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ORIGINAL ARTICLE

Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder

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Brief intensive cognitive-behavioral therapy (CBT) using exposure and response prevention significantly improves obsessive-compulsive disorder (OCD) symptoms in as little as 4 weeks. However, it has been thought that much longer treatment was needed to produce the changes in brain function seen in neuroimaging studies of OCD. We sought to elucidate the brain mediation of response to brief intensive CBT for OCD and determine whether this treatment could induce functional brain changes previously seen after longer trials of pharmacotherapy or standard CBT. [^{18}F]-fluorodeoxyglucose positron emission tomography brain scans were obtained on 10 OCD patients before and after 4 weeks of intensive individual CBT. Twelve normal controls were scanned twice, several weeks apart, without treatment. Regional glucose metabolic changes were compared between groups. OCD symptoms, depression, anxiety and overall functioning improved robustly with treatment. Significant changes in normalized regional glucose metabolism were seen after brief intensive CBT ($P=0.04$). Compared to controls, OCD patients showed significant bilateral decreases in normalized thalamic metabolism with intensive CBT but had a significant increase in right dorsal anterior cingulate cortex activity that correlated strongly with the degree of improvement in OCD symptoms ($P=0.02$). The rapid response of OCD to intensive CBT is mediated by a distinct pattern of changes in regional brain function. Reduction of thalamic activity may be a final common pathway for improvement in OCD, but response to intensive CBT may require activation of dorsal anterior cingulate cortex, a region involved in reappraisal and suppression of negative emotions.

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Introduction

Functional brain imaging studies of patients with obsessive-compulsive disorder (OCD) have repeatedly found elevated cerebral glucose metabolism and blood flow in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), basal ganglia and thalamus[1–7] that decrease with response to treatment with serotonin reuptake inhibitor (SRI) medications[5,8–15] or cognitive-behavioral therapy (CBT).[9,16,17] These findings and others have led to the theory that the symptomatic expression of OCD is mediated by hyperactivity along frontal-subcortical circuits connecting the OFC, caudate, globus pallidus and the medial dorsal nucleus of the thalamus.[18,19]

Clinical response of OCD symptoms usually requires up to 12 weeks of treatment with SRI medications and standard, weekly outpatient CBT.[20] The response of OCD symptoms to SRI medications is thought to depend on the downregulation of terminal serotonin $1d_{\beta}$ receptors and subsequent increase in serotonin release in the OFC, which require at least 8 weeks of SRI administration.[21] However, very little is known about the brain mediation of response to CBT in OCD. Baxter and colleagues[9,16] performed positron emission tomography (PET) scans on a total of 18 OCD patients before and after 8–12 weeks of weekly CBT and found that the 12 patients who responded to treatment showed significant, pre- to posttreatment decreases in normalized right caudate glucose metabolism. A study of 22 treatment-refractory OCD

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patients with Xenon-enhanced computerized tomography before and after 7–8 months of CBT also found significant reductions in right caudate blood flow, as well as smaller decreases in left frontal cortex and thalamus.[17]

However, it is not known if the functional changes in OFC, basal ganglia and thalamus associated with response to prolonged treatment in OCD can be produced or accelerated by an intensive, short-term treatment. If such changes could be demonstrated after only a few weeks of treatment, it would be a significant advance in our understanding of the cerebral mechanisms and time course of treatment response in OCD that could have important clinical implications.

The effectiveness of brief, intensive, daily CBT using exposure and response prevention (ERP) for OCD is well established, and it is considered one of the standard, frontline treatments for OCD.[22] Intensive CBT produces improvement in 60–80% of OCD patients in as little as 4 weeks, with symptom improvement ranging from 50–80%.[23–25] We sought to elucidate the brain mediation of response to brief intensive CBT in OCD by measuring cerebral glucose metabolism with PET before and after 4 weeks of intensive CBT, and to determine whether intensive CBT could rapidly induce the changes previously seen after much longer trials of pharmacotherapy or standard, weekly CBT. We hypothesized that normalized glucose metabolism in OFC, caudate and thalamus would decrease in OCD patients who responded to intensive CBT.

Materials and methods

Subjects

This study was approved by the UCLA Medical Institutional Review Board. Ten adult patients with OCD (six men, four women, mean age 40.6 ± 12.3 years) and 12 normal controls (four men, eight women, mean age 46.4 ± 9.9 years) completed all study procedures. Initially, 12 OCD patients were enrolled, but 2 dropped out during their first week of treatment and therefore did not receive any posttreatment procedures or assessments. All subjects gave informed consent after the procedures and possible side effects were explained by the study physician (SS). Diagnoses were made by a clinical diagnostic interview and confirmed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (SCID).[26] For inclusion into the study, OCD patients needed to have a pretreatment Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[27] score $\geqslant 16$. All subjects were in good physical health. Subjects with major medical conditions, current or recent substance abuse, or any other concurrent Axis I diagnosis were excluded, except for one OCD patient who had comorbid major depressive disorder. Six OCD patients were taking medications, but all medication doses were unchanged for at least 12 weeks prior to starting CBT and were not changed during the study. Six patients were taking SRI medications, three were also taking adjunctive buspirone, two were on adjunctive risperidone and two were on adjunctive clonazepam. None were on mood stabilizers, tricyclics or other antidepressants. Of the twelve OCD patients initially enrolled, seven had received CBT in the past, and six reported prior response to CBT. Controls had scores <6 on all symptom rating scales and no history of any psychiatric disorder or substance abuse, and no current major medical conditions or psychoactive medications.

Symptom severity was rated with the Y-BOCS, Hamilton Depressive Rating Scale (HDRS),[28] Hamilton Anxiety Scale (HAS),[29] Global Assessment Scale (GAS)[30] and Clinical Global Impressions/Improvement scale (CGI),[31] immediately before each subject's pretreatment and posttreatment PET scans, by a trained rater who was not involved in the treatment.

Treatment

All OCD patients had 90-min individual CBT sessions, 5 days a week for 4 weeks, with a therapist with expertise in CBT for OCD (EG). Treatment consisted of ERP with homework exercises, as well as cognitive techniques and mindful awareness. ERP involved graded exposures to both imagined and real situations and stimuli that typically provoked compulsive behaviors or avoidance, accompanied by prevention of compulsions or avoidance. In addition to their daily ERP sessions with the therapist, patients were assigned 4 hours of ERP homework daily, and were instructed that it was imperative for them to follow all instructions and homework assignments carefully, to maximize the benefit of the treatment.

Intensive CBT was conducted for every patient according to a set protocol and sequence.[25] Sessions no. 1–3 included a comprehensive behavioral assessment, education for the patient in self-monitoring of obsessions, compulsions and triggers, and a discussion of the rationale and specific goals of CBT for each individual. A hierarchy of feared and avoided situations and stimuli was created for each patient, using a 'subjective units of distress' scale. Sessions no. 4–15 consisted of *in vivo* and imaginal ERP sessions of gradually increasing difficulty, as well as review of daily homework assignments. Sessions no. 16–20 focused on relapse prevention and included continued ERP practice, cognitive restructuring and assessment of progress. Patients were also taught to recognize internal and external cues that triggered their OCD symptoms (mindful awareness), so that they could anticipate their over-appraisal of fear and anxiety when their obsessions occurred.

Response to treatment was defined *a priori* as a $\geqslant 35\%$ drop in Y-BOCS score and a CGI rating of 'much improved' or 'very much improved,' the standard response criteria used in clinical trials for OCD.[32]

Imaging methods

Cerebral glucose metabolism was measured with [^{18}F]-fluorodeoxyglucose (FDG)-PET in all subjects

before and after 4 weeks of intensive, daily CBT. Normal controls were scanned before and after 10–12 weeks without any treatment, to control for the effects of habituation to the scanning procedures and environment on brain metabolism. PET methods were as detailed in our previous reports.[6,11] In brief, each subject received 5 mCi of FDG while in supine position with eyes and ears open, in a dimmed room with no specific stimuli. Subjects were closely monitored to make sure that they remained awake, lying still without moving or talking during the 40-min FDG-uptake period. No cognitive task was given. PET scanning was performed on a Siemens-CTI EXACT HR1 961 PET tomograph (CTI, Knoxville, TN, USA), yielding 63 transverse sections spaced 3.5 mm apart, with 3.6 mm in-plane spatial resolution, with a 15.5 cm field of view (FOV) in 3D mode. Images were acquired at an angle parallel to the canthomeatal plane and reconstructed using a Hann filter (cutoff frequency 0.5 cycles per pixel) into 128×128 pixel images. Each subject's head was held in a special head holder during scanning. A plastic mask was molded to each subject's face to ensure that his/her head would be in the identical position during the first and second scans. Face masks were held in place with velcro fastens to minimize head motion. Accurate head positioning was ensured by aligning markings on the mask to a low-power neon laser beam. A ^{63}Ge transmission scan was performed for positioning and attenuation correction, prior to injection of FDG. After the 40-min FDG-uptake period, dynamic emission PET scan acquisition occurred over 30 min and was summed (six frames, 5 minutes each).

Each subject also received a 3D magnetic resonance imaging (MRI) scan of the brain without contrast, performed on a Siemens Symphony or Sonata 1.5 Tesla scanner (Siemens, New York, NY, USA), using the following protocol: (1) multiplanar whole-brain scout; (2) axial-oblique whole-brain T2-weighted fast spin echo sequence—0 angle slices parallel to the canthomeatal line in parasagittal view (repetition time (TR) = 2000–2500 ms, echo time (TE) = 90–110 ms, FOV = 25 cm, slice thickness = 3 mm with 0 mm separation between slices, reconstructed to a 256×192 matrix) and (3) axial-oblique whole-brain 3D spoiled-gradient recall parallel to the canthomeatal line (TR = 24 ms, TE = 4 ms, flip angle = 35°, slice thickness = 1.2 mm, yielding 124 slices in a 25 cm FOV; 256×256 matrix). All MRI scans were reviewed by a neuroradiologist (NS). One prospective subject with MRI evidence of structural CNS lesions was excluded from the study.

An MRI-based region-of-interest (ROI) analysis was employed for comparisons of glucose metabolic changes in brain regions chosen *a priori*, based on previous findings in OCD. This method involved coregistering each subject's pre- and posttreatment FDG-PET scans within the 3D orientation of his/her MRI scan, using MedX software (Sensor Systems, Arlington, VA, USA), then manually outlining gray matter ROIs on transaxial planes of the MRI scan, as previously described.[6,11] Cerebrospinal fluid (CSF) and white matter were excluded from the hand-drawn outlines of all gray matter ROIs (Figure 1).

ROIs were drawn by technicians blind to subject identity and diagnosis and were reviewed to ensure interrater reliability. Eight bilateral ROIs were selected *a priori*, based on previous associations with OCD symptoms or response to treatment: dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), OFC, dorsal anterior cingulate cortex (dACC), ventral anterior cingulate cortex (vACC), caudate nucleus, putamen and thalamus. Boundaries for these regions were defined using standard atlases.[33,34] The DLPFC consisted of the dorsal half of the middle frontal gyrus, while the VLPFC consisted of its ventral half.[35] The OFC ROI included the medial and lateral orbital gyri, the orbital part of the inferior frontal gyrus and the most inferior part of frontal pole, but excluded gyrus rectus. The ACC was divided evenly into dorsal and ventral portions. The horizontal midplane of the genu of the corpus callosum divided the dACC from the vACC. The cingulate sulcus was the dorsal boundary of the dACC; and the callosal sulcus was the ventral boundary of the vACC. The vACC ROI thus included subgenual cingulate cortex but not gyrus rectus. The caudate ROI included the entire head but excluded the body and tail of the caudate nucleus. Both supratentorial hemispheres were also drawn.

ROIs drawn on each subject's MRI were transferred to his/her coregistered, first and second PET scans. Ratios of each ROI normalized to ipsilateral hemispheric glucose metabolism (ROI/Hem) were calculated. This technique took intersubject neuroanatomical variability into account and ensured that pre- and posttreatment values for a given ROI were measured in exactly the same neuroanatomical volume.

Statistical methods

The data were first screened for distributional properties, outliers and missing values. No variables were rejected by this process. Only data from subjects who completed the study were analyzed for pre- to posttreatment changes. Demographic variables were compared between the two subject groups: OCD patients ($n = 10$) and normal controls ($n = 12$). Age was compared between the two groups with *t*-tests (two-tailed) for independent samples, while the proportion of men in each group was compared with a Fisher's exact test (SPSS 11.0). Symptom severity scores (Y-BOCS, HDRS, HAS and GAS) were compared between the two groups with an omnibus repeated-measures multivariate analysis of variance (MANOVA), using diagnostic group as the between-subject factor, time (before vs after treatment) as the within-subjects factor, and symptom severity scores as the dependent variables.

ROI/Hem data were analyzed to identify significant pre- to posttreatment changes in normalized regional

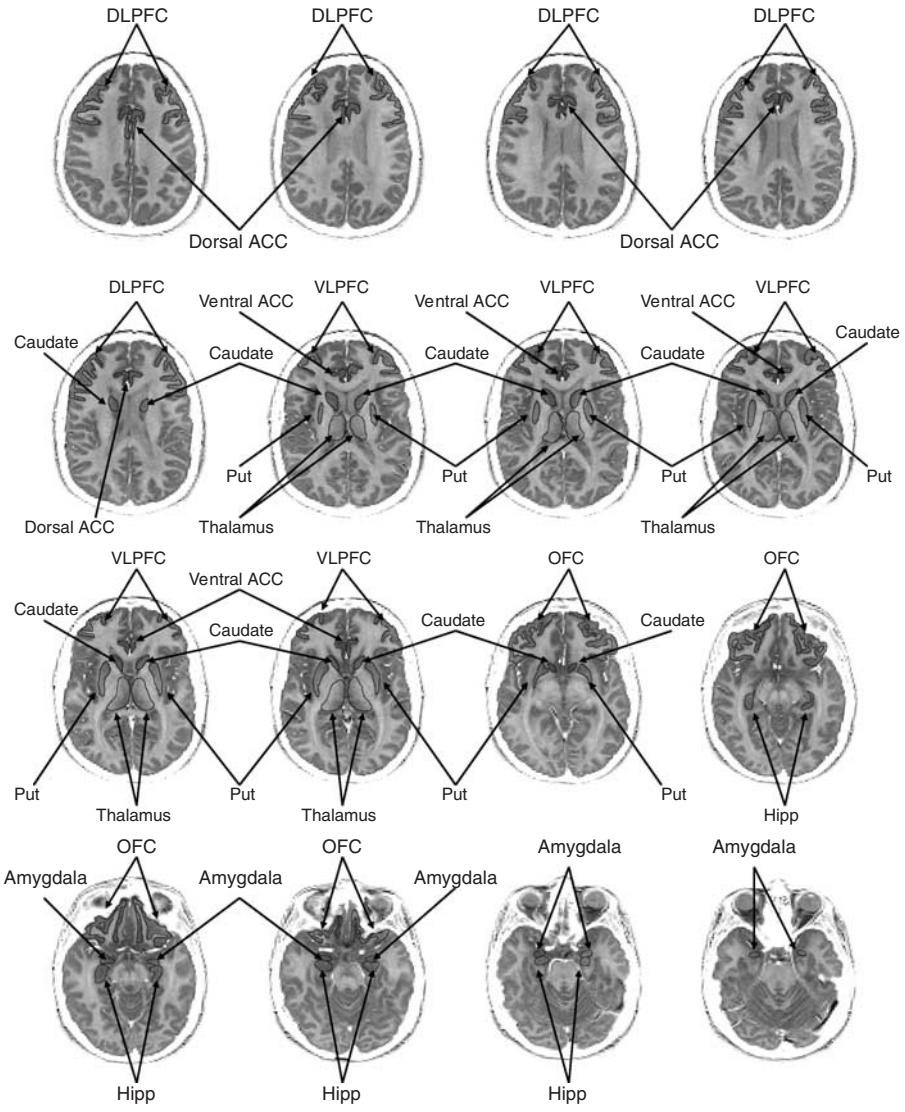

Figure 1 Regions of interest (ROIs) drawn on magnetic resonance imaging (MRI) scans. ROIs outlining gray matter structures were manually on transaxial planes of the MRI scan of every subject. Cerebrospinal fluid (CSF) and white matter were excluded from the outlines of all ROIs. Bilateral ROIs were selected *a priori*, based on previous associations with OCD symptoms or response to treatment. Hippocampus and amygdala ROIs were not included in the data analysis but are shown here as neuroanatomical reference points. Both supratentorial hemispheres were also drawn. Each subject's ROIs were transferred to their coregistered, first and second positron emission tomography (PET) scans, for calculation of glucose metabolic rates in their specific regional volumes. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; ACC, anterior cingulate cortex; Put, putamen; Hipp, hippocampus.

cerebral glucose metabolism. Pre- and posttreatment ROI/Hem values were compared between the two groups with an omnibus repeated-measures MANOVA, using diagnostic group as the between-subject factor, time (before vs after treatment) as the within-subjects factor, and ROI/Hem values as the dependent variables. Wilk's λ statistic for the interaction effect of diagnostic group $\times$ time was used to determine whether OCD patients and controls had significantly different, pre- to posttreatment changes in normalized regional cerebral glucose metabolism across all 16 ROIs tested. Univariate repeated-measures analyses of variance were then performed for only those ROIs found to have significant diagnosis $\times$ time interactions in the omnibus MANOVA, to determine which ROIs accounted for the significant difference between groups ($P < 0.05$). The use of the omnibus MANOVA reduced the likelihood of Type II error from multiple comparisons.

Partial correlations, covarying for pretreatment HDRS-17 score, were calculated between pre- to posttreatment changes in Y-BOCS scores and pre- to posttreatment changes in ROI/Hem values in the 10 OCD patients, to identify significant associations between improvement in OCD severity and changes in regional brain activity.

Results

OCD patients did not differ significantly from controls in age (Student's $t = 1.2$, $P = 0.23$) or male:female ratio (Fisher's exact test, $P = 0.39$).

Treatment response

OCD patients responded very well to intensive CBT, with robust improvements on all outcome measures. OCD patients had highly significant, pre- to posttreatment decreases on the Y-BOCS, HDRS and HAS, and significant increases in GAS scores, compared to untreated controls (all $P < 0.001$; Table 1). Nine of the ten OCD patients who completed treatment met criteria for classification as responders to intensive CBT. Normal controls did not show significant changes on any symptom rating scale.

Changes in relative regional cerebral glucose metabolism

Pre- to posttreatment changes in normalized cerebral glucose metabolism differed significantly between OCD patients and controls. A significant interaction effect of diagnosis × time was found in the omnibus repeated-measures MANOVA comparing changes in all pre- to posttreatment ROI/Hem values in OCD patients vs controls (Wilk's $\lambda = 0.06$, $F_{16,5} = 5.0$, $P = 0.04$). Four regions accounted for this difference between groups: left dACC (time × diagnosis F = 4.8, d.f. = 1,20, $P = 0.04$), right dACC (F = 4.7, d.f. = 1,20, $P = 0.04$), left thalamus (F = 5.3, d.f. = 1,20, $P = 0.03$) and right thalamus (F = 4.5, d.f. = 1,20, $P = 0.047$). Compared with controls, OCD patients showed significant decreases in bilateral thalamus/Hem values but had a significant increase in right dACC/Hem (Table 2). Controls, on the other hand, showed a significant decrease in left dACC/Hem values, compared to OCD patients.

In OCD patients, there was a significant inverse correlation between change in Y-BOCS scores and change in right dACC/Hem values (partial $r = -0.76$, d.f. = 7, $P = 0.02$), indicating a strong association between improvement in OCD symptoms and increasing normalized glucose metabolism in right dACC. No other significant correlations between symptom improvement and changes in regional brain activity were found.

Table 1 Clinical variables of study population before and after treatment

Clinical variable	*OCD patients* (n = *10*)	*Normal controls* (n = *12*)	Repeated-measures MANOVA (*Diagnosis × time*)	
			F (d.f. = 20)	P
Y-BOCS				
Pre	25.2 (±3.3)	0.4 (±1.4)		
Post	11.0 (±5.1)	0.2 (±0.6)	265.9	<0.001
HDRS-17				
Pre	11.8 (±5.4)	1.3 (±1.2)		
Post	6.1 (±6.5)	2.1 (±2.1)	29.6	<0.001
HDRS-28				
Pre	17.7 (±7.0)	1.6 (±1.6)		
Post	8.0 (±5.9)	3.0 (±2.9)	51.7	<0.001
HAS				
Pre	13.7 (±7.0)	1.8 (±1.8)		
Post	6.3 (±5.3)	2.6 (±2.4)	28.5	<0.001
GAS				
Pre	51.9 (±5.1)	86.8 (±3.9)		
Post	64.5 (±7.3)	84.7 (±6.1)	70.6	<0.001

Abbreviations: GAS, Global Assessment Scale; HAS, Hamilton Anxiety Scale; HDRS, Hamilton Depressive Rating Scale; MANOVA, multivariate analysis of variance; OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.
Mean ± s.d.

Discussion

There were two novel findings of this study. First, significant changes in brain activity were achieved after just 4 weeks of intensive CBT, much faster than previously seen with SRI treatment or standard, weekly CBT. Second, brief intensive CBT resulted in a unique pattern of changes in normalized regional glucose metabolism: significant increases in dACC activity that correlated with improvement in OCD symptoms, accompanied by significant declines in bilateral thalamic activity. This pattern suggests that intensive CBT shares some common sites of anti-obsessional action with SRIs but has different effects in the dACC. Reduction of thalamic activity may be a final common pathway to improvement in OCD symptoms, regardless of the treatment modality used, but CBT may lead to this end result through very different mechanisms and loci of action than pharmacotherapy.

The declines in thalamic activity seen with brief intensive CBT in this study replicated the results of several previous functional neuroimaging studies of OCD treatment using pharmacotherapy[9,11,15] or neurosurgery.[36,37] Taken together, the results of these studies suggest that reduction of thalamic activity, and a resultant decrease in thalamocortical excitation,[18] may represent a final common pathway to response to a variety of different treatments in nondepressed OCD patients.[19,38] As in many prior studies,[5,8–10,12,17,36] the magnitude of change in thalamic metabolism did not correlate with the degree of response of OCD symptoms to intensive CBT. This suggests that while decreasing thalamic activity may be a marker of response to treatment in OCD it is not specifically related to the extent of symptom improvement.

However, the increase in dACC activity seen after brief intensive CBT was opposite to changes

Table 2 Pre- and posttreatment region/hemisphere glucose metabolic ratios

Region of interest	*OCD patients*		*Normal controls*	
	Pretreatment	*Posttreatment*	*First scan*	*Second scan*
Right amygdala	0.75 ± 0.04	0.74 ± 0.05	0.77 ± 0.05	0.78 ± 0.05
Left amygdala	0.80 ± 0.07	0.78 ± 0.06	0.81 ± 0.05	0.81 ± 0.05
Right caudate	1.11 ± 0.08	1.12 ± 0.07	1.16 ± 0.08	1.16 ± 0.06
Left caudate	1.07 ± 0.09	1.07 ± 0.06	1.15 ± 0.05	1.14 ± 0.07
Right dACC[a]	1.03 ± 0.08	1.05 ± 0.08	1.07 ± 0.05	1.06 ± 0.06
Left dACC[a]	1.05 ± 0.12	1.06 ± 0.09	1.08 ± 0.11	1.05 ± 0.11
Right DLPFC	1.17 ± 0.08	1.19 ± 0.09	1.21 ± 0.07	1.21 ± 0.07
Left DLPFC	1.19 ± 0.08	1.20 ± 0.09	1.22 ± 0.08	1.22 ± 0.08
Right hippocampus	0.80 ± 0.05	0.80 ± 0.05	0.83 ± 0.05	0.84 ± 0.05
Left hippocampus	0.84 ± 0.04	0.85 ± 0.04	0.86 ± 0.04	0.85 ± 0.03
Right OFC	1.03 ± 0.07	1.02 ± 0.06	1.05 ± 0.07	1.05 ± 0.10
Left OFC	1.05 ± 0.05	1.05 ± 0.06	1.05 ± 0.09	1.05 ± 0.10
Right putamen	1.30 ± 0.10	1.30 ± 0.09	1.35 ± 0.09	1.34 ± 0.07
Left putamen	1.32 ± 0.12	1.33 ± 0.08	1.36 ± 0.10	1.36 ± 0.07
Right thalamus[a]	0.99 ± 0.08	0.95 ± 0.07	1.01 ± 0.04	1.01 ± 0.04
Left thalamus[a]	1.01 ± 0.09	0.98 ± 0.08	1.02 ± 0.05	1.04 ± 0.05
Right vACC	1.08 ± 0.08	1.10 ± 0.08	1.09 ± 0.04	1.09 ± 0.05
Left vACC	1.11 ± 0.12	1.10 ± 0.10	1.13 ± 0.07	1.13 ± 0.07
Right VLPFC	1.07 ± 0.11	1.08 ± 0.09	1.12 ± 0.09	1.11 ± 0.11
Left VLPFC	1.10 ± 0.12	1.09 ± 0.11	1.12 ± 0.05	1.12 ± 0.09

Abbreviations: dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; vACC, ventral anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex.
[a]Repeated-measures MANOVA, diagnosis × time interaction, $P < 0.05$.

sometimes seen with pharmacotherapy of OCD. While the majority of pre- and post treatment functional neuroimaging studies published to date found no changes in cingulate activity with pharmacotherapy of OCD (see Saxena *et al*.[39] for review), three of the nine pre- to posttreatment PET studies[5,9,12] and three of the eight pre- to posttreatment single-photon emission computed tomography studies[14,40,41] found significant decreases in cingulate activity in OCD responders to SRI treatment. Thus, decreasing cingulate activity may sometimes be associated with improvement in OCD symptoms but does not appear to be a necessary mechanism of action for treatment response. Instead, the functional changes most strongly associated with treatment response in OCD are decreases in activity in the right OFC,[8,10–13,36,37,42,43] right caudate[9,11,12,14,16,17,36,37,42] and thalamus.[9,11,15,36,37]

In contrast to the effects of pharmacotherapy on brain function, enhancement of dACC activity may be a primary mechanism of action of CBT for OCD. Treatment with CBT appears to enhance dACC activation in OCD patients during certain cognitive tasks.[44,45] Moreover, a significant increase in glucose metabolism in the dACC was seen in responders to CBT for major depression.[46] Taken together with these prior findings, our results suggest that dACC activation might be a common mechanism of action required for response to CBT across disorders.

The dorsal part of the ACC includes two anatomically and functionally distinct subregions: the perigenual ACC and the anterior middle cingulate cortex (aMCC) (see Vogt *et al*.[47] for nomenclature and definitions of subregions). Our dACC ROI encompassed a relatively large section of cingulate cortex that included the aMCC and the superior half of the perigenual cingulate cortex. Different subdivisions of the cingulate cortex clearly have different roles.[47–49]

The aMCC, described as limbic motor cortex that governs response selection,[47] has been shown to be involved in conscious regulation of emotion. The aMCC is activated by several cognitive tasks that are required and emphasized in CBT for OCD: selective attention to one's own emotional responses,[50,51] mindful awareness of one's own emotional state, reappraisal of negative stimuli,[52] and suppression of arousal[53] and negative affect.[54] Efferent projections from the aMCC to the amygdala appear to modulate amygdala activity.[55] Activity in the aMCC is positively correlated with the magnitude of decrease in negative affect when subjects reappraise their emotional responses to negative photographs,[52,54] and is negatively correlated with left amygdala activity when subjects label threatening photographs.[56] Thus, in OCD patients, an increase in aMCC activity after intensive CBT could represent an improved ability to reappraise and suppress negative emotional responses, perhaps by inhibiting exaggerated amygdala responses to stimuli that previously provoked obsessional fears and compulsive urges.[57–59]

Other functions of the aMCC include monitoring response conflict, error detection, focused attention,

executive control and willed motivation.[55,60–62] Nakao *et al*.[44] found that after treatment with fluvoxamine or CBT, OCD patients activated the right aMCC and left posterior MCC during a Chinese version of the Stroop task. Enhanced posttreatment aMCC activity may, therefore, also reflect improved cognitive functioning associated with response to OCD treatment.

One surprising result was the lack of significant pre- to posttreatment changes in normalized caudate or OFC metabolism in the OCD patients. This may be because 6 of the 10 OCD patients were on medications, which likely influenced pretreatment caudate and OFC activity and may have precluded further major metabolic changes in these regions. Indeed, pretreatment normalized glucose metabolism in bilateral caudate and right OFC was somewhat lower in the OCD group than in the controls, suggesting that the OCD patients' previous and ongoing medications may have already decreased activity in these brain regions prior to their entry into the present study. However, no subject in this study had any change in medications or doses for at least 12 weeks prior to their first PET scan and initiating intensive CBT, nor were medication changes allowed during the CBT treatment period. Therefore, it is very unlikely that medication effects alone could account for the specific pre- to post-CBT changes in brain activity seen in this study. The fact that the six medicated OCD patients had not adequately responded to pharmacotherapy and still had moderate to severe OCD symptoms at study entry suggests that they might represent a relatively medication-refractory group that might be neurobiologically different from more SRI-responsive OCD patients.[63] However, approximately 50% of all OCD patients have similarly inadequate responses to SRI medications,[20,64] indicating that it is more the rule than the exception. So our sample is likely quite representative of the range of SRI responsivity found in among OCD patients in the 'real world.' Nonetheless, regional brain metabolic responses to CBT in medicated patients may well be different than those of unmedicated patients.

Another possibility is that striatal changes may take a longer time to manifest and may be preceded by changes in the aMCC and thalamus in patients treated with intensive CBT. The two previous functional imaging studies of CBT effects on brain activity in OCD, which both found decreased caudate activity after CBT, were of 12 weeks'[9,16] and 7–8 months'[17] durations, respectively, whereas the present study lasted only 4 weeks. Neither of those prior studies found pre- to posttreatment changes in OFC activity, suggesting that CBT might not significantly alter OFC function in OCD. Our findings suggest that activation of the aMCC occurs rapidly with intensive CBT and is strongly correlated with treatment response after 4 weeks. Unfortunately, the Nakatani *et al*.[17] study did not measure cingulate activity, so it remains unknown whether prolonged weekly CBT produces similar effects in this region. Future studies that measure brain activity with multiple, serial scans during and after treatment will be required to establish the dynamics and chronological pattern of regional brain responses to CBT.

This study had several limitations. The sample size was relatively small. One OCD patient in this study had comorbid major depression, but exclusion of this patient's data from analysis of changes in regional brain metabolism did not significantly change the results. The inter-scan interval for controls was longer than for OCD patients. However, there is no reason to suspect that the regional cerebral metabolic changes seen in controls would have been significantly different if the period between their first and second scans was shorter. The decrease in ACC metabolism seen in controls replicated the findings of several prior PET studies[65–68] and likely reflects habituation to the scanning environment and procedures.[67]

However, this study also had several strengths that afford confidence in its findings. All OCD patients were treated by the same CBT therapist (EG), eliminating confounds from inter-therapist variance in treatment. Medication changes were not allowed for 12 weeks prior to the first PET scan, nor during the 4 weeks of intensive CBT between the first and second PET scan. As in prior studies of intensive CBT for OCD, a high proportion of patients in this responded to treatment. Of 12 OCD patients initially enrolled, only two dropped out, and nine of the ten completers were responders to brief intensive CBT. This response rate is quite typical for prior studies of intensive, daily CBT for OCD.[23–25] For example, Foa *et al*.[25] also studied OCD patients treated with intensive ERP for 4 weeks. Their intent-to-treat and completer response rates were 62 and 86%, respectively, similar to our response rates.

MRI-based localization of ROIs for each subject was used to measure regional activity in brain structures chosen *a priori*, and to identify significant changes in regional activity, rather than relying on whole-brain voxel-based methods that may not account for structural neuroanatomical abnormalities and variability that are present in OCD.[38] Several studies have found systematic errors in the localization of regional cerebral metabolic abnormalities when voxel-based methods were used, compared to individual subject MRI-based ROI methods.[69,70] Such errors are often due to failed spatial alignment of small structures, such as the caudate nucleus and hippocampus, which are prone to high anatomic variability.[69] Our ROI method also partially corrected for regional atrophy, because CSF and white matter were excluded from the outlines of all gray matter structures, and ensured that pre- and posttreatment values for each ROI were measured in exactly the same neuroanatomical volume in each subject. Symptom severity was assessed in each subject with standardized rating scales immediately prior to their pre- and posttreatment PET scans, so that the brain activity measured on the PET scan would reflect the current symptomatic state of the subject. Thus, we were able to correlate pre- to posttreatment changes in symptom

severity with corresponding changes in regional cerebral glucose metabolism.

In conclusion, the findings of this study suggest that the rapid response of OCD to brief intensive CBT may be mediated by a distinct pattern of functional neuroanatomical changes: decreases in thalamic activity accompanied by an increase in dACC activity that correlates with the degree of symptomatic improvement. Decreasing thalamic activity may represent a common pathway to response of OCD symptoms to a variety of treatment modalities, while activation of the dACC may be a mechanism of action required for response to CBT across mood and anxiety disorders.

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