



BRIEF REPORT

Functional magnetic resonance imaging of tics and tic suppression in Gilles de la Tourette syndrome

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Abstract

Tics are defined as involuntary, quick, sudden, and stereotypical movements or phonic productions. Despite the fact that tic suppression plays an important role for the patient's ability to cope with tic disorders, investigations of the underlying neural correlates using functional imaging focused on tic generation rather than tic suppression. We examined a patient with Gilles de la Tourette syndrome with regard to neural mechanisms of tic generation and tic suppression using fMRI. Three different conditions were compared: "tics", "tics suppressed", and "tics imitated". The comparisons of "tics" to "tics suppressed" and of "tics" to "tics imitated" showed similar activation in the anterior cingulate cortex. This leads to distinct suggestions concerning the neural network involved in tic suppression. Similar mechanisms may be involved in tic suppression via mental efforts or active movements.

Key words: *Anterior cingulate cortex, fMRI, Gilles de la Tourette syndrome, tic, tic suppression*

Introduction

Tics are involuntary, quick, sudden, and stereotypical movements or phonic productions that often lead to severe impairment of motor behaviour and to social stigmatization of the affected person. Regarding the high burden of the patients, it is of major importance to reveal the underlying neurobiology of tics and to develop strategies for their control. Tics have been described as "isolated disinhibited fragments of normal motor or vocal behaviours" (Leckman et al. 1999). This accentuates the importance of inhibition or control for the occurrence of tics.

The feeling which arises before the occurrence of many tics is described as "pressure" or "urge" by patients. Premonitory urges that are reported to occur before the execution of a tic have been interpreted as the involuntary component (Kwak et al. 2003), with the performance of the tic itself as a voluntary response to this urge (Lang 1991). Tics can be suppressed to a certain degree, they worsen under conditions of distress, emotional involvement and when the patient feels unobserved (Kawohl et al.

2007). The suppression of tics is reported to be more or less stressful and resource consuming by many patients. It is, next to the social stigmatization by the tics itself, one of the most straining features of tic disorders. Many patients with tic disorders highlight their ability to control or suppress their tics when describing the impairment caused by tics in everyday life. However, research efforts have usually focused on tic generation instead of tic suppression: the neural mechanism of tic generation have been subject of various functional imaging studies (for a review see Adams et al. (2004)). There is, to our knowledge, only one functional magnetic resonance imaging (fMRI) study investigating tic suppression (Peterson et al. 1998). However, that study did not take into account the role of active movements in tic suppression. The absence of tics during voluntary motor tasks coinciding with supplementary motor activation has been reported for Gilles de la Tourette syndrome (Fattapposta et al. 2005). This leads to the assumption that tic suppression may be linked to the performance of other movements. Nevertheless, tics can be suppressed by mental efforts, as reported by many patients. The aim of our investigation was

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to uncover mechanisms underlying tic generation and tic suppression.

Methods

Patient

A 28-year-old, right handed male with Gilles de la Tourette syndrome according to DSM-IV (307.22) participated in the investigation after giving written informed consent. At the time of the fMRI acquisition, the patient had been unmedicated for 2 weeks, after having taken aripiprazole for 17 months. After suffering from severe periods of the disorder with pronounced and frequent motor and vocal tics in the past, the patient reported the preponderance of a simple motor tic of the thumbs (right >> left) at the time of the investigation. He showed good tic control and was able to easily suppress the tics by mere mental effort. However, tic frequency and interference worsened under distress and when alone. He scored 26 points on the Yale Global Tic Severity Scale (YGTSS) (Leckman et al. 1989).

Task

While being scanned with fMRI, the patient exerted three conditions, each lasting 3 min in a block design. In the first condition, “tics”, the patient gave free rein to the tics. In the second condition, “tics suppressed”, he mentally suppressed the tics. In the third condition, “tics imitated”, he imitated the tics by actively and voluntarily moving the right thumb in the way it would be done by the tic. Due to the frequent occurrence of tic at rest no real resting condition was possible. The time in between the different conditions was approximately 1 min.

fMRI acquisition and analysis

Imaging was performed with a 3.0-Tesla General Electrics Signa HD whole body scanner (GE Health Care, Munich, Germany) equipped with a head coil. Initially, high-resolution three-dimensional T1* weighted anatomical volumes were acquired (TR/TE 9.4/2.1 ms; matrix size 256 × 256; 1 × 1 × 1 mm resolution, axial orientation) for later coregistration with the fMRI. T2* weighted functional MR images were obtained using echoplanar imaging (EPI, TR/TE 1980/32 ms, flip angle 70°, 22 sequential axial slices covering the whole brain, slice thickness 5 mm, 0.5 mm gap, matrix 64 × 64 pixels, FOV 220 mm, resulting voxel size 3.4 × 3.4 × 5.5 mm). Altogether 270 volumes were obtained, 90 volumes per condition. During the session, the patient watched a neutral blank screen via digital video goggles (Resonance Technology Inc., Northridge, USA).

fMRI data were analyzed using BrainVoyager QX 1.8 (Brain Innovation, Maastricht, The Netherlands). Preprocessing of the functional scans included motion correction (translation and rotation did not exceed 3 mm), slice scan time correction, high frequency temporal filtering, and removal of linear trends. The three different conditions were compared by building contrasts within the block design.

Results

An increased signal in the “tic” condition compared to the condition “tics suppressed” was observed in the left anterior cingulate cortex (ACC) (Talairach coordinates $-11/24/26$, BA 24, 135 voxels of 1 mm³ voxel size, $P < 0.001$, Bonferroni-corrected; Figure 1a). For the same area, a similarly increased signal in the “tic” condition compared to the condition “tics imitated” was observed (Talairach coordinates $-9/23/28$, BA 24, 357 voxels; $P < 0.001$, Bonferroni-corrected; Figure 1b). No statistically significant difference was observed between the signal changes during the conditions “tics suppressed” and “tics imitated”.

Discussion

The “tics” condition was associated with an activation in the left middle anterior cingulate cortex (ACC) when compared to both other conditions, “tics suppressed” (by mental effort) and “tics imitated” (by voluntary action). This area matches the rostral cingulate motor area (CMA, BA24c (Vogt and Vogt 2003)). In the first gaze this similarity between tic suppression and imitation appears to be counterintuitive, but it may be explained within the frame of feedback models. Earlier, electrical stimulation in the cingulate motor area (CMA) was reported to produce involuntary movements and complex gestures (Vogt and Vogt 2003), which could be modified or resisted. Moreover, it is part of a network of paralimbic areas which are activated before tic onset (Bohlhalter et al. 2006), which is in accordance with our results. The mediating role of the CMA between emotional and motivational influences on the one hand, and motor control on the other hand may correspond to the differential influences on tic severity by various emotional states (Wood et al. 2003). Within the frame of our conservative statistical threshold, the ACC was the one area more active during the involuntary happening of tics compared to the suppressed state. We assume that there may be either a dysfunction of the CMA causing continuous pathological activity propagating the tics, or an afferent dysfunctional input

to the CMA. The latter might arise mainly from the basal ganglia or the thalamus (Leckman et al. 2006) and cause a continuous pathological discrepancy between the actual and the desired state. The ACC detects this discrepancy and accordingly initiates the correcting movement in form of a tic. This view would fit with the role of the ACC, especially the caudal or midcingulate area, as an error or conflict detector (Carter et al. 1998; van Veen and Carter 2002).

In our design we cannot determine whether a pathological intrinsic activity is generated in the CMA itself or if it would activate the CMA via

afferences from the striatum or the thalamus, because the afferent areas would be active continuously and would not present themselves in any behavioural comparison. An influence by “higher” cortical areas during suppression of tics is also conceivable: The ACC has a strong bidirectional connection with the prefrontal cortex, especially the dorsolateral prefrontal cortex (DLPFC) (Bates and Goldman-Rakic 1993; Devinsky et al. 1995; Paus 2001), which is involved in important processes of cognitive and executive control (Brass et al. 2005; Egner and Hirsch 2005). The motor action of tics is assumed to be caused by a propagation of the ACC

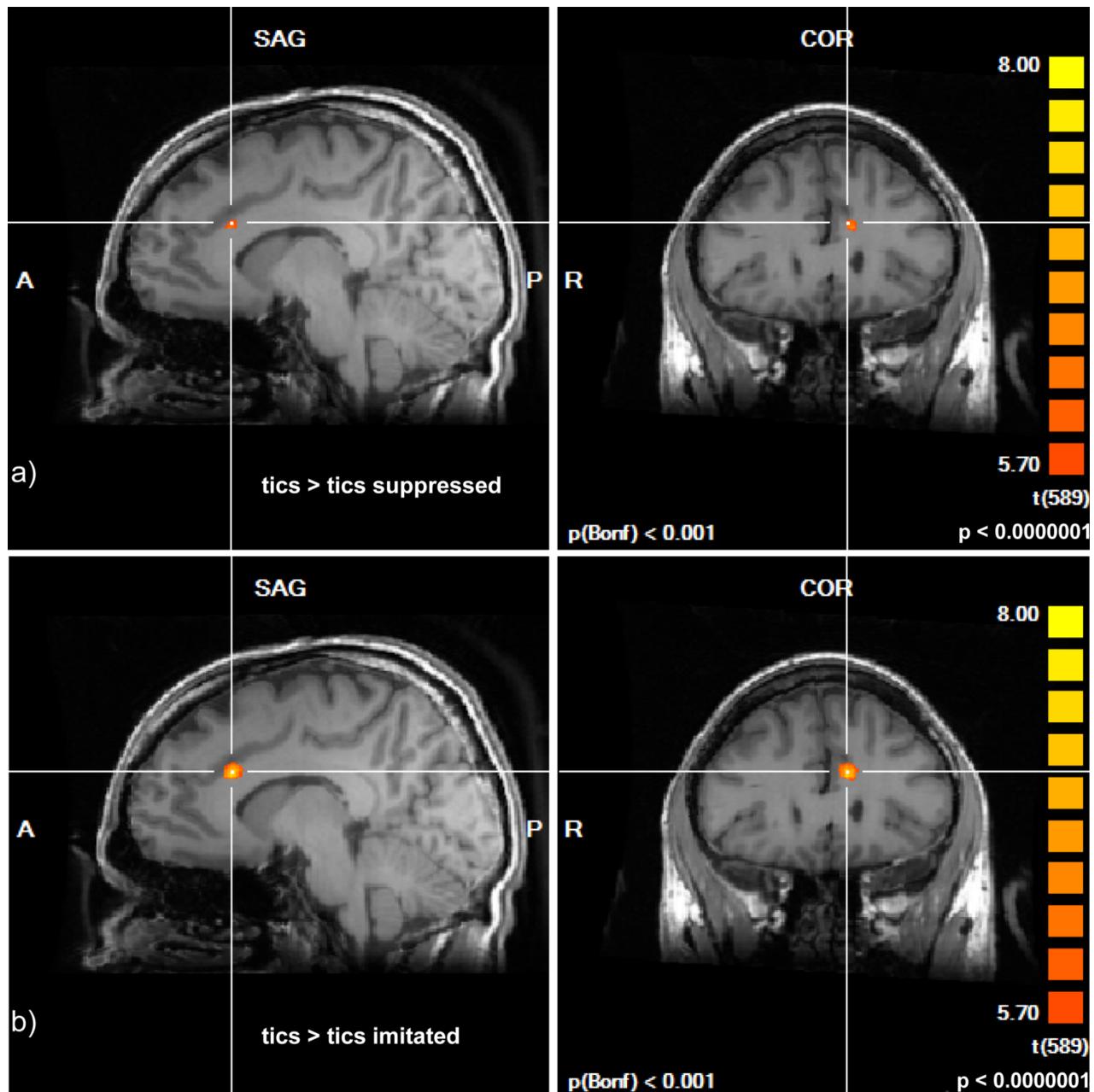


Figure 1. (a) Comparison of the conditions “tics” and “tics suppressed”, (b) comparison of the conditions “tics” and “tics imitated”.

information to the DLPFC and subsequently to premotor (PMC) and supplementary motor area (SMA), and finally to the motor cortex (MC). Our findings would further fit with the assumption of a voluntarily induced suppression of the dysfunctional ACC signal by top-down control from the DLPFC (MacDonald et al. 2000; Paus et al. 2001). Accordingly, in the suppression condition compared with the native tics condition the activity of the ACC would be reduced. During “tics imitated” the subject made the same movements he normally did involuntarily now by actively and voluntarily moving the thumb. We assume in this condition an executive signal by the DLPFC towards the PMC, SMA and MC to initiate a moving of the thumb. Now, the SMA, which is cytoarchitectonally similar to the CMA (BA 24c–BA 6a (Vogt and Vogt 2003)), may be the source of a so called efferential copy of this information to the ACC. This leads to a reduction of the discrepancy between actual and target state. Alternatively, the efferential copy could also arise from the MC (Morecraft and Van Hoesen 1992). Thus, the decreased activity of the ACC of both conditions, “tics suppressed” and “tics imitated” compared to the resting condition “tics” would explain the activation shown in Figure 1.

This is also in accordance to clinical descriptions of patients about tic control by voluntary movements and is used in habit reversal training, a behaviour therapy using voluntary movements to control tics. This leads to the conclusion that similar mechanisms are likely to be involved in tic suppression via mental efforts or active movements.

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Statement of interest

The authors declare that they have no conflict of interest concerning commercial or financial involvements.

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