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Distinctive tics suppression network in Gilles de la Tourette syndrome distinguished from suppression of natural urges using multimodal imaging

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ABSTRACT

Background and objectives: Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterized by tics. A hallmark of GTS is the ability to voluntarily suppress tics. Our aim was to distinguish the neural circuits involved in the voluntary suppression of ocular tics in GTS patients from blink suppression in healthy subjects.
Methods: Fifteen GTS patients and 22 healthy control subjects were included in a multimodal study using eye-tracker recordings during functional MRI (fMRI). The ability to suppress tics/blinks was compared both on subjective (self-rating) and objective (eye-tracker) performance. For fMRI analysis we used a novel designed performance-adapted block design analysis of tic/blink suppression and release based on eye-tracker monitoring.
Results: We found that the subjective self-reported ability to suppress tics or blinks showed no significant correlation with objective task performance. In GTS during successful suppression of tics, the dorsal anterior cingulate cortex and associated limbic areas showed increased activation. During successful suppression of eye blinks in healthy subjects, the right ventrolateral prefrontal cortex and supplementary and cingulate motor areas showed increased activation.
Conclusions: These findings demonstrate that GTS patients use a characteristic limbic suppression strategy. In contrast, control subjects use the voluntary sensorimotor circuits and the classical 'stop' network to suppress natural urges. The employment of different neural suppression networks provides support for cognitive behavioral therapy in GTS.

1. Introduction

Gilles de la Tourette Syndrome (GTS) is a neuropsychiatric disorder defined by the presence of multiple motor and vocal tics. Tics typically develop during childhood and wax and wane over time (Singer, 2005). The first tics to develop in childhood usually encompass simple facial tics, for instance ocular tics or nose twitching (Jankovic, 1997). Ocular tics are present in almost all patients with GTS and include forceful eye blinking, eye rolling, or squinting (Karson et al., 1985; Martino et al., 2012). One of the key clinical features of tics is the ability to suppress the unwanted movement. Notably, ocular tics are the most difficult tics to suppress in GTS. Tics are often preceded by a premonitory sensation or an urge and tic execution may provide temporary relief (Singer, 1997). The urge to tic increases during tic suppression. Patients often

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report that the premonitory urge to tic increases during tic suppression, although tic self- rating by patients has been proven to be unreliable (Muller-Vahl et al., 2014). It is assumed that the relief from premonitory urges functions as a negative reinforcer, which leads to tic maintenance (negative reinforcement model) (Beetsma et al., 2014; Brandt et al., 2016; Capriotti et al., 2014). During adolescence the awareness of premonitory urges increases with increasing age, and there is some evidence that this improves the ability to suppress tics (Banaschewski et al., 2003). Although it is true that the awareness of urges increases with age, it is unclear whether this increases the ability for tic suppression. There is even some conflicting evidence that urges and tic inhibition are not directly related (Ganos et al., 2012).

The pathophysiology of GTS remains unclear (Ganos et al., 2013). GTS is hypothesized as a disorder of inhibition, in which patients have impaired capability to restrain their urges to tic. Based on post-mortem pathology and imaging studies a primary dysfunction of the basal ganglia (BG) and their output pathways via the corticostriatal circuits is suggested (Bohlhalter et al., 2006; Peterson et al., 1998; Wang et al., 2011; Worbe et al., 2012). The clinical observation that GTS patients are capable to temporarily overrule their tics by suppression, while their disorder can in essence be regarded as a disinhibition of motor control, is a poorly understood paradox.

Few neuroimaging studies have investigated the mechanisms by which patients are capable to temporarily suppress tics (Ganos et al., 2014a; Kawohl et al., 2009; Peterson et al., 1998). Peterson and colleagues studied 22 GTS patients during suppression of tics during functional Magnetic Resonance Imaging (fMRI) showing increased activity of the caudate nucleus, and a decrease of activity in the putamen, globus pallidus and thalamus (Peterson et al., 1998). Another study in a single GTS patient, found the anterior cingulate cortex (ACC) to be active during tic suppression (Kawohl et al., 2009). A third study found in 14 GTS patients increased activity of the left inferior frontal gyrus as a sole finding during tic suppression compared to the release of tics (Ganos et al., 2014a). These papers, however, lack comparison to control subjects. As a model to study tic suppression in healthy controls, several studies have investigated the suppression of natural urges such as normal eye blinking. Intuitively, the premonitory tension and urge experienced just prior to tic onset appear to be similar to the somatosensory tension experienced during sustained voluntary suppression of eye blinks (Mazzone et al., 2010). Lerner and colleagues found a central role for the insula and the ACC in blink suppression (Lerner et al., 2009). Mazzone and colleagues observed increased activation of the right middle frontal gyrus (Brodmann area, BA 9), left dorsal anterior cingulate cortex (BA32) and the bilateral superior frontal gyrus (BA10) during blink suppression in GTS compared to control subjects (Mazzone et al., 2010). However, it remains unclear to what extent this increased frontostriatal activity in GTS is specific for tic suppression.

The current study is the first to directly compare the neural correlates of suppression of ocular tics in patients with GTS with the suppression of eye blinks in healthy controls. Another novelty of this study is that we ensure a true comparison of motor output suppression versus release during task performance since we incorporate task performance, as objectively measured with the eye-tracker, in the analyses of the fMRI. This also enables us to compare the participants' self-report measures of suppression ability with their objective ability to follow task instruction.

Our first objective is to explore the neural correlates of tic suppression in GTS. We hypothesize that GTS patients during suppression will demonstrate increased activation in the caudate nucleus and ACC. Second, we aim to explore the neural correlates of blink suppression as a model of the suppression of natural urges in control subjects, and we hypothesize that healthy control subjects demonstrate increased activation of the insula and the ACC. Our third objective is to compare the suppression strategy of tics in GTS patients with blink suppression in healthy control subjects. We hypothesize that frontostriatal activity is increased in GTS compared to controls during suppression. To validate our task and confirm previous findings on tic generation we also investigate tic release (Bohlhalter et al., 2006; Hampson et al., 2009; Neuner et al., 2014; Stern et al., 2000; Wang et al., 2011). Three separate processes are hypothesized to be active during tic release. The first is the prime tic generator (mediated by BG (Ganos et al., 2013)), the second mediates release of tic control (predominantly controlled by supplementary motor area (SMA) (Bohlhalter et al., 2006; Hampson et al., 2009; Wang et al., 2011), and a third process is responsible for tic execution (encompassing the sensorimotor system, consisting of the cerebellum, somatosensory and (pre)motor cortex (Bohlhalter et al., 2006; Hampson et al., 2009; Wang et al., 2011)). Thus, during release of tics we hypothesize that GTS patients show increased activity in the BG and sensorimotor system, in particular the SMA.

2. Materials and methods

2.1. Participants

Sixteen patients fulfilling DSM-IV-TR criteria of GTS participated in this study. Twenty-two healthy controls without neurological or psychiatric conditions and without psycho-active medication were included. Patients were recruited from a previously performed video and EEG study, measuring the Bereitschaftspotential (BP) prior to the onset of motor tics (for a full description of the participants see (van der Salm et al., 2013a; van der Salm et al., 2012; van der Salm et al., 2016)). Inclusion criteria for patients the presence of both eye and motor tics and the ability to suppress and release their motor and ocular tics on demand. The ability to suppress tics was tested and clinically judged during the previous EEG and video studies. (van der Salm et al., 2013a; van der Salm et al., 2012; van der Salm et al., 2016) We excluded one patient because of technical eye-tracker malfunction. Data of 15 patients and 22 controls were analyzed on task performance (see below). Patients and controls were matched at group level on gender, age, education level (Verhage, 1964) and handedness (Oldfield, 1971) (see Table 1 for demographic characteristics). Prior to scanning medical history and psychiatric history or current psychiatric symptoms (exclusion criteria) were inquired in healthy control subjects. Psychiatric co-morbidity in patients was assessed with the MINI plus (van Vliet et al., 2000). Three out of fifteen GTS patients were diagnosed with co-morbid OCD, and one patient with co-morbid ADHD. Thirteen patients were medication free during testing. The GTS patient with ADHD was on methylphenidate which was continued during scanning. Two

Table 1
Demographic and clinical characteristics of patients and controls.

Characteristics	GTS patients (n = 15)	Control subjects (n = 22)
Age in years (SD)	34.8(8.9)	42.7(15.1)
Gender (M/F)	13/2	13/9
Education (SD)	5.3 (0.8)	5.4 (1.2)
Comorbidity		–
OCD	3	–
ADHD	1	–
Psycho-active medication (%) during scanning	1 (7%)	0 (0%)

Legend: ADHD = attention deficit hyperactivity disorder; F = female; GTS = Gilles de la Tourette syndrome M = male; OCD = obsessive compulsive disorder.

There was no significant difference between groups in age (p = .262 Mann Whitney U test), gender (p = .075 chi-squared test) or educational level (p = .453; Mann Whitney U test). Education was scored in the Dutch classification system according to Verhage, encompassing 7 categories. 1 = did not finish primary school, 2 = finished primary school, 3 = did not finish secondary school, 4 = finished secondary school, low level, 5 = finished secondary school, medium level, 6 = finished secondary school, highest level, and/or college degree, 7 = university degree. (Verhage, 1964).