Published in final edited form as:

Am J Psychiatry. 2007 June ; 164(6): 955–966.

A Developmental fMRI Study of Self-Regulatory Control in Tourette's Syndrome

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Abstract

Objective—Disturbances in the maturation of neural systems that mediate self-regulatory processes may contribute to the development of Tourette's syndrome by releasing motor and vocal tics from regulatory control. The purpose of this study was to examine the age correlates of functional activity in neural circuits that subserve self-regulatory control in children and adults with Tourette's syndrome.

Method—The participants were 136 children and adults, which included 66 Tourette's syndrome patients and 70 healthy comparison subjects. During performance of the Stroop interference task, the authors compared the functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent response in patients with Tourette's syndrome with that of healthy comparison subjects. General linear modeling of Stroop-related activations was used to compare the differential effects of age and behavioral performance on changes in self-regulatory control between the two diagnostic groups.

Results—Although the correlations of age with behavioral performance on the Stroop task were similar between patients with Tourette's syndrome and healthy comparison subjects, the two groups differed significantly in their correlations of age with the magnitude of regional brain activation during the task. Interactions of age with diagnosis were detected in the ventral prefrontal (Brodmann's areas 10 and 24) and posterior cingulate cortices (Brodmann's area 31), and post hoc analyses indicated that subjects with Tourette's syndrome deactivated these regions less with advancing age. Greater activation of bilateral frontostriatal regions (Brodmann's areas 9/46, 45/46; lenticular nucleus; and thalamus) accompanied poorer performance in the patient group, which—in the presence of normal behavioral performance on the Stroop task—suggests that greater activation of the frontostriatal systems helps to maintain task performance in individuals with Tourette's syndrome.

Conclusions—Normative developmental correlates of activity in frontostriatal circuits that subserve self-regulatory control are disturbed in persons with Tourette's syndrome. These aberrant developmental correlates are likely a consequence of greater anatomical and functional disturbances in these circuits in adults with Tourette's syndrome, which leads to impaired regulation of tic behaviors. Reduced default-mode processing in ventral prefrontal and posterior cingulate cortices in adults with Tourette's syndrome suggests the presence of greater difficulty in engaging mental processes that become active when freed from the demands of more challenging cognitive tasks.

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The authors report no competing interests.

However, individuals with Tourette's syndrome appear to co-opt normal developmental processes in circuits that subserve age-related improvement in self-regulatory control while presumably struggling to maintain adequate task performance.

Disturbances in the maturation of frontostriatal systems in individuals with Tourette's syndrome likely contribute to impairments in self-regulatory control processes that, in turn, contribute to difficulty in suppressing tics. Tics are typically brief, nonpurposeful or semipurposeful fragments of motor behaviors that often occur in response to stimuli or environmental cues originating from within an individual's own body or from the outside world. Sensitivity to these cues is commonly experienced as a compulsory urge that is relieved only by the performance of a tic. Tics can be suppressed voluntarily but not indefinitely, and the internal struggle to control the urge of a tic is often as debilitating as the tic itself.

Findings from anatomical neuroimaging and postmortem studies indicate that children and adults with Tourette's syndrome have smaller volumes and reduced densities of inhibitory neurons in their caudate nuclei, which are thought to generate the repetitive, fragmented behavioral routines that constitute tics and that determine their clinical course (1). The continual need to suppress tics is thought to induce compensatory neural plasticity within the prefrontal cortices, as indicated by the presence of larger prefrontal volumes in children with Tourette's syndrome (2-4). The failure of this plastic response is thought to contribute to more severe symptoms and to the persistence of Tourette's syndrome into adulthood, thereby accounting for findings of smaller prefrontal volumes in adults with persistent Tourette's syndrome (2). Thus, the continued presence of frontostriatal disturbances into adulthood may preclude individuals with Tourette's syndrome from developing the requisite degree of self-regulatory control over their urges to perform tics and other semicompulsory behaviors that is needed for their symptoms to remit by young adulthood.

The Stroop test (5) engages self-regulatory control processes by requiring subjects to inhibit an automatized response (reading) in favor of another less automatic response (color naming). In a large cohort of healthy individuals ages 7 to 57 years, task performance improved with increasing age and was accompanied by increasing activation of frontostriatal systems and more prominent deactivations in a so-called "default-mode" system within ventral and posterior cingulate cortices. A large number of imaging studies suggest that these default-mode deactivations likely represent the more self-monitoring and free associative thought processes during the easier baseline task (6-10). Changes with age in these neural systems likely underlie the improvement in self-regulatory control that characterizes normal human development. Therefore, disturbances in the maturation of these systems may contribute to the development and persistence of Tourette's syndrome symptoms in the relatively small subgroup of individuals with a lifetime history of Tourette's syndrome whose symptoms do not remit or significantly attenuate by young adulthood.

We report a functional magnetic resonance imaging (fMRI) study in which we used the Stroop task to investigate differences in the development of self-regulatory control processes between individuals with and without Tourette's syndrome. We hypothesized that the correlations of age with brain activity during performance of the Stroop task would differ in patients relative to comparison subjects in frontostriatal and default-mode circuits.

Method

Subject Recruitment and Characterization

Tourette's syndrome subjects were recruited through the Tic Disorder Clinic of the Yale Child Study Center and through the local chapter of the Tourette Syndrome Association. The comparison cohort, consisting of the same children and adults described in our study of self-

regulatory control in normal development (6), were recruited through phone calls to randomly selected names on a telemarketing list of approximately 10,000 families in the local community. Comparison subjects were group matched with the patients by age, gender, and socioeconomic status. Those with a history of neurological illness, past seizures or history of head trauma with loss of consciousness, mental retardation, pervasive developmental disorder, psychosis, or current axis I disorders were excluded. Written informed consent was obtained from adult subjects and the parents of participating children, and assent was obtained from the children.

Neuropsychiatric diagnoses were established for all subjects using the Schedule for Tourette and Other Behavioral Syndromes (11), which contains the Schedule for Affective Disorders and Schizophrenia for adult subjects (12) and the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version for subjects under 18 years of age (13). Two child psychiatrists performed a best-estimate procedure to establish diagnoses using all available clinical and investigational materials. The Yale Global Tic Severity Scale (14), the Children's Yale-Brown Obsessive Compulsive Scale (15), and the DuPaul-Barkley Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale (16) were used, respectively, to rate current and worst ever severity of tics, obsessive-compulsive disorder (OCD), and ADHD symptoms. Full-scale IQs were estimated using the Wechsler Abbreviated Scale of Intelligence (17), and socioeconomic status was quantified using the Hollingshead Four-Factor Index of Social Status (18).

Stimulus Presentation

Four color words (red, green, yellow, and blue) were presented randomly against a black background and back-projected onto a screen that the subjects viewed through a mirror located on the scanner's head coil. The words were situated directly above a gaze-fixation white cross-hair and subtended about 2.2 vertical and 3.75 horizontal degrees of the visual field. Colored word stimulus and interstimulus durations were 1300 and 350 msec, respectively. Following a 1-second presentation of the cross-hair, colored word stimuli were presented in "congruent" and "incongruent" blocks of 16 trials each. Congruent trial blocks consisted of words written in the corresponding color (e.g., the word "red" displayed in red ink), and incongruent blocks consisted of words written in a randomly selected mismatched color (e.g., the word "red" written in blue, green, or yellow ink), with the constraint that no word or color was the same as the preceding word or color. The frequencies of presentation of colors and words were balanced between congruent and incongruent blocks. Four blocks, each of congruent and incongruent stimuli, were presented in each of two runs, and each run was 3 minutes and 44 seconds. Consistent with previous studies, subjects were instructed to name the color of the stimulus on each presentation, regardless of the meaning of the written word, quietly and with as little mouth movement as possible (19).

The presentation of stimuli within the scanner was strictly paced so that the number of stimuli would be equal across conditions (congruent and incongruent trial blocks). This method of stimulus presentation did not permit us to measure the response time that is typically used to assess the degree of interference experienced by subjects performing the task. We therefore measured behavioral interference outside of the scanner using a standard clinical format of the Stroop task. In task A (color naming), subjects were asked to name, as quickly as possible, the color (red, green, or blue) of 126 dots, 5.6 mm in diameter, arrayed randomly in nine columns and 14 rows on a sheet of white paper (8.5×11 inches) and scanned left to right and then top to bottom. In task B (word reading), subjects were asked to read, as quickly as possible, an equal number of similarly arrayed words ("red," "green," or "blue") printed in black ink. In task C (color-word naming), they were asked to name a similar array of words written in incongruent colors as quickly as possible. The time to completion of each task was recorded.

Stroop interference was calculated as $C - [(A \times B) / (A + C)]$ (20). These behavioral measures were conducted after the scanning session so as not to introduce practice and habituation effects into the functional imaging data. They were then used for correlation analyses with the magnitudes of brain activation detected inside the scanner.

Image Acquisition and Preprocessing

Acquisition—Head positioning in the magnet was standardized using the canthomeatal line. A T1-weighted sagittal localizing scan was used to position the axial images that were acquired, using a sagittal spoiled-gradient-recall sequence. Images were acquired on a GE Signa 1.5 Tesla LX scanner (General Electric, Milwaukee) and a standard quadrature head coil. The functional images were obtained using a T2*-sensitive gradient-recalled, single-shot echoplanar pulse sequence (TR=1750 msec, echo time=45 msec, flip angle=60° [single execution per image] field of view=20×40 cm, matrix=64×128, in-plane resolution=3.1×3.1 mm). In all 136 subjects, six axial slices were acquired to correspond with axial slices in the z direction of Talairach space (21), beginning at the anterior commissure-posterior commissure line and extending dorsally six-ninths of the distance to the vertex. Six slices were slices that were acquired in all subjects and used for image analysis. Slice thickness was a constant 7 mm, while the skip among slices varied between 0.5 and 2 mm in order to maintain a strict correspondence with the Talairach coordinate system, thus each axial slice represented the same plane within stereotaxic space between subjects.

Preprocessing—Images were visually inspected and discarded if artifacts such as ghosting occurred or if the subject moved >0.5 pixels in any direction. Images were then motion corrected using statistical parametric mapping (SPM) 99 software for three translational directions and three possible rotations. Corrected images were spatially filtered using a Gaussian filter with a full-width half-maximum of 6.3 mm. The drift of baseline image intensity was removed using an eighth-order, high-pass Butterworth filter with a frequency cutoff equal to three-fourths of the task frequency.

The T1-weighted axial anatomical images and corresponding echoplanar functional images for each subject were transformed into a common stereotactic space using a piece-wise linear warping to a common bounding box (21).

The mean percent change in fMRI signal acquired during blocks of congruent and incongruent stimuli was calculated at each pixel for every subject (19). Group composite activation maps were generated by calculating t statistics at each pixel of the image. To avoid the need to assume a specific distribution and variance of the data, a randomization procedure was used to estimate p values (22).

Behavioral Analyses

Stroop interference scores for each subject were entered as dependent variables in a linear-mixed model using SAS, version 9.0 (SAS Institute, Inc., Carey, N.C.), with diagnosis (Tourette's syndrome versus healthy comparison), age², full-scale IQ, and sex included as covariates. The difference in the improvement in performance with age between subjects with Tourette's syndrome and comparison subjects was tested by assessing the statistical significance of the diagnosis-by-age² interaction. Mixed-models analyses were also performed using the times to completion for each of the Stroop subtests (word reading, color naming, and color-word naming), with the same covariates included in each model. In the subjects with Tourette's syndrome, the association of behavioral performance with the severity of symptoms was assessed in correlation analyses. Pearson's partial correlation coefficients were calculated between interference scores and Yale Global Tic Severity Scale scores to determine whether performance was correlated with symptom severity.

A Priori Hypothesis Testing

We hypothesized that subjects with Tourette's syndrome would not exhibit the previously described (6) normative developmental patterns of brain activations that underlie the improvement in self-regulatory control. We tested this hypothesis by assessing whether correlations of Stroop-related activations with age differed between the patient group and comparison subjects. At each voxel, the mean percent signal change was entered as the dependent variable in a linear-mixed model (23), with diagnosis (Tourette's syndrome versus healthy comparison) as a between-subjects factor. Covariates included age and sex. We also considered all two- and three-way interactions of diagnosis, age, and sex for inclusion in the model. Terms that were not significant were eliminated via backward stepwise regression, with the constraint that the models had to be well formulated hierarchically at each step (i.e., all possible lower-order component terms had to be included in the model regardless of their statistical significance) (24). The differential effect of age on Stroop-related activations between the groups was tested by the statistical significance of the age-by-diagnosis interaction. In the present study, we report voxels that were identified on maps using a p value threshold <0.05 , together with the requirement that the activation occurred in a spatial cluster of at least (25) adjacent pixels, a conjoint requirement that, based on an approximation formula (25), yields a highly conservative effective p value <0.000005 . The volume of this cluster ($3.1 \text{ mm} \times 3.1 \text{ mm} \times 7 \text{ mm} \times 25 \text{ mm} = 1.68 \text{ cm}^3$) was well below that of the caudate and lenticular nuclei (5 to 6 cm^3), permitting detection of significant activation in those regions (26). The combined application of a statistical threshold and cluster filter substantially reduces the false positive identification of activated pixels at any given threshold (27).

Exploratory Analyses

Performance correlates—At each voxel, Stroop-related signal changes were entered as the dependent variable in another linear-mixed model with diagnosis (Tourette's syndrome versus healthy comparison) as a between-subjects factor. Interference scores obtained outside the scanner and age were entered as covariates. This analysis was intended to identify effects that were independent of age, allowing us to identify brain areas that contributed to improved performance. To assess whether activation in the same brain regions accounted for the variance in behavioral performance between groups, we tested the statistical significance of the diagnosis-by-interference interaction.

Correlates of symptom severity—To determine whether Stroop-related changes in signal were associated with illness severity, we included age and the Yale Global Tic Severity Scale scores in another voxel-wise regression analysis using general linear modeling. The correlates of symptom severity were assessed by testing the statistical significance of the Yale Global Tic Severity Scale term in the model. We also assessed the statistical significance of the age-by-Yale Global Tic Severity Scale interaction at each voxel to determine whether the correlates of symptom severity with activation varied with age. In addition, group composite activation maps were generated to explore differences in Stroop-related brain activity of the Tourette's syndrome subjects who had the lowest or highest Yale Global Tic Severity Scale scores (those within the lowest or highest quartiles of the distribution of Yale Global Tic Severity Scale scores).

Medication and comorbidity effects—We included medication (receiving medication or not receiving medication) as an independent variable in another voxel-wise regression analysis and assessed the significance of its main effect and interaction with other variables. We also assessed the statistical significance of the group-by-age interaction in a model that included only subjects with Tourette's syndrome who were or were not receiving medication at the time of the study (alpha-antagonists, neuroleptics, or selective serotonin reuptake inhibitors). We conducted this analysis to ensure that the findings of a priori hypothesis testing were stable

and not driven by medication effects. The effects of comorbidity (ADHD or OCD) were similarly assessed.

Results

Subjects

Seventy-six patients with Tourette's syndrome and 76 comparison subjects were scanned, but nine children (six Tourette's syndrome subjects and three comparison subjects) moved excessively during the procedure, and seven more (four Tourette's syndrome adults and three comparison children) had ghosting artifact that precluded inclusion in the analyses. Thus, 66 subjects with Tourette's syndrome (32 children and 34 adults) and 70 comparison subjects (20 children and 50 adults) remained for statistical analyses. Tourette's syndrome and comparison subjects were group-matched according to cohort characteristics (Table 1).

Behavioral Performance

A mixed-model analysis of Stroop interference scores did not reveal a significant main effect of diagnosis ($p=0.28$) or a significant diagnosis-by-age² interaction ($p=0.69$), indicating that the groups performed similarly on the Stroop task and that the improvement in performance with age was similar between the groups (Figure 1). Performance in both groups improved (interference lessened) during adolescence and stabilized in adulthood. Mixed-model analyses showed that the improvement in performance with age was also similar between groups on the Stroop subtests (color naming: $p=0.62$; word reading: $p=0.30$; color-word naming: $p=0.82$). The Full Scale Intelligence Quotient and sex did not account for significant variance in interference scores (Full Scale Intelligence Quotient: $p=0.23$; sex: $p=0.75$) or scores from any of the three subtests (in all cases: $p>0.1$). Performance of Tourette's syndrome patients did not correlate with symptom severity ($r=-0.19$, $p=0.15$).

A Priori Hypothesis Testing

Age effects—Significant interactions of age with diagnosis (Figure 2, Table 2) included the ventral prefrontal regions (mesial prefrontal cortex: $p=0.002$, Brodmann's area 10, $z_{\text{tal}}=0$; ventral anterior cingulate cortex: $p<0.05$, Brodmann's areas 24/32, $z_{\text{tal}}=9$, 18, and 27) and the dorsal posterior cingulate cortex ($p<0.01$, Brodmann's area 31, $z_{\text{tal}}=27$ and 36). Scatter plots indicated that deactivation in the mesial prefrontal cortex and ventral anterior cingulate cortex strengthened with age in the comparison subjects but remained stable with age in the Tourette's syndrome group (Figure 3). Deactivation in the posterior cingulate cortex increased with age in comparison subjects but attenuated with age in Tourette's syndrome subjects (Figure 3). Interactions of age with diagnosis were also detected in the right inferolateral prefrontal cortex ($p=0.007$, Brodmann's area 45, $z_{\text{tal}}=0$) and lenticular nucleus ($p=0.03$, $z_{\text{tal}}=9$), frontostriatal circuits that were engaged progressively more with increasing age among healthy comparison subjects but not Tourette's syndrome patients. After eliminating 26 of the adults in the comparison group to ensure more comparable proportions of adults between the diagnostic groups, these group differences in age correlates of activation in the ventral prefrontal and posterior cingulate cortices and in the frontostriatal regions remained significant.

Performance correlates—In subjects with Tourette's syndrome, poorer performance (i.e., higher interference scores) accompanied greater activation of frontostriatal regions (Figure 4, Table 3), including the inferolateral prefrontal cortex ($p<5$, Brodmann's areas 44/45, $z_{\text{tal}}=0$ and 9), mesial frontal gyrus ($p=0.001$, Brodmann's area 46, $z_{\text{tal}}=18$), dorsolateral prefrontal cortex ($p=0.001$, Brodmann's areas 9/46, $z_{\text{tal}}=27$ and 36), lenticular nucleus ($p=0.001$, $z_{\text{tal}}=0$ and 18), and thalamus ($p=0.001$, $z_{\text{tal}}=0$). In contrast, more activation of the right inferolateral prefrontal cortex accompanied better performance in the comparison subjects (Figure 4). Interactions of diagnosis with performance were also detected in the mesial prefrontal cortex

($p=0.02$, Brodman's area 10, $z_{\text{tal}}=0$) and posterior cingulate cortex ($p<0.05$, Brodman's area 31, $z_{\text{tal}}=18$ and 27). However, maps viewed separately of performance effects in the two cohorts indicated that activation of these regions accompanied better performance in the Tourette's syndrome patients, and more activation of these regions accompanied poorer performance in the healthy comparison subjects.

Exploratory Analyses

Correlations with symptom severity—The severity of symptoms correlated significantly with Stroop-task activation in the left dorsolateral prefrontal cortex ($p=0.03$, Brodman's area 46, $z_{\text{tal}}=27$ [Figure 4]), reflecting its greater activation in patients with more severe symptoms. Maps viewed separately in patients with the highest and lowest scores for symptom severity corroborated this finding (Figure 4).

Medication and comorbidity effects—A comparison of maps of diagnosis-by-age interactions, including maps viewed separately of the subjects with Tourette's syndrome who were or were not receiving medication or all subjects with Tourette's syndrome combined, revealed that medication did not contribute to results from our a priori hypothesis testing. Likewise, a comparison of the maps of diagnosis-by-age interactions, including the map of individuals with pure Tourette's syndrome or those with comorbid ADHD and/or OCD and of the map including all individuals with Tourette's syndrome, suggests that comorbidity did not produce the differential effects of age on Stroop-related activations between Tourette's syndrome and healthy comparison subjects. Similar comparisons revealed that comorbid illnesses did not moderate the associations of performance with Stroop-related activations in the Tourette's syndrome cohort. (These maps are available from the authors upon request.)

Discussion

The correlations of age with regional brain activity during performance of the Stroop task differed between the Tourette's syndrome and comparison groups. We detected interactions of age with diagnosis in a neural system comprising the medial prefrontal [Brodman's area 10], ventral anterior cingulate [Brodman's areas 24/32], and posterior cingulate [Brodman's area 31] cortices. We also detected group differences in the correlations of activation with performance in these same regions. In the comparison group, deactivations increased with age in these regions and were associated with better performance. In the Tourette's syndrome group, however, deactivations attenuated with age in these regions and were associated with poorer performance. In addition, group differences in the correlations of activation with performance were detected in frontostriatal circuits (right inferolateral prefrontal cortex [Brodman's areas 44/45], left mesial frontal gyrus [Brodman's area 46], left dorsolateral prefrontal cortex [Brodman's areas 9/46], lenticular nucleus, and thalamus). In healthy comparison subjects, greater activation of these regions accompanied better performance, whereas greater activation of these regions accompanied poorer performance in the Tourette's syndrome subjects. We interpret these differences in performance correlates as indicating that the individuals with Tourette's syndrome were compensating for a relative inefficiency of neural processing within frontostriatal circuits in order to maintain their normal level of performance on the self-regulatory task. We also suspect that this putative inefficiency of neural processing within frontostriatal systems contributed to the relative inability to regulate tic behaviors among Tourette's syndrome patients (28).

Behavioral Performance

Performance on the Stroop task correlated inversely with age in both groups, likely reflecting the maturation of neural systems that subserve response inhibition (29,30). In addition, correlations of age with the speed of performance was similar between groups for all three

subtests (word reading, color naming, and color-word naming) of the task, suggesting comparable improvement in all component processes that the task engages. These findings are consistent with previous behavioral studies that reported normal Stroop task performance in persons with Tourette's syndrome (31,32).

Group Differences in Age Correlates

In healthy comparison subjects, age correlated inversely with activation of the ventral prefrontal and subgenual cortices (Figure 2), indicating that deactivation of these regions increased progressively with age. Deactivations reflect either increased activity during the baseline task (naming of congruent stimuli) or greater suppression of activity during the active task (naming of incongruent stimuli) or a combination of both. The presence of greater neural activity during the performance of a baseline or "resting" condition, relative to activity during the performance of a more cognitively demanding active task, within the ventral prefrontal, subgenual, and posterior cingulate cortices is consistent with numerous prior reports of deactivations in these same regions (7-10). The greater neural activity during a baseline condition compared with an active task has been termed default-mode processing because it is presumed to reflect mental processes that become more active when freed from the demands of a more challenging cognitive task. Default-mode processing was prominent in the healthy adults in our study but absent in the healthy children. We have previously interpreted these findings as suggesting that healthy adults more readily engage these mental processes than do children during performance of the baseline task, perhaps because they more readily free up attentional resources during the baseline condition compared with the active task (6). Additionally, adults may more strongly suppress this activity than children during a more difficult active task.

The age correlates of default-mode processing in the Tourette's syndrome group differed significantly from those in the healthy comparison group. Scatter plots indicated that an absence of default-mode activity in Tourette's syndrome adults accounted for these group differences (Figure 2). Exploratory analyses revealed that these differences in default-mode processing were not moderated by the presence of comorbid OCD or ADHD in the Tourette's syndrome subjects. A similar failure to generate default-mode activity has been reported in patients with dementia, in healthy elderly individuals (33), in persons who are sleep-deprived (34), and in individuals with autism (35). Similar to interpretations offered in these prior studies, we suspect that the reduced or absent default-mode activity in Tourette's syndrome adults in our study likely represents either the presence of inefficient neural processing in brain regions that require greater activity during the more active task, perhaps as some sort of neural compensation, or difficulty in more actively suppressing neural activity during the more active task. Alternatively, attenuated deactivations could represent less activity during the baseline task in the Tourette's syndrome adults, perhaps reflecting difficulty with engaging the mental processes during the baseline task when freed from more difficult task demands, which would occur if the adult patients found the baseline task more difficult than did the comparison subjects. Either hypothesis suggests that, in Tourette's syndrome adults, there is a presence of impaired neural processing in the default-mode system or in the related neural circuits that regulate it.

Group differences in age correlates were also detected in frontostriatal circuits. In the healthy comparison subjects, activations in the right inferolateral prefrontal cortex and right lenticular nucleus strengthened with increasing age (Figure 2), which is consistent with findings from previous imaging studies of response inhibition during normal development (6). These age correlates were not observed in the Tourette's syndrome cohort because of a failure to increase activation of these regions in Tourette's syndrome adults. This observation is consistent with

our understanding of frontostriatal disturbances in individuals with Tourette's syndrome whose tic symptoms fail to remit or to attenuate with age².

Group Differences in Performance Correlates

Group differences in performance correlates were most significant in frontostriatal regions (Figure 4). In Tourette's syndrome subjects, activation of large expanses of the inferolateral and dorsolateral prefrontal cortices and basal ganglia was associated with worse task performance (Figure 4), whereas in healthy comparison subjects frontostriatal activation increased with better performance (Figure 4). In addition, the presence of comorbid OCD or ADHD did not contribute to these performance correlates in the Tourette's syndrome cohort. Furthermore, activity in the dorsolateral prefrontal cortex was associated positively with the severity of symptoms, indicating that patients with more severe symptoms engaged this frontostriatal region most. These findings are consistent with the reliance of the task on frontostriatal control circuits and suggest that these circuits activate more in individuals with Tourette's syndrome who have the greatest inherent difficulty with self-regulatory control—in those individuals whose tics are the most symptomatic and the most enduring.

Interactions of performance with diagnosis were also detected in the medial prefrontal and posterior cingulate cortices, corresponding to the observed group differences in age correlates within default-mode systems. Deactivations in these brain regions accompanied better performance only in the healthy adults. These group differences in performance-related activity further suggest that the excessive reliance of Tourette's syndrome subjects on activating frontostriatal circuits while maintaining task performance accompanies less efficient regulatory control of default-mode processing.

In a previous fMRI study, the willful suppression of tics also produced changes in activity of frontostriatal systems, with the magnitude of change correlating with the severity of tic symptoms (36). This prior finding suggests that when frontostriatal control systems fail, tics, and possibly other behaviors, are more likely to be released from inhibitory influences of the frontal cortex. Thus, findings from this prior study as well as the present one suggest that individuals with Tourette's syndrome may have difficulty engaging these regulatory systems not only to suppress their urges to tic, but also to control their response to cognitive interference during incongruent trials of the Stroop task and to regulate default-mode activity during this attention-demanding, self-regulatory task.

The association of greater activation in the prefrontal cortex and basal ganglia with poorer performance in both children and adults with Tourette's syndrome suggests that the continued presence of abnormalities in frontostriatal functioning may contribute to the continued presence of impaired self-regulatory control in Tourette's syndrome adults. Smaller prefrontal volumes in adults with Tourette's syndrome are thought to provide a neural and functional reserve that is insufficient for controlling the urges to tic that derive from the striatum (36). Thereby, smaller prefrontal volumes likely contribute to the release of tic symptoms from top-down control and to the persistence of Tourette's syndrome into adulthood (2). However, the excess reliance on frontostriatal circuits to maintain Stroop task performance in individuals with Tourette's syndrome may represent a co-opting of the developmental circuits that subserve normal age-related improvements in self-regulatory control, thereby accounting for similar improvements in behavioral performance with advancing age between both diagnostic groups in our study.

Associations With the Severity of Symptoms

The magnitude of signal change in the dorsolateral prefrontal cortex (Brodmann's areas 9/46) correlated positively with tic severity and was associated with worse task performance in the Tourette's syndrome group. These findings suggest that, in order to maintain performance, the

most symptomatic Tourette's syndrome patients needed to engage more of the attentional resources that the dorsolateral prefrontal cortex provides, which is consistent with prior findings that Tourette's syndrome subjects must engage this region during the successful inhibitory control of tic symptoms (2,36). Alternatively, dorsolateral prefrontal cortex engagement by individuals who have the most severe symptoms may represent a compensatory effort to overcome distraction from their tics while performing an attention-demanding task. Previous Stroop task studies indicate that the left dorsolateral prefrontal cortex may subserve the attentional demands of the task (37). In addition, stimulation of the left dorsolateral prefrontal cortex during performance of the Stroop task decreases reaction times during both congruent and incongruent trials (38), further indicating that the dorsolateral prefrontal cortex plays an important role in implementing top-down attentional control in this task.

Strengths and Limitations

Our study of 136 subjects is, to our knowledge, the largest developmental fMRI study of self-regulatory control and the largest fMRI study of individuals with Tourette's syndrome to date. The findings in this study improve our understanding of how the abnormal development of self-regulatory processes may contribute to the pathophysiology of Tourette's syndrome. Our findings of different age-related changes in brain activation may reflect the use of different strategies across ages or diagnostic groups rather than differences in the maturation of self-regulatory processes *per se*. We did not assess or compare the differential use of competing strategies between the groups of children or adults or between Tourette's syndrome and healthy comparison groups, and thus our findings should be considered in light of this limitation. Other developmental studies of cognitive functions attempted to address this limitation through performance-matching (39) or the manipulation of task difficulty (40). Our diagnostic groups were in fact comparable in task performance, thereby supporting the attribution of group differences in activation to inefficiencies in neural processing within regulatory systems of the Tourette's syndrome subjects.

Another limitation to this study was the use of a subvocal response to the Stroop stimuli, which we chose to use because overt speech can cause significant fMRI signal artifacts (41). A subvocal response, however, precluded the online measurement of task performance during scanning. Because our behavioral measures were conducted after the scanning session, we cannot exclude the possibility that differential practice or habituation effects between the groups may have confounded or contributed to our findings of similar age-related improvement in the behavioral performance between the groups. To our knowledge, however, no previous block-design studies have correlated online reaction time data with fMRI signal change. Moreover, Stroop task studies that have used overt and covert verbal responses have demonstrated similar measures of cognitive load and patterns of fMRI activation when they have been compared directly with one another (42), and subvocal responses have been used in numerous other fMRI studies of the Stroop task in both adults (19) and children (43). The use of a manual response such as a button press, an alternative to a vocal response, would introduce a complex mapping function of color names to a pattern of finger response that would fundamentally change the nature of the task in a way that could interact profoundly with age and diagnosis.

We included both correct and incorrect responses in our analyses, which is consistent with prior Stroop task studies (19,43) that have demonstrated error rates of approximately 3% (37), a rate that is consistent with the error rates noted outside of the scanner in our cohort. Inclusion of erroneous trials at these low rates likely had a negligible effect on our activation maps. Additionally, the observed group differences in Stroop-related brain activations may have been attributed to differences in reading proficiency, given that reading skills are typically more disturbed in clinical populations. However, none of the Tourette's syndrome subjects had

a clinical diagnosis of dyslexia, and their scores on the word reading subtest were comparable with those of the comparison subjects ($p=0.30$), suggesting that group differences in reading ability were unlikely to have produced our findings. Last, because our findings are based on associations, we cannot conclude from this study that increased frontostriatal activations represent compensatory responses for inefficient neural processing in Tourette's syndrome subjects or that inefficient neural processing causes more severe or more persistent tic symptoms. However, our findings are consistent with an extensive literature documenting compensatory neural responses in individuals with Tourette's syndrome (2,26).

Conclusions

The findings in this study have important implications for understanding the developmental trajectory of brain functioning in persons with Tourette's syndrome. Taken together with a large body of evidence from other Tourette's syndrome imaging studies, our observations are consistent with the hypothesis that disturbances in the maturation of the frontostriatal systems that mediate self-regulatory control contribute to the development, persistence, and severity of tic symptoms. Frontostriatal disturbances may also contribute to the inability of individuals with Tourette's syndrome to regulate default-mode brain activity during this attention-demanding task. Both the improvement in task performance with age and the greater activation of frontostriatal regions when individuals with Tourette's syndrome are struggling with the task likely reflect compensatory responses to the presence of subtle functional disturbances in the efficiency of neural processing within frontostriatal regulatory circuits. Compensatory responses may serve to enhance self-regulatory control, thereby allowing individuals with Tourette's syndrome to maintain task performance and, as indicated in a prior study of tic suppression (36), to regulate the severity of their tics.

Acknowledgements

Supported in part by NIMH grants MH-01232, MH-59139, MH-068318, K-02-74677, and K01-MH-077652; the Suzanne Crosby Murphy Endowment at Columbia University College of Physicians and Surgeons; and the Thomas D. Klingenstein and Nancy D. Perlman Family Fund.

The authors thank James Leckman, M.D., Robert King, M.D., Larry Schahill, Ph.D., Diane Findley, Ph.D., as well as the Tourette Syndrome Association, for help with recruitment. The authors also thank John Gore, Ph.D., and Cheryl Lacadie, Ph.D., for technical assistance.

References

1. Kalanithi PS, Zheng W, Kataoka Y, DiFiglia M, Grantz H, Saper CB, Schwartz ML, Leckman JF, Vaccarino FM. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. *Proc Natl Acad Sci U S A* 2005;102:13307–13312. [PubMed: 16131542]
2. Peterson BS, Staib L, Scahill L, Zhang H, Anderson C, Leckman JF, Cohen DJ, Gore JC, Albert J, Webster R. Regional brain and ventricular volumes in Tourette syndrome. *Arch Gen Psychiatry* 2001;58:427–440. [PubMed: 11343521]
3. Fredericksen KA, Cutting LE, Kates WR, Mostofsky SH, Singer HS, Cooper KL, Lanham DC, Denckla MB, Kaufmann WE. Disproportionate increases of white matter in right frontal lobe in Tourette syndrome. *Neurology* 2002;58:85–89. [PubMed: 11781410]
4. Hong KE, Ock SM, Kang MH, Kim CE, Bae JN, Lim MK, Suh CH, Chung SJ, Cho SC, Lee JS. The segmented regional volumes of the cerebrum and cerebellum in boys with Tourette syndrome. *J Korean Med Sci* 2002;17:530–536. [PubMed: 12172051]
5. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643–662.
6. Marsh R, Zhu H, Schultz RT, Quackenbush G, Royal J, Skudlarski P, Peterson BS. A developmental fMRI study of self-regulatory control. *Hum Brain Mapp* 2006;27:848–863. [PubMed: 16421886]
7. Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci* 2004;16:1484–1492. [PubMed: 15601513]

8. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A* 2001;98:4259–4264. [PubMed: 11259662]
9. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, Petersen SE. Common blood flow changes across visual tasks, II: decreases in cerebral cortex. *J Cogn Neurosci* 1997;9:648–663.
10. McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci* 2003;15:394–408. [PubMed: 12729491]
11. Pauls, DL.; Hurst, CR. Schedule for Tourette and Other Behavioral Syndromes. New Haven, Conn: Yale University Child Study Center; 1996.
12. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 1978;35:837–844. [PubMed: 678037]
13. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. The Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980–988. [PubMed: 9204677]
14. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1989;28:566–573. [PubMed: 2768151]
15. Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, Cicchetti D, Leckman JF. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* 1997;36:844–852. [PubMed: 9183141]
16. DuPaul GJ. Parent and teacher ratings of ADHD symptoms: psychometric properties in a community-based sample. *J Clin Child Psychol* 1991;20:245–253.
17. Wechsler, D. Wechsler Adult Intelligence Scale—Revised (WAIS-R) Manual. San Antonio, Tex: Psychological Corp; 1981.
18. Hollingshead, AB. Four-Factor Index of Social Status. New Haven, Conn: Yale University Press; 1975.
19. Peterson BS, Skudlarski P, Zhang H, Gatenby JC, Anderson AW, Gore JC. An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Biol Psychiatry* 1999;45:1237–1258. [PubMed: 10349031]
20. Golden, CJ. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Wood Dale, Ill: Stoelting; 1978.
21. Talairach, J.; Tournoux, P. Co-Planar Stereotaxic Atlas of the Human Brain. New York: Thieme Medical; 1988.
22. Manly, B. Randomization, Bootstrap and Monte Carlo Methods in Biology. London: Chapman and Hall; 1997.
23. Worsley K, Marret S, Neelin P, Vandal K, Friston K, Evans A. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 1996;4:58–73.
24. Morrell CH, Pearson JD, Brant LJ. Linear transformations of linear mixed-effects models. *Am Statistician* 1997;51:338–343.
25. Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp* 1994;1:214–220.
26. Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang Z, Bronen R, King R, Leckman JF, Staib L. Basal ganglia volumes in patients with Gilles de la Tourette syndrome. *Arch Gen Psychiatry* 2003;60:415–424. [PubMed: 12695320]
27. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 1995;33:636–647. [PubMed: 7596267]
28. Leckman JF. Phenomenology of tics and natural history of tic disorders. *Brain Dev* 2003;25(suppl 1):s24–s28. [PubMed: 14980368]
29. Comalli PE Jr, Wapner S, Werner H. Interference effects of Stroop Color-Word Test in childhood, adulthood, and aging. *J Genet Psychol* 1962;100:47–53. [PubMed: 13880724]

30. Schiller PH. Developmental study of color-word interference. *J Exp Psychol* 1966;72:105–108. [PubMed: 5967713]
31. Channon S, Flynn C, Robertson MM. Attentional deficits in Gilles de la Tourette syndrome. *Neuropsychiatry Neuropsychol Behav Neurol* 1992;5:170–177.
32. Ozonoff S, Jensen J. Brief report: specific executive function profiles in three neurodevelopmental disorders. *J Autism Dev Disord* 1999;29:171–177. [PubMed: 10382139]
33. Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL. Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A* 2003;100:14504–14509. [PubMed: 14608034]
34. Chee MW, Choo WC. Functional imaging of working memory after 24 hours of total sleep deprivation. *J Neurosci* 2004;24:4560–4567. [PubMed: 15140927]
35. Kennedy DP, Redcay E, Courchesne E. Failing to deactivate: resting functional abnormalities in autism. *Proc Natl Acad Sci U S A* 2006;103:8275–8280. [PubMed: 16702548]
36. Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, Leckman JF, Gore JC. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. *Arch Gen Psychiatry* 1998;55:326–333. [PubMed: 9554428]
37. MacDonald AW III, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 2000;288:1835–1838. [PubMed: 10846167]
38. Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'Haenen H. The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. *Exp Brain Res* 2006;169:279–282. [PubMed: 16418843]
39. Darcy Burgund E, Lugar HM, Schlaggar BL, Petersen SE. Task demands modulate sustained and transient neural activity during visual-matching tasks. *Neuroimage* 2005;25:511–519. [PubMed: 15784430]
40. Durston S, Thomas KM, Yang Y, Ulug AZ, Zimmerman RD, Casey BJ. A neural basis for the development of inhibitory control. *Developmental Sci* 2002;5:F9–F16.
41. Barch DM, Sabb FW, Carter CS, Braver TS, Noll DC, Cohen JD. Overt verbal responding during fMRI scanning: empirical investigations of problems and potential solutions. *Neuroimage* 1999;10:642–657. [PubMed: 10600410]
42. Laird AR, McMillan KM, Lancaster JL, Kochunov P, Turkeltaub PE, Pardo JV, Fox PE. A comparison of label-based review and ALE meta-analysis in the Stroop task. *Hum Brain Mapp* 2005;25:6–12. [PubMed: 15846823]
43. Adelman NE, Menon V, Blasey CM, White CD, Warsofsky IS, Glover GH, Reiss AL. A developmental fMRI study of the Stroop Color-Word Task. *Neuroimage* 2002;16:61–75. [PubMed: 11969318]

FIGURE 1. Interference Scores Plotted Against Age in Tourette's Syndrome and Healthy Comparison Subjects Showing Similar Patterns of Improvement in Behavioral Performance^a

^a Plots of correlations with subtest scores of Tourette's syndrome and healthy comparison subjects show that much of the variance in interference scores derives from the color-word naming scores in both groups.

FIGURE 2. Group Average Brain Activations in Tourette's Syndrome and Healthy Comparison Children and Adults^a

^a Shown are the group composite t maps for fMRI signal change associated with incongruent compared with congruent stimuli. These are axial slices (parallel to the floor in a standing person) positioned "superiorly to inferiorly" (top to bottom). Increases in signal during the incongruent relative to congruent stimuli are coded in yellow, and decreases are coded in purple or blue. For the main effects of age in Tourette's syndrome and healthy comparison groups, positive correlations with age are in yellow, and inverse correlations with age are in purple or blue. Posterior cingulate cortex=PCC; anterior cingulate cortex=ACC; inferior frontal gyrus=IFG; superior temporal gyrus=STG; lenticular nucleus=Lent; lateral prefrontal cortex=LPFC; mesial prefrontal cortex=MPFC; inferolateral prefrontal cortex=ILPFC; mesial temporal gyrus=MTG; ventral anterior cingulate cortex=VACC; occipital cortex=OCC.

FIGURE 3. Interactions of Diagnosis With Age Plotted in Mesial Prefrontal (Brodmann's Area 10), Ventral Anterior Cingulate (Brodmann's Area 24), and Posterior Cingulate Cortices^a

^a Deactivations in these regions increased with age in healthy comparison subjects. In subjects with Tourette's syndrome, signal change in the mesial prefrontal and ventral anterior cingulate cortices remained stable, and deactivations attenuated with age in the posterior cingulate cortex.

FIGURE 4. Main Effects of Behavioral Performance in Tourette's Syndrome and Healthy Comparison Subjects^a

^a Diagnosis-by-performance interactions were detected in frontostriatal and posterior cingulate regions in which interactions of diagnosis with age were observed. Tourette's syndrome subjects likely needed to engage frontostriatal regions more to maintain task performance. Main effect of symptom severity in the left dorsolateral prefrontal cortex, indicating that the patients with the worst symptoms activated this region most, is shown. These are axial slices (parallel to the floor in a standing person) positioned superiorly "to inferiorly" (top to bottom). Increases in signal change are coded in yellow, decreases coded in blue/purple. Posterior cingulate cortex=PCC; inferior frontal gyrus=IFG; lenticular nucleus=Lent; lateral prefrontal

cortex=LPFC; inferolateral prefrontal cortex=ILPFC; mesial prefrontal cortex=MPFC; putamen=Put; cuneate=Cun; thalamus=Thal; dorsolateral prefrontal cortex=DLPFC.

TABLE 1

Demographic and Clinical Characteristics of Subjects

Characteristic	Group									
	Children					Adults				
	Individuals With Tourette's Syndrome (N=32)		Healthy Comparison Subjects (N=20)			Individuals With Tourette's Syndrome (N=34)		Healthy Comparison Subjects (N=50)		
	Mean	SD	Mean	SD	%	Mean	SD	Mean	SD	%
Age (years) ^a	12.82	2.8	13.52	3.2		35.27	11.1	31.91	11.4	
Socioeconomic status ^b	47.54	12.1	47.53	12.0		48.48	13.3	52.00	10.9	
Wechsler Abbreviated Scale of Intelligence score	113.09	13.2	117.5	12.3		118.8	13.9	123.2	14.9	
Yale Global Tic Severity Scale score										
Motor/phonic (current)	18.50	10.2				20.54	10.1			
Motor/phonic (worst ever)	28.41	9.9				29.55	8.9			
	N	%	N	%		N	%	N	%	
Sex (male:female) ^c	27:5		11:9			20:14		23:27		
Race (Caucasian) ^d	29	90.6	20	100		34	100	43	86	
Comorbidity										
OCD	10	31				15	44			
ADHD	6	18				2	5			
OCD/ADHD	4	12				1	3			
Pure Tourette's syndrome	20	63				16	54			
Medication ^e										
Stimulants	3	9								
Haloperidol/pimozide	6	18				3	8			
Risperidone	5	15				1	2			
Alpha-adrenergic agonists	6	18								
SSRIs	8	25				6	17			
Medication free	9	28				21	61			

^aThe mean age range for children with Tourette's syndrome and healthy comparison children, respectively, was 8.4 to 17.5 years and 7.1 to 17.9 years. The mean age range for adults with Tourette's syndrome and healthy comparison adults, respectively, was 17 to 52.6 years and 18.3 to 57.2 years.

^bValues for socioeconomic status were quantified using the Hollingshead Four Factor Index of Social Status, which calculates socioeconomic status based on the following formula: $[(\text{maternal education} \times 3) + (\text{paternal education} \times 5)] + [(\text{maternal occupation} \times 5) + (\text{paternal occupation} \times 5)]/2$.

^cSignificant between-group difference in gender ratio in the group of children ($\chi^2=5.78$, $df=1$, $p=0.02$).

^dSignificant between-group difference in race in the adult group ($\chi^2=5.19$, $df=1$, $p=0.02$).

^eMedications were not mutually exclusive.

TABLE 2

Diagnosis-by-Age Interactions

Region of Interest	Side	Slice	Talairach Coordinates			Brodmann's Area	Signal Change	p
			x	y	z			
Mesial prefrontal cortex	Left/right	1	6	52	0	10	Increase	0.002
Inferolateral prefrontal cortex	Right	1	-42	43	0	45	Decrease	0.007
Ventral anterior cingulate cortex	Left/right	2	5	46	9	24	Increase	0.001
		3	5	46	18	32	Increase	0.04
		4	5	46	27	32	Increase	0.03
Inferior frontal gyrus	Left	3	42	14	32	44	Decrease	0.006
Superior temporal gyrus	Right	1	-51	-11.5	0	22	Decrease	0.04
Dorsal posterior cingulate	Left/right	3	9	-46	27	31	Increase	0.001
	Left/right	4	9	-46	36	31	Increase	0.007
Lenticular nucleus	Right	2	-31	4	9	N/A	Decrease	0.03

TABLE 3

Diagnosis-by-Performance Interactions

Region of Interest	Side	Slice	Talairach Coordinates			Brodmann's Area	Signal Change	p
			x	y	z			
Mesial prefrontal cortex	Left/right	1	1	59	0	10	Decrease	0.02
Inferolateral prefrontal cortex	Right	1	-24	37	0	44/45	Increase	0.01
	Right	2	-29	39	9	45	Increase	0.001
	Right	3	-29	39	9	45	Increase	0.02
Dorsolateral prefrontal	Left	4	29	39	27	9/46	Increase	0.001
	Left	5	31	10	36	9/46	Increase	0.001
Mesial frontal gyrus	Left	3	31	11	18	46	Increase	0.001
Posterior cingulate cortex	Left/right	3	2	-61	18	31	Decrease	0.02
	Left/right	4	4	-47	27	31	Decrease	0.01
Lenticular nucleus	Right	1	-23	6	0	N/A	Increase	0.001
	Right	3	-33	1	18	N/A	Increase	0.001
Thalamus	Left	1	31	-11	0	N/A	Increase	0.001