Psychiatry Research: Neuroimaging 224 (2014) 269–274

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Neural correlates of behavior therapy for Tourette's disorder

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ARTICLE INFO

Article history:
Received 25 February 2014
Received in revised form
19 August 2014
Accepted 5 September 2014
Available online 16 September 2014

Keywords:
Behavior therapy
Habit reversal
Tourette's disorder
Neuroimaging

ABSTRACT

Tourette's disorder, also called Tourette syndrome (TS), is characterized by motor and vocal tics that can cause significant impairment in daily functioning. Tics are believed to be due to failed inhibition of both associative and motor cortico-striato-thalamo-cortical pathways. Comprehensive Behavioral Intervention for Tics (CBIT), which is an extension of Habit Reversal Therapy (HRT), teaches patients to become more aware of sensations that reliably precede tics (premonitory urges) and to initiate competing movements that inhibit the occurrence of tics. In this study, we used functional magnetic resonance imaging (fMRI) to investigate the neural changes associated with CBIT treatment in subjects with TS. Eight subjects with TS were matched with eight healthy controls in gender, education, age, and handedness. Subjects completed the Visuospatial Priming (VSP) task, a measure of response inhibition, during fMRI scanning before and after CBIT treatment (or waiting period for controls). For TS subjects, we found a significant decrease in striatal (putamen) activation from pre- to post-treatment. Change in VSP task-related activation from pre- to post-treatment in Brodmann's area 47 (the inferior frontal gyrus) was negatively correlated with changes in tic severity. CBIT may promote normalization of aberrant cortico-striato-thalamo-cortical associative and motor pathways in individuals with TS.

1. Introduction

Tourette's disorder, also called Tourette syndrome (TS), is characterized by motor and vocal tics that can cause significant impairment in daily functioning. Traditionally, pharmacotherapy has been considered the first line of treatment for tic suppression. However, available medications often fail to bring about sustained remission, and many patients are reluctant to take medications because of possible unwanted side effects. Habit Reversal Therapy (HRT), a behavioral treatment, has become the nonpharmacological treatment of choice (Verdellen et al., 2011; Steeves et al., 2012). In brief, the primary strategies of HRT consist of (a) awareness training (to help the patient detect tics as early as possible) and (b) competing response training (which encourages the patient to engage in a behavior that is physically incompatible with the tic, and thus prevents the tic from occurring). These strategies are often supplemented with (c) relaxation and (d) contingency management (*e.g.*, a reward system to enhance treatment compliance). The efficacy of HRT has been evaluated in a number of smaller trials with promising results (*e.g.*, Azrin and Peterson, 1990; Wilhelm et al., 2003; Deckersbach et al., 2006).

Recently, two large randomized multi-site trials funded by the National Institute of Mental Health (NIMH) investigated the efficacy of an expanded form of HRT, the Comprehensive Behavioral Intervention for Tics (CBIT). These two studies, one in children and the other one in adults, found that CBIT was associated with significantly greater reductions in tic severity and impairment relative to standardized psychoeducation plus

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http://dx.doi.org/10.1016/j.pscychresns.2014.09.003
0925-4927/

supportive therapy (Piacentini et al., 2010; Wilhelm et al., 2012). Treatment gains were well maintained at 6-month follow-up. The present study was a supplement to the study on adults with TS (Wilhelm et al., 2012). Specifically, we investigated the neural correlates of CBIT with functional magnetic resonance imaging (fMRI).

Prior research indicates that tics are due to failed inhibition within cortico-striato-thalamo-cortical pathways (Mink, 2001). The basal ganglia, *via* thalamo-cortical projection neurons, facilitate the release of desired motor movements and the inhibition of unwanted motor movements. In TS, clusters of abnormally active striatal neurons within the basal ganglia lead to aberrant inhibition of neurons in the globus pallidus, pars interna (GPi; the major output of the basal ganglia). Increased inhibition of GPi neurons in turn disinhibits thalamo-cortical projection neurons, resulting in the release of unwanted motor patterns (Mink, 2001). In addition, frontal regions appear to modulate aberrant cortico-striato-thalamo-cortical circuits in a top-down manner in the service of tic suppression (*i.e.*, Casey et al., 1997; Bush et al., 1998; Peterson et al., 1998; Konishi et al., 1999; Rubia et al., 2001; Bunge et al., 2002; Fischer et al., 2003; Ridderinkhof et al., 2004; Serrien et al., 2005; Wright et al., 2005a; Wright et al., 2005b).

The Visuospatial Priming (VSP) task has been repeatedly used to assess response inhibition (Swerdlow et al., 1996; Wright et al., 2005a; Wright et al., 2005b). Less inhibition and greater facilitation has been found in children and adults with TS, compared with healthy controls (Swerdlow et al., 1996). In addition, VSP performance is correlated with response to behavior therapy but not supportive psychotherapy for TS (Deckersbach et al., 2006). In the present study, participants with TS and healthy controls completed the VSP during fMRI scanning before and after CBIT treatment (or an equivalent waiting period for healthy controls) to investigate neural changes in the basal ganglia and frontal cortex associated with CBIT treatment.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of Massachusetts General Hospital (MGH). Eight individuals with TS were recruited from the adult CBIT study at MGH. After complete description of the study to the subjects, written informed consent was obtained. The diagnoses of TS and co-occurring Axis I disorders were ascertained with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (First et al., 2002). We also recruited eight healthy control participants who were matched with TS subjects based on gender, age, education and estimated IQ. The mean age of the TS subject group was 26.88 ± 5.41 years (range of 21–37 years old). The mean age of the healthy control group was 25.63 ± 4.00 years (range of 23–35 years old). All participants with TS and controls were right-handed. Concomitant conditions for participants with TS included major depressive disorder ($n=4$), generalized anxiety disorder ($n=2$), obsessive–compulsive disorder ($n=1$), and specific phobia ($n=2$). Five TS subjects were also taking psychotropic medications at the time of the study, including citalopram ($n=1$), clomipramine ($n=1$), escitalopram ($n=1$), venlafaxine ($n=1$), and guanfacine ($n=1$). Of the participants with TS, three were medication-free. Medication changes were not allowed during the course of the CBIT study. All healthy controls were psychotropic medication-free and had no history of Axis I disorders.

2.2. Procedures

A full description of the procedures involved in CBIT can be found in Wilhelm et al. (2012). Briefly, before CBIT or a waiting period for healthy controls, subjects completed a battery of clinical scales and questionnaires. Participants with TS completed a measure of tic severity, the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989), a measure of premonitory urges preceding tics, the Premonitory Urge for Tics Scale (PUTS; Woods et al., 2005), and a measure of obsessive–compulsive symptom severity, the Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). In addition, all subjects completed the Beck Depression Inventory (BDI; Beck et al., 1961), the Beck Anxiety Inventory (BAI; Beck et al., 1988), the Sheehan Disability Scale (Leon et al., 1992), and the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale (Barkley, 1990).

The primary outcome measure for the CBIT treatment study was the YGTSS Total Tic score, which is the most commonly used endpoint measure to detect change in clinical trials (Lin et al., 2002). The YGTSS (Leckman et al., 1989) is a clinician-rated scale used to assess current tic severity. Motor and phonic tics were rated separately on a scale from 0 to 5 for number, frequency, intensity, complexity, and interference. Thus, motor and phonic tic scores can range from 0 to 25, with the combined Total Tic score ranging from 0 to 50. At baseline, the mean YGTSS Total Tic score for these eight participants was 21.63 (S.D.=6.05), corresponding to moderate tic severity. After 10 weeks of CBIT, the mean YGTSS Total Tic score was 18.63 (S.D.=6.89) (paired $t(7)=5.02$, $p<0.005$, Cohen's $d=0.46$). Two TS subjects had a $\geq 25\%$ reduction in the YGTSS Total Tic score, four had a 10–20% reduction, and two subjects had a $<10\%$ reduction.

The Premonitory Urge for Tics Scale (Woods et al., 2005) is a self-report questionnaire assessing the presence of premonitory sensory urges, with higher scores representing greater levels of premonitory urges. The mean Premonitory Urge score before CBIT was 26.00 (S.D.=6.91) and the mean score post-CBIT was 25.57 (S.D.=5.47).

All secondary clinical measure scores can be found in Table 1.

2.3. MRI imaging procedures

Subjects were scanned once before treatment and once after treatment (or after a 10-week waiting period for healthy controls) using a 3.0 T Siemens Trio "Tim" system whole body high-speed imaging device equipped for echo planar imaging (EPI; Siemens Medical Systems, Iselin, NJ) at MGH's Athinoula A. Martinos Center for Biomedical Imaging.

After automated scout and shimming procedures to optimize field homogeneity (Reese et al., 1995), two high-resolution 3D MPRAGE sequences (TR/TE/flip angle=2530 ms/3.39 ms/7°) with an in-plane resolution of 1.3 mm, and 1 mm slice thickness were collected to be used for co-registration with fMRI data. Functional MRI images were acquired using a gradient echo T2*-weighted sequence (TR/TE/flip angle=1600 ms/30 ms/90°) with an in-plane resolution of 3.125 mm and foot-to-head excitation order. Before each scan, four functional images were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

2.4. fMRI paradigm

2.4.1. Visuospatial priming task

The VSP task assesses the effects of an inhibitory or facilitory "prime" on the reactions to a subsequently presented probe (Swerdlow et al., 1996; Wright et al., 2005a; Wright et al., 2005b) (Fig. 1).

The first set of stimuli (S1) served as a "prime" for the second set (S2). In both S1 and S2, an "X" and an "O" were presented simultaneously in two of four different positions on a screen. Participants were instructed to ignore the "X" (the distractor) and press the button corresponding to the position of the "O" (the target stimulus). In negative prime trials, the "O" appeared in the location previously occupied by the distractor "X". In positive prime trials, the "O" appeared in the same location as in the prime, S1. In the neutral trials, the "O" appeared in a position unrelated to its position in the prime, S1.

The sequence and timing of the stimuli were pseudo-randomized and counterbalanced by scheduled optimization (Dale, 1999). Additional presentations of a low-level fixation condition, where no motor response was required, were inserted between trials in a pseudo-randomized fashion to serve as baseline. All subjects performed four sessions of the VSP task lasting 5 min and 46 s. In total, there were 144 trials (36 positive primes, 36 negative primes, and 72 neutral trials) spread

Table 1
Secondary clinical measures before and after treatment/waiting period

	Pre-treatment MRI				Post-treatment/waiting period MRI			
	TS		Controls		TS		Controls	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
BDI	5.38	4.69	2.38	2.83	4.00	5.98	2.13	3.09
BAI	8.00	6.35	4.25	4.80	5.13	2.53	2.88	3.56
Y-BOCS	5.88	11.04	–	–	5.13	9.58	–	–
Disability Scale	6.06	4.69	2.13	4.52	4.13	4.12	1.63	2.92
ADHD	9.00	8.68	5.38	4.26	8.00	7.89	5.13	4.26

Mean scores for the secondary clinical measures in healthy controls and TS subjects before and after treatment/waiting period.
Note. BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory, Y-BOCS=Yale-Brown Obsessive–Compulsive Scale, Disability scale=Sheehan Disability Scale, ADHD=Attention Deficit Hyperactivity Disorder Rating Scale.