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Neural correlates of behavior therapy for Tourette's disorder

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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.

Keywords

Behavior therapy; Habit reversal; Tourette's disorder; Neuroimaging

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 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 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 across two runs within each session. A 5 min practice trial was undertaken to familiarize the subjects with the task, before fMRI data acquisition began.

2.5. MRI data analysis

Functional data were processed using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK). The fMRI images were motion-corrected, spatially normalized to the standardized normalized space established by the Montreal Neurological Institute (MNI), and smoothed using a 6 mm full-width half-maximum Gaussian kernel. For each subject, we investigated VSP task-related changes by creating contrast images comparing all VSP conditions (*i.e.*, negative, positive, and neutral) relative to the fixation cross. We also explored the unique aspects of negative and positive priming by creating contrasts for negative vs. neutral prime, and positive vs. neutral prime.

For our second level analysis, we conducted a flexible factorial analysis using each individual subject’s *t*-contrast images. Based on previous studies investigating inhibitory changes in TS (Peterson et al., 1998; Mink, 2001; Wright et al., 2005a; Wright et al., 2005b), the *a priori* regions of interest were the basal ganglia (caudate and putamen) and selected regions in the prefrontal cortex (Brodmann area (BA) 11, 44, 47). To control for multiple statistical comparisons, we maintained a cluster-level false positive detection rate at $p < 0.005$ with a cluster (*k*) extent empirically determined by Monte Carlo simulations in the AFNI program AlphaSim (Ward, <http://afni.nimh.nih.gov/afni/docpdf/alphasim.pdf>). This correction was conducted within our *a priori* regions of interest (Brodmann areas 11, 44, 47,

caudate, and putamen) using anatomical masks from the Wake Forest University Pick Atlas (Maldjian et al., 2003). This was followed by a post-hoc AlphaSim whole brain corrected analysis. For any significant activation, we included medication status, anxiety, depressive, obsessive-compulsive, and ADHD symptoms as covariates to investigate if the findings remained significant after controlling for these variables.

In TS subjects, we also investigated correlations between change in tic severity, change in premonitory urge levels and change in VSP task related activations from pre- to post-CBIT. We also conducted predictor analyses by using the pre-treatment YGTSS tic severity and PUTS scores in the same method of analysis. For this analysis, due to the fact that only the TS participants were included, we maintained a cluster level false positive detection rate at $p < 0.05$ using similarly described methods in AFNI (Cox, 1996). Post-hoc whole-brain analyses were also conducted to identify significant *a posteriori* activations.

2.6. Statistical analysis of behavioral data

Reaction times and accuracy were analyzed using a $2 \times 2 \times 3$ mixed-model analysis of variance (ANOVA) with group (TS vs. controls) as the between-subjects factor, time (pre-CBIT or baseline for controls vs. post-CBIT and post-waiting period for controls) and prime (negative, positive, neutral) as the within-subjects factors, and response times (s) and accuracy rates as the dependent variable. As needed, pairwise group comparisons were run for each of the prime conditions. Significance was determined using two-tailed tests and $\alpha = 0.05$.

3. Results

3.1. Behavioral data

The mixed model ANOVA analyzing reaction times revealed no main effect of group (TS vs. controls; $F(1, 14) = 0.86, p = 0.37$). There was a main effect of time (pre-CBIT and baseline for controls vs. post-CBIT and post-waiting period for controls). Both controls and TS subjects showed faster reaction times after compared with before CBIT and waiting period for controls, suggesting a practice effect ($F(1, 14) = 5.96, p = 0.029$; mean pre-CBIT RT = 520.47 s, S.D. = 19.95 s, mean post-CBIT RT = 495.98 s, S.D. = 20.88 s). There was also a main effect of prime ($F(1, 14) = 20.65, p < 0.001$). Pairwise comparisons revealed that all participants had slower reaction times for negative prime trials compared with neutral trials and had faster reaction times on positive prime trials than neutral trials (mean RT for negative prime = 531.24 s, S.D. = 20.70 s, mean RT for positive prime = 492.49 s, S.D. = 20.80 s; mean RT for neutral = 500.94 s, S.D. = 18.83 s; Fig. 2). There were no significant interactions.

The mixed model ANOVA analyzing percent accuracy also revealed no main effect of group (TS vs. controls) ($F(1, 14) = 0.01, p = 0.91$). There was a main effect of prime; both TS subjects and healthy controls were more accurate for the positive prime trials than the neutral trials, which were more accurate than the negative prime trials ($F(2, 28) = 8.20, p = 0.002$; mean accuracy for negative prime = 91.84, S.D. = 1.45, mean accuracy for positive prime = 94.57, S.D. = 0.95, mean accuracy for neutral trial = 93.53, S.D. = 1.16; Fig. 2). There were no significant interactions.

3.2. fMRI data

3.2.1. Group main effects—For VSP task-related changes (VSP task vs. fixation), we did not find any significant between-group differences in our *a priori* regions of interest before or after CBIT/baseline for healthy controls. However, we found a significant interaction between group (TS vs. controls) and time (pre- vs. post-CBIT). As shown in Fig. 3, TS subjects showed a decrease in activation from pre- to post-CBIT and controls showed an increase in activation from pre- to post-waiting period in the putamen (MNI coordinates= $-22, 0, 10$, $k=107$, $Z\text{-score}=3.67$, $p<0.001$). For the TS subjects, this finding remained even after controlling for whether the TS subjects were taking medication or were medication-free ($F(1, 13)=9.05$, $p=0.01$).

There were no significant activations in *a priori* regions that exceeded AlphaSim correction for multiple comparisons specific to VSP negative priming or positive priming.

3.2.2. Neural correlates of treatment-related changes in tic severity and premonitory urges—We also investigated correlations between the change in tic severity and premonitory urge levels (pre-CBIT minus post-CBIT YGTSS Total Tic and PUTS scores) and the change in VSP task-related activations from pre to post. We found a significant negative correlation between the change in YGTSS Total Tic scores and a region in BA 47 in the inferior frontal gyrus (MNI coordinates= $56, 20, 0$, $k=35$, $Z\text{-score}=2.68$, Pearson's $r=-0.85$, and $p=0.007$; Fig. 4). Changes in scores on the BDI, BAI, Sheehan Disability Scale, and ADHD Rating Scale from pre- to post-CBIT were not correlated with the change in putamen activation (all p values >0.16). However, the change in Y-BOCS scores was negatively correlated with the change in putamen activation, such that the greater the change in obsessive-compulsive symptoms, the less of a change in putamen activation from pre- to post-CBIT (Pearson's $r=-0.81$, and $p=0.015$). There were no significant correlations with changes in premonitory urge levels.

3.2.3. Predictors of change in tic severity and premonitory urges—We also conducted predictor analyses to see if initial YGTSS Total Tic scores and initial premonitory urge levels were significantly correlated with CBIT associated changes in VSP task-related activations (pre- minus post-CBIT) in our *a priori* regions of interest (BA 11, 44, 47, caudate, and putamen). Initial tic severity and premonitory urge levels were not significantly correlated with the change in VSP task-related activation in our *a priori* regions (all p values >0.62). Correlations between pre-treatment Y-BOCS, BDI, BAI, Sheehan Disability Scale, and ADHD Rating Scale scores and changes in activation in the putamen were nonsignificant (all p values >0.11). For *a posteriori* regions there was a significant positive correlation between initial tic severity and VSP task-related activation in the middle temporal gyrus (MNI coordinates= $-62, -14, -8$, $k=722$, $Z\text{-score}=3.42$, Pearson's $r=0.94$, and $p=0.001$) and a significant negative correlation between initial premonitory urge levels and VSP task-related activation in the superior temporal gyrus (MNI coordinates= $50, 14, -16$, $k=601$, $Z\text{-score}=3.90$, Pearson's $r=-0.97$, and $p<0.001$).

4. Discussion

We aimed to investigate the neural changes in cortico-striatal circuitry following CBIT. Based on previous research on the neural correlates of tic suppression and VSP task activation, our *a priori* regions were the basal ganglia (caudate and putamen) and pre-frontal regions (BA 11, 44, 47). For VSP task-related activation (all conditions >fixation), we found significantly greater putamen changes in activation in TS subjects from pre- to post-CBIT. Whereas TS subjects had greater putamen activation before CBIT compared with controls, after CBIT, TS subjects had less putamen activation than controls. This finding remained significant after controlling for medication, anxiety, depressive, obsessive-compulsive, and ADHD symptoms.

Our finding of decreased putamen activation from pre- to post-CBIT is consistent with previous research implicating abnormal basal ganglia activation in tics (Mink, 2001). CBIT may promote a decrease in the elevated activation in the putamen observed at baseline. Since group differences were limited to the overall VSP contrast, the specific identification of aberrant processing in TS subjects was not possible (*i.e.*, increased facilitation or reduced inhibition are not suggested by our results). Null findings about specific VSP task conditions were supported by the lack of no significant differences between TS subjects and controls in VSP reaction times or percent accuracy for the different conditions. These findings are inconsistent with previous studies (*e.g.*, Swerdlow et al., 1996; Deckersbach et al., 2006).

We also observed a negative correlation between the change in YGTSS Total Tic scores and change in the inferior frontal gyral activation in BA 47 from pre- to post-CBIT. The greater the change in tic severity, the less the change in inferior frontal gyral activation. This finding is somewhat inconsistent with prior research implicating the role of frontal regions in modulating aberrant cortico-striato-thalamo-cortical circuits for tic suppression (*e.g.*, Wright et al., 2005a; Wright et al., 2005b). It is possible, however, that adequate inferior frontal gyral activation is a necessary precondition for CBIT to work, instead of reflecting CBIT-related changes in this region. The inferior frontal gyrus is implicated in task-switching and set-shifting and may be recruited to disengage attention from distracting information (Britton et al., 2010; Britton et al., 2012). Therefore, greater prefrontal activation may be associated with less impairment.

Limitations of this study include the small sample size, which prevented a more thorough exploration of potential effects of concomitant psychiatric disorders. All TS participants were treatment-seeking individuals. Likewise, because CBIT was the only active treatment in this study, it is not possible to infer whether effects are specific to the active tic-suppressing components in CBIT or reflect nonspecific aspects of psychotherapy. Due to these limitations, the findings should be considered as preliminary.

In summary, CBIT may be involved in normalizing aberrant basal ganglia activation implicated in tics. This change was not influenced by other factors such as medication or symptoms related to depression, obsessive-compulsive disorder, ADHD, or anxiety. The change in tic severity was negatively correlated with change in VSP task-related inferior

frontal gyral activation. These findings support the idea that CBIT, a form of behavior therapy, might help target deficit neural circuitry in adults with TS.

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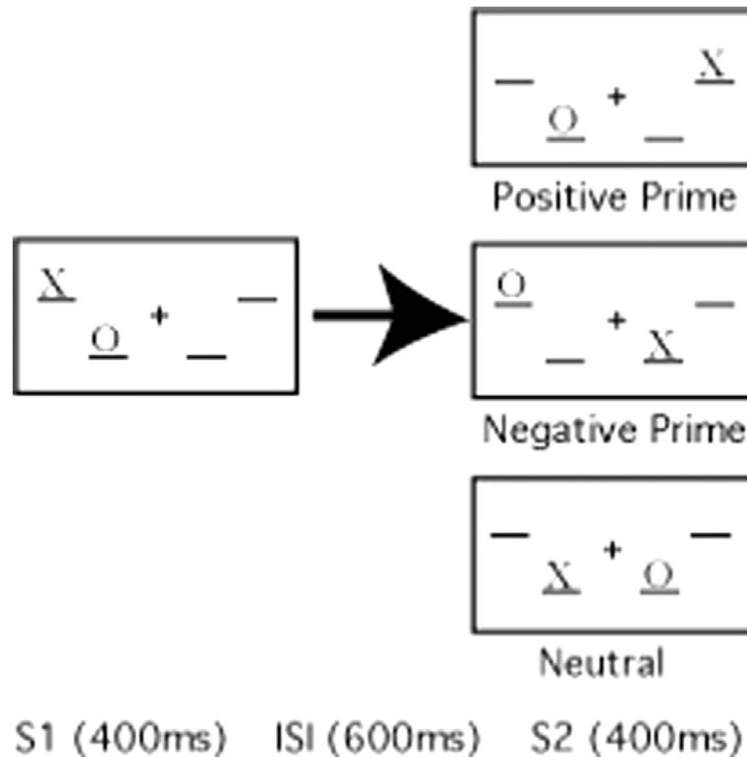
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**Fig. 1.**

The visuospatial priming (VSP) task. VSP task assesses the effects of an inhibitory or facilitory pre-signal (“prime”) on the reactions to a subsequently presented probe. The first set of stimuli (S1) served as a “prime” for the second set (S2). S1 and S2 were presented for 400 ms and separated by an interstimulus interval (ISI) of 600 ms. In both S1 and S2, an “X” and an “O” 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.

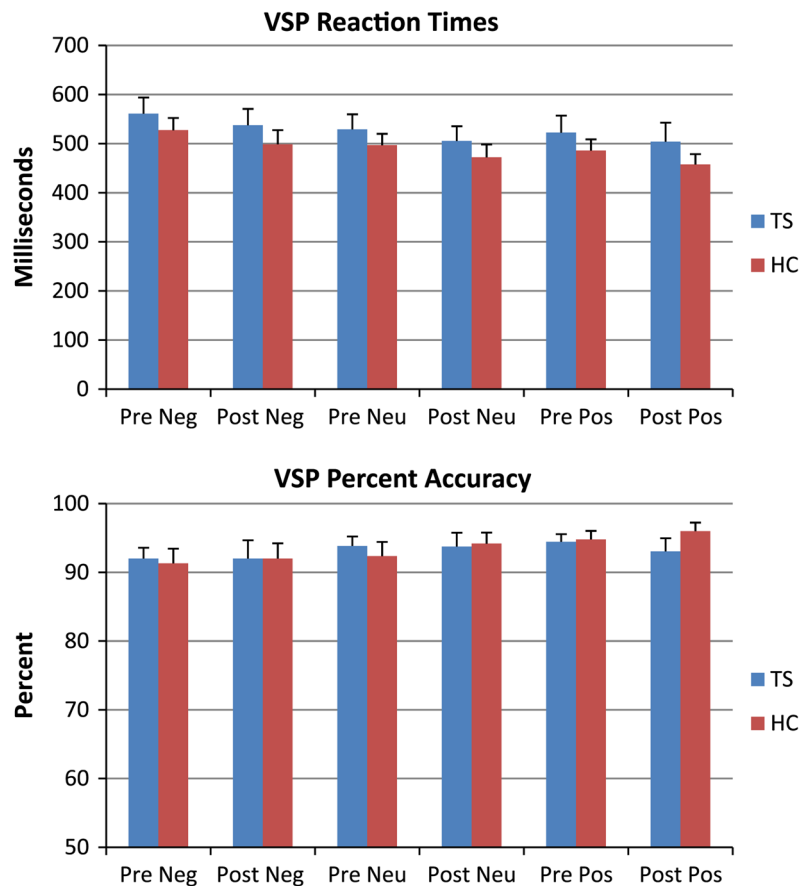


Fig. 2.

Visuospatial priming task performance before and after CBIT. TS patients and healthy controls (HC) did not differ on overall reaction times or percent accuracy, but both HC and TS subjects showed faster reaction times after CBIT compared to before CBIT (waiting period for HC), suggesting a practice effect ($F(1, 14)=5.96, p=0.029$). There was also a main effect of prime for reaction times ($F(1, 14)=20.65, p<0.001$) and percent accuracy ($F(2, 28)=8.20, p=0.002$). All participants had slower reaction times for negative prime trials compared to neutral trials and had faster reaction times on positive prime trials than neutral trials. Both TS subjects and healthy controls were also more accurate for the positive prime trials than the neutral trials, which were more accurate than the negative prime trials. *Note.* TS=Tourette's disorder; HC=healthy control; VSP=Visuospatial Priming task; neg=negative, neu=neutral, pos=positive.

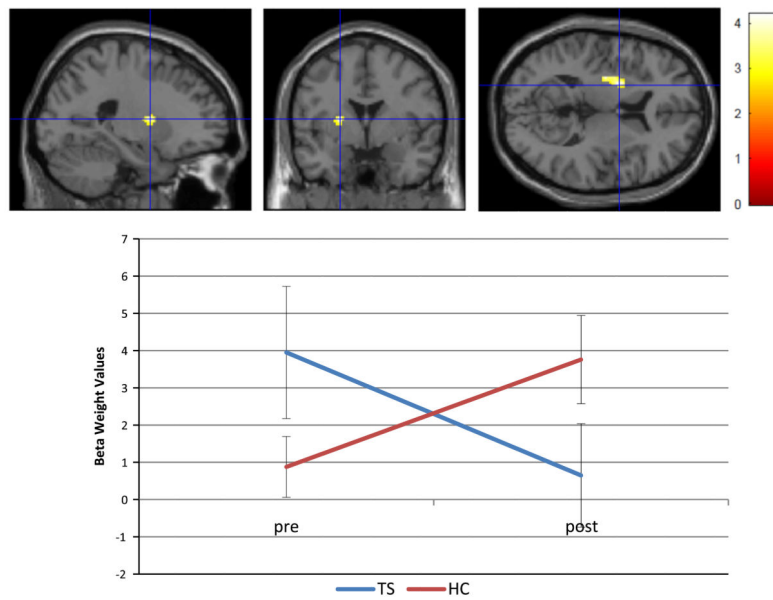


Fig. 3. Treatment associated putamen activation. For VSP task-related changes (VSP task vs. fixation), we found a significant interaction between group (TS vs. controls) and time (pre- vs. post-treatment) in the putamen (MNI coordinates=-22, 0, 10, $k=107$, $Z\text{-score}=3.67$, and $p=0.016$). Whereas TS subjects initially had greater putamen activation prior to treatment compared to controls, after treatment, TS subjects had less putamen activation than controls. *Note.* TS=Tourette’s disorder; HC=healthy control; VSP=Visuospatial Priming task; MNI=Montreal Neurological Institute.

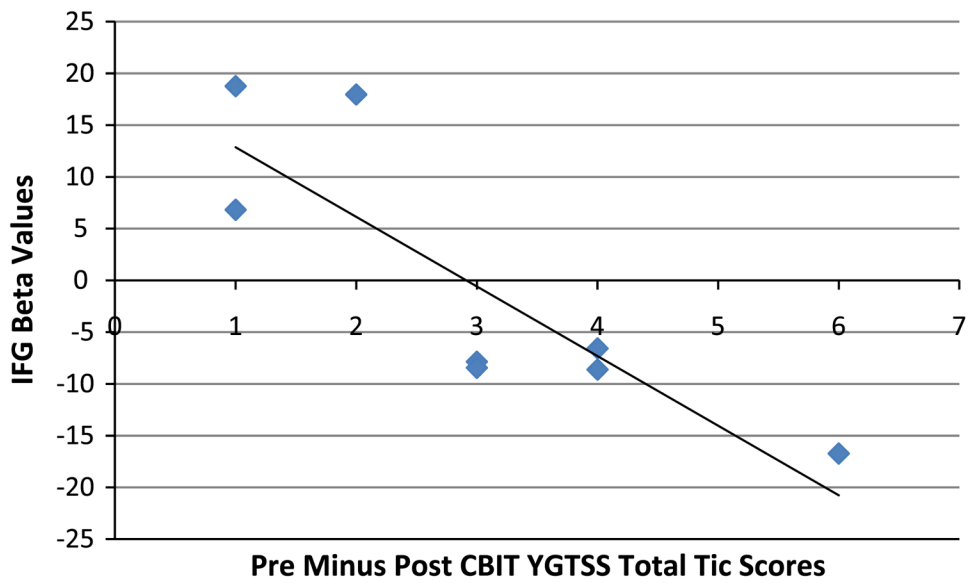


Fig. 4. Treatment related change in tic severity in the inferior frontal gyrus. We found a significant negative correlation between the change in YGTSS Total Tic scores and a region in the inferior frontal gyrus (MNI coordinates=56, 20, 0, $k=35$, Z -score=2.68, Pearson's $r=-0.85$, and $p=0.007$). *Note.* IFG=inferior frontal gyrus; CBIT=Comprehensive Behavioral Intervention for Tics; YGTSS=Yale Global Tic Severity Scale; MNI=Montreal Neurological Institute.

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.