

Functional and Biochemical Alterations of the Medial Frontal Cortex in Obsessive-Compulsive Disorder

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Context: The medial frontal cortex (MFC), including the dorsal anterior cingulate and the supplementary motor area, is critical for adaptive and inhibitory control of behavior. Abnormally high MFC activity has been a consistent finding in functional neuroimaging studies of obsessive-compulsive disorder (OCD). However, the precise regions and the neural alterations associated with this abnormality remain unclear.

Objective: To examine the functional and biochemical properties of the MFC in patients with OCD.

Design: Cross-sectional study combining volume-localized proton magnetic resonance spectroscopy and functional magnetic resonance imaging with a task encompassing inhibitory control processes (the Multi-Source Interference Task) designed to activate the MFC.

Setting: Healthy control participants and OCD patients recruited from the general community.

Participants: Nineteen OCD patients (10 males and 9 females) and 19 age-, sex-, education-, and intelligence-matched control participants recruited from the general community.

Main Outcome Measures: Psychometric measures of symptom severity, Multi-Source Interference Task be-

havioral performance, blood oxygen level-dependent activation, and proton magnetic resonance spectroscopy brain metabolite concentrations.

Results: Multi-Source Interference Task behavioral performance did not differ between OCD patients and control subjects. Reaction time interference and response errors were correlated with blood oxygen level-dependent activation in the dorsal anterior cingulate region in both groups. Compared with controls, OCD patients had greater relative activation of the supplementary motor area and deactivation of the rostral anterior cingulate during high- vs low-conflict (incongruent > congruent) trials. Patients with OCD also showed reduced levels of neuronal *N*-acetylaspartate in the dorsal anterior cingulate region, which was negatively correlated with their blood oxygen level-dependent activation of the region.

Conclusions: Hyperactivation of the MFC during high- vs low-conflict conditions in patients with OCD may be a compensatory response to a neuronal abnormality in the region. This relationship may partly explain the nature of inhibitory control deficits that are frequently seen in this group and may serve as a focus of future treatment studies.

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NEUROBIOLOGIC AND NEUROPSYCHOLOGIC models of obsessive-compulsive disorder (OCD) have linked obsessive and compulsive symptoms to deficits of response control and inhibition.¹⁻⁹ Such deficits putatively reflect a reduced capacity of patients with OCD to inhibit intrusive or ritualistic cognitions and motor response tendencies² and have been linked to increased volume¹⁰ and excessive activity of some brain regions, including the medial frontal cortex (MFC), ventral frontal cortex, and basal ganglia.^{2,11-17} Recent functional magnetic resonance imaging

(fMRI) studies of OCD patients have associated MFC-related hyperactivations in the dorsal (dAC) and rostral (rAC) anterior cingulate regions with specific dimensions of inhibitory control, such as response conflict detection and resolution and sensitivity to errors.¹⁸⁻²¹

Although the neural basis of inhibitory control deficits in OCD remains largely unknown, studies using proton magnetic resonance spectroscopy (¹H-MRS) have found specific reductions in AC levels of *N*-acetylaspartate (NAA) in medicated²² and drug-naïve OCD patients.²³ *N*-acetylaspartate is a metabolite found primarily in neurons, and reduced levels are

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Table 1. Sample Characteristics^a

Characteristic	OCD (n = 19)	Control (n = 19)	F _{1,36}	P Value
Sex, M/F, No.	10/9	10/9	NA	NA
Handedness, right/left, No.	19/0	19/0	NA	NA
Age, y	33.7 ± 10.7	30.6 ± 7.2	1.10	.30
Education, y	14.6 ± 2.2	15.4 ± 2.6	0.91	.35
Intelligence–Verbal Scale	109.3 ± 6.3	112.7 ± 10.1	1.61	.21
Intelligence–Performance Scale	109.1 ± 13.9	115.2 ± 11.6	2.16	.15
Intelligence–Full Scale	110.2 ± 9.4	115.5 ± 10.3	2.80	.10
BDI-II	9.0 ± 6.7	6.3 ± 5.8	1.73	.19
BAI	9.7 ± 9.2	5.5 ± 5.7	2.94	.10
Duration of illness, y	13.4 ± 11.3	NA	NA	NA
YBOCS–Obsessions	7.7 ± 3.5	NA	NA	NA
YBOCS–Compulsions	8.6 ± 2.9	NA	NA	NA
YBOCS–Total	16.3 ± 5.7	NA	NA	NA
PI–Obsessional Thoughts	5.35 ± 4.90	NA	NA	NA
PI–Obsessional Impulses	1.30 ± 1.78	NA	NA	NA
PI–Contamination Compulsions	11.85 ± 10.45	NA	NA	NA
PI–Checking Compulsions	16.90 ± 13.63	NA	NA	NA
PI–Dressing/Grooming Compulsions	3.80 ± 3.45	NA	NA	NA
PI–Total	39.20 ± 29.48	NA	NA	NA

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; NA, not applicable; OCD, obsessive-compulsive disorder; PI, Padua Inventory; YBOCS, Yale-Brown Obsessive-Compulsive Scale.

^aData are given as mean ± SD except where indicated otherwise.

thought to index neuronal loss, dysfunction, or both.^{24,25} This suggests that hyperactivation of the MFC, which is commonly seen in fMRI studies of OCD patients, may reflect a compensatory response to a primary neuronal deficit.^{11,26} However, direct associations between these 2 measures have not previously been demonstrated as no study to date, to our knowledge, has acquired both functional and biochemical indices of neuronal integrity in the same individual.

In this study, we sought to clarify the nature of MFC hyperactivation in OCD patients using a multimodal approach combining fMRI and ¹H-MRS. We focused primarily on the superior MFC, incorporating the paralimbic component of the dAC, given strong previous evidence for its involvement in inhibitory control and dysfunction in OCD.^{11,19,20,27-31} We used a functional paradigm, the Multi-Source Interference Task (MSIT), that has been shown to robustly activate the dAC and the supplementary motor area (SMA), including the pre-SMA, in individual healthy and neuropsychiatric individuals³²⁻³⁴ and that incorporates elements of inhibitory control (eg, response conflict detection and resolution) that are relevant for understanding the behavioral disturbances seen in patients with OCD.¹⁹ Concurrently, we acquired volume-localized ¹H-MRS measures from the medial wall region that we expected would be activated by the functional task.

Based on previous work, we hypothesized that patients would show increased activation of this medial wall complex during MSIT performance compared with controls,^{27,35,36} that concentrations of NAA would be reduced in the patient group,²² and that there would be an inverse relationship between concentrations of NAA and dAC activation. Such a relationship would constitute preliminary evidence supporting the notion of compensatory MFC hyperactivation driven by a neuronal deficit.

METHODS

PARTICIPANTS

We recruited 21 patients with OCD from the general community through advertisements in local newspapers and community services. All the patients were required to (1) have a current IQ greater than 80, (2) be medication free or stable on their medication dose for at least 1 month, and (3) have no other current Axis I psychiatric diagnosis. All participants with a history of significant head injury (ie, loss of consciousness for >5 minutes, hospitalization requiring a >1-night stay, or significant post-concussion syndrome), neurologic disease, electroconvulsive therapy, impaired thyroid function, and corticosteroid use were excluded. All the participants gave written informed consent to participate in this study, which was approved by the Melbourne Health Research and Ethics Committee.

One patient with OCD was excluded because of an incidental MRI finding (an infarct in the superior parietal area), and 1 was excluded owing to inability to complete the task (1 arm became numb while in the scanner and the patient could not respond properly). The remaining OCD patients were case matched based on age, sex, education, and intelligence to a sample of 19 controls selected from a larger control sample obtained as a part of an ongoing program of research³⁷ such that there were no significant group differences on any of these measures (matching was done before any analyses were performed) (**Table 1**). At the time of scanning, the OCD group reported mild to moderate levels of OCD symptoms (as indexed by the Yale-Brown Obsessive-Compulsive Scale), characterized predominantly by contamination and checking compulsions (indexed using the Padua Inventory), and moderate levels of cognitive and affective symptoms of depression and physiologic and psychological symptoms of anxiety (measured using the Beck Depression Inventory and the Beck Anxiety Inventory). There were no patients with prominent hoarding symptoms. Eleven patients were receiving stable doses of

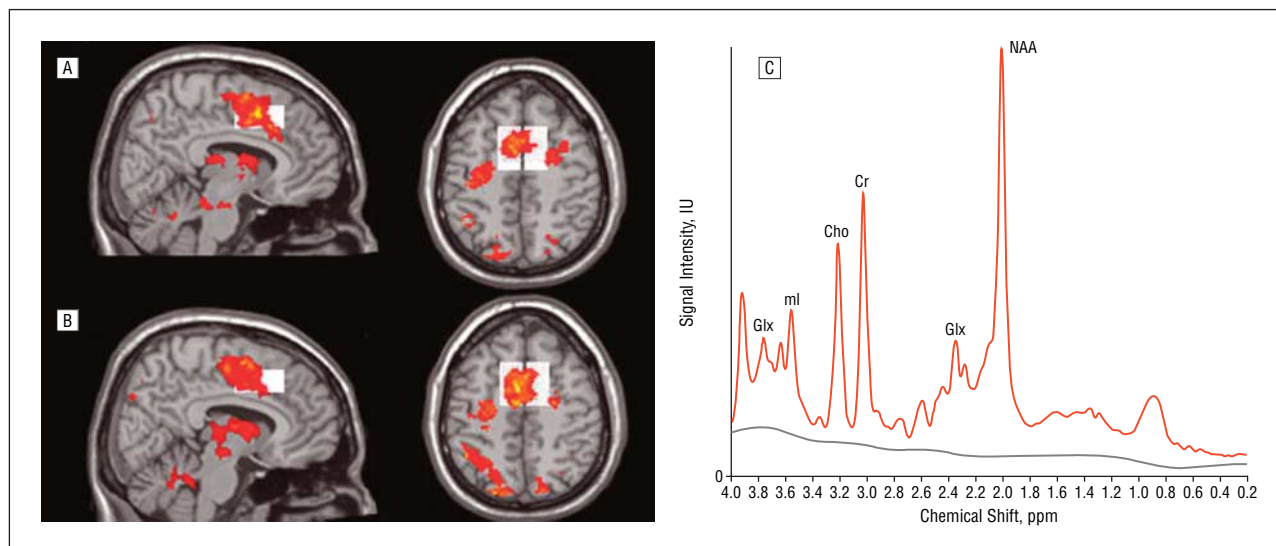


Figure 1. Volume-localized proton magnetic resonance spectroscopy (sagittal and axial orientations) shows considerable overlap with the group of activated clusters in the dorsal anterior cingulate region (displayed at the commonly reported threshold of $z > 3.0$) for controls (A) and patients with obsessive-compulsive disorder (B). Images are displayed on a canonical structural magnetic resonance image (Montreal Neurological Institute, Talairach brain). C, Sample magnetic resonance spectroscopy spectrum from the dorsal anterior cingulate region highlighting the 5 main metabolite peaks: *N*-acetylaspartate compounds (NAA), creatine + phosphocreatine (Cr), choline compounds (Cho), glutamate + glutamine (Glx), and myoinositol (ml). IU indicates arbitrary institutional units.

medication at the time of scanning (fluoxetine hydrochloride [$n=4$], fluvoxamine maleate [$n=1$], citalopram hydrobromide [$n=2$], venlafaxine hydrochloride [$n=1$], and clomipramine hydrochloride [$n=3$]).

Diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I disorders (including impulse spectrum disorders), Patient Edition.³⁸ All the controls also underwent a Structured Clinical Interview for DSM-IV Axis I disorders, Nonpatient Edition. No control subject had an Axis I or II disorder, and no patient had comorbid Axis I or II disorders. General intelligence (IQ) was estimated using the Wechsler Abbreviated Scale of Intelligence.³⁹

FUNCTIONAL TASK

Full details of the MSIT appear elsewhere.^{32,33} Briefly, the MSIT is a task that encompasses inhibitory control processes designed specifically to probe the human MFC, particularly the dACC-SMA complex, in fMRI experiments. The MSIT combines sources of interference from a variety of well-known paradigms (ie, the Stroop, Flanker, and Simon tasks) and generates a state of high response conflict by engaging competing response tendencies that code correct and incorrect outcomes. During scanning, participants viewed sets of 3 numbers from 0 to 3, presented in strings of 3, with 1 number always being different from the other 2. Participants were instructed to indicate the identity (not the position) of the number that was different by pressing the appropriate button on a response box. Responses were made with 1 of 3 fingers: the index finger to indicate 1, the middle finger to indicate 2, and the ring (fourth) finger to indicate 3. During congruent (C) task trials, the number always matched the position on the response box and was flanked by the number 0. During incongruent (I) task trials, the number never matched the response position and was flanked by incongruent numbers. Participants were informed that scans would begin and end with fixation for 60 seconds, between which they would see 8 alternating block pairs of C and I trials (ie, 16 blocks) lasting 30 seconds per block (eg, FCICICIFCICICIF). Stimulus and interstimulus intervals were 2000 and 500 milliseconds, respectively. For all the trials, participants were instructed to answer

as quickly and accurately as possible. During the scanning trials, behavioral reaction times (RTs) and percentage error scores were recorded via a notebook computer. Before scanning, all the participants completed a practice run of the task consisting of 1 block of 12 C trials and 1 block of 12 I trials.

IMAGING ACQUISITION AND PREPROCESSING

All individual MRI sequences were acquired in a single scanning session using a 3-T magnetic resonance scanner (GE Signa Horizon LX; GE Healthcare, Milwaukee, Wisconsin). Before scanning, participants were introduced to a “mock scanner” to familiarize them with the MRI environment (for approximately 30 minutes). After the mock session, participants were taken to the actual scanner and had their head stabilized using a Velcro strap over the forehead. Scanning sequences consisted of a scout localizer, fMRI, T1-weighted anatomical sequence, and ¹H-MRS, in that order. Imaging data were transferred to a Linux 2.4.27 workstation (Debian Sarge) for image preprocessing and analysis.

Functional MRI data were acquired as a series of single-shot gradient-recalled echo-echo planar imaging volumes providing T2*-weighted blood oxygen level-dependent (BOLD) contrast. The image acquisition parameters for the functional scans were repetition time, 3000 milliseconds; echo time, 40 milliseconds; flip angle, 60°; field of view, 24 cm; and a 128 × 128 matrix, producing a voxel size of 1.875 × 1.875 × 4.0 mm and 25 sections for full-brain coverage. The first 4 images in each run were automatically discarded to allow the magnetization to reach steady-state equilibrium. For each 30-second block in the experiment, 10 volumes were acquired, resulting in a total of 80 volumes for the C condition and 80 volumes for the I condition.

Volume-localized ¹H-MRS findings were recorded using a short-echo point resolved spectroscopy sequence (repetition time, 3000 milliseconds; echo time, 30 milliseconds; number of signals acquired, 128; and nominal voxel size, approximately 6.5 cm³) from the dACC bilaterally (**Figure 1**). The MRS voxels were placed in each hemisphere, separated by the medial wall boundary of the frontal lobes, to encompass the dACC. The posterior boundary of the voxel was approximately 10 mm posterior to a vertical line from the anterior commissure orthogonal to the an-

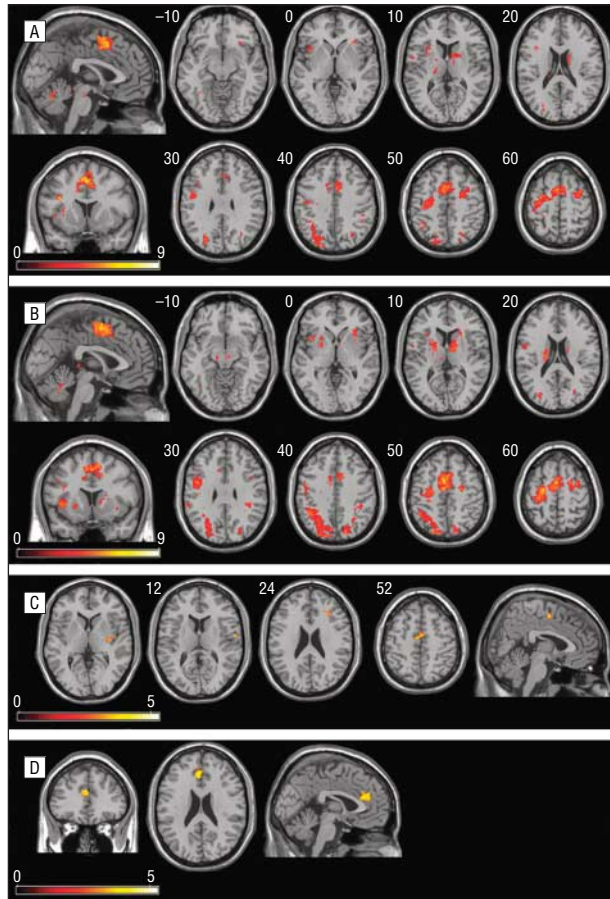


Figure 2. Areas of brain activation during performance of the Multi-Source Interference Task in controls (A) and patients with obsessive-compulsive disorder (OCD) (B). Both groups showed robust activation of the medial walls of the frontal lobes and superior parietal regions. In OCD patients areas of relative hyperactivation are shown, including the putamen, inferior frontal, and supplementary motor area (C), as is apparent hypoactivation in the rostral anterior cingulate (D). Images are displayed in radiologic format. Numbers at the top of each row indicate the section number in Montreal Neurological Institute space. Color bars indicate the z score ranges.

terior commissure–posterior commissure line. The inferior border was approximately 5 mm superior to the top edge of the corpus callosum, and the medial border was 1 to 2 sections lateral to the parasagittal section on the T1 structural image for each hemisphere. For volume-localized spectra, absolute levels of NAA, glutamate + glutamine, creatine + phosphocreatine, choline, and myoinositol were measured.

STATISTICAL ANALYSES

Individual demographic measures of sex, handedness, age, education, and IQ were compared across groups using univariate analyses of variance in SPSS version 11.0 (SPSS Inc, Chicago, Illinois). Analyses of behavioral data were conducted using repeated-measures analysis of variance, with task condition (C vs I blocks) as the within-subject effect and group (controls vs OCD patients) as the between-subject effect. Response errors were calculated by summing all commission (eg, responding “1” when the correct answer was “2”) and omission errors (missed responses) across the C and I trials. The response error variable was \log_{10} transformed to ensure normality of distribution.⁴⁰ Interference effects were calculated by subtracting the mean RT for the C trials across all blocks from the mean RT of the I trials across all blocks.

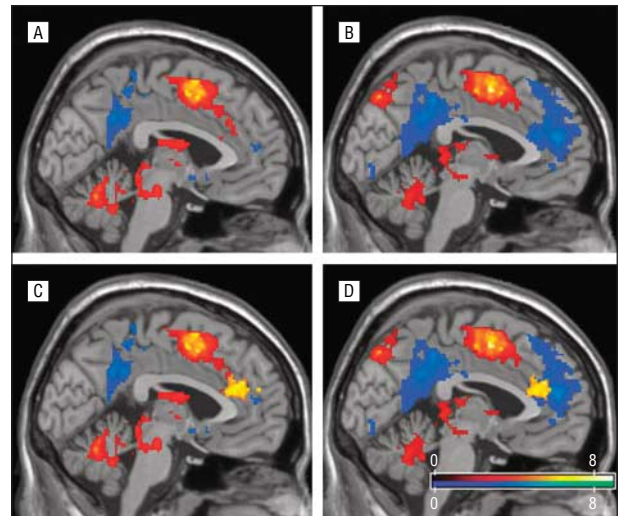


Figure 3. Patterns of task-related activation (hot colors) and deactivation (cold colors) during high- vs low-conflict trials (incongruent > congruent) in both groups. Patterns are shown for controls (A) and patients with obsessive-compulsive disorder (OCD) (B) and for controls (C) and OCD patients (D) with the rostral anterior cingulate cluster differentiating the 2 groups superimposed in yellow. It can be seen that this rostral anterior cingulate cluster represents a portion of the significant medial frontal cortex deactivation in OCD patients. Images are displayed in radiologic format. Color bars indicate the z-score ranges (hot colors for activation and cold colors for deactivation).

Analysis of the fMRI data was performed using FEAT (fMRI Expert Analysis Tool) Version 5.4 (FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl>). The following preprocessing was applied before statistical analysis: motion correction using MCFLIRT,⁴¹ nonbrain removal using the BET (Brain Extraction Tool),⁴² spatial smoothing using a gaussian kernel of full width at half maximum of 5 mm, mean-based intensity normalization of all volumes by the same factor, and high-pass temporal filtering (gaussian-weighted least squares fit straight line fitting, with $\sigma = 30.0$ seconds). Time series statistical analysis was performed using FILM (FMRIB Improved Linear Model) with local autocorrelation correction.⁴³ Individual participant z (gaussian-transformed) statistical images were thresholded using clusters determined by $z > 2.7$ and a whole-brain (corrected) cluster significance threshold of $P < .05$.⁴⁴ For controls, 16 showed activation of the dAC-SMA region at this threshold, and 3 controls showed activation at a lowered z score of 2.33 (whole-brain clusterwise corrected). For OCD patients, 16 showed activation of the dAC-SMA region at the higher $z > 2.7$ threshold, 2 showed activation at the lower level, and 1 showed no activity above either threshold. In addition, we extracted a converted percentage signal change value of the BOLD response (I > C) from the dAC cluster maximum of each individual using Featquery in FSL. We used the peak voxel for each individual in preference to summing activity over a larger area in a standard space (eg, an area around the peak voxel or the MRS volume of interest) to minimize averaging over nonsignificant voxels. Preliminary analyses indicated that an individually tailored voxel is representative of the overall activated cluster and provides a more reliable association with the behavioral indices of the MSIT.

Group-level analysis was performed using FLAME (FMRIB Local Analysis of Mixed Effects).^{45,46} For within-group analyses, z (gaussianized T/F) statistical images were determined using a threshold of $z > 4.0$, $P < .05$ (whole-brain clusterwise corrected).⁴⁴ To facilitate comparisons with existing literature,^{18,19} clusters were visually displayed (eg, **Figure 2** and **Figure 3**) at a commonly reported threshold of $z > 3.0$. For between-group comparisons (OCD vs control), z (gaussianized T/F) statistical images were determined using a whole-

Table 2. Medial Frontal Wall Activation and Relative Group Differences During Task Performance in Controls and Patients With OCD^a

Group and Region	Approximate Area ^b	Cluster Size ^c	Maximum z Score	Anatomical Coordinates		
				x	y	z
Controls (n = 19)						
dAC	32/6	357	7.79	0	12	48
	32		6.76	-8	16	46
	32		6.72	4	10	48
	32		6.56	-2	4	48
	6		7.09	6	0	58
Pre-SMA	6	357	6.61	4	6	54
	6					
OCD (n = 19)						
dAC/pre-SMA	32/6	747	8.96	2	0	52
	32/6		8.94	4	4	52
	32/6		8.52	-2	8	52
	32		7.81	4	2	46
dAC ^d	6	17	8.22	6	0	58
	6		7.45	0	0	60
Pre-SMA	6	17	5.15	-12	10	40
	32					
OCD > control						
SMA	32/6	60	4.67	2	-10	52
Control > OCD						
rAC ^f	24/32	232	4.95	2	40	26

Abbreviations: dAC, dorsal anterior cingulate; OCD, obsessive-compulsive disorder; rAC, rostral anterior cingulate; SMA, supplementary motor area.

^aThe first listed entry for each group reflects the cluster maxima, and following entries reflect significant, associated subcluster peaks.

^bRefers to approximation of Brodmann areas. Some entries have 2 numbers because the exact Brodmann area was difficult to determine based on the peak location of activation.

^cRefers to the cluster size in number of activated voxels.

^dRefers to the right hemisphere.

^eRefers to the left hemisphere.

^fThis finding actually reflects greater relative deactivation of this region in patients during high-conflict trials (incongruent > congruent).

brain (uncorrected) threshold of $z > 3.0$, $P < .0001$. Registration to standard space images was performed using FLIRT.^{41,47}

Metabolite concentrations derived from ¹H-MRS were determined for each region of interest (corrected for estimated tissue content) using LCModel software.⁴⁸ This software used a library of reference spectra in a basis set recorded specifically for the scanner and calibrated using the tissue water signal as an internal standard. The LCModel-fitting algorithm uses the multiple peaks contributing to an individual metabolite spectrum to estimate the tissue content of each metabolite.⁴⁸ The residual signal corresponds to, and is fitted by, additional broad peaks representing unknown metabolites and other factors, such as macromolecular components with short T1 relaxation times. In the analyses, the mean of the left and right hemisphere values for each metabolite was used because the values were highly correlated ($r = 0.45-0.86$; $P < .05$), with no significant differences between them. The MRS parameters used for this study provided robust signals for the control and OCD groups, with mean \pm SD signal-to-noise ratios of 15.94 ± 2.01 and 16.45 ± 2.86 , respectively, and a mean \pm SD full width at half maximum of 0.06 ± 0.01 ppm for both groups. All the metabolites showed good reliability of fit as judged from the mean Cramer-Rao lower bounds. The mean Cramer-Rao lower bounds values (estimates of the SD of the fit) for NAA, creatine + phosphocreatine, choline compounds, myoinositol, and glutamate + glutamine were 5.2, 5.2, 6.0, 8.4, and 10.3, respectively, for controls and 5.0, 4.9, 5.1, 7.2, and 9.1, respectively, for patients with OCD.

Examination of brain behavior-metabolite associations were conducted using Pearson product moment correlations between the percentage signal change value of the BOLD response from the dAC cluster maxima of each individual, behavioral indices of RT interference and response errors, brain metabolites from ¹H-MRS, and symptom severity measures from the Yale-Brown Obsessive-Compulsive Scale.

RESULTS

BEHAVIORAL

Both groups had faster mean \pm SD RTs to the C trials (controls: 865 ± 134.99 milliseconds; OCD patients: 930 ± 110.62 milliseconds) than to I trials (controls: 1203 ± 187.58 milliseconds; OCD patients: 1287 ± 153.39 milliseconds; main effect of condition: $F_{1,35} = 514.50$; $P < .001$). Both groups displayed large and comparable mean \pm SD RT interference effects (controls: 338 ± 85.31 milliseconds; OCD patients: 357 ± 100.57 milliseconds; main effect of group: $F_{1,35} = 2.52$; $P = .12$; task by group interaction: $F_{1,35} = 0.39$; $P = .54$). Both groups made fewer response errors (mean \pm SD) to C trials (controls: $0.47\% \pm 0.77\%$; OCD patients: $2.0\% \pm 2.38\%$) than to I trials (controls: $4.79\% \pm 5.89\%$; OCD patients: $7.39\% \pm 7.18\%$; main effect of condition: $F_{1,35} = 20.92$; $P < .001$). There was no difference in response accuracy between the 2 groups (main effect of group: $F_{1,35} = 3.13$; $P = .09$; task by group interaction: $F_{1,35} = 0.26$; $P = .62$).

FUNCTIONAL

Within Group

Both groups showed the largest task-related activation ($I > C$) in the MFC region encompassing the dAC and the SMA (**Table 2** and Figure 2A and B). This medial cluster of activation was primarily in the dAC for con-

Table 3. Additional Areas of Brain Activation and Relative Group Differences During Task Performance in Patients With OCD and Controls^a

Group and Region	Approximate Area ^b	Cluster Size ^c	Maximum z Score	Anatomical Coordinates		
				x	y	z
Controls (n = 19)						
Superior parietal/occipital	7/19	243	7.52	24	-76	32
Middle frontal gyrus	6	141	7.75	28	-6	60
	6	104	7.17	-28	0	56
	6	40	6.20	20	-6	58
Inferior frontal gyrus	45	32	5.48	36	16	22
Precentral gyrus	6	28	6.50	50	-4	34
Cerebellum	NA	28	5.21	36	-62	-26
Caudate/putamen	NA	25	4.95	-16	4	14
Fusiform gyrus	37	22	5.09	34	-58	-14
OCD (n = 19)						
Superior parietal/occipital	7/19	519	8.69	20	-80	50
Middle frontal gyrus	6	451	8.03	20	-10	60
Caudate/putamen	NA	155	5.94	-16	0	12
	NA	104	5.45	18	-4	12
	NA	35	5.36	34	14	2
	NA	29	4.96	22	8	12
Precentral gyrus	6	110	6.84	48	-4	26
	4	18	5.41	38	-22	56
Insula	NA	24	5.89	-32	20	2
Inferior parietal lobe	40	21	4.78	-42	-34	34
OCD > control						
Superior parietal/occipital	7/19	39	4.39	-10	-86	40
Precentral gyrus	43	15	4.02	-60	-6	12
Middle frontal gyrus	6	14	5.26	24	-14	60
Inferior frontal gyrus	47	10	3.73	-34	30	26
Putamen	NA	10	3.49	-36	-12	4
Control > OCD						
Inferior frontal gyrus	47	11	3.78	-26	26	-14
Fusiform gyrus	37	10	3.69	54	-54	-14

Abbreviations: NA, not applicable; OCD, obsessive-compulsive disorder.

^aThe first listed entry for each group reflects the cluster maxima, and following entries reflect significant, associated subcluster peaks.

^bRefers to approximation of Brodmann areas.

^cRefers to the cluster size in number of activated voxels.

trols and was larger and extended more posteriorly into the pre-SMA and SMA proper for OCD patients.

The MFC activation was part of a larger network of activated regions for controls, including 9 other suprathreshold clusters ($P < 5.87 \times 10^{-9}$ to $P < 1.0 \times 10^{-3}$, clusterwise corrected) in the prefrontal, superior parietal, fusiform, cerebellar, and caudate/putamen regions. For OCD patients, 10 suprathreshold clusters were identified ($P < 2.04 \times 10^{-14}$ to $P < 1.0 \times 10^{-3}$) in regions similar to those displayed by controls, with additional clusters in the insula and inferior parietal areas (Table 3 and Figure 2A and B).

Between Group

The OCD group showed relative hyperactivation ($I > C$) in a cluster located in the SMA. Patients also showed relative hypoactivation in the rAC (Table 2 and Figure 2C and D). This latter finding was contrary to expectations and the results of previous studies, which led us to further investigate patterns of task-related activation and deactivation in both groups. These patterns are displayed in Figure 3 together with the rAC cluster that differentiated the 2

groups. As can be seen, the apparent rAC hypoactivation in OCD patients resulted from greater relative deactivation of this region in the patient group during the high- vs low-conflict trials (ie, the $I > C$ contrast revealed greater relative rAC deactivation in the OCD group).

The OCD group showed relatively greater activation in 5 other regional clusters ($P < 1.0 \times 10^{-3}$), with the largest being in the superior parietal area. Controls showed greater relative activation in 2 other regional clusters ($P < 1.0 \times 10^{-3}$), including the inferior frontal cortex and fusiform gyrus (Table 3 and Figure 2C and D).

Metabolites

Compared with controls, OCD patients showed significant ($P = .01$) decreases in NAA concentrations (a mean reduction of 6.3%) (Table 4). No other group differences were observed for the other metabolites.

Brain-Behavioral Associations

There was no group difference in the mean magnitude of dAC BOLD signal change ($I > C$) for each individual

Table 4. Absolute Metabolite Concentrations Obtained From the dAC^a

Metabolite	OCD (n = 19)	Controls (n = 19)	ANOVA	
			F _{1,36}	P Value
NAA	7.87 ± 0.52	8.40 ± 0.69	7.15	.01
Cho	1.57 ± 0.22	1.52 ± 0.19	0.55	.46
Cr	5.54 ± 0.29	5.52 ± 0.33	0.03	.87
Glx	9.79 ± 1.13	9.98 ± 1.01	0.29	.59
ml	4.05 ± 0.61	3.93 ± 0.48	0.42	.52

Abbreviations: ANOVA, analysis of variance; Cho, choline containing metabolites; Cr, creatine + phosphocreatine; dAC, dorsal anterior cingulate; Glx, glutamate + glutamine; ml, myoinositol; NAA, *N*-acetylaspartate; OCD, obsessive-compulsive disorder.

^aMean ± SD absolute concentrations are expressed as institutional units approximating millimoles per kilogram.

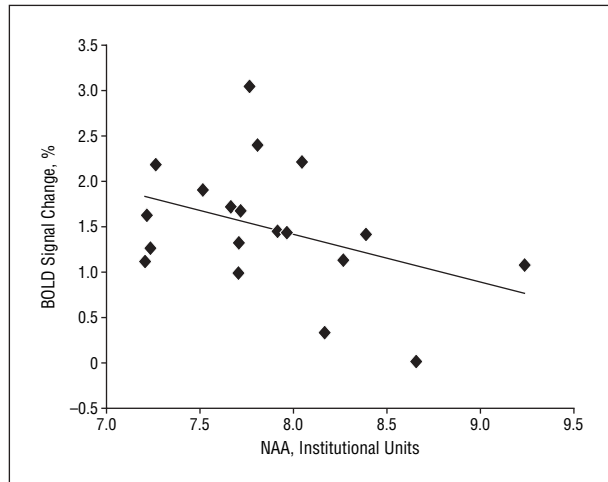


Figure 4. Scatterplot of the relationship between the percentage of blood oxygen level-dependent (BOLD) signal change and *N*-acetylaspartate (NAA) concentrations in the dorsal anterior cingulate of patients with obsessive-compulsive disorder.

participant's maximal cluster of activation (controls: 1.53%; OCD patients: 1.48%; main effect of group: $F_{1,36}=0.06$; $P=.81$). For controls, there was a positive correlation between dAC BOLD signal change and RT interference and total response errors ($r=0.68$, $P=.001$; $r=0.61$, $P=.005$, respectively). Similarly, OCD patients also showed a significant correlation between dAC BOLD signal change and RT interference and response errors ($r=0.46$, $P=.03$; $r=0.47$, $P=.03$, respectively).

As predicted, OCD patients showed a negative association between dAC BOLD signal change and levels of dAC NAA ($r=-0.39$; $P=.05$) (**Figure 4**). This association was not apparent in the control group ($r=-0.10$; $P=.69$). A direct between-group comparison of the 2 correlation coefficients was not significant ($z=-0.88$; $P=.19$) and would require a sample size of 59 to achieve significance at $P<.05$.

Controls showed a trend-level association between behavioral performance and concentrations of myoinositol (RT interference: $r=0.36$, $P=.07$; response errors: $r=0.49$, $P=.02$) that was not apparent in OCD patients (RT interference: $r=0.20$, $P=.21$; response errors: $r=0.02$, $P=.50$). The differences between groups for the 2 correlation coefficients were not significant for the association between myoinositol and response errors ($z=1.46$;

$P=.07$) or for the association between NAA and BOLD signal change ($z=-0.09$; $P=.19$). The sample size required to achieve significance at $P<.05$ would be 24 for the myoinositol-response errors association and 59 for the NAA-BOLD signal change association. No other brain-behavior associations between measures (including symptom severity and depressive symptoms) were identified.

Effects of Psychotropic Treatment

Eleven OCD patients were receiving psychotropic therapy at the time of testing, which may have affected their behavioral performance, brain function, or biochemistry. Reanalysis of the data comparing the 11 medicated OCD patients with the 8 unmedicated patients did not reveal any differences between these 2 OCD groups on measures of task performance, symptom severity, dAC activation, or metabolite concentrations. However, there was a trend for medicated patients to have lower glutamate + glutamine concentrations relative to unmedicated patients (mean ± SD, 9.41 ± 1.17 vs 10.32 ± 0.87 institutional units; $F_{1,13}=3.48$; $P=.08$).

COMMENT

To our knowledge, this is the first study to combine fMRI and ¹H-MRS measurements to investigate the neural correlates of inhibitory control in OCD patients. We found that during performance of a task encompassing inhibitory control processes, OCD patients showed evidence of relative hyperactivation of the MFC during high- vs low-conflict conditions. Although the peak group difference was in the SMA, inspection of the within-group results suggests that this effect resulted from OCD patients activating a more spatially extended dAC/SMA region rather than a focal difference in the SMA alone. Consistent with the predictions, OCD patients showed a reduction in the concentration of dAC NAA that was inversely correlated with the BOLD signal change in the same region. Taken together, these findings provide new evidence for a biochemical basis to the MFC hyperactivation seen in OCD and suggest that this excessive activation may reflect a compensatory response to underlying neuronal abnormalities. This results in patients recruiting a larger region of the MFC (ie, as defined by a greater spatial extent or number of activated voxels) to

perform at appropriate levels. However, given the modest strength of the association between dAC BOLD signal change and dAC levels of NAA, we consider this a novel finding that requires replication.

Similar to other studies^{33,34} of the MSIT in controls and psychiatric patients, both groups in this study showed significant and robust activation of the dAC and the closely connected dorsal premotor regions (pre-SMA/SMA). The relative hyperactivation of the MFC in OCD patients was consistent with the predictions and previous findings.^{11,19,20,31} Overall, the group-level analysis showed that the extent of activation (ie, the number of activated voxels) in OCD patients was approximately twice that in control subjects (747 vs 357 voxels), with no significant group differences in the magnitude of the dAC BOLD response. When taken together with the present findings of decreased NAA levels in the dAC of individuals with OCD, 1 possibility is that to achieve adequate task performance, the patient group recruited a larger cluster of medial wall regions (ie, pre-SMA/SMA) to compensate for biochemical abnormalities in the region. Alternatively, it is possible that the heightened activation of dorsal premotor regions in patients has primary, rather than compensatory, relevance to the pathogenesis of OCD. This would be consistent with other studies of premotor cortex hyperexcitability in OCD patients,⁴⁹⁻⁵² particularly during response-generation tasks.²⁶ In either case, it is clear that further studies are needed to clarify the specificity of functional abnormalities of the MFC in OCD in the context of cognitive and psychomotor demands.

The magnitude of this dAC BOLD response was associated with task performance in both groups and was unrelated to symptom severity in patients. This latter finding contrasts with recent studies^{18,20} that have reported associations between the magnitude of increased dAC activity and severity of illness. The OCD sample was characterized by moderate levels of symptom severity, comparable with these studies, suggesting that differences in symptom severity are unlikely to explain the discrepancy in findings. The present findings are consistent with those of Maltby et al,¹⁹ who investigated more severely ill patients using the go/no-go task of inhibitory control. These researchers found hyperactivity in the MFC, which was unrelated to symptom severity. Future studies using similar tasks in the context of symptom provocation paradigms or different symptom profiles may elicit patterns of activation that are more closely related to symptom measures.⁵³⁻⁵⁷ In addition, studies that focus on specific events (eg, using an event-related fMRI paradigm to model brain activity associated specifically with response errors) may have greater sensitivity in extracting such relationships.^{18,20}

The finding of reduced NAA levels is consistent with the 2 previous ¹H-MRS studies of the AC in OCD.^{22,23} We extended this work by demonstrating a negative correlation, apparent only in patients, between dAC NAA levels and function, as indexed by the BOLD response. N-acetylaspartate is a metabolite produced in neuronal mitochondria and is thought to reflect neuronal density and functional viability.^{24,58} It remains unclear whether reduced levels reflect neuronal loss or a state of (potentially reversible) neuronal dysfunction. Whereas Ebert

et al²² interpreted their findings of reduced NAA levels in OCD patients as evidence of neuronal loss in the AC region, histopathologic data on this issue are lacking. More recently, Jang et al²³ found that the baseline NAA reductions in the dAC of drug-naïve OCD patients could be partly reversed with 12 weeks of citalopram treatment, suggesting that the reduced NAA levels in this study may reflect neuronal dysfunction rather than loss. More specifically, it has been suggested that NAA concentration reflects mitochondrial function.⁵⁹ After its release from neurons, NAA is taken up and hydrolyzed by oligodendrocytes^{60,61} to act as a source of acetyl groups in a variety of metabolic processes, including myelin synthesis,⁶² lipid repair/fatty acid synthesis,⁶³ osmotic regulation,⁶⁴ and anti-inflammatory action.⁶⁵ Reduced dAC NAA levels may, thus, reflect a variety of underlying metabolic and biochemical changes that, when considered in the context of the present findings, suggest that OCD patients have fewer healthy neurons in the region, necessitating the recruitment of adjacent and other task-related brain regions (eg, the SMA, the lateral premotor, and the superior parietal) to perform at levels comparable with controls. This finding is supported by increasing evidence that NAA is critical for optimal cognitive functioning (for reviews, see Yeo et al⁶⁶ and Valenzuela et al⁶⁷). However, the precise nature of the relationships among BOLD signal change, neuronal activity levels, and the physiologic role of NAA in neurons has yet to be fully elucidated. Further investigations of the exact relationship between BOLD signal change (measured by means of fMRI) and NAA concentration (measured by means of ¹H-MRS) in controls or patients with focal brain regions is warranted before more conclusive statements can be made.

As a secondary finding of this study, the whole-brain comparison of OCD patients and controls also showed significantly greater deactivation of the rAC region during the high- vs low-conflict trials. This pattern of task-related deactivation of the rAC and adjacent MFC is a typical finding in functional neuroimaging experiments and is thought to reflect a shift from greater self-referential, or self-directed, mental activity (including subjective anxiety)⁶⁸ to focused attention during task performance.⁶⁹ The increased rAC deactivation seen in OCD patients may reflect abnormally high levels of performance anxiety, which may form a part of the primary functional abnormality of the disorder. However, whether such activity relates to task anticipation or performance appraisal cannot be determined herein. A focus for future studies will be to undertake more detailed characterizations of the baseline default state in OCD patients.

One limitation of the present study was the long duration of illness in patients (average illness duration of approximately 13 years), which means that the effects of prolonged illness and treatment on the findings cannot be excluded. However, note that serotonergic antidepressant medication tends to decrease activation in the MFC of OCD patients,^{70,71} which is, therefore, unlikely to account for the finding of hyperactivation of the MFC in patients. A second limitation was the focus on the MFC, particularly the dAC, meaning that we did not acquire MRS data from other brain regions that are also impor-

tant in the inhibitory control network implicated in OCD (eg, the inferior frontal gyrus).^{2,72} Thus, the anatomical specificity of the MRS findings is unclear. Finally, some of the analyses (eg, comparison of medicated vs unmedicated patients) may have been underpowered and warrant more comprehensive examination. Future studies examining the relationship between neuronal and functional markers of AC integrity in OCD, and how these vary as a function of symptom profile and treatment history, will represent a useful extension to this study.

Taken together, the behavioral, functional, and biochemical measures of the MFC indicate that OCD is associated with increased, presumably compensatory, activation in this region that may be underpinned by reduced neuronal integrity and viability. Future studies should consider the effects of treatment on brain metabolites and differences in brain activation during baseline or control conditions in OCD patients, as these may provide complementary data about the functional neuropathologic features of OCD. Future OCD research should also use tasks that encompass other and more specific aspects of inhibitory control (eg, the stop-signal paradigm)⁷² and further evaluate the state vs trait nature of dysfunction (eg, by examining unaffected relatives of affected patients).

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