

"In the photographs the island is covered in vegetation. True/False?"

A response was made using a button box in the participant's right hand. Stories alternated between FB and FP conditions and were interleaved with a 13.5 s rest period. There were four acquisition fMRI runs each containing three FB and three FP vignettes.

Brain imaging protocol

Participants' data were acquired during a single scanning session using an 8 channel head coil. Stimuli were presented using Presentation software (Version 14.9, Neurobehavioral Systems, CA) which also recorded behavioral responses. 71 T2*-weighted gradient echo planar imaging volumes were obtained for each of the four acquisition runs of the task (3 mins each). Scan protocol parameters were selected to achieve whole brain coverage (42 axial slices, obtained consecutively in a bottom up sequence) with TR=2.5 s, TE=35 ms, flip angle=79°, SENSE factor=2, FOV 240 x 240 mm, acquisition matrix=80×80, reconstructed to give isotropic voxels of size=3×3×3mm^3. On completion, high resolution T1-weighted gradient echo anatomical images were collected with 175 x 1mm sagittal slices (TE=3.8 ms, FOV=288 x 232 x 175mm, reconstructed to 1×1×1 mm^3 isotropic voxels).

Neuroimaging analysis

Raw structural and functional data were converted from Phillips PAR/REC format into NIfTI format. All data processing was carried out using FEAT v6.00, part of FSL v5.0.6 (Smith et

al., 2004). Processing steps included slice timing correction and MCFLIRT inter-volume motion correction using rigid body transformations (Jenkinson et al., 2002). Data were high-pass filtered using a Gaussian-weighted least-squares filter (sigma=21 s), spatially smoothed using a 3D Gaussian kernel (FWHM=5 mm) and grand-mean intensity normalized across the 4D dataset. Using FLIRT, the functional data were registered to their respective participant's T1 structural images using a 6-DOF linear transformation and to the standard template Montreal Neurological Institute (MNI) reference brain using a 12-DOF affine transformation (Jenkinson & Smith, 2001; Jenkinson et al., 2002). In-scanner movement for each task block was examined. One patients and one control were excluded because their within-task mean absolute movement across 3D space was greater than 50% of the size of the fMRI voxel dimensions used (i.e. 1.5mm). A comparison of maximum movement per block showed no significant group difference.

The neuroimaging data was modelled according to the customary method employed for this specific ToM task by Saxe and Kanwisher (2003) and later work (e.g. Hartwright et al., 2012) in order to facilitate inter-study comparison. A general linear model (GLM) was utilised to model the principal experimental conditions of interest: FB and FP. As per the standard analysis path, button responses were not explicitly modelled and there was no separate regressor for response errors. Nonetheless, additional models that regressed out button responses and incorrect trials were explored for comparison. As these yielded consistent findings which did not alter interpretation, we report the results generated by the standard analysis method for historical continuity. The timeseries for when each principal condition was active (14 s epochs) were convolved with a standard gamma-derived haemodynamic response function and high pass temporal filtering (sigma=21 s) was applied to the model. The temporal derivatives of each of the two principal conditions were additionally added to the GLM in order to create a better fit for the overall model and reduce unexplained noise. Finally, the 6 motion parameters of rotation and translation generated by MCFLIRT were added to the overall GLM as separate regressors of no interest, to help reduce any residual uncorrected motion-related artefacts (Johnstone et al., 2006).

Second level modelling used a simple fixed effects model to aggregate the data across the four acquisition runs within participants to create a main effect of interest for FB and FP transformed into MNI space. At the third level, two separate models were used to investigate effects of interest (McLaren et al., 2011). The first complex higher order mixed-effects model modelled the between condition effect (contrasting FB with FP, collapsing across group; Results Table 1 below) and the group by condition interaction (contrasting FB with FP and

controls with patients; Results Table 3 below). The second, simple higher order mixed-effects (between groups) model merged the two conditions in the ToM experiment into one "active" period (implicitly contrasted with the rest periods) and modelled the two participant groups (controls and patients) as two separate regressors with independent sources of (non-pooled) variance. This model was used to generate the data for Table 2 below.

Group Z statistic images from these two models were subsequently corrected for multiple comparisons using a two step family wise error (FWE) correction process to control for false positives. The 3dClustSim program, part of the AFNI toolkit (Cox, 1996), was used to control the FWE rate. The smoothing kernel size (5.5mm) was estimated by means of the AFNI 3dFWHMx program using an average calculated from the residuals of the first level GLM analyses. A particular voxel-wise threshold was chosen and together with the voxel dimensions and kernel size estimate above the probability of a cluster of specific size arising by chance was estimated by means of a Monte Carlo simulation. All data are reported here with FWE corrected $p < 0.05$, equivalent to a voxel-wise threshold of $p < 0.005$ ($Z > 2.6$) and cluster size > 65.

TPJ Covariate Analysis

Pre-planned covariate analysis was undertaken to explore the relationship between brain areas showing an activation difference between patients and controls during ToM (i.e. based on ROIs from Table 3; FB > FP), and core clinical symptoms related to TS. We therefore investigated three specific brain regions selected post-hoc from Table 3 (Figure 2): the right angular gyrus (TPJ), right amygdala and posterior cingulate, as well as the left TPJ and left amygdala for comparison. We selected these three areas because they showed the most significant group differences and are more traditionally associated with ToM than the other remaining areas in Table 3 (which are more generally associated with visual processing and motor function). In addition, we were able to avoid circularity when examining these areas by using healthy participant data collected during the task. We created masks based on areas that were functionally localised using only the control group data for the left and right TPJ and the posterior cingulate (this means that we are therefore likely to be examining areas that are specifically involved in ToM). The masks for the amygdalae were based on the Harvard-Oxford Subcortical Atlas. These masks are shown in Supplementary Figure 2. Symptom measures were lifetime ratings for tics and common compulsive and impulsive behavioral problems including socially relevant urges: tic severity (YGTSS), premonitory urge severity

(PUTS), obsessive-compulsive behaviors (YBOCS), attention problems (Adult Self Report Scale six item score), non-obscene socially inappropriate symptoms ratings (scored 0-3 based on 0=absent or 1/2/3 of insults; other remarks; actions), impulse control disorders (MIDI total count) and echophenomena ratings (scored 0-2 based on 0=absent or 1/2 of echolalia; echopraxia). Using the nlme package in R, one mixed-effects model was fitted for each of the five masks, with the percentage BOLD signal change as the dependent variable, the participant identity as a random factor, and the seven symptom measures as initial covariates in a stepwise backwards elimination to create the minimal adequate model in which all surviving measures are significant.

RESULTS

Behavioral performance

Each of the 48 participants included in the fMRI analysis completed 24 individual ToM task trials. There were 8 missed responses and 25 trials were excluded as outliers (having a response time outside 2.5 SDs per person) leaving 1119 valid responses out of a possible 1152 (97.1%).

Accuracy

Healthy controls (HC) answered correctly on 88.7% of false-belief trials and on 84.6% of FP trials. Patients with TS answered correctly on 85.3% of FB trials and on 81.6% of FP trials. When pooling correct and incorrect responses across conditions, there was no difference (X^2=1.888, df=1, p-value= 0.170) between patients (91 errors) and controls (75 errors). When comparing the two groups for correct responses for each condition separately, there were no significant differences (FB: X^2=0.962, df=1, p-value=0.327; FP: X^2=0.721, df=1, p-value=0.396). When considering accuracy across conditions and averaging over group, Pearson's Chi-squared test with Yates' continuity correction was not significant (X^2=3.344, df=1, p-value=0.067) with just a weak trend for more errors in the FP condition (Supplementary Table 2).

Reaction Times

Reaction times for HC were quicker for correct compared to incorrect responses for both FB (correct mean=2.95s, SE=0.06s; incorrect mean=3.58s, SE=0.21s) and FP trials (correct mean=3.03s, SE=.06s; incorrect mean=3.60s, SE=0.18s). Patients were also faster when answering correctly on FB trials (correct mean=3.03s, SE=.05s; incorrect mean=3.84s, SE=0.19s) and FP trials (correct mean=3.16s, SE=.06s; incorrect mean=3.42s, SE=0.15s). A mixed effects model was run, treating group (patient/control), condition (FB/FP) and response (correct/incorrect) as fixed factors and participant identity as a random factor in a full factorial model. Model comparisons indicated no significant effect of group (likelihood ratio=7.11, p=0.13) or condition (likelihood ratio=9.19; p=0.06). However, the effect of response was significant (likelihood ratio 36.4, p<0.0001) and this was the only factor remaining in the final, minimally adequate, model (F(1070, 1)=28.6, p<0.0001).

Neuroimaging data

Main effect of ToM task

For patients and controls combined a mixed effects analysis identified cortical regions that showed greater activation for mental versus physical representation (FB>FP, p_{corr} <0.05). These results (Table 1) are consistent with previous studies (e.g. Saxe & Kanwisher, 2003), showing enhanced recruitment of regions within the mentalizing network for FB, including bilateral TPJ, precuneus and medial prefrontal cortex (Supplementary Figure 1). The reverse contrast results (FP>FB) are shown in Supplementary Table 3.

Main effect of group

When comparing task related activation (regardless of condition) between groups, less activation was apparent in multiple regions in TS (Figure 1). Some differences were in areas previously implicated in tic release and suppression, including supplementary motor cortex and parietal operculum (see Table 2). Other regions revealed by this group comparison are involved in language and memory (e.g. planum polare, temporal fusiform cortex, frontal

pole), visual attention and imagery (e.g. intracalcarine cortex, inferior occipital fusiform). There were no significant differences for the reverse contrast TS>HC.

Interaction between group and condition

To identify differences between the groups during ToM, we conducted a further whole-brain analysis to specifically identify areas where HC>TS interacted with FB>FP (Figure 2). Five neural regions exhibited clusters surviving corrected thresholding (Table 3). There were differences in right side regions of the mentalizing network, and left side regions linked to visual attention and executive functions. No significant differences were apparent for the negative interaction.

Differential activation of the TPJ has not previously been highlighted in TS, yet our data revealed multiple areas showing a group difference around the right TPJ in TS, including right supramarginal gyrus which showed a group difference over the whole task (Table 2 and blue area in Figure 3) and right angular gyrus which showed an interaction between task condition and group (Figure 2, Table 3, and red area in Figure 3).

Covariate Analysis

Group differences were apparent in two areas around the right TPJ in TS. As shown in Figure 3, a group difference across both task conditions was seen in right supramarginal gyrus, with a more inferior area of right angular gyrus being revealed by the interaction contrast. To avoid circularity, the covariate analysis examined whether TPJ activity was linked to patients' symptoms using the right TPJ area as localised by the ToM task in the control group (FB>FP). Additional areas that were examined were right amygdala and posterior cingulate (which showed a group difference for FB>FP), plus left TPJ and left amygdala. Right TPJ activation was found to covary strongly with premonitory urges and echophenomena, and less strongly with some other impulsive behaviors (Table 4). Left TPJ activity covaried with NOSIS ratings, and activity in both amygdalae was also found to co-vary with the urge to tic. There were no significant covariation findings for the posterior cingulate. Multicollinearity was not significant when correlations between symptom covariates and the model variance inflation factors were examined.

DISCUSSION

When compared to controls, patients with TS exhibited differential activation of regions including posterior cingulate, right angular gyrus and right amygdala (Table 3) during ToM. Such activations are frequently linked to perspective taking (Mano et al., 2009) and distinguishing between intentional and physical causality (e.g. Den Ouden et al., 2005; Vogeley et al., 2001) in healthy participants. Two other areas which exhibited a group difference were the left superior frontal gyrus and occipital pole. The left medio-dorsal frontal cortex is active during mentalizing (e.g. Fletcher et al., 1995), but this could be related to working memory (du Boisgueheneuc et al., 2006). Hypoactivation of the occipital lobe could indicate reduced visual attention to task stimuli in TS, although there were no group differences in behavioral performance. This latter finding is in accordance with intact understanding of false-belief as previously reported in this patient population (Eddy et al., 2010a). Patients with TS are more likely to exhibit subtle behavioral differences to controls on complex tests of ToM involving emotion (see Eddy and Cavanna, 2013b), or on tasks where mentalizing is not explicitly requested (Eddy and Cavanna, 2015).

Differential activation of the right amygdala during a ToM task in TS may be of particular interest given that previous studies have highlighted both functional and structural abnormalities of the amygdala in Tourette syndrome (Peterson et al., 2007; Ludolph et al., 2008; Werner et al., 2010; Neuner et al., 2010; Neuner et al., 2011; Wittfoth et al., 2012). The right amygdala specifically can generate automatic emotional arousal to stimuli with limited conscious appraisal (Bradley et al., 1991; Bradley et al., 1996; Funayama et al., 2001; Sander & Scheich, 2001). However, whilst many studies emphasise its involvement in social cognition (e.g. Stone et al., 2003) recent studies suggest this structure may not play a critical role in adults during some ToM tasks (e.g. Spunt et al., 2015). The relationship between urges to tic and amygdala activation during the ToM task could reflect an emotional component involved in tics, or perhaps be related to startle-response (e.g. Angrilli et al., 1996).

One interpretation of our findings is that there is a relationship between tics and social cognition. However, right TPJ activation is also frequent in attention orienting paradigms (e.g. Geng & Vossel, 2013; Corbetta et al., 2008) so it is possible that attention differences between the groups influenced some of our results. While previous studies (Saxe and

Kanwisher, 2003; Saxe and Wexler, 2005; Aichhorn et al., 2006) have suggested that the right TPJ makes a critical contribution to ToM, a role in the domain general control of self and other representations (e.g. Sowden and Shah, 2014) helps explain activations during tasks involving imitation and attribution of agency. Right TPJ activations may aid social cognition by allowing the blending or separation of the perspectives, actions or emotions of oneself and other people. Blending with another person's action will enable imitation, while overlap between emotion in oneself and another may underlie empathy. However, in some cases it is important to distinguish the perspective of the self and the other e.g. for the understanding of false-belief.

Spengler et al. (2010) showed that lesions to right TPJ can lead to deficits in cognitive perspective taking while empathy remains intact. Furthermore, these patients show difficulty in resisting motor interference from observed movements (i.e. deficits in imitation inhibition). Differential right TPJ activity in TS during ToM could similarly affect control of representations relating to the self and other (Eddy, submitted). Firstly, while empathy is enhanced when witnessing other people's distress, these patients report less spontaneous cognitive perspective taking than controls in everyday life (Eddy et al., 2015). Secondly, patients with TS can show greater susceptibility than controls to interference from observed biological movements that are incompatible with their own movements (Jonas et al., 2010). Indeed, in the current study, a measure of echophenomena (tics involving imitation) was linked to right TPJ activation. Mirroring tics could therefore involve problems differentiating between actions linked to the self and to the observed other.

Premonitory urges to tic co-varied strongly with right TPJ activations during the ToM task. The TPJ exhibits a peak in gray matter between 8.5 and 13 years (see Segheir, 2013) so it is interesting to note that these sensations usually become apparent around 10 years of age (Leckman et al., 1993). Our findings could imply that premonitory urges are associated with problems with multisensory integration, another suggested function of the TPJ (e.g. Ionta et al., 2011; Ionta et al., 2014). When TPJ dysfunction leads to problems differentiating between actions linked to the self and other, this can affect our sense of agency or action ownership (Blakemore et al., 2003; Farrer and Frith, 2002). Therefore, our finding of an association between right TPJ activity and patients' ratings on the MIDI could imply that many of their behavioral symptoms are linked to a disturbed sense of agency. The evidence of a relationship between activity in left TPJ during a ToM task and the number of different types of compulsive socially inappropriate behaviours experienced by patients also encourages

further research into the possible relationships between TPJ function, social cognition and complex context-dependent tics.

Limitations of this study include the use of medication, which is important to consider, given the potential relationships between dopamine function and ToM (e.g. Abu-Akel, 2003). However, dopamine antagonists were only being taken by a small proportion of patients (7/24) in the current study. In addition, our findings may only characterise adults with mild to moderate TS and some mild obsessive-compulsive behaviors. We could not measure the occurrence of tics, tic urges or suppression during scanning owing to the challenge of collecting such data when patients are undertaking a complex task. Some group activation differences were apparent in brain regions which could be associated with tics, but as these observations were not unexpected, we have focused on novel findings relevant to ToM. In relation to the specificity of neural activations covarying with premonitory urges during ToM reasoning, although these symptoms were linked to activity in right TPJ and both amygdalae, no such association was apparent for other regions involved in ToM (i.e. posterior cingulate, left TPJ). Finally, it should be noted that the cortical regions activated by the false-belief task partly overlap with the default mode network (e.g. Raichle, 2015), which is commonly linked to mentalizing and introspection.

In conclusion, patients with uncomplicated TS exhibit neural activation differences to controls during ToM, which is in line with previous evidence that some aspects of social cognition are altered in TS. Furthermore, our findings highlight the possibility that right TPJ could contribute to symptoms including echophenomena. Future studies should seek to further elucidate the role of the TPJ in driving symptomatology along the continuum of compulsive disorders.

FIGURE LEGENDS

Figure 1.

Activation differences between patients with TS and healthy controls across the whole task (HC>TS). Axial slices shown from z=-40mm (top left slice shown) in ascending order with each successive slice 2mm superior.

Figure 2.

Activation differences healthy controls and patients with TS (HC > TS) during Theory of Mind reasoning (FB: false-belief > FP: false-photo). Slice co-ordinates are as per Table 3. Right hand column shows interaction plots for each ROI.

Figure 3.

Right hemisphere temporo-parietal ROIs showing activation differences between patients with TS (TS) and healthy controls (HC). Left lighter bar shows activation for false-belief condition; right side darker bar shows activation for false-photo condition.Yellow ROI and barchart shows activation in right temporo-parietal junction as defined by the theory of mind task (i.e. significant task condition difference: Table 1) but not by group. Blue ROI and barchart shows right supramarginal gyrus activation, which differs only for group (but not for task condition: in Table 2). Red ROI and barchart shows activation in right angular gyrus which exhibited an interaction for group and condition (in Table 3). This overlaps with the yellow area. Overlap between blue and yellow shown in green. ROIs are shown on slices at y=-52, x=52, z=40).

Supplementary Figure 1.

Theory of Mind network localised across the groups using the task (i.e. false belief > false photo). Axial slices shown from z=-40mm (top left slice shown) in ascending order with each successive slice 2mm superior.

Supplementary Figure 2.

Masks used in the covariate analysis. These were extracted from the Harvard-Oxford subcortical atlas for the left and right amygdala and from the ToM task (false-belief > false-photo) for the control group for the left and right TPJ and the posterior cingulate. Left column (showing slices at y=-62 and z=30) depicts the left and right TPJ ROIs in pink and purple and the posterior cingulate ROI in blue. Right column (showing slices at y=0 and z=-22) depicts the left and right amygdala in green.

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Table 1. Results for whole brain analysis; False Belief > False Photo (all participants)

Label	Hemisphere	Brodmann Area	Cluster size (voxels)	MNI coordinates			Z-value
				x	y	z	
Precuneus	L/R	23	3952	8	-52	34	9.37
Temporo-parietal junction	R	39	2545	52	-54	18	7.38
Temporo-parietal junction	L	39	1988	-48	-60	18	6.07
Middle temporal gyrus/temporal pole	L	21	1882	-50	4	-32	5.76
Middle temporal gyrus/temporal pole	R	21	2685	58	-6	-20	5.65
Frontal pole (medial prefrontal cortex)	L/R	10/11	6021	-2	62	-12	5.46
Middle frontal gyrus	L	46	367	-38	22	40	4.81
Frontal pole	L	9	69	-20	40	30	4.08
Posterior cingulate gyrus	L/R	23	66	0	-18	34	3.95
Frontal pole	L	11	78	-36	56	-14	3.51

Table 2. Results for group comparison collapsed across task conditions; controls > patients

Label	Hemisphere	Brodmann Area	Cluster size (voxels)	MNI coordinates			Z-value
				x	y	z	
Temporal pole	L	38	355	-30	12	-28	4.95
Planum polare	R	20	84	44	4	-24	4.29
Precentral gyrus	L	48	896	-58	8	6	4.25
Inferior occipital fusiform cortex	R	19	908	20	-60	-16	4.23
Postcentral gyrus	R	48	128	64	-6	14	4.19
Supramarginal gyrus	R	40	224	56	-44	42	4.16
Anterior cingulate gyrus*	R	24	456	4	26	18	4.02
Supramarginal gyrus	L	40	774	-40	-42	46	3.96
Anterior cingulate gyrus	L/R	24	230	2	-4	28	3.82
Supplementary motor cortex*	L	6	127	-4	2	52	3.81
Precentral gyrus*	L	6	131	-44	2	42	3.65
Frontal pole	L	45	207	-40	40	20	3.63
Precentral gyrus*	R	6	89	28	-6	46	3.58
Middle frontal gyrus*	R	9	54	44	26	42	3.53
Superior frontal gyrus*	L	8	160	-26	16	62	3.46
Intracalcarine cortex	L	18	130	-22	-72	10	3.41
Posterior temporal fusiform cortex	L	37	60	-44	-42	-26	3.40
Precuneus	R	7	198	12	-72	42	3.33
Superior lateral occipital cortex	L	19	62	-18	-84	50	3.32
Parietal operculum cortex*	L	48	81	-48	-28	22	3.25
Superior lateral occipital cortex	L	39	62	-46	-68	28	3.22
Middle temporal gyrus (temporo-occipital)	L	37	54	-54	-56	-8	3.12
Precuneus	L	7	64	-14	-70	34	3.12

regions linked to tics/tic suppression (Baym et al., 2008; Bohlhalter et al., 2006; Stern et al., 2000; Wang et al., 2011)

Table 3. Results for whole brain analysis; interaction of controls > patients and False Belief > False Photo

Label	Hemisphere	Brodmann Area	Cluster size (voxels)	MNI coordinates			Z-value
				x	y	z	
Angular gyrus	R	39/41	149	44	-48	16	3.87
Amygdala	R	38	101	34	4	-26	3.86
Posterior cingulate	R	23	295	6	-40	36	3.39
Occipital pole	L	17	129	-12	-104	8	3.29
Superior frontal gyrus	L	8	81	-20	18	54	3.17

Table 4. Covariate analysis in Tourette syndrome group: Minimal adequate model results

Region	Variables	DF	F-value	p-value
Right temporo-parietal junction	ECHO	1,20	7.55	0.012
	MIDI	1,20	5.11	0.035
	PUTS	1,20	13.02	0.002
Left temporo-parietal junction	NOSIS	1,17	4.61	0.047
Right amygdala	PUTS	1,17	10.30	0.005
Left amygdala	PUTS	1,17	6.46	0.021

KEY= ECHO: echophenomena rating, number of types; MIDI: Minnesota Impulsive Disorders; Interview number of disorders; NOSIS: non-obscence socially inappropriate symptoms number of types; PUTS: Premonitory Urge for Tics Scale total score. Masks obtained using healthy control group data for the ToM task (false-belief > false-photo).
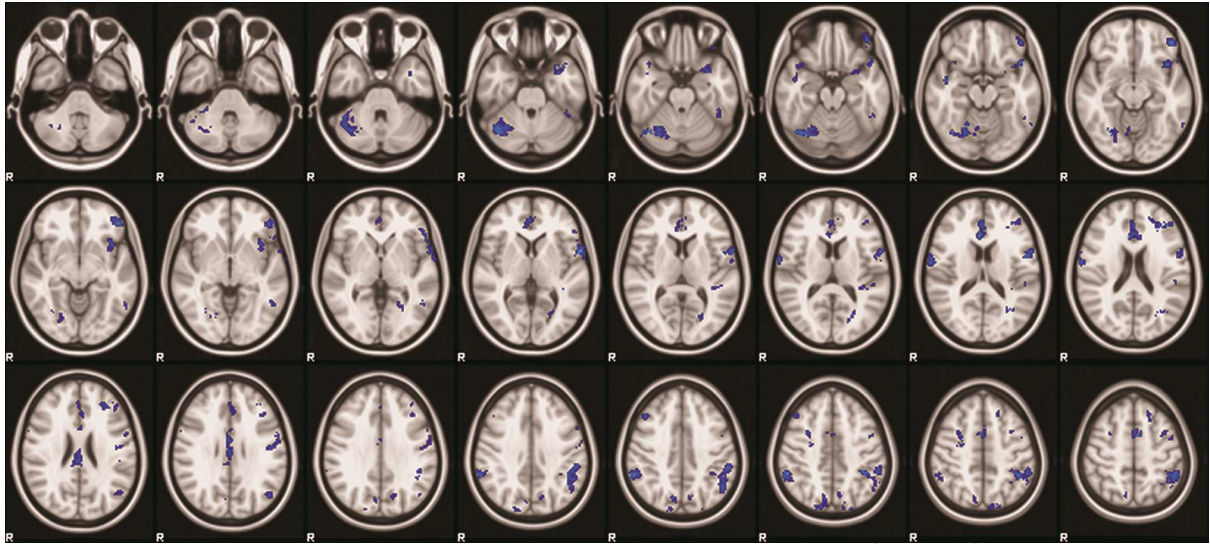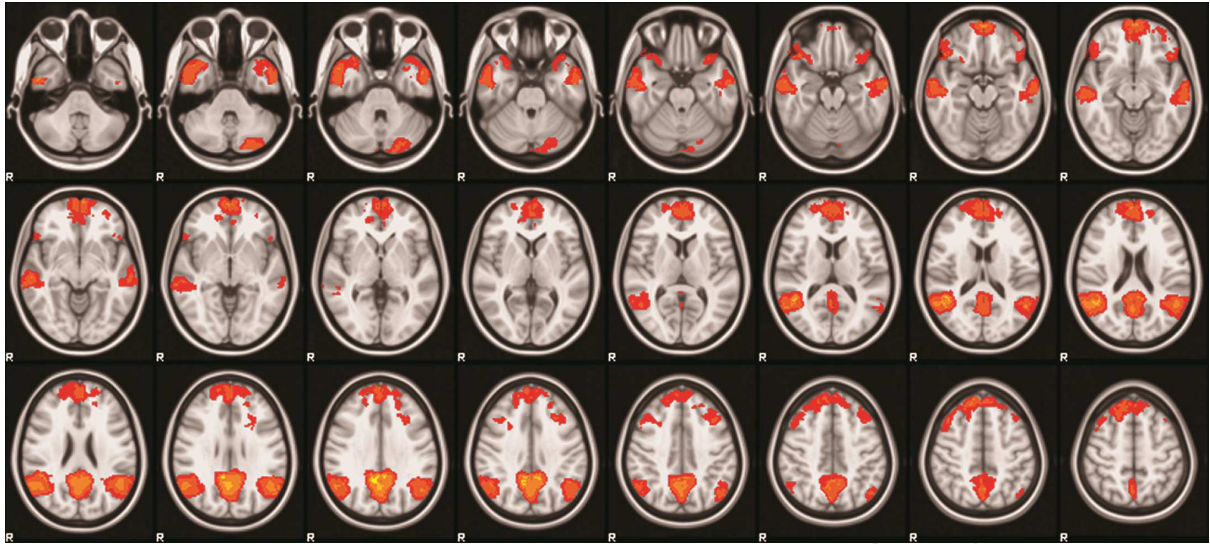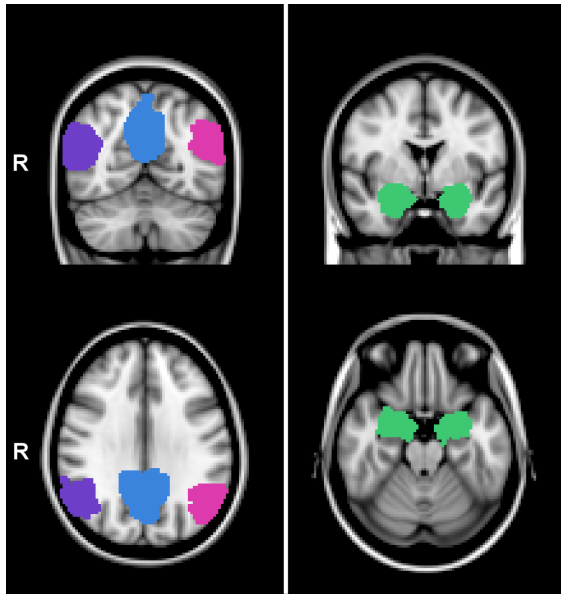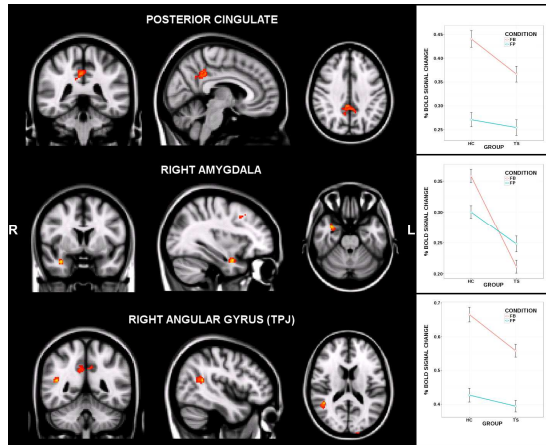
CONTRIBUTORS

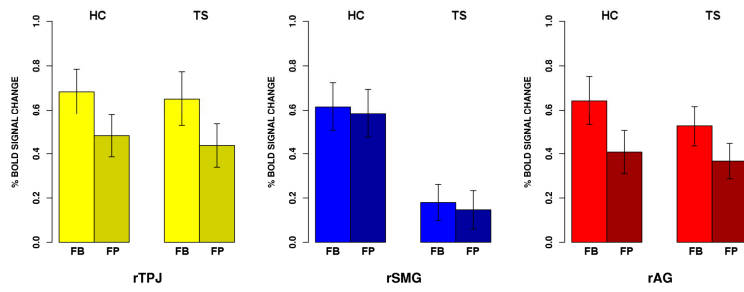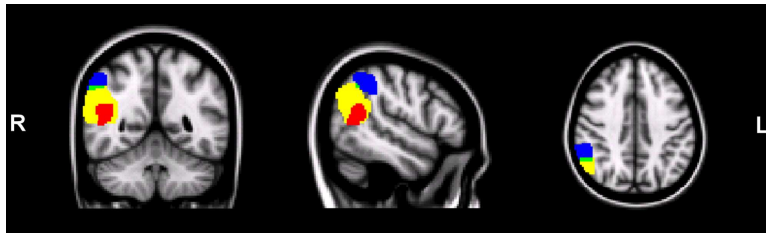CME: Conceptualization, project administration, methodology, investigation, analysis, writing (original draft and editing); AEC: Methodology, investigation, resources, supervision, writing (review and editing); HER: Resources, supervision, writing (review and editing); PCH: Methodology, software, investigation, resources, writing (original draft and editing).

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