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The neural correlates of tic inhibition in Gilles de la Tourette syndrome

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ABSTRACT

Tics in Gilles de la Tourette syndrome (GTS) resemble fragments of normal motor behaviour but appear in an intrusive, repetitive and context-inappropriate manner. Although tics can be voluntarily inhibited *on demand*, the neural correlates of this process remain unclear. 14 GTS adults without relevant comorbidities participated in this study. First, tic severity and voluntary tic inhibitory capacity were evaluated outside the scanner. Second, patients were examined with resting state functional magnetic resonance imaging (RS-fMRI) in two states, free ticcing and voluntary tic inhibition. Local synchronization of spontaneous fMRI-signal was analysed with regional homogeneity (ReHo) and differences between both states (free ticcing < tic inhibition) were contrasted. Clinical correlations of the resulting differential ReHo parameters between both states and clinical measures of tic frequency, voluntary tic inhibition and premonitory urges were also performed. ReHo of the left inferior frontal gyrus (IFG) was increased during voluntary tic inhibition compared to free ticcing. ReHo increases were positively correlated with participants' ability to inhibit their tics during scanning sessions but also outside the scanner. There was no correlation with ratings of premonitory urges. Voluntary tic inhibition is associated with increased ReHo of the left IFG. Premonitory urges are unrelated to this process.

1. Introduction

Goal-directed motor behaviour involves the appropriate selection and execution of intended actions. An important, but often neglected, aspect of these processes is the cancellation or inhibition of competing motor programs (Badre, 2008; Filevich, Kuhn, & Haggard, 2012; Munakata et al., 2011). Volition, i.e. choosing one's own actions based on internal processes or "free will", may strongly depend on these inhibitory processes, since producing an intentional action necessarily involves inhibiting other voluntary and involuntary movements. This "intentional inhibition" emerges via a clear developmental trajectory both in anatomy and function (Leisman, Machado, Melillo, & Mualem, 2012). For example, the seemingly involuntary, uncoordinated, hyperkinetic nature of infants transforms to well-orchestrated and context-appropriated motor output in adolescents and adults, subserving the achievement of internally set goals. However, in neurodevelopmental disorders, not all elements of motor development undergo this developmental process. Many such disorders involve seemingly superfluous extra movements, behavioural deficits and aberrant motor control.

One of the most striking examples in this regard is Gilles de la Tourette syndrome (GTS), which is characterised by the presence of motor and phonic tics with childhood or adolescence onset, and commonly associated with neuropsychiatric comorbidities including attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Tics share many kinematic and most neurophysiological properties with normal movements and complex tics may resemble voluntary actions (Paszek et al., 2010). However, they lack the flexibility and context-appropriateness that typifies human voluntary action control. They are experienced as involuntary, repetitive movements.

Although the debate on the voluntariness of tics is ongoing, evidence suggests disinhibition of the cortico-striato-thalamo-cortical loops (Ganos, Roessner, & Munchau, 2013). The 'tic generator' has been seen not as a unique alteration in a single brain

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area, but as a disinhibited cortico-striato-thalamo-cortical loop. Against this background, GTS patients would need to recruit additional control mechanisms to achieve useful goal-directed action. In particular, they might need to strategically compensate for involuntary movements by enhanced cognitive control. Consistent with this view, GTS subjects, particularly in the absence of comorbid disorders, were reported to show normal or even supranormal motor performance in manual and saccadic control tasks (Baym, Corbett, Wright, & Bunge, 2008; Buse et al., 2012; Ganos et al., 2014b; Jackson, Mueller, Hambleton, & Hollis, 2007; Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007; Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006; Watkins et al., 2005), suggesting that they learn to efficiently control their actions.

However, previous studies of cognitive control in GTS used task-switching, and response-inhibition experiments. These paradigms are rather different from the central feature of real-life action control in GTS: i.e., the requirement to intentionally inhibit involuntary movements. In fact, while it is widely agreed that many GTS patients can voluntary inhibit tics *on demand* at least for short periods, the cognitive mechanism of this unique form of motor control has hardly been studied. With increasing age many GTS patients report a 'premonitory urge' prior to tics. One classical view (Bliss, 1980) proposed that tic inhibition involves a voluntary response to the conscious experience of urge to tic. However, the capacity for tic inhibition was recently shown to be unrelated to sensations preceding tics (Ganos et al., 2012). Thus, despite previous efforts, the cortical underpinning of tic inhibition remains elusive (Peterson et al., 1998; Serrien, Orth, Evans, Lees, & Brown, 2005).

Tic inhibition is difficult to study using fMRI. By definition, there is no behavioural marker of tic inhibition to serve as an event for event-related designs. However, the characteristic brain processes underlying the ongoing state of voluntary tic inhibition may be studied using resting state fMRI (RS-fMRI). RS-fMRI records brain activations in more or less natural conditions and is thought to reflect the "intrinsic" functional organisation of the brain (Fox and Raichle, 2007; Gusnard and Raichle, 2001; Zang, Jiang, Lu, He, & Tian, 2004). Regional homogeneity (ReHo) is a specific method of analysing RS-fMRI. It captures the synchrony of resting state brain activity in neighbouring voxels. While functional connectivity reveals synchronization of remote predefined brain regions, ReHo measures the local synchronization of spontaneous fMRI signals (Zang et al., 2004; Zou, Wu, Stein, Zang, & Yang, 2009), and can therefore be considered a measure of local connectivity. Importantly, ReHo circumvents the necessity to define a priori seed region. It is therefore appropriate for unbiased, whole-brain analyses of resting state data.

We therefore employed ReHo to compare the neural properties of "tic inhibition" versus "free ticcing" (i.e., no instruction to inhibit tics) in a group of patients with uncomplicated GTS.

2. Material and methods

2.1. Subjects

14 Adult GTS patients (1 female), aged between 18 and 47 years (mean age 30.6 years ± 8.8 years SD) and previously described in detail (Ganos et al., 2014a) participated in the study. They were recruited from the GTS outpatient clinic of the Department of Neurology, University Medical Centre Hamburg-Eppendorf. Written informed consent was given prior to study attendance. The study was performed with ethical permission and in accordance with the Declaration of Helsinki.

Thorough clinical assessment was performed by A.M. and C.G. as described elsewhere (Ganos et al., 2014a) based on a semi-structured neuropsychiatric interview. The DSM-IV-TR criteria were employed for a diagnosis of GTS (American Psychiatric Association., 2000). Current tic severity was assessed by means of the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and the Modified Rush Video Scale (MRVS) (Goetz, Pappert, Louis, Raman, & Leurgans, 1999). Tic-inhibition capacity was evaluated by asking patients to maximally inhibit their tics for 2 × 2.5 min while being videotaped as previously described (Ganos et al., 2012). Outside the scanner motor tic inhibition potential (IPmotor) was calculated from the numbers of motor tics during the free ticcing (TFmotor) and the tic inhibition conditions outside the scanner (TImotor): IPmotor = (TFmotor − TImotor)/TFmotor.

During the scanning sessions tics were monitored and registered by means of a button press by an independent medical student well trained in tic recognition (U.K.). Tic counts were separately summed for the two conditions (free ticcing, tic inhibition). Similar to IPmotor outside the scanner, an inhibition index during the scanning procedure (IPscan) was also build: IPscan = (TFscan − TIscan)/TFscan, where TFscan and TIscan are the number of motor tics during the free ticcing and the tic suppression conditions inside the scanner, respectively.

Premonitory urges were assessed using the validated German version of the Premonitory Urge for Tics Scale (PUTS) (Rössner Müller-Vahl & Neuner, 2010; Woods, Piacentini, Himle, & Chang, 2005).

GTS associated comorbidities were additionally screened for by using the ADHD self assessment scale (German version; ADHS Selbstbeurteilungsskala) (Rösler et al., 2004), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) and the Beck Depression Inventory (BDI) (Beck, Guth, Steer, & Ball, 1997).

2.2. Scanning procedure

Study participants were positioned head first and supine in the scanner. Imaging was performed with a 3 T Magnetom Trio MRI scanner system (Siemens, Erlangen, Germany) using a 12-channel radiofrequency head coil. In order to effectively minimise head movements foam pads were positioned next to the head. Functional imaging was employed for the GTS group in 2 behavioural conditions, each repeated once in a pseudorandomized order in a total of 4 imaging blocks. In one condition subjects were instructed to simply close their eyes (Free Ticcing Condition), whereas in the other condition they were asked, again with closed eyes, to maximally inhibit their tics (Tic Inhibition Condition). Functional whole brain images were acquired using an echo planar imaging (EPI) sequence (TR = 2280 ms, TE = 30 ms, image matrix = 64 × 64, FOV = 224 mm, flip angle = 80°, slice thickness = 3 mm, distance factor = 17%, voxel size = 3.5 mm × 3.5 mm × 3.0 mm, 36 axial slices). A total of 80 images aligned to PC-AC were acquired per functional imaging block. Anatomical images were collected in all participants using a 3D, T1-weighted MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm × 256 mm, flip angle = 9°, slice thickness = 1.00 mm, voxel size = 1.0 mm × 1.0 mm × 1.0 mm).

2.3. Resting state analysis

The first 5 volumes were discarded to allow the magnetisation to approach a dynamic equilibrium, and for the subjects to get used to the scanner noise. Part of the data pre-processing, including slice timing, head motion correction (a least squares approach and a 6-parameter spatial transformation) and spatial normalisation to the Montreal Neurological Institute (MNI) template (resampling voxel size of 3 mm × 3 mm × 3 mm), were conducted using SPM8 and Data Processing Assistant for Resting State fMRI (DPARSF) (Chao-Gan and Yu-Feng, 2010). A spatial filter of 4 mm FWHM (full-width at half maximum) was used. Participants showing head motion above 3.5 mm of maximal translation (in any direction of x, y or z) and 1.0° of maximal rotation throughout the course of scanning would have been excluded.

After pre-processing, linear trends were removed. Then the fMRI data were temporally band-pass filtered (0.01–0.08 Hz) to reduce the very low-frequency drift and high-frequency respiratory and cardiac noise (Biswal, Yetkin, Haughton, & Hyde, 1995). ReHo analysis (Liu et al., 2006; Wu et al., 2009; Zang et al., 2004) was performed using DPARSF. ReHo is based on previous reports that fMRI activity is more likely to occur in clusters of several spatially contiguous voxels than in a single voxel (Katanoda, Matsuda, & Sugishita, 2002; Tononi, McIntosh, & Russell, 1998). Therefore, ReHo assumes that activation in a given voxel is temporally similar to that of its neighbours. For each participant ReHo analysis was performed on a voxel-wise basis by calculating Kendall's coefficient of concordance (KKC) (Kendall and Gibbons, 1990) of the time series of a given voxel with those of its nearest neighbours (26 voxels). Then, the KKC value was given to this voxel and individual KKC maps were obtained. ReHo was calculated within a brain-mask, which was obtained by removing the tissues outside the brain using the software MRIcro (by Chris Rorden, http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html).

We obtained separate ReHo maps for the tic suppression and free tic condition. These images were subtracted within each subject, to provide a contrast image (tic suppression – free ticcing), which was then subjected to a one-sample *t*-test. A height threshold of $p < 0.001$ was used, and the cluster-size corrected by means of Monte Carlo simulation. Significant effects were reported when the volume of the cluster was greater than the Monte Carlo simulation determined minimum cluster size on the whole brain volume (> 30 voxels), above which the probability of type I error was below 0.05 (AlphaSim) (Ward, 2000). Coordinates reported are in MNI space.