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DOI:
10.1017/S0033291716002725

Document Version
Peer reviewed version

Citation for published version (Harvard):
Eddy, C, Cavanna, AE & Hansen, P 2016, 'Empathy and aversion: the neural signature of mentalizing in Tourette syndrome', *Psychological Medicine*. https://doi.org/10.1017/S0033291716002725

Empathy and aversion: the neural signature of mentalizing in Tourette syndrome

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Running head: Empathy and aversion in Tourette syndrome

Manuscript word count: abstract = 249; main text = 4625; 4 tables and 1 figure; supplementary information (separate files): 3 tables and 1 figure

This study was unfunded.

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ABSTRACT

BACKGROUND: Previous studies suggest that adults with Tourette syndrome (TS) can respond unconventionally on tasks involving social cognition. We therefore hypothesised that these patients would exhibit different neural responses to healthy controls in response to emotionally salient expressions of human eyes. METHODS: Twenty-five adults with TS and twenty-five matched healthy controls were scanned using fMRI during the standard version of the Reading the Mind in the Eyes Task which requires mental state judgments, and a novel comparison version requiring judgments about age. RESULTS: During prompted mental state recognition, greater activity was apparent in TS within left orbitofrontal cortex, posterior cingulate, right amygdala and right temporo-parietal junction (TPJ), while reduced activity was apparent in regions including left inferior parietal cortex. Age judgment elicited greater activity in TS within precuneus, medial prefrontal and temporal regions involved in mentalizing. The interaction between group and task revealed differential activity in areas including right inferior frontal gyrus. Task related activity in the TPJ covaried with global ratings of the urge to tic. CONCLUSIONS: While recognising mental states, adults with TS exhibit greater activity than controls in brain areas involved in motor control and the processing of negative emotion, in addition to reduced activity in regions associated with the attribution of agency. In addition, increased recruitment of areas involved in mental state reasoning is apparent in these patients when mentalizing is not a task requirement. Our findings highlight differential neural reactivity in response to emotive social cues in TS, which may interact with tic expression.

KEY WORDS: Emotion, Social cognition, Theory of Mind, Tics, Tourette syndrome

INTRODUCTION

Tourette syndrome (TS) is characterised by involuntary movements and vocalizations, which are commonly preceded by sensory-psychological urges termed premonitory sensations. Tics are thought to reflect dysfunction within motor regions including the basal ganglia (Albin and Mink, 2006; Wang *et al.*, 2011). However, the behavioral spectrum of TS frequently involves complex tics or compulsions including swearing tics (coprolalia), mirroring behaviors (echophenomena) and context-dependent socially inappropriate urges (Kurlan *et al.*, 1996; Eddy and Cavanna, 2013a). The neural mechanisms underlying these latter features are yet to be determined.

Urges to carry out socially inappropriate behaviors could be linked to reasoning about people's mental states such as beliefs and emotions. For example, a socially inappropriate remark (e.g. "big nose") is likely to prompt a negative emotional reaction in the subject, and inferences about the beliefs or intentions of the speaker. The speaker may also experience a negative emotional reaction on realising the consequences of their remark. Adults with TS can respond differently to controls on tasks involving social cognition, such that their interpretations of socially inappropriate faux pas, humour, sarcasm and emotional facial expressions can be unconventional (Eddy *et al.*, 2010a, b; Eddy *et al.*, 2011). However, people with TS do not demonstrate a 'lack' of Theory of Mind (ToM, i.e. the ability to reason about mental states), but rather subtle differences to controls in when drawing inferences relating to social interaction (Eddy and Cavanna, 2013b). One study (Eddy and Cavanna, 2015) examined patients' behavioural responses to a task that required participants to describe the ambiguous movements of animated shapes. When shown videos featuring random movement, patients with TS were more likely than controls to attribute emotions and intentions to the shapes. This raises the possibility of hyper-mentalizing in TS, i.e. a tendency

towards excessive attribution of mental states, which may be associated with inaccurate conclusions about social behaviour (e.g. Sharp *et al*., 2011). Hyper-mentalizing may also help to explain why patients can report the occurrence of socially inappropriate actions in benign control stories containing no faux pas (Eddy *et al.*, 2010a; Eddy *et al.*, 2011), and attribute more negative intentions to imaginary conspecifics during cooperative games (Eddy *et al.*, 2011). Furthermore, people with TS report increased personal distress during every-day social interactions, indicating increased susceptibility to negative emotions in the self when witnessing other people in distress i.e. enhanced empathy or emotional contagion (Eddy *et al.*, 2015). Hyper-mentalizing or increased personal distress could help explain social anxiety in TS (e.g. Thibert *et al*., 1995) or insecure attachment styles involving relationship anxiety and avoidance (e.g. Dehning *et al*., 2015).

Previous research has raised the possibility of dissociation between different aspects of social cognition in TS. For example, despite evidence of hyper-mentalizing, people with TS can self-report doing less everyday cognitive perspective taking than healthy controls (Eddy *et al.*, 2015). This finding could help explain why activity in the posterior cingulate, right amygdala and right temporo-parietal junction (TPJ) increased to a lesser degree in patients with TS than in healthy controls when these patients were asked to reason about story character's beliefs (Eddy et al., 2016). The aim of the current study was to further investigate social cognition in TS using fMRI and a different measure: the Reading the Mind in the Eyes Task (RMET: Baron-Cohen *et al.*, 2001). This task was selected as it is quite different to the story-based false-belief task used in these authors' previous experiment, and relies upon the use of visual cues to infer mental state (Eddy *et al*., 2016). Furthermore, the RMET may more accurately be described as a test of emotion recognition rather than ToM (Oakley *et al*., 2016), suggesting it may offer greater insight into affective aspects of social cognition, such as empathy, or the ability to relate to others' emotions. The standard version

of the RMET may elicit mild behavioral differences in TS (Eddy *et al.*, 2011), which could reflect dysfunction in regions typically activated by this task such as the orbitofrontal cortex (OFC), amygdala or temporal lobe (see Schurz *et al.*, 2013). Indeed, some of these neural regions may be activated by facial expressions even when mental state recognition is not relevant to the task goal as a result of implicit ToM (Tseng *et al.*, 2014). In the current study, a newly developed version of the eyes task which required judgments about age rather than mental states was included for comparison. We hypothesised that patients with TS would show neural differences to controls during both versions of the task (given that salient emotional expressions were present in both), but that this would vary according to whether they were prompted to consider mental or physical states.

MATERIALS AND METHODS

Participants

Twenty-five outpatients with uncomplicated TS and twenty-five healthy controls matched (mostly one-to-one) for gender (6 females, 19 males) age (TS: mean=31.48 years, SD=11.50, median=29, range=17-59; Controls: mean=31.76, SD=12.65, median=28, range=18-59) and education (TS: mean=14.68 years, SD=2.06, median=15, range=11-19; controls: mean=14.64, SD=1.95, median=14, range=11-19) took part. All were English first-language speakers with no history of head injury, seizure or substance abuse. Patients were recruited through a specialist outpatient clinic in Birmingham, UK and healthy controls were recruited through the Queen Elizabeth Hospital, Birmingham and University of Birmingham, UK. Controls had no psychiatric or neurological diagnoses and were not taking psychoactive

medication. Patients (**Table 1**) had TS diagnosed by an experienced neurologist (AEC) 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 as screened for using the National Hospital Interview Schedule for Tourette syndrome (Robertson and Eapen, 1996), therefore the sample may be considered to comprise participants with 'uncomplicated' TS. There was no significant difference in age between the two groups (Wilcoxon-Mann-Whitney value=274, p=.386). Group comparisons for performance on neuropsychological tests, which indicated limited differences on some tests assessing set-shifting, are reported in an earlier study (Eddy et al., 2016).

Protocol

The protocol received NHS approvals and all participants gave written informed consent. After neuropsychological assessment (see Eddy *et al.*, 2016), participants were shown task instructions and example stimuli, before being made comfortable in the scanner.

Eyes Tasks

The in-scanner task was based on the Reading the Mind in the Eyes Task (Baron-Cohen *et al.*, 2001). This task contains 36 photographs of eyes surrounded by four mental state terms (e.g. interested, flirtatious, doubtful, preoccupied). One option is the conventional 'correct' answer as based on healthy control responses. We included a matched version that required judgments about physical rather than mental states (i.e. the age of the eyes), similar to previous studies (e.g. Moor *et al.*, 2012). However, our comparison stimuli differed from those used in the Moor *et al*. study as that study used a combination of age (older/younger)

and gender (male/female) to create four options. The age version used in the current study was developed through testing 135 healthy participants (77 females, 58 males; mean age=22.5 years, SD=10.72; mean education=13.5 years, SD=1.47). First, 60 healthy participants estimated the approximate age of each pair of eyes. Sample means and modes were used to generate a 'conventional' answer for each photo. The three other forced-choice options were similar to the original task: one age option was close to the conventional answer (e.g. within 5 years) and two others were more different (e.g. within 8-20 years). The pilot age task was tested on a further 75 healthy participants along with the mental state version. Responses were reviewed periodically and the multiple choice options for the age version were adjusted, until the matched trials for age and mental state yielded a very similar number of errors. The 21 trial photographs with the most closely matched mean errors for the two versions comprised the final task (one practice item; original stimuli numbered 1, 2, 3, 5, 6, 7, 11, 13, 14, 15, 17, 18, 23, 25, 26, 27, 30, 31, 33, 34, 36; The stimuli set with age options is available on request). Participants completed four blocks containing ten trials (age; mental state; age; mental state). Instructions at the start of each block told participants to consider each photo and respond to the question mark cue by pressing one of four buttons, selecting the age/mental state that best matched the image. Each photo with four answer options was onscreen for 10 seconds, and then replaced by a question mark cue for two seconds. Each trial was followed by a blank period with a fixation point in the middle of the screen (15.5 seconds) before the next photo appeared.

Data acquisition protocol

Sponge pads were used to reduce head movement, and patients were told the best time to tic was in between trials and scanning phases. Data were acquired during a single scanning

session in a Phillips Achieva 3.0T MRI scanner using an eight-channel head coil. Stimuli were presented using Presentation software (Version 14.9, Neurobehavioral Systems, CA) which also recorded behavioural responses. 110 T2*-weighted gradient echo planar imaging volumes were obtained for each of the four acquisition runs of the task. 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=t, FOV 240 x 240 mm, acquisition matrix=80×80, reconstructed to give isotropic voxels of size=3×3×3mm^3. On completion of the task, 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

Movement artefact (mean absolute movement across each run) was examined and participants were excluded if they had more than one run where they moved more than 1.5mm (i.e. half a voxel or more). Exclusions left data from 23 patients and 24 controls. A comparison of maximum movement per block showed no significant group difference ($p=0.210$).

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 v5.0.9 (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=24 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 Boundary-Based Registration transformation. A non-linear FNIRT transformation with a warp resolution of 10mm was used to register between participants' T1 image and MNI space.

Button responses were modelled into the neuroimaging data as a covariate of no interest. The timeseries for when each principal condition was active (10 second epochs) were convolved with a standard gamma-derived haemodynamic response function and high pass temporal filtering (sigma=24 seconds) 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 motion parameters generated by MCFLIRT were added to the overall GLM as separate regressors of no interest, in order to help reduce any residual uncorrected motion-related artefacts (Johnstone *et al.*, 2006). This model was used to generate the data for Results Tables 1 and 2 below, which show group activation differences for each version of the task.

Group Z statistic images from these models were subsequently corrected for multiple comparisons by means of a two step family wise error (FWE) correction process in order to control for false positives. The AlphaSim program, part of the AFNI toolkit (Cox, 1996), was used to control the FWE rate. A particular voxel-wise threshold was chosen and, together with the voxel dimensions and spatial smoothing kernel size used in the fMRI analysis, 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 Z >2.1 and cluster size >130.

Finally, we previously scanned this sample of patients during a ToM task involving false-belief, and found that right TPJ activity covaried with echophenomena, impulsivity ratings and urges to tic; left TPJ activity co-varied with socially inappropriate urges; and

amygdala activity co-varied with premonitory urges (Eddy *et al.*, 2016). We therefore examined whether similar relationships were apparent for the RMET, using the same TPJ masks based on healthy control data from this previous study, and masks for the amygdalae based on the Harvard-Oxford Atlas. Symptom ratings were for lifetime tic severity on the Yale Global Tic Severity Scale (YGTSS: Leckman *et al.*, 1989); tic urge severity on the Premonitory Urge for Tics Scale (PUTS: Woods *et al.*, 2005); obsessive-compulsive behaviours on the Yale-Brown Obsessive Compulsive Scale (YBOCS: Storch *et al.*, 2007); 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 according to Minnesota Impulsive Disorders Interview (MIDI total count; Christenson *et al.*, 1994) 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 four masks, with percentage BOLD signal change as the dependent variable, participant identity as a random factor, and the six symptom measures as initial covariates in a stepwise backwards elimination to create the minimal adequate model where all surviving measures were significant.

RESULTS

Behavioural performance

Behavioural data are shown in **Supplementary Table 1**. Each of the 47 participants included in neuroimaging analysis completed 20 trials for each version of the eyes task. There were four missing responses. All responses within 5 s following the question mark cue were

included, yielding 1790 valid responses out of 1880 (95.2%). Patients and controls showed no significant differences on either the mental state version (X^2=2.784, df=1, p-value=0.0952) or the age judgment version (X^2 =0.0125, df =1, p-value=0.911) of the task in terms of accuracy. For reaction times, a mixed effects model was run with RT regressed against dependent variables of population group, task condition and error status (whether the trial was correct or not). This indicated no significant effect of group (F(45,1)=1.4657, p=0.2323) or task (F(1737,1)=0.3586, p=0.549) but correct responses were faster (F(1737,1)=37.964, p<0.0001) by approximately 131milliseconds on average.

Neuroimaging data

In healthy controls, the standard (mental state judgment) eyes task activated similar brain regions (**Supplementary Table 2**) to those reported in previous studies, including posterior superior temporal gyrus (STG) and inferior frontal gyrus (e.g. Schurz *et al.*, 2013; Moor *et al.*, 2012). The age judgment task led to activity in many regions overlapping with the mental state version (e.g. visual, inferior frontal and anterior cingulate cortices), plus additional activity in areas such as middle frontal and dorsolateral prefrontal cortex (**Supplementary Table 3**). The general effects of task appear in line with those of Harris and Fiske (2007), who used a different picture-based task in healthy participants and observed more superior frontal, middle temporal and parahippocampal activation for judging mental state (preference) and greater activity in bilateral precentral gyrus, middle frontal gyrus and insula for age judgments.

For the standard version of the eyes task (**Table 2; Supplementary Figure 1**), patients with TS showed greater activation than controls in the left lateral OFC, posterior cingulate, right angular gyrus, and a cluster spanning the right amygdala and putamen. The

opposite contrast revealed reduced activation (to baseline) in areas including the lingual gyrus, precentral gyrus and left inferior parietal cortex in TS.

During the age judgment version of the task (**Table 2; Supplementary Figure 1**), patients with TS exhibited more activity than controls in precuneus, medial prefrontal cortex, left inferior frontal gyrus (IFG), angular and supramaginal gyri, and regions within left occipital cortex. Healthy controls showed greater activation than patients in areas including left precentral gyrus, right supplementary motor cortex, left superior parietal cortex, left and right intracalcarine cortex and right occipital areas.

Statistically significant differences relating to the interaction between group and version of the eyes task are shown in **Table 3.** Differential activity was apparent in TS in right IFG, right STG (planum temporale), left precentral gyrus and bilateral occipital areas. Interaction plots are shown in **Figure 1**. For the right IFG, brain activity increased more in TS for age judgment than mental state judgment, which is the opposite pattern to controls. For the other four regions, activity increases in TS are greater for the mental state version and smaller in the age version, with less difference between the two versions of the task in controls.

Finally, covariate analysis was performed on the left and right TPJ, and left and right amygdalae, based on previous findings (Eddy *et al.*, 2016). One mixed effects model was generated for each of the four masks for activity across both versions of the eyes task, with six symptom ratings as listed previously. Three regions (right TPJ, left TPJ and left amygdala) showed significant covariation between at least one symptom measure and activity across the eyes task (**Table 4**). Right TPJ activity covaried negatively with echophenomena, but positively covaried with premonitory urges and impulse control disorders. Activity in left TPJ covaried positively only with urges to tic, and left amygdala activity covaried positively with echophenomena ratings.

DISCUSSION

During mental state recognition on the standard version of the eyes task, adults with TS exhibited greater activity than healthy controls in left OFC, posterior cingulate, right amygdala and putamen, and right TPJ. Reduced activity was apparent in TS in areas including left inferior parietal cortex. Age judgment elicited other group differences, including greater activity in TS within precuneus, medial prefrontal and temporal regions frequently implicated in ToM. The exact abilities and processes assessed by the RMET are still debated. For example, one recent study (Oakley et al., 2016) found that alexithymia (i.e. difficulties in interpreting and explaining one's own emotions) can be more closely related to impairments on the RMET than a diagnosis of autistic spectrum disorder, emphasising the importance of emotional processes. However, as a previous study found no evidence of elevated rates of alexithymia in TS (Eddy *et al.*, 2015), differential neural activity in TS in response to the eyes stimuli may be related to group differences in empathy or emotional contagion, complementing existing reports of neural differences on traditional tests of ToM (e.g. Eddy *et al.*, 2016).

Both the OFC and amygdala are associated with operant conditioning and learning about aversive outcomes (e.g. Schoenbaum *et al.*, 1998). More specifically, the left OFC is linked to recognition of negative emotions such as fear, anger and disgust (e.g. Sprengelmeyer *et al.*, 1998; Wicker *et al.*, 2003) and awareness of threatening social interactions (e.g. Suguira *et al.*, 2009). Greater OFC activity is seen in healthy adults when they control behavioural responses which are naturally incompatible with emotional facial expressions e.g. approach responses towards angry faces (Roelofs *et al.*, 2009). More

precisely, the left OFC peak in the current study matches that differentially activated for deceptive versus co-operative interactions in healthy participants (Lissek *et al.*, 2008). This is notable given that patients with TS are more likely than controls to report accidental anti-social remarks as being motivated by negative intent (Eddy *et al.*, 2010; Eddy *et al.*, 2011). Increased activity in a brain area linked to the processing of negative emotional interactions could imply that being prompted to consider mental states has aversive associations in TS, perhaps because this could make patients more aware of unpleasant social attention due to tics. However, patients with TS also experience more personal distress than controls when witnessing other people's negative emotional experiences (Eddy *et al.*, 2015), so increased reactivity to other people's emotions in general may be a more parsimonious interpretation of our findings.

Patients with TS also exhibited differential activity in a cluster encompassing right amygdala and putamen during prompted mental state recognition. Previous studies have reported amygdala dysfunction during emotional face processing in TS (Neuner *et al.*, 2010). The right amygdala has been linked to subconscious processing of emotional expressions (Pegna *et al.*, 2005) and shows enhanced activation when social phobics view emotional expressions (Bertolino *et al.*, 2005). As well as supporting the suggestion that tics could involve orbitofrontal or amygdala reactivity to environmental cues (Eddy *et al.*, 2013b), these findings further raise the possibility that associated putamen activations could link emotional cues to motor responses, or perhaps prompt tics. In other words, the cardinal motor signs of TS (i.e. tics), may at least partly reflect underlying changes in limbic activity. However, as tic occurrence was not measured during scanning further research is needed to confirm this possibility.

Activity in the left amygdala was found to covary strongly with echophenomena ratings, while activity in left and right TPJ covaried with ratings of premonitory urges, and

right TPJ activity was also linked to echophenomena and impulsive behaviours (similar findings for right TPJ were recently reported using a story-based ToM task: Eddy *et al.*, 2016). More specifically, activity in right TPJ covaried negatively with echophenomena ratings, but positively with tic urges and impulse control problems. Right TPJ activity is reduced in association with greater self-other blending (Cheng et al., 2010). Therefore our findings are in line with an association between increased self-other blending and echophenomena. The positive relationship between right TPJ activity, tic urges and impulsive behaviours is harder to interpret, but may suggest these symptoms are linked to achieving a state of self-other distinction (Eddy, 2016). In summary, during tasks involving social cognition, activity within medial and lateral temporal regions in TS covaries with core symptoms (i.e. premonitory urges) and characteristics that may be related to social cognition (i.e. echophenomena).

Individuals with TS exhibited less activity than controls in left inferior parietal cortex during prompted mental state recognition. This region may contribute to motor simulation when understanding action goals and related mental states (e.g. Cerri *et al.*, 2015). Moreover, there is stronger left inferior parietal activation when healthy participants imagine themself carrying out an action, and reduced activity when imagining another person as the acting agent (Ruby and Decety, 2001). Differential inferior parietal activity in patients during mental state recognition could therefore further reflect differences in attributing agency for the observed actions or emotions. Problems disentangling the actions of one-self and another person could help to explain echophenomena. Furthermore, difficulties in disciminating between actor and observer when perceiving other people's negative emotions could lead to unpleasant emotions being over-attributed to the self, helping to explain increased personal distress in TS (Eddy *et al.*, 2015).

The precuneus is frequently associated with social cognition (Cavanna and Trimble, 2006) and exhibits increased activation for third-person versus first-person simulation in healthy participants (Ruby and Decety, 2001). The posterior cingulate and precuneus showed greater activity in TS during both versions of the eyes task, perhaps indicating a predisposition towards ToM. Patients with TS also exhibited more activity than controls in medial prefrontal and posterior temporal areas frequently implicated in ToM specifically during age judgments. These findings support the suggestion that people with TS spontaneously hyper-mentalize (Eddy and Cavanna, 2015).

Group and task interactions indicated that while controls showed little difference in premotor activity across each eyes task, activity in left precentral gyrus increased more in TS during mental state judgment, but increased less than in controls for age judgment. This further links social cognition to motor activity in TS. In addition, controls showed similar increases in occipital activity for each task version, whereas in TS a greater increase was seen during mental state recognition, with less of an increase for age judgment. This could reflect comparatively greater attention and visual processing in TS specifically during mental state recognition.

The right IFG exhibited more of an increase in activity in TS during age judgment than mental state judgment, whereas the opposite pattern was apparent in controls. Right IFG has been implicated in the control of impulsive motor responses (Aron *et al.*, 2004; Aron *et al.*, 2014) and inhibition of distracting emotional stimuli (Mitchell *et al.*, 2008). Indeed, response inhibition and aversive emotional stimulus processing may combine additively in IFG (Brown *et al*., 2012). Therefore differential activity in this area in TS could reflect efforts to control emotional or motor responses elicited by the eyes stimuli. For example, perhaps greater right IFG engagement during age judgment may underpin patients' efforts to reduce interference linked to emotion processing. As there were no significant behavioural

differences between the groups for either version of the eyes task, at least some of our findings could reflect activation patterns which enabled adults with TS to maintain good task performance. If the pattern of right IFG activity across the two versions of the eyes test in TS did relate to attempts to control hyper-mentalizing or emotion processing, one interpretation is that this reflects a compensation mechanism.

The right STG (planum temporale) also showed in the condition and group interaction, with greater activity in TS, especially during mental state recognition. The right STG is activated by the standard version of the eyes task (e.g. Gallagher and Frith, 2003) and may play a role in inferring meaning from gaze direction and facial expression (Allison *et al.*, 2000). However, the left planum temporale is implicated in speech and language comprehension (e.g. Sommer *et al.*, 2008). In the current study, mental state options were presented as words whereas age options were numbers. Therefore the possibility that this interaction effect could be related to a group difference in hemisphere specialisation for language cannot be ruled out. Indeed, the contribution of the right hemisphere to language processing in TS, and a possible relationship with symptoms such as coprolalia, is worthy of investigation.

Limitations of the current study include that the age judgment task was newly developed, and although some of our findings are in accordance with previous studies using a similarly designed task (e.g. Moor *et al.*, 2012), caution is needed in interpretation. For example, it would be naive to assume that emotional expressions would definitely not elicit some degree of automatic emotional processing even when judging age (e.g. Wagenbreth et al., 2014). In addition, our ability to assess the link between tics, brain activity and social cognition is limited because we did not assess tics or urges during scanning. Furthermore, our patient sample was restricted to adults with moderate tic severity and no diagnosed co-morbid disorders. The prevalence of co-morbidities in TS can be as high as 90% (Cavanna &

Rickards, 2013), although the rate may be lower in adults, or in community samples containing less severe cases (e.g. Scharf *et al.*, 2012). Despite limiting generalizability, studying patients without co-morbid disorders may help determine whether TS *per se* is likely to explain differences to healthy controls. One important point is that studies of social cognition in children with TS are lacking, and would offer further insight into the role of social cognition in this disorder.

In conclusion, TS is associated with greater activity in neural regions important for ToM when visual cues to mental state reasoning are available but are not required by the task. Furthermore, during prompted mental state recognition these patients exhibit dysfunction in brain regions involved in attributing agency alongside increased activity in areas that process negative emotion. Increased susceptibility to emotive social cues could help explain why patients experience elevated personal distress in interpersonal situations, and why tics worsen with negative emotions and social stress. Right IFG activations may reflect patients' attempts to control their emotional reactions and related motor responses. Our findings once again highlight the right TPJ as an area of interest in relation to core symptoms of TS. Future studies seeking to clarify the precise relationship between tics, social cognition and emotional reactivity will make a unique and important contribution to our understanding of this neurodevelopmental condition.

ACKNOWLEDGMENTS

We are grateful to Nina Salman for assistance with MRI data collection, to Tourettes Action UK for publicising the study, and to all of our participants. We also thank Birmingham University Imaging Centre for facilitating this study.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

This study was unfunded. Scanning costs were met in house by Birmingham University Imaging Centre, UK: This was a BUIC development project.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Table 1. Patient group clinical characteristics

Measure	Mean; SD	Median; range
YGTSS total score*	53.60; 13.57	52; 31-90/100
YGTSS tic score*	28.40; 5.78	28; 21-40/50
PUTS total score	20.48; 2.97	21; 15-29/9-36
YBOCS total score	8.80; 5.27	9; 0-19
HADS depression subscale	7.04; 3.83	7; 1-15
HADS anxiety subscale	7.96; 5.04	7; 3-15
Duration of TS (years)	23.76; 11.24	22; 8-49
Complex tic-related symptoms	Non-obscene socially inappropriate behaviors=15; palilalia=16; palipraxia=16; echolalia=13; impulse control disorders=12; self-injurious behaviors=10; echopraxia=10; coprolalia=6; copropraxia=5	
Medications (n=10/25)	3 clonidine, 2 risperidone, 1 haloperidol, 1 sulpiride, 1 risperidone + aripiprazole, 1 risperidone + clonidine, 1 aripiprazole + clonidine	

KEY = HADS: Hospital anxiety and Depression Scale; PUTS: Premonitory Urge for Tics Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale; YGTSS: Yale Global Tic Severity Scale. * Measure was clinician rated. All other scales were self-report.

Table 2. Eyes task mental state judgments group activation differences

Label	Side	BA	Cluster size	MNI X	MNI Y	MNI Z	Peak Z-value
MENTAL STATE JUDGMENT							
Healthy controls > Tourette syndrome							
Lingual gyrus	R	19	233	22	-72	-2	3.83
Precentral gyrus (premotor area)	L	6	241	-58	4	36	3.58
Inferior parietal cortex	L	40	566	-52	-44	50	3.56
Somatosensory cortex	L	3	166	-24	-22	46	3.27
Temporo-occipital fusiform	R	37	149	28	-52	-22	3.19
Tourette syndrome patients > Healthy controls							
Lateral orbitofrontal cortex	L	47	311	-38	28	-8	4.17
Posterior cingulate	L	30	460	-12	-52	20	3.62
Right amygdala/putamen	R	34	501	26	-4	-8	3.51
Angular gyrus	R	42	139	54	-46	22	3.29
AGE JUDGMENT							
Healthy controls > Tourette syndrome							
Supplementary motor cortex	R	6	179	4	0	58	4.30
Intracalcarine cortex	L	19	877	-26	-60	6	4.04
Precentral gyrus	L	48	414	-62	10	0	4.01
Superior parietal cortex	L	2	807	-36	-44	64	3.79
Precentral gyrus	L	4	231	-30	-18	40	3.67
Lateral occipital cortex (superior)	R	19	181	16	-82	42	3.66
Occipital fusiform gyrus	R	19	470	22	-72	-4	3.58
Intracalcarine cortex	R	17	218	10	-74	8	3.51
Occipito-temporal area	R	37	185	32	-54	-24	3.33
Tourette syndrome > Healthy controls							
Precuneus	R	23	348	6	-60	26	4.71
Anterior medial prefrontal cortex	R	10	134	8	58	16	4.12
Superior lateral occipital cortex	L	7	130	-30	-72	48	3.97
Inferior frontal gyrus	L	45	289	-50	22	16	3.83
Occipital pole	L	18	145	-20	-92	34	3.65
Posterior supramarginal gyrus	R	22	130	66	-44	22	3.53
Angular gyrus	L	39	132	-64	-62	8	3.39

KEY = Threshold z>=2.1, cluster size >130; p<.05 corrected. BA: Brodmann areas are approximate.

Table 3. Interaction between task (mental state/age judgment) and group (Tourette syndrome; healthy controls)

Label	Side	BA	Cluster size	MNI			Peak Z-value
				X	Y	Z	
Inferior frontal gyrus	R	44	210	56	16	24	3.94
Superior lateral occipital cortex	L	19	618	-32	-82	16	3.56
Lingual gyrus	R	18	575	18	-82	0	3.47
Right superior temporal gyrus (planum temporale)	R	42	155	60	-24	14	3.40
Precentral gyrus	L	6	131	-44	-6	46	3.38

KEY = Threshold z>=2.1, cluster size >130; p<.05 corrected. BA: Brodmann areas are approximate.

Table 4. Significant models from covariate analysis for the Tourette syndrome group

ROI	Variable	Value	Standard error	DF	t-value	p-value
Right TPJ	Intercept	0.025	0.170	23	0.150	0.883
	ECHO	-0.152	0.051	19	-3.004	0.007
	MIDI	0.056	0.024	19	2.385	0.028
	PUTS	0.022	0.008	19	2.913	0.009
Left TPJ	Intercept	0.030	0.215	23	0.142	0.889
	PUTS	0.019	0.009	21	2.229	0.037
Left amygdala	Intercept	0.552	0.061	23	9.073	<0.001
	ECHO	0.150	0.051	21	2.957	0.008

KEY = ECHO: echo-phenomena rating, number of types; MIDI: Minnesota Impulsive Disorders Interview number of disorders; PUTS: premonitory urge for tics scale total score; TPJ: Temporo-parietal junction.

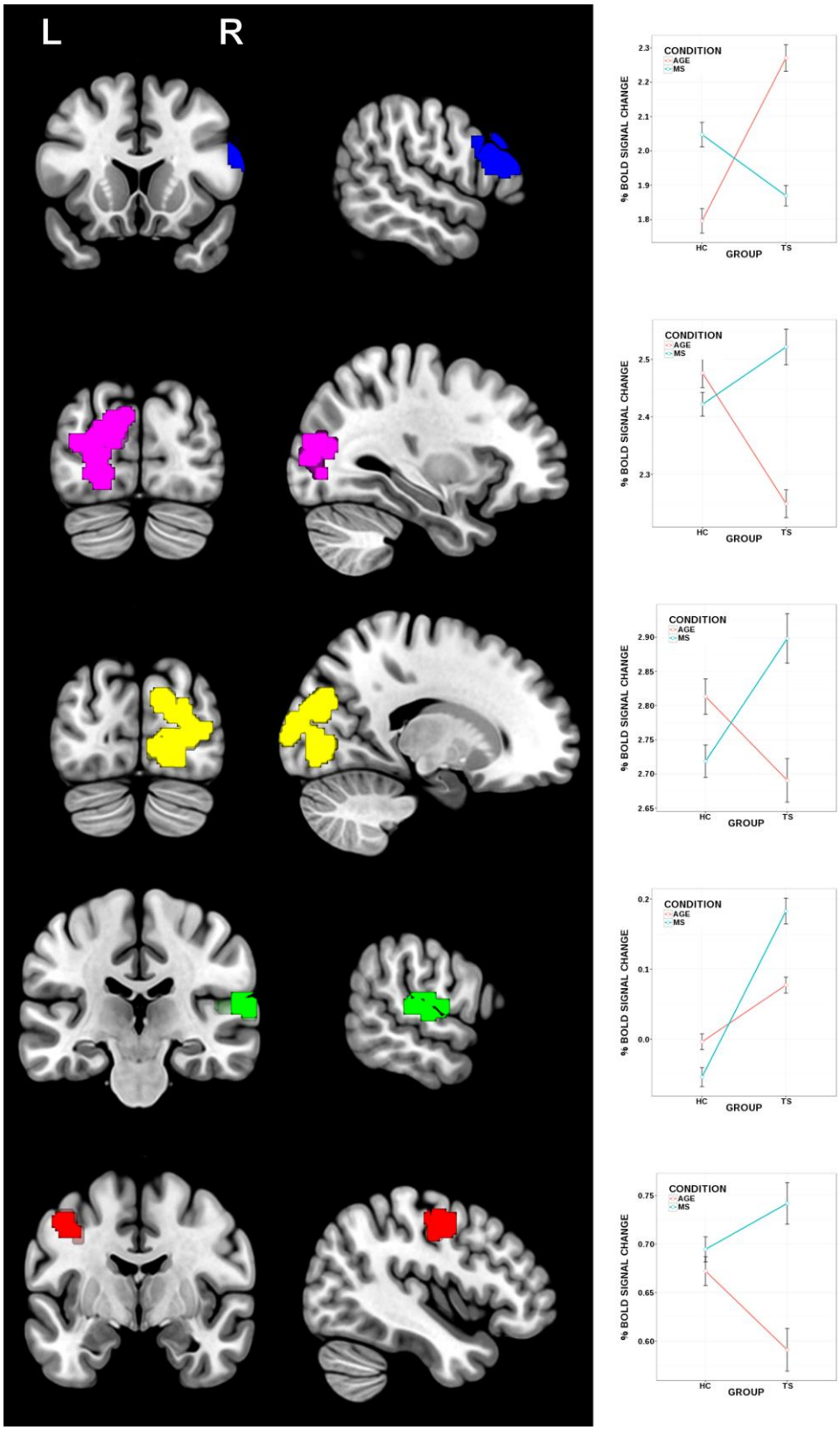

Figure 1. Interaction plots for the five areas showing an interaction between type of eyes task (mental state judgment or age judgment) and group

Brain regions correspond to Table 3. From the top going down: Right inferior frontal gyrus in blue; Left superior lateral occipital cortex in pink; Right lingual gyrus in yellow; Right superior temporal gyrus (plaum temporale) in green; Left precentral gyrus in red. AGE: age judgment task; HC: Healthy controls; MS: mental state judgment task; TS: Tourette syndrome.

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Supplementary Table 1. Behavioural data for patients and controls on both versions of the Eyes Task

Group	Mental state judgments				Age judgments			
	Correct	RT	Incorrect	RT	Correct	RT	Incorrect	RT
Healthy controls	357	0.718 (0.020)	105	0.849 (0.050)	265	0.722 (0.023)	189	0.852 (0.032)
Tourette syndrome	320	0.790 (0.024)	123	0.981 (0.058)	249	0.811 (0.026)	182	0.889 (0.038)

KEY: mean (standard error), RT: reaction time in seconds

Supplementary Table 2. Eyes Task mental state judgments activity change from baseline for the healthy control group

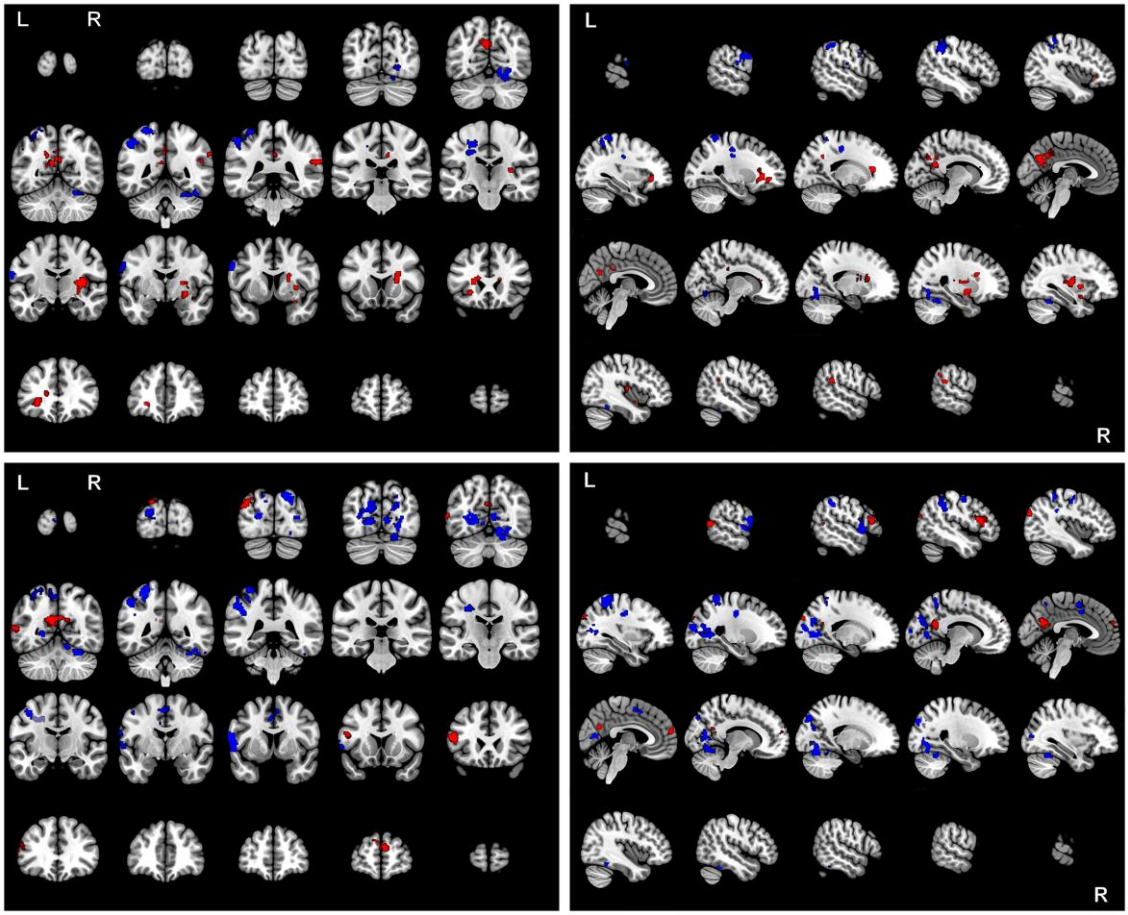
LABEL	HEMI	BA	CLUSTER SIZE	MNI			PEAK Z-SCORE
				X	Y	Z	
Occipital fusiform gyrus	R	19	19639	26	-68	-12	11.40
Inferior frontal gyrus (pars opercularis)	R	44	1930	56	18	26	9.99
Hippocampus	R	/	298	22	-28	0	9.08
Hippocampus	L	27	462	-20	-30	-2	8.89
Inferior frontal gyrus (pars opercularis)	L	48	3640	-40	10	26	8.45
Dorsal anterior cingulate gyrus	L	32	957	-4	14	48	8.40
Ventral striatum (NA)	L	/	349	-16	8	8	7.01
Posterior superior temporal gyrus	L	21	345	-50	-36	2	6.90
Caudate	R	/	254	14	4	12	6.72
Thalamus	L	/	90	-12	-14	10	6.43
Thalamus	R	/	40	12	-12	8	6.34
Anterior cingulate cortex	L	/	12	-14	8	26	5.82
Midbrain	L/R	/	4	0	-16	-22	5.67
Caudate	R	/	9	18	-10	20	5.55
Amygdala	L	/	5	-16	-8	-10	5.54
Supplementary motor cortex	L/R	/	7	0	14	72	5.47
Midbrain	L	/	7	-8	-32	-24	5.45

Threshold z>=5.0, cluster size >3; p<.001 corrected; BA: Brodmann's areas are approximate

Supplementary Table 3. Eyes Task age judgments activity change from baseline for the healthy control group

LABEL	HEMI	BA	CLUSTER SIZE	MNI			PEAK Z-SCORE
				X	Y	Z	
Occipital fusiform gyrus	R	18	23865	26	-70	-14	12.90
Hippocampus	R	/	2987	20	-30	2	8.95
Dorsal anterior cingulate gyrus	L	32	1116	-4	20	44	8.94
Anterior insula	R	47	487	34	20	2	8.71
Posterior cingulate	L/R	/	6	0	-46	8	8.16
Anterior insula	L	47	299	-28	26	0	8.08
Precentral gyrus (primary motor area)	R	44	1067	36	10	28	7.66
Middle frontal gyrus (premotor area)	R	6	267	32	0	58	7.41
Middle frontal gyrus (premotor area)	L	6	426	-28	0	58	7.35
Precentral gyrus (primary motor area)	L	44	374	-46	10	34	7.09
Anterior cingulate gyrus	L	/	93	-4	6	28	6.98
Midbrain	R	/	16	4	-34	-26	5.77
Dorsolateral prefrontal cortex	L	48	49	-38	20	26	5.50
Precuneus	R	7	9	4	-64	60	5.28

Threshold z>=5.0, cluster size >3; p<.001 corrected; Brodmann's areas are approximate



Supplementary Figure 1. Neural differences between patients with Tourette syndrome and healthy controls for each version of the eyes task

Mental state judgment top; age judgment version below. Red = TS> HC; blue = TS<HC.