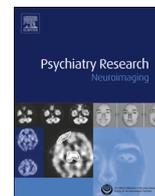




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Brain mechanisms for prepulse inhibition in adults with Tourette syndrome: Initial findings



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ABSTRACT

Prepulse inhibition (PPI) of the startle reflex is disrupted in a number of developmental neuropsychiatric disorders, including Tourette syndrome (TS). This disruption is hypothesized to reflect abnormalities in sensorimotor gating. We applied whole-brain functional magnetic resonance imaging (fMRI) to elucidate the neural correlates of PPI in adult TS subjects using airpuff stimuli to the throat to elicit a tactile startle response. We used a cross-sectional, case-control study design and a blocked-design fMRI paradigm. There were 33 participants: 17 with TS and 16 healthy individuals. As a measure of PPI-related brain activity, we looked for differential cerebral activation to prepulse-plus-pulse stimuli versus activation to pulse-alone stimuli. In healthy subjects, PPI was associated with increased activity in multiple brain regions, of which activation in the left middle frontal gyrus in the healthy controls showed a significant linear correlation with the degree of PPI measured outside of the magnet. Group comparisons identified nine regions where brain activity during PPI differed significantly between TS and healthy subjects. Among the TS subjects, activation in the left caudate was significantly correlated with current tic severity as measured by the total score on the Yale Global Tic Severity Scale. Differential activation of the caudate nucleus associated with current tic severity is consistent with neuropathological data and suggests that portions of cortical-striatal circuits may modulate the severity of tic symptoms in adulthood.

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1. Introduction

Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder characterized by multiple motor tics and at least one phonic tic (Leckman, 2002,2012). Estimates of TS prevalence indicate prevalence in childhood on the order of 0.1% to 1.0% with a much lower prevalence in adulthood (Khalifa and von Knorring, 2003, 2006; Mol Debes et al., 2008; Scahill et al., 2007). The onset of TS is typically prepubertal, and boys are more commonly affected than girls. In both clinical and population-based samples, tic severity usually peaks between 8 and 12 years of age with many affected individuals showing a marked reduction in severity by the end of adolescence (Leckman et al., 1998; Bloch et al., 2006).

Indeed, by the age of 20 years, tic severity is generally greatly reduced in a majority of individuals with TS (Leckman et al., 1998; Bloch et al., 2006).

Recent neuropathology studies have highlighted the loss of GABAergic and cholinergic interneurons in the caudate and putamen of individuals with TS (Kalanithi et al., 2005; Kataoka et al., 2010). Although structural and functional brain imaging studies have also implicated striatal involvement in the pathobiology and persistence of TS (Bloch et al., 2005), a number of other cortical and subcortical regions, including the hippocampus, have also been implicated (Peterson et al., 2007; Bansal et al., 2012). Indeed, multiple lines of evidence suggest that disturbances in the development of the sensorimotor portions of cortical-subcortical circuits likely predispose to the development TS, and that neuroplastic changes in the limbic and associative circuits may help to modulate the severity of symptom expression over the lifespan (Graybiel, 2008; Plessen et al., 2009; Leckman et al., 2010; Wang et al., 2011; Bansal et al., 2012). Hypothesized abnormalities

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in cortical–striatal circuits in TS have led to behavioral paradigms to detect inhibitory deficits, such as prepulse inhibition (PPI). PPI is a simple behavioral measure of inhibition of the startle blink reflex, referring to reduction in startle blink magnitude when a stimulus (prepulse) occurs 30–500 ms before a startle stimulus (Swerdlow et al., 2001). The prepulse is believed to activate automatic brain mechanisms that protect or “gate” the processing of that stimulus for a brief window of time. Animal studies show that PPI is mediated by brain stem circuits as well as forebrain circuits involving the prefrontal cortex, thalamus, hippocampus, amygdala, nucleus accumbens, striatum, ventral pallidum, and globus pallidus (Swerdlow et al., 2001, 2008). Although the neural substrates of PPI may vary to some degree between animals and humans (Swerdlow et al. 2008), imaging studies (Hazlett and Buchsbaum, 2001; Kumari et al., 2003, 2005; Campbell et al., 2007; Hazlett et al., 2008) support the involvement of similar brain regions in the modulation of human PPI.

In schizophrenia research PPI has played an important role in strategic efforts to develop and characterize new treatments as well as to identify valid endophenotypes (Postma et al., 2006; Swerdlow et al., 2008; Kumari et al., 2008; Greenwood et al., 2011). Similar opportunities may exist in efforts to understand and treat TS. Specifically, several studies have shown reduced PPI in TS subjects compared to control subjects (Smith and Lees, 1989; Castellanos et al., 1996; Swerdlow et al., 2001; Swerdlow, 2012).

We studied PPI in healthy controls and individuals with TS using functional magnetic resonance imaging (fMRI) to determine if a deficit in sensorimotor gating is a characteristic of TS in adulthood and if brain regions displaying differential activation to prepulse-plus-pulse vs. pulse-alone stimuli were associated with current levels of tic severity. Based on the available neuropathological and structural imaging studies, we were particularly interested in the possible association of current tic severity, PPI and differential BOLD responses in striatal and hippocampal regions.

2. Methods

2.1. Study subjects

Thirty-eight subjects were recruited to voluntarily participate in this fMRI study (18 TS and 20 healthy control subjects). There were 11 males and 7 female subjects with TS who ranged from 21 to 59, averaging 33.2 years of age. Healthy normal participants (12 male, 8 female) ranged from 21 to 44, averaging 30.4 years of age. The two groups did not differ significantly in age ($p > 0.2$) or gender ($p > 0.2$). We recruited persons with a lifetime diagnosis of TS and who were being followed in the Tic Disorder Specialty Clinic at the Yale Child Study Center in New Haven, CT, excluding persons who had an axis I disorder other than obsessive-compulsive disorder (OCD) or attention deficit hyperactivity disorder (ADHD) before the onset of TS (comorbid OCD: $N=12$, comorbid ADHD: $N=9$, both OCD and ADHD: $N=7$). We did not exclude individuals with a lifetime history of a mood disorder as long as the disorder was not currently a source of impairment (lifetime mood disorder: $N=7$). We recruited comparison subjects through advertisements on Craigslist <<http://newhaven.craigslist.org/>> and by word-of-mouth. We excluded those who reported a history of tic disorder, OCD, or ADHD, or who met diagnostic criteria for any axis I psychiatric disorder at the time of the Baseline assessment. Additional exclusionary criteria for both groups were a lifetime history of substance abuse or head trauma.

We administered the Schedule for Tourette and Other Behavioral Disorders (STOBD) (Pauls and Hurst, 1993), as well as clinical evaluations, to establish diagnoses through a consensus procedure of expert clinicians (Leckman et al., 1982). The STOBD includes the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) for adults, as well as sections on TS and OCD. Ratings of current and worst-ever symptom severity of tic and obsessive–compulsive symptoms were obtained using the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989).

All subjects were screened for illicit drug abuse. Written informed consent was obtained at the time of the evaluation assessment. Compensation for participation was provided at both time points under the guidelines of the Yale University Human Investigation Committee. Data from four control subjects and one TS participant (who fell asleep) who startled on fewer than 36% pulse-alone trials

during the psychophysiological assessment outside the scanner were excluded (see below). The demographic and clinical characteristics (including medication status) for these 33 subjects are presented in Table 1.

2.2. Startle task

A tactile (airpuff) startle paradigm in an fMRI setting similar to that used by Kumari et al. (2003) was employed to measure PPI. A block design with three conditions was used: pulse-alone, prepulse+pulse (PPI), and rest. The pulse-alone condition involved presentations of the pulse stimulus. The PPI condition involved presentation of the prepulse stimulus 100 ms before the pulse stimulus. Each condition was presented to the participant six times in 30-s blocks in pseudorandom order across two runs. The pulse-alone, PPI and rest blocks each occurred three times in run 1 and three times in run 2. Run 1 began with six pulse-alone stimuli (30 s). Each of the runs began with a 10-s resting baseline period. Within each 30-s block, six stimuli were presented with an inter-stimulus interval of 3 s to 6 s. Air puffs to the throat area were used as both pulse and prepulse. Stimulus presentation inside and outside the scanner was controlled by identical San Diego Instruments Human Startle Response Monitoring Systems (SR-Lab, San Diego Instruments, San Diego, CA, USA). The air-puff delivery system consisted of two cylinders of compressed breathable air (one for the pulse, one for the prepulse) and regulators for setting the psi level (pulse stimulus regulator range 0–240 psi; prepulse stimulus regulator range 0–30 psi). Solenoid-controlled valves and 10-m-long plastic tubes delivered the air. The pulse tube consisted of rigid nylon-11 material (6 mm I.D.). The prepulse tube consisted of flexible Tygon tubing (3 mm I.D.). To maintain comparable placement across participants, each tube was fastened to a customized protective ice hockey collar. Each participant wore the collar so that the air tubes were midline, over the larynx. Inside the collar, two parallel 1.5 cm × 3 cm foam pads kept the tubing at 1.5 cm from the participant's larynx. Pulse-alone stimuli were 80 psi at the regulator and 40 ms in duration. Prepulses were 7 psi at the regulator and 20 ms in duration. Following Kumari et al. (2003), the startle responses were measured outside the fMRI setting. Since it was not possible to safely use electrodes to acquire electromyographic (EMG) activity during MRI scanning, the eye-blink reflex response was measured on the same day as the imaging scan, approximately 2.5 h post-scan. The startle assessment took place in a quiet, dimly lit room (60 W bulb). The individual sat in a comfortable chair with the EMG electrodes and tactile startle apparatus attached (Borelli et al., 2010).

Due to technical difficulties, one TS patient was scanned on a different day than his startle response measurement. In addition, three controls and one TS participant (who fell asleep) who startled on fewer than 36% pulse-alone trials during the psychophysiological assessment were excluded. In terms of cases, we had originally

Table 1
Demographic and clinical characteristics at baseline.

Variable	Normal controls (N=16)	TS subjects (N=17) ^b	p-value
Age in years (SD)	28.3 (7.4)	32.5 (11.3)	0.22
Gender (% female)	62.5%	41.2%	0.22
Race (% Caucasian)	85%	94.2%	
Age of tic onset in yrs, mean (SD)	NA	7.9 (3.6)	
Comorbid OCD lifetime, current ^a (%)	NA	64.7%, 29.4%	
Comorbid ADHD (%)	NA	52.9%	
Comorbid OCD and ADHD (%)	NA	41.2%	
Comorbid mood disorder lifetime (%)	NA	41.2%	
Current symptom severity ^b			
TS, mean (SD)	NA	21.4 (11.9)	
OCD, mean (SD)	NA	7.6 (7.6)	
Psychotropic medications			
Alpha-2 agonists (%)	NA	5.9%	
Neuroleptics (%)	NA	11.8%	
Selective serotonin reuptake inhibitors (%)	NA	41.2%	
Benzodiazepines (%)	NA	17.6%	

TS=Tourette syndrome, OCD=obsessive–compulsive disorder, ADHD=attention deficit hyperactivity disorder; Mood disorder=a past history of major depressive disorder or depressive disorder not otherwise specified.

^a Subjects with a core on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) > 16 at time of study were considered to have current comorbid OCD.

^b Total score of the current Yale Global Tic Severity Scale (YGTSS) and total score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). However, only the YGTSS total tic severity score was used in analyzing the tactile startle and fMRI data (see text).

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