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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 include environmentally dependent social behaviors 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). In this study, twenty-five adults with uncomplicated TS (no co-morbid disorders, moderate tic severity), and twenty-five healthy age and gender matched controls were scanned with fMRI during an established ToM task. Neural activity 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 localised by this task covaried with the severity of symptoms including echophenomena, 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.

1. 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, 2013; 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, 2014), 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 and 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

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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, 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 prefrontal cortex, temporo-parietal 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 have 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 activity 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 and 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.

2. Materials and methods

2.1. 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 (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).

2.2. Protocol

The study was conducted in accordance with the Declaration of Helsinki and received regional National Health Service 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 and Wolfson, 1985), the Stroop test (Stroop, 1935), the Hayling task (Burgess and Shallice, 1996), the Wisconsin card sorting test (Greve, 2001), tests of regular and irregular word reading (Torgeson et al., 1999; Reynolds and 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., 2010), attention deficit hyperactivity disorder symptoms (Adult Self Report Scale for ADHD: Kessler et al., 2005), anxiety and depression (Hospital Anxiety and Depression Scale: Zigmond and 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 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.