A Functional Magnetic Resonance Imaging Study of Tic Suppression in Tourette Syndrome

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Background: The inability to inhibit unwanted behaviors and impulses produces functional debility in a broad range of neuropsychiatric disorders. A potentially important model of impulse control is volitional tic suppression in Tourette syndrome.

Methods: Tic suppression was studied in 22 adult subjects with Tourette syndrome by using functional magnetic resonance imaging. Images acquired during periods of voluntary tic suppression were compared with images acquired when subjects allowed the spontaneous expression of their tics. The magnitudes of signal change in the images were then correlated with measures of the severity of tic symptoms.

Conclusions: Significant changes in signal intensity were seen in the basal ganglia and thalamus and in anatomically connected cortical regions believed to subserve attention-demanding tasks. The magnitudes of regional signal change in the basal ganglia and thalamus correlated inversely with the severity of tic symptoms. These findings suggest that the pathogenesis of tics involves an impaired modulation of neuronal activity in subcortical neural circuits.

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The most frequent cause of functional debility associated with many neuropsychiatric disorders is the inability to inhibit unwanted impulses and behaviors. Compulsions, stereotypes, impulsivity, hyperactivity, and aggression are broad classes of behavioral problems that have been variously attributed to the failed inhibition of normal brain processes. Neuroimaging studies of these behaviors through task activation paradigms have been hindered by the inability to inhibit the behaviors rapidly and reversibly on demand during a scanning protocol. Semicompulsory behaviors that can be rapidly and voluntarily suppressed for brief periods, and that are therefore amenable to study in functional imaging protocols, are the tics of Tourette syndrome (TS).1

The motor and vocal tics of TS are typically heralded by a localized and vaguely defined discomfort that is often described as an irresistible urge to perform the movement.2 This urge increases during tic suppression until an inevitable capitulation brings rapid, albeit temporary, relief. Other behavioral features of TS can also be seen as capitulations to irresistible, extraneous, and unwanted urges. These include motoric hyperactivity and impulsivity, obsessions and compulsions, and hypersexual and aggressive behaviors.3 4 Some or all of these symptoms are purported to be variant expressions of the putative TS vulnerability gene.5 6 Understanding the volitional suppression of tics therefore may have important implications for the broader understanding of the suppression of other unwanted impulses and behaviors. We report a functional magnetic resonance imaging (MRI) study of volitional tic suppression in TS.

RESULTS

The omnibus test of statistical significance demonstrated significant increases and decreases in the global functional MRI signal change (Table). Post hoc testing of regional significance demonstrated bilateral decreased subcortical neuronal activity associated with tic suppression in the ventral globus pallidus and the putamen, as well as in the midbody of each hemithalamus. Increased subcortical activity during tic suppression was seen in the ventral head of the right caudate nucleus. Significantly increased cortical activity was evident in the right midfrontal cortex, the right middle temporal gyrus, the supe-
SUBJECTS AND METHODS

SUBJECTS

Subjects were identified through a review of medical records of the Yale TS Specialty Clinic (Yale University School of Medicine, New Haven, Conn) and through advertisements with local chapters of the Tourette Syndrome Association, Bayside NY. Preferentially recruited were subjects without tic repertoires that would likely produce movement artifact, ie, head- or neck-jerking motor tics, explosive vocal tics, and highly complex tics. Thus, almost all subjects had typical simple motor and vocal tics that included eye blinking, facial twitching, lip pursing, ling or toe movements, sniffling, soft grunting, or throat clearing. Subjects with a history of concussion, mental retardation, substance abuse, or current affective disorder and subjects who could not voluntarily suppress their tics (n=4) were excluded from participation in the study. All subjects gave informed written consent for their participation. Twenty-six subjects were scanned, but 4 moved excessively during the procedure and were not included in further analyses.

The remaining subjects included 11 men and 11 women with TS, 18 to 55 years old (mean±SD, 35.7±10.9 years), who had a broad range of severity of current tic symptoms (mean±SD tic scores: total, 24.6±8.9 [range, 8-39 of a possible 50]; motor, 15.2±4.5 [range, 8-23 of a possible 25]; phonic, 9.4±5.8 [range, 0-19 of a possible 25]). Men did not differ significantly from women in mean tic severity. Ten subjects (6 men and 4 women) met the diagnostic criteria of the DSM-IV9 for obsessive-compulsive disorder (OCD), and 3 retrospectively met the criteria for attention deficit hyperactivity disorder during childhood but did not currently meet the criteria. Fourteen (8 men and 6 women) were right-handed and 8 (3 men and 5 women) were left-handed. Five were taking fluoxetine hydrochloride (mean±SD, 32±22 mg/d, mean±SD duration, 37±25 months) for the treatment of OCD, and 2 were taking low-dose haloperidol (<2 mg/d for several months) for the control of tics.

TASK ACTIVATION

Subjects alternated 40-second epochs of allowing tics to occur freely with 40-second epochs of volitional tic suppression. Epochs alternated on hearing the verbal command “now” for tic and suppression epochs. This comparison of epochs controlled for the instantaneous variance in signal intensity that contributed to the stochastic noise of the signal and for any potential long-term drift of the baseline of the signal that could produce false-positive activation. Before comparisons of the t maps, a threshold of t=0.4 and a cluster filter of 8 adjacent pixels (pixels above threshold corresponding with 6 sections of the Talairach coordinate system9) was used to position the axial images beginning at the anterior commissure–posterior commissure line, extending dorsally two thirds of the distance to the vertex. The thickness of the slices was a constant 7 mm, while the skip between slices varied between 1 and 2 mm to maintain strict correspondence to the Talairach coordinate system.

Images were acquired on a 1.5-T scanner (GE Signa, General Electric, Milwaukee, Wis) that was equipped with echoplanar imaging hardware (Advanced NMR Inc, Wilmington, Mass). The functional images were obtained with a gradient echoplanar pulse sequence: repetition time of 2000 milliseconds, echo time of 45 milliseconds, 60° flip angle, 7-mm slice thickness, single excitation per image, 20×40-cm field of view, 64×128 matrix, providing a 3.1×3.1-mm in-plane resolution. During each experiment, 320 echoplanar images were acquired in each slice, providing 160 images per trial and 40 images per cycle of tic suppression.

IMAGE ACQUISITION

To minimize activation from eye movements, subjects were instructed to fix their gaze during the entire experiment on a crosshair located on the wall of the bore of the magnet. Head positioning in the magnet was standardized using the canthomeatal line. Six axial slices were acquired to correspond with 6 sections of the Talairach coordinate system. A T1-weighted sagittal localizing scan was used to position the axial images beginning at the anterior commissure–posterior commissure line, extending dorsally two thirds of the distance to the vertex. The thickness of the slices was a constant 7 mm, while the skip between slices varied between 1 and 2 mm to maintain strict correspondence to the Talairach coordinate system.

Functional MRI signal changes reflect changes in blood flow and oxygen concentration that are an indirect measure of neuronal activity. A method of image analysis was devised to assess the statistical significance of the signal changes related to the task, both experiment-wide and within individual regions of interest. First, all images were motion corrected by using a standard computerized algorithm. The intensities of each pixel of the echoplanar images were then grouped into tic and tic-suppression epochs. The first 3 images at the beginning of each epoch were discarded to minimize effects from the delay of onset and offset of changes in blood flow. The mean difference between tic and tic-suppression epochs for each pixel was normalized by its pooled variance to form the standardized difference, which was then transformed to a t statistic for that particular pixel relative to the standardized difference scores for all the other pixels in the entire functional MRI data set for each subject.

An omnibus test of statistical significance was performed to set a study-wide probability of error at P<.05. The omnibus test was designed to compare the task-related signal change with signal change that was not task-related for each pixel; this was accomplished by comparing the t maps of the tic-suppression cycles for each subject with the analogous 2 maps constructed from adjacent tic-tic and suppression-suppression epochs. This comparison of t maps controlled for the instantaneous variance in signal intensity that contributed to the stochastic noise of the signal and for any potential long-term drift of the baseline of the signal that could produce false-positive activation. Before comparisons of the t maps, a threshold of t=0.4 and a cluster filter of 8 adjacent pixels (pixels above threshold identified in post hoc testing (F 20,1=5.20; P=.04). Univariate tests of these same regions revealed that the men had significantly greater spatial extents of activation in the left putamen (z=2.7; P=.01), left hemithalamus (z=3.4; P=.005), right posterior cingulate (z=2.3; P=.01), right middle temporal gyrus (z=2.3; P=.02), and the left hippocampal and parahippocampal cortices (z=2.1; P=.04). Separate univariate exploratory analy-
that connect in any fashion) were applied to each map. Pixels meeting these t-value and cluster criteria for the first half of the experiment were also required to meet the same criteria for the second half of the experiment; this additional constraint, typically referred to as the split-t criterion, therefore stipulates that the change in signal intensity for a cluster of pixels replicates independently within individual subjects between both halves of the experiment. The threshold, cluster filter, and split-t criteria in combination strongly limit the number of spurious activations present in the t maps. The number of pixels that survived application of these criteria in the task-related tic-suppression maps were compared with the number that survived application of identical criteria to the 2 control t maps (ie, to the tic-tic and suppression-suppression maps). The nonparametric Wilcoxon signed rank test was used to make these comparisons because the surviving t values of the 3 maps were not normally distributed. For signal changes in the tic-suppression map to be deemed significant and task-related study-wide, we required that both signed rank tests be significant (ie, each P<.05). Requiring the activations in the tic-suppression map to outnumber significantly the activations in the 2 control maps was an additional stringent constraint on the number of spurious activations that appeared in the final data set.

An analogous analytic strategy was used in post hoc testing of the significance of changes in signal intensity for individual subregions of the brain. Cortical regions were predefined by using a standard stereotactic proportional grid system, which was constructed relative to the anterior commissure–posterior commissure landmarks and a box bounding the cortical surface (Figure 1). The putamen, globus pallidus, and thalamus were hand circumscribed, blind to characteristics of the subject and the t-maps (Figure 2). The post hoc probability values were assigned to the number of activations found in each region without correction for multiple comparisons because the overall study-wide experimental error of <.05 had already been established in the omnibus test. Similar strategies designed to address the issue of multiple comparisons are invoked in standard multivariate tests of significance. Moreover, the stringent requirement that the tic-suppression maps for each region activate significantly more than both of the control maps helped protect against type I errors in the post hoc testing.

CONSTRUCTION OF THE GROUP MEAN ACTIVATION MAP

For visual depiction of the mean group activation at each pixel, individual activation maps were warped into a common stereotactic space. The T1-weighted anatomic images for each subject underwent a piecewise linear warping transformation to a common bounding box. The same transformations were then applied to the corresponding functional activation maps (Figure 1), which were then averaged.

EXPLORATORY ANALYSES

Possible sex differences in regional activation were assessed by using a repeated-measures multivariate analysis of variance (MANOVA). Regions identified in the post hoc analyses as significantly active were entered as 20 levels in a “region” within-subjects factor, and sex was entered as a between-subjects factor. Univariate analyses were performed with Mann-Whitney U tests. The effects on regional activations of OCD comorbidity and the use of fluoxetine were similarly assessed. Possible laterality effects in regional activation were assessed by using the Wilcoxon signed rank test comparing activations in the corresponding regions of each hemisphere. A confirmatory repeated-measures MANOVA was performed with regions and hemisphere as within-subjects factors; the analysis was run with and without sex as a between-subjects factor.

CORRELATIONS

Correlation analyses were undertaken only for regions determined to be significantly active in the omnibus and post hoc regional analyses. Because the activation data were not normally distributed, the Efron bootstrap method was used to assess the significance of the Pearson correlation coefficients of the severity of tic symptoms with regional activation. Recalculation of Pearson correlations and significance levels and resampling of the population with replacement were repeated 10 000 times, producing an equal number of correlation matrices. Probability values were computed using the 10 000 correlation matrices as a reference distribution. Similar analyses were used to assess the significance of intercorrelations between activations in basal ganglia subregions.

ASSESSMENT OF MOTION-RELATED ARTIFACT

In-plane motion was assessed by examining the consistency of the brain border in all images and by plotting the center of the mass of image intensity. Motion perpendicular to the imaging planes was assessed by counting the number of pixels within the brain boundaries. Movement greater than 0.25 pixels resulted in the exclusion of 2 subjects. In addition, an index of motion for each subject was defined as the sum of motion of 8 points arranged on the vertices of a cube with 100-mm sides, centered within the brain to yield a single numerical index of motion. Displacements of each point were integrated in time by using the 6 parameters obtained from the motion correction algorithm (x, y, and z displacements, and roll, yaw, and pitch rotations). A motion index larger than 2 SDs from the group mean excluded an additional 2 subjects.
tently with the severity of tic symptoms than did changes in cortical activity. The directions of correlation throughout the cerebrum indicated that with increasing severity of symptoms outside of the scanner, the magnitude of task-related changes in neuronal activity while in the scanner was less—whether activity increased in the cortical regions and the caudate nucleus or whether it decreased in the lenticular nucleus and the thalamus. Correlations of whole-brain and regional activations with an index of total motion during the scan\(^{10}\) and correlations of symptom severity with the motion index did not approach the level of statistical significance, indicating that motion of the subject was not likely responsible for the robust correlations between regional activation and the severity of symptoms.

Increased activity in the right frontal cortex was associated with increased activity in the right caudate nucleus \((r=0.48; P=.03)\), and increased activity in the right caudate nucleus in turn was associated with greater decreases in activity of the globus pallidus \((r=0.84; P<.001)\), the putamen \((r=0.86; P<.001)\), and the thalamus \((r=0.51; P=.02)\) during tic suppression. The activities of the globus pallidus and the putamen were correlated \((r=0.95; P<.001)\), and both positively predicted thalamic activity \((r=0.90; P<.001)\).

<table>
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<th>Region</th>
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<th>Slice‡</th>
<th>z∥</th>
<th>P</th>
<th>Severity of Motor Tic§</th>
<th>r¶</th>
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*All statistically significant regional analyses are presented, including omnibus (whole brain) and post hoc regional analyses. Regions that did not reach the level of statistical significance \(P<.05\) are not included; therefore, data are presented bilaterally for some regions but unilaterally for others.
†For each analysis, separate analyses were performed to test for increased and decreased signal intensity as a measure of changed neuronal activity.
‡The slices are numbered as shown in Figure 1; slices 1 through 6 correspond to Talairach slices 8 through 3, respectively.
§Total motor tic subscale of the Yale Global Tic Symptom Severity Scale (Yale University School of Medicine, New Haven, Conn).
∥The z statistic from the Wilcoxon signed rank test. It is the smallest (ie, the least significant and most conservative) of the 2 z statistics calculated in the comparisons of the tic-suppression map with the tic-tic and suppression-suppression maps.
¶Pearson correlation coefficient assessing the strength of the relationship between the absolute value of the magnitude of activation and the severity of motor tic symptoms. A negative correlation coefficient indicates that as the severity of symptoms increases, the magnitude of the regional signal change (and neuronal activity) during tic suppression decreases. Therefore during tic suppression, the magnitude of the increased neuronal activity of the right caudate is reduced, just as the magnitude of the decrease in the remaining subcortical regions is reduced, in subjects who have more severe motor tics. The associated probability values were determined using bootstrap resampling methods.
The brain regions that are activated during tic suppression are those that have been described as belonging to a quadripartite distributed neural circuit that participates in the inhibition of unwanted impulses. This circuit consists of the prefrontal, parietal, temporal, and cingulate cortices, for which the role in behavioral inhibition is believed to depend critically on the modulation of activity in the basal ganglia and thalamus. Subcortical modulation is effected through excitatory projections primarily from the prefrontal cortex to the caudate nucleus, which in turn sends inhibitory GABAergic projections to the globus pallidus and substantia nigra; the globus pallidus and substantia nigra then project to the thalamus, and the thalamus projects back to the cortex. Precisely how this circuit initiates and regulates an appropriate behavioral response in the motor cortex is not entirely clear, although possibilities include the integration and cross talk of the prefrontal circuits with the

Figure 1. Group mean activation map and definition of cortical regions of interest. The map uses an arbitrary t statistic cutoff of 0.2 and a 25-pixel cluster filter. Although this format for data presentation provides an indication of consistent regional activation for all subjects, variability between subjects in the location of anatomical regions, such as the basal ganglia, and variability in the spatial location of activation within subcortical and stereotactically defined cortical regions make intersubject averaging an imperfect visual representation of the regional significance testing used in this study. This is particularly evident in the left basal ganglia, in which the group mean map fails to indicate activation. Red indicates increased activity during tic suppression; blue, decreased activity; and green outlines, the Talairach stereotactic definitions of cortical regions of interest using the anterior commissure–posterior commissure and bounding cortical surface landmarks. The regions of interest are numbered as follows: anterior cingulate, 1, 7, 14, 21, 28, and 35; posterior cingulate, 20, 27, 34, and 40; frontal cortex, 2, 8, 15, 22, 29, and 36; superior temporal gyrus, 3, 10, and 17; middle temporal gyrus, 4, 11, and 25; precentral gyrus, 9; sensorimotor cortex, 16, 23, 30, and 37; inferior parietal cortex, 24, 31, and 38; occipital cortex, 5, 12, 18, 26, and 32; hippocampus and parahippocampus, 6; cuneus, 13 and 19; and precuneus, 33 and 39.
sensorimotor circuits in the basal ganglia and thalamus, the influence of projections from the prefrontal cortex directly to motor relay nuclei in the thalamus, or through direct projections from the prefrontal cortex to the supplementary motor, premotor, or cingulate motor cortices.

Neurocognitive functions of the prefrontal cortex that may contribute to the suppression of unwanted behaviors include modulating selective attention, suppressing automatic or involuntary actions, monitoring self-behavior, or holding “online” in working memory the mental representations of the task. Hippocampal and parahippocampal portions of the circuit are believed to provide long-term declarative or episodic memory representations, and the superior temporal and inferior parietal cortices are believed to contribute contemporaneous visuospatial and somatosensory information that is relevant to the task. The anterior motor portion of the cingulate is believed to subserve the attentional, affective, and motivational aspects of goal-directed task performance, while functions of the posterior portion are believed to include the monitoring and assigning of mnemonic associations to somatic and other sensory input.

Tic suppression is an attention-demanding task that requires a constant update of somatosensory information, thereby accounting for the task-related increases in the activity of the frontal, superior temporal, and anterior cingulate cortices. The preoccupation with contemporaneous somatosensory information during tic suppression may reduce the need for retrieval of memory traces from long-term storage, thereby decreasing the activity of the hippocampal, parahippocampal, and posterior cingulate cortices. While these various cortical regions seem to be involved in tic suppression, in general their changes in activity correlated poorly with the severity of tic symptoms, suggesting that the regions are unlikely to be primarily involved in the failure to inhibit tic behaviors outside of the scanner.

In contrast, the much more robust inverse correlations of the severity of symptoms with task-related signal changes throughout the subcortex suggest that a failure to inhibit tics in TS may result from an impaired ability to alter subcortical neuronal activity (ie, less subcortical change in activity is accompanied by more severe symptoms, whether that signal change produces increased activity in the caudate nucleus or decreased activity in the other subcortical regions during tic suppression). These functional findings are generally consistent with the findings of previous structural imaging studies of singletons with TS that demonstrated volume reductions in the lenticular nucleus. They are also consistent with a study of monozygotic twins with TS in whom MRI demonstrated volume reduction in the right caudate nucleus, and increased dopamine receptor availability in the caudate nucleus in the more severely affected co-twins documented with single photon emission computed tomography using the ligand (5-N-(methyl-2-pyrrolidinyl)-methyl-2-hydroxy-3-iodo-6-methoxy-benzamide.

Discerning the changes in neural activity of the numerous complex pathways within the basal ganglia during tic suppression from blood flow data alone may be difficult or impossible, because the determinants of blood flow change can be presynaptic or postsynaptic, and projections to basal ganglia target regions are both inhibitory and excitatory. Moreover, striatal neurons (including those in the caudate nucleus) project to the internal and external globus pallidus, as well as to the substantia nigra, and highly variable behavioral effects are produced depending on which portion of the pathway is excited. The positive correlations between increased activity in the frontal cortex and the right caudate nucleus and between increased activity in the right caudate nucleus and decreased activity in the globus pallidus are consistent with the known presence of excitatory projections from the frontal cortex to the caudate nucleus and the known inhibitory projections from the caudate nucleus to the globus pallidus. The significant correlations of the severity of symptoms with activity in all subregions of the basal ganglia suggest insufficient activity upstream in the pathway at the right caudate nucleus in the initial prefrontal-striatal or the subsequent striatopallidal projections. Although our study cannot further specify which of these projections is more likely the culprit, the functional consequence of each alternative is the same—

Figure 2. Representative single-subject activation map and subcortical regions of interest. Because of the limitations of the group mean activation map in representing the regional significance testing (Figure 1), the activation map of a single subject is shown with the same threshold and filtering used in the regional significance testing. Left, Basal ganglia and thalamus as defined by hand tracing on the T-weighted anatomical images. Definitions of the regions are shown for the most inferior slice, in which activation of the basal ganglia was seen. Yellow indicates the putamen; blue, the globus pallidus; and red, the caudate nucleus. Right, Activation map showing bilateral decreased activity of the putamen and globus pallidus (blue) and increased activity in the right portion of the caudate nucleus during tic suppression (red).
insufficient activity in the inhibitory striatopallidal neurons projecting to the rest of the basal ganglia.28

Interpretation of the changes in neuronal activity that occurred with tic suppression possibly was confounded by our comparison of 2 states, tic suppression and spontaneous tic activity; the measured changes in signal intensity might therefore reflect the differing frequency of tics between subjects. However, our comparison of the 2 states is an unlikely confounding factor, because a higher frequency of spontaneous tics would be expected to produce a greater change in MRI signal intensity during successful tic suppression (and all subjects suppressed their tics successfully on demand); this greater signal change, owing to more frequent tics during the baseline measurement, would correlate positively with the severity of tic symptoms and not negatively, as we found in all regions of the subcortex.

Another potential confounding factor is that undetected motion during the tic epochs increased regional signal variance, thereby lessening signal differences between tic and tic-suppression epochs and erroneously producing the observed correlations between signal change and the severity of symptoms. This possibility cannot be excluded entirely, although our diligent attempts at appropriate selection of subjects, the detection of and correction for motion, the absence of correlation between the extent of subject motion and brain activation or the severity of symptoms, and the absence of significant inverse correlations between the severity of symptoms and whole-brain activation (Table) suggest that motion was not responsible for the observed correlations of activation with the severity of symptoms in the subcortex.

The preliminary findings of sex differences in regional activation must be interpreted with caution because left-handed subjects were included in the study. The left-sided differences between men and women in the putamen and thalamus may relate to previous findings that volume reductions in the lenticular nucleus are more prominent on the left side of the brain and in males.23 The relative rarity of TS in females (males are 4-10 times more likely to have TS) and the consistently smaller activations in women during tic suppression suggest that the functional activity of the left subcortical regions may need to be significantly more impaired if females are to exhibit clinically significant symptoms.

The findings for regional activations and the correlations of regional activity with the severity of symptoms are preliminary and must be replicated. Nevertheless, the findings may suggest alternative interpretations of the findings of previous imaging studies in TS and OCD. Positron emission tomography studies of subjects with TS, for example, typically require that the subjects suppress their tics during the scan to help minimize motion artifact. Those studies have consistently demonstrated striatal hypometabolism in subjects with TS compared with healthy control subjects,29,30 and I study reported a bilateral decrease in regional metabolism of the parahippocampal cortex—both findings that were seen here. Similarly, positron emission tomography and functional MRI studies of subjects with OCD generally require the subjects to suppress their compulsions during the scan or during the period of radioligand uptake before the scan, implicitly making the scanning protocol similar to the protocol we used. Studies using a within-subjects symptom provocation paradigm, in which the need for behavioral inhibition is greatest during epochs of symptom provocation, are particularly similar in design and in their findings.31,32 Like the results of our study, the imaging findings for subjects with OCD have generally included increased metabolism and blood flow in the frontal cortex and the caudate nucleus,33-34 as well as increased activity in the anterior cingulate cortex.31,33,34 That regional hypermetabolism normalized after successful anxiobessional therapy,35-40 when the need to suppress less severe compulsions was attenuated, is of little surprise.

The similarities of previous imaging findings with the findings we report highlight the importance of making explicit the demands of any scanning protocol, which may include behavioral inhibition. The similarities also underscore the involvement of cortical and subcortical circuitry in the inhibition of semicompulsory acts, not just in TS and OCD, but possibly in a much broader range of disorders that are characterized by repetitive stereotyped behaviors and impaired impulse control.

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