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ORIGINAL ARTICLE

Predicting response to cognitive behavioral therapy in contamination-based obsessive–compulsive disorder from functional magnetic resonance imaging

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Background. Although cognitive behavioral therapy (CBT) is an effective treatment for obsessive–compulsive disorder (OCD), few reliable predictors of treatment outcome have been identified. The present study examined the neural correlates of symptom improvement with CBT among OCD patients with predominantly contamination obsessions and washing compulsions, the most common OCD symptom dimension.

Method. Participants consisted of 12 OCD patients who underwent symptom provocation with contamination-related images during functional magnetic resonance imaging (fMRI) scanning prior to 12 weeks of CBT.

Results. Patterns of brain activity during symptom provocation were correlated with a decrease on the Yale–Brown Obsessive Compulsive Scale (YBOCS) after treatment, even when controlling for baseline scores on the YBOCS and the Beck Depression Inventory (BDI) and improvement on the BDI during treatment. Specifically, activation in brain regions involved in emotional processing, such as the anterior temporal pole and amygdala, was most strongly associated with better treatment response. By contrast, activity in areas involved in emotion regulation, such as the dorsolateral prefrontal cortex, correlated negatively with treatment response mainly in the later stages within each block of exposure during symptom provocation.

Conclusions. Successful recruitment of limbic regions during exposure to threat cues in patients with contamination-based OCD may facilitate a better response to CBT, whereas excessive activation of dorsolateral prefrontal regions involved in cognitive control may hinder response to treatment. The theoretical implications of the findings and their potential relevance to personalized care approaches are discussed.

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Key words: Cognitive behavioral therapy, contamination, fMRI, obsessive–compulsive disorder, predictors, symptom dimensions, washing.

Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric condition that affects between 0.3% and 3.1% of the general population (Fontenelle *et al.* 2006). The onset of OCD is usually gradual and, if left untreated, the course can be chronic, resulting in lower quality of life (Olatunji *et al.* 2007). Fear of contamination, the most common presentation of OCD, can be complex, difficult to control and extraordinarily persistent (Rachman, 2004). Contamination fear in OCD is often characterized by overt compulsive acts of cleaning, washing and disinfecting, which function to alleviate distress from obsessions about contact (real or perceived) with stimuli perceived to be dirty, impure or infectious. Although effective treatments can help a large proportion of patients with OCD, at least 40% remain unimproved with medications and/or cognitive

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behavioral therapy (CBT) (Greist *et al.* 1995; Mataix-Cols *et al.* 2002).

CBT that focuses on exposure and response prevention (ERP) is currently the psychological treatment of choice for OCD (NICE, 2006). Given that some patients do not respond to CBT, various characteristics of the individuals presenting for treatment may influence its efficacy to some degree. Several studies have attempted to identify variables that predict treatment outcome in OCD (Olatunji *et al.* 2012). However, the identification of reliable predictors of treatment outcome in OCD remains elusive. In fact, most of the variables examined to date (age, gender, severity of symptoms, depression, personality disorder, symptom duration, pure obsessiveness, and most symptom dimensions) have not been consistently predictive of improvement with CBT in OCD (Foa & Goldstein, 1978; Christensen *et al.* 1987; Basoglu *et al.* 1988; van Balkom *et al.* 1994; Steketee & Shapiro, 1995; Mataix-Cols *et al.* 2002).

Another important line of research has focused on the identification of neural biomarkers that may predict pharmacological treatment outcomes. For example, resting-state positron emission tomography (PET) studies have found that decreased pre-treatment regional cerebral blood flow (rCBF) in the orbitofrontal cortex is associated with a better response to serotonin reuptake inhibitors (Swedo *et al.* 1992; Brody *et al.* 1998; Saxena *et al.* 1999; Rauch *et al.* 2002). Studies have also found that increased rCBF in the posterior cingulate gyrus correlates with clinical improvement after treatment with cingulotomy and fluvoxamine (Rauch *et al.* 2001, 2002). Higher pre-treatment rCBF in the right caudate nucleus has also been found to be significantly associated with improvement in OCD symptoms with paroxetine (Saxena *et al.* 2003). A more recent extension of this body of research found that pre-treatment activation in the right cerebellum and the left superior temporal gyrus predicted subsequent reduction in OCD symptoms with fluvoxamine (Sanematsu *et al.* 2010).

However, few studies have examined neuroimaging predictors of response to CBT in OCD. In an earlier PET study, Brody *et al.* (1998) found that increased rCBF in the left orbitofrontal cortex correlated positively with clinical improvement. A recent structural neuroimaging study found that pre-treatment gray matter volume within the right medial prefrontal cortex was associated positively with symptom improvement following CBT, whereas gray matter volume within the right middle lateral orbitofrontal cortex was associated negatively with improvement after treatment with fluoxetine (Hoexter *et al.* 2013). Taken together, these preliminary findings suggest that it may be possible to identify neural biomarkers of response to different treatment modalities in OCD. This may lead to more targeted and personalized treatment approaches, fewer treatment failures and better overall outcomes. Clearly, this research is in its infancy and more research is required before such ambition can become a reality. For example, prior research does suggest that different OCD symptom dimensions are mediated by distinct neural processes (Mataix-Cols *et al.* 2004; van den Heuvel *et al.* 2009; Harrison *et al.* 2013). This suggests that currently available studies may be limited by use of a heterogeneous sample of patients with OCD, given that different OCD symptom dimensions may have different neural predictors of treatment outcome.

The present study examined the neural correlates of response to CBT among patients with contamination-based OCD during symptom provocation by visual exposure using functional magnetic resonance imaging (fMRI). As different symptom dimensions of OCD may derive from distinct neural systems (Rauch *et al.* 1998; Phillips *et al.* 2000; Mataix-Cols *et al.* 2003, 2004; van den Heuvel *et al.* 2009), only patients with predominant contamination/washing symptoms were examined to limit the potential confound associated with variability in OCD symptom dimensions. It was predicted that brain regions identified as dysfunctional in prior neuroimaging studies on fear and anxiety more broadly and contamination-based OCD more specifically (Schienle *et al.* 2005; Husted *et al.* 2006) might provide predictive information about CBT treatment response. Based on emotional processing theory (EPT), which postulates that physiological activation is a crucial requirement for extinction learning during exposure-based treatments for anxiety disorders (Foa & Kozak, 1986), it was predicted that greater activation in limbic and paralimbic brain regions during symptom provocation would be associated with better outcomes after CBT.

Method

Participants

Participants were 12 patients with primary OCD and contamination fears who completed an open trial of CBT at the in-patient CBT unit of Bethlem Royal Hospital, London, UK (n=11) or at an out-patient clinic in West London (n=1). Although only patients with predominantly contamination and cleaning symptoms were included in the present study, most had other concurrent symptoms [obsessions: aggressive (55%), sexual (18%), religious (27%), symmetry (55%), somatic (46%), hoarding (27%); compulsions: checking (82%), repeating (73%), counting (36%), arranging (36%), hoarding (27%)]. The Ethics Committee (Research) of

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the Maudsley Hospital and Institute of Psychiatry approved the study protocol and all subjects signed an informed consent form prior to their participation. Axis I and II diagnoses were made according to DSM-IV criteria by a psychiatrist or nurse therapist using the SCID-CV (First *et al*. 1996). Patients with co-morbid diagnoses other than psychosis or substance abuse were not excluded provided that OCD was the main problem for which treatment was sought. Exclusion criteria were brain injury, any neurological condition, psychosis or substance abuse.

Nine (75%) patients had one or more co-morbid Axis I disorders, and four (33.3%) met the criteria for one or more Axis II disorders. Table 1 shows the demographic and clinical characteristics of the sample. All patients were substantially symptomatic at the time of the scan as indicated by scores on the Yale–Brown Obsessive Compulsive Scale (YBOCS; mean=32.25, S.D.=5.73), a rating scale designed to assess the severity of symptoms in patients with OCD (Goodman *et al*. 1989*a*, *b*). Depression symptoms were mild to moderate among OCD patients at the time of the scan as indicated by scores on the Beck Depression Inventory (BDI; mean=23.25, S.D.=11.10), one of the most widely used instruments for measuring the severity of depression (Beck *et al*. 1961).

Treatment and outcome measures

The patients were scanned before an open trial of CBT. Consistent with a cognitive approach, ERP strategies were used as a means of helping the patient discover the way in which neutralizing behavior acts to maintain their beliefs and the associated discomfort, and that stopping such behaviors is beneficial (Salkovskis, 1999). The majority of the participants (n=11) received CBT during in-patient treatment with a maximum duration of 12 weeks, each receiving approximately 24 individual treatment sessions. These treatment sessions were more frequent during the first few weeks of admission. One additional patient was treated with ERP techniques guided by a telephone-accessed computer system (Greist *et al*. 2002) plus telephone clinician support over eight sessions lasting a total of 90 min. The outcome measures included the percentage decrease in YBOCS and BDI scores from pre- to post-treatment.

Most patients (n=8, 66.7%) had been on stable doses of medications for at least 6 weeks before starting CBT and, for the most part, these medications were maintained stable during the CBT trial. Doses of benzodiazepines were reduced in two cases as part of a withdrawal schedule. One previously unmedicated patient was started on sertraline up to 150 mg/day for 2 weeks before discharge as he had failed to improve with CBT. This patient was not excluded from the study because 2 weeks are usually considered insufficient for a sustained clinical response, as was indeed confirmed in this case (i.e. no clinical response was observed during this 2-week period).

Symptom provocation paradigm

All subjects participated in a 6-min symptom provocation task in which they viewed 10 alternating blocks (each lasting 60 s) of contamination-related or neutral images before undergoing CBT. These images are well validated and have been used effectively in prior research (Mataix-Cols *et al*. 2003, 2004, 2009). The order in which the contamination and neutral blocks were presented was balanced between subjects. Prior to the presentation of each set of images, participants listened to the following pre-recorded instructions through high-fidelity pneumatic headphones: 'Imagine that you must come into contact with what's shown in the following pictures without washing yourself afterwards' (contamination), and 'Imagine that you are completely relaxed while looking at the following scenes' (neutral). After each set of images, another pre-recorded sound file of the question 'How anxious do you feel?' was played and participants rated their subjective anxiety on a scale from 0 (no anxiety) to 8 (extreme anxiety). Previous research has shown that this provocation procedure is highly effective in provoking contamination-related anxiety and that the patients' severity of contamination-related fears correlates with the degree of provoked anxiety during this procedure (Mataix-Cols *et al*. 2009).

Image acquisition

Gradient-echo echo-planar imaging (EPI) was performed on a GE Signa 1.5-T Neuro-optimized MR system (General Electric, USA) at the Maudsley Hospital, London. One hundred T2*-weighted whole-brain volumes depicting blood oxygen level-dependent (BOLD) contrast, consisting of 16 slices oriented according to the bicommissural plane (thickness 7 mm, 0.7-mm gap), were acquired over 6 min [repetition time (TR)=2.0 s, echo time (TE)=40 ms, field of view (FOV)=24 cm, flip angle=70°, 64×64 matrix size]. This EPI dataset provided almost complete brain coverage.

In each 20-s stimulus presentation block, subjects viewed either 10 provocative or 10 neutral pictures. Each picture was presented for 1950 ms, with an interstimulus interval of 50 ms. Ten whole-brain volumes were acquired during each block. Each block was followed by: (*a*) an 8-s period of complete silence during which subjects were asked to rate their level of anxiety; (*b*) a further 8-s period during which the subjects listened to a sound file containing instructions pertinent

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Table 1. *Demographic and clinical characteristics of 12 patients with OCD before and after a trial of CBT*

Subject	Sex	Age (years)	Handedness	Illness duration (years)	Axis I co-morbidity	Axis II co-morbidity	Pre-treatment YBOCS	Post-treatment YBOCS	% Improvement on YBOCS	Pre-treatment BDI	Post-treatment BDI	% Improvement on BDI
1	M	23	Right	Since childhood	SP, MD, BDD	AV, DE, OC, DEP, NA, BO	21	20	5	23	28	–22
2	M	24	Right	10–15	None	None	37	30	19	14	20	43
3	F	41	Right	10–15	SOP	AV, DE, OC	39	28	28	29	19	34
4	F	34	Left	Since childhood	MD	AN	36	17	53	37	7	81
5	F	33	Right	10–15	None	None	33	15	55	23	18	22
6	F	39	Right	> 20	None	None	30	24	20	29	23	21
7	M	18	–	–	SP	None	34	28	18	8	12	–50
8	M	36	Right	31	None	None	27	14	48	9	17	–88
9	F	53	Right	10–15	None	None	40	35	12	38	26	32
10	M	37	Right	10–15	None	AV, OC, DEP	31	29	6	38	22	42
11	F	27	Right	5–10	None	None	34	24	29	12	7	42
12	M	22	Right	–	None	None	25	19	24	19	12	37

OCD, Obsessive–compulsive disorder; CBT, cognitive behavioral therapy; YBOCS, Yale–Brown Obsessive Compulsive Scale; BDI, Beck Depression Inventory; M, male; F, female; SOP, social phobia; GAD, generalized anxiety disorder; MD, major depressive episode; PD, panic disorder without agoraphobia; SP, specific phobia; BDD, body dysmorphic disorder; AG, agoraphobia without panic; AV, avoidant; OC, obsessive–compulsive; DEP, depressive; DE, dependent; BO, borderline; PA, paranoid; NA, narcissistic; AN, antisocial; –, missing information.

to the next stimulus block. Four 'dummy volumes' were excited during this 8-s period using the same radio frequency envelope and gradient slice selection parameter, with the same repetition time of 2 s to allow the magnetization to reach an equilibrium amplitude prior to the next period of data acquisition. The frequency-encoding gradient was turned off during this period to minimize acoustic noise and ensure that the instructions were heard clearly by the subjects. The four dummy volumes were later discarded from the time series and this was taken into account during data analysis.

Individual brain activation maps in native space were co-registered to a structural scan with the following acquisition parameters: TE=40 ms, TR=3000 ms, FOV=24 cm, matrix size=128×128, number of slices=43, slice thickness=3.0 mm, interslice gap=0.3 mm, number of signal averages=8.

Statistical analyses

Prior research has shown that the timing of exposure may modulate the magnitude of the BOLD response during exposure to threat-relevant stimuli among anxious participants (Larson *et al*. 2006; Caseras *et al*. 2010). Furthermore, such temporal considerations in neural activation have been found to be relevant in predicting treatment outcome (Siegle *et al*. 2006). Accordingly, for data analysis, provocation and neutral blocks were split in half into 'early' and 'late' phases, resulting in two active phases of 10 s (five volumes) each.

Data were analyzed with the XBAM software developed at the Institute of Psychiatry, King's College London, which implements a permutation-based non-parametric approach to fMRI data analysis (Bullmore *et al*. 1999*a*, 2001; Breakspear *et al*. 2003). Individual brain activation maps (BAMs) were produced for each subject for each contamination phase *versus* the neutral condition. These were then normalized into standard space (Talairach & Tournoux, 1988) by a two-stage process (Brammer *et al*. 1997) using spatial transformations computed for each subject's high-resolution structural scan. From the statistic maps in standard space, a generic brain activation map (GBAM) was produced for each experimental condition by testing the median observed statistic [called the sum of squares (SSQ) ratio] over all subjects at each voxel (median values were used to minimize outlier effects), against a critical value derived from the permutation distribution for the median SSQ ratio generated from the spatially transformed wavelet-permuted data (Brammer *et al*. 1997). For greater sensitivity and to reduce the multiple comparison problem encountered in fMRI, hypothesis testing was carried out at the cluster level using methods developed by Bullmore *et al*. (1999*b*). Image-wise expectation of the number of false-positive three-dimensional (3D) clusters under the null hypothesis is set for each analysis at less than one (that is, the statistical thresholds are adjusted in such a way as to obtain less than one false-positive 3D cluster for each map).

Partial correlation analyses

In each phase ('early' and 'late'), the Pearson product-moment correlation coefficient at each voxel between the standardized power of the fMRI response (SSQ ratio) and the percentage improvement on the YBOCS for each subject was determined. The following covariates were used in three further partial correlation analyses: (1) the YBOCS score at the time of the scan, (2) the BDI score at the time of the scan, and (3) the percentage improvement in BDI from pre- to post-treatment. Only regions that survived all four analyses are reported here. Cluster-level maps of significant correlations were then computed as described in Bullmore *et al*. (1999*b*). Voxel and cluster statistical thresholds were again adjusted in such a way as to obtain less than one false-positive 3D cluster per map. Scatterplots were visually inspected to ensure that the results were not due to outliers.

Results

Treatment efficacy

Overall, there was a significant improvement in OCD symptom severity, as assessed by the YBOCS, from pre- to post-treatment (t=5.24, df=11, p<0.001). Three patients exhibited a greater than 35% reduction in total YBOCS scores, and seven exhibited improvement greater than 20%. Patients also experienced a marginally significant reduction in BDI scores (t=1.81, df=11, p=0.09). Table 1 shows the individual pre- and post-treatment scores on these measures.

Validation of the provocation procedure

A paired-sample t test indicated that anxiety ratings for the contamination provocation images (mean=6.06, S.D.=1.66) were significantly higher than anxiety ratings for the neutral images (mean=1.68, S.D.=1.66, t_{11}=7.49, p<0.001).

A hierarchical regression analysis was conducted to examine if anxiety ratings for the contamination and neutral images predicted a percentage drop in YBOCS scores after CBT. This analysis was conducted to delineate the extent to which neural biomarkers predict improvement with CBT above and beyond self-report. Anxiety ratings for the contamination and

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neutral images were entered simultaneously as predictors. The model was not significant (R^2=0.05, $F_{2,9}$=0.24, p=0.79), and anxiety ratings of neither contamination (β=0.01, p=0.98) nor neutral (β=–0.23, p=0.51) images emerged as a significant predictor of percentage drop in YBOCS scores after CBT.

Neural predictors of treatment outcome

Early symptom provocation phase

Table 2 and Fig. 1 show the brain regions with significant positive correlations with the percentage decrease in total YBOCS scores during the early phase of symptom provocation. These include the right anterior temporal lobe [inferior temporal gyrus (Brodmann area, BA 20) and middle temporal gyrus (BA 21)]; left posterior temporal lobe [fusiform gyrus (BA 20) and superior temporal gyrus (BA 22)]; ventromedial prefrontal cortex (inferior frontal gyri bilaterally, BA 11); right subcalosal gyrus (BA 47); left inferior postcentral gyrus (BA 3); parastriate cortex bilaterally (middle occipital gyri, BA19); right supramarginal gyrus (BA 40); left postcentral gyrus (BA2); left posterior cingulate (BA 31); right precuneus (BA 7); caudate nucleus (bilaterally); and left pulvinar thalamus.

Table 3 and Fig. 2 show the brain regions with significant negative correlations with percentage decrease in total YBOCS scores during the early phase of symptom provocation. These include the anterior cingulate gyrus bilaterally (BA 32); right medial frontal gyrus (BA 10); left inferior temporal gyrus (BA 21); right fusiform gyrus (BA 19); and middle occipital gyrus (BA 18).

Late symptom provocation phase

Table 2 and Fig. 1 show the brain regions with significant positive correlations with percentage decrease in total YBOCS scores during the late phase of symptom provocation. These include the temporal pole bilaterally [superior temporal gyrus (BA 38) and middle temporal gyrus (BA 21)]; on the left parahippocampal gyrus and uncus (BA 36) and right amygdala; in the left posterior temporal lobe [inferior (BA 20) and middle (BA 21) temporal gyri]; right inferior frontal gyrus (BA 47); posterior cingulate bilaterally (BA 30, 23); left insula (BA 13); left postcentral gyrus (BA 3); bilateral precuneus (BA 31, 19); and left cuneus (BA 18).

Negative correlations with symptom reduction in the 'late' phase (Table 2 and Fig. 2) were observed in the left dorsolateral prefrontal cortex (BA 46); right middle and superior frontal gyri (BA 9, 10); right anterior cingulate (BA 24); right cuneus (BA 17); left superior temporal gyrus (BA 41); right thalamus (pulvinar), left caudate; precentral gyri (BA 6) bilaterally; and right postcentral gyrus (BA 3).

Discussion

Although CBT that focuses on ERP is very effective for the treatment of OCD, a large proportion of patients remain symptomatic (Mataix-Cols *et al*. 2002). Several studies have attempted to identify patient characteristics that may reliably predict treatment outcome in OCD. However, such efforts have generally been unsuccessful (Olatunji *et al*. 2012). Building on existing research examining self-report and behavioral predictors, the present study examined the neural correlates of symptom improvement with CBT among patients with contamination-based OCD. Examination of treatment outcome revealed that OCD patients who underwent CBT including ERP experienced significant reductions in OC symptoms and marginally significant reductions in depression. Examination of neural correlates revealed positive associations between improvement in OCD severity and activation in areas such as the right anterior temporal cortex, the ventromedial prefrontal cortex and the posterior cingulate during the 'early' phase of symptom provocation with contamination threat. This pattern of findings was intensified in the 'late' phase of exposure to threat with strong bilateral correlations between improvement in OCD severity and activation in temporal pole regions. Significant correlations between activation in the right amygdala, left uncus and the insula during the 'late' phase of symptom provocation and improvement in OCD severity were also observed.

Activation of areas such as the anterior temporal pole and amygdala have been implicated in emotional encoding and processing (Sergerie *et al.* 2008; Visser *et al.* 2009). The present findings suggest that heightened encoding and processing during symptom provocation in OCD may predict greater CBT treatment effects. These findings are consistent with mechanisms that have been articulated in the context of EPT (Foa & Kozak, 1986). According to EPT, the effects of CBT that focuses on ERP derive from activation of a 'fear structure' and integration of information that is incompatible with it, resulting in a non-fear structure that replaces or competes with the original one (Foa & McNally, 1996). Thus the process of fear activation, which is characterized by physiological reactivity, is a vital mechanism underlying extinction learning during exposure-based treatments for anxiety disorders (Alpers & Sell, 2008). This view is consistent with the finding that activation in visual areas such as the precuneus and cuneus also correlated positively with treatment response in the present study. Previous research has shown that arousal modulates activity in

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Table 2. *Significant positive correlations between percentage improvement on the YBOCS and the BOLD signal during early and late phases, controlling for pretreatment BDI and YBOCS scores and percentage improvement in the BDI*

Cerebral region	Size	Talaraich coordinates			Cluster probability
		x	y	z	
Early					
Right inferior temporal gyrus (BA 20)	5	36	–7	–35	0.000083
Right superior temporal gyrus (BA 38)	11	40	7	–29	0.000083
Cerebellum	4	–18	–74	–29	0.000166
Left fusiform gyrus (BA 20)	4	–43	–33	–18	0.002412
Left inferior frontal gyrus (BA 11)	7	–25	33	–18	0.000582
Right subcallosal gyrus (BA 47)	9	22	15	–13	0.001913
Right superior frontal gyrus (BA 11)	9	14	52	–13	0.000083
Left middle temporal gyrus (BA 37)	4	–51	–56	–7	0.002495
Left primary visual (parastriate) cortex (BA 19)	4	–43	–67	9	0.000083
Right primary visual (parastriate) cortex (BA 19)	3	43	–63	9	0.005405
Right caudate	8	4	0	15	0.000083
Left superior temporal gyrus (BA 13)	10	–40	–48	20	0.000083
Posterior cingulate gyrus (BA 23)	8	–4	–19	20	0.000083
Left inferior postcentral gyrus (gustatory) (BA 43)	10	–58	–15	20	0.000083
Left inferior postcentral gyrus (BA 1)	5	–65	–15	26	0.001746
Left precuneus (BA 31)	13	–22	–63	20	0.000083
Right supramarginal gyrus (BA 40)	8	29	–41	37	0.000083
Right precuneus (BA 7)	16	18	–78	37	0.000083
Left postcentral gyrus (BA 2)	2	40	–26	43	0.003410
Late					
Cerebellum	6	0	–81	–29	0.000060
Left uncus (BA 36)	7	–22	–7	–29	0.000298
Right amygdala	12	29	–4	–24	0.000060
Right anterior temporal pole (BA 38)	15	43	11	–29	0.000060
Cerebellum	18	–14	–78	–24	0.000060
Left parahippocampal gyrus (BA 36)	9	–36	–30	–18	0.000060
Right inferior frontal gyrus (BA 47)	8	36	22	–18	0.000060
Cerebellum	34	–14	–48	–13	0.000060
Left inferior temporal gyrus (BA 20)	10	–47	–19	–13	0.000179
Left middle temporal gyrus (BA 21)	4	–54	–7	–13	0.003097
Left inferior frontal gyrus (BA 47)	44	–29	26	–24	0.000060
Right inferior frontal gyrus (BA 47)	5	50	22	–7	0.001787
Left insula (BA 13)	14	–40	–4	–7	0.000060
Left posterior cingulate (BA 29)	11	–11	–63	9	0.000060
Right posterior cingulate (BA 23)	4	7	–26	20	0.000179
Left postcentral gyrus (BA 4)	4	–51	–11	26	0.001787
Right angular gyrus (BA 39)	4	36	–52	31	0.003693
Left precuneus (BA 7)	16	–14	–52	37	0.000060
Right cingulate gyrus (BA 23)	8	7	–26	31	0.000060
Right precuneus (BA 19)	14	18	–81	37	0.000060
Left cuneus (BA 18)	23	–7	–74	9	0.000060
Left superior temporal gyrus (BA 13)	20	–40	–44	20	0.000060
Left supramarginal gyrus (BA 40)	7	29	–41	37	0.000060
Left inferior parietal lobule (BA 40)	3	–51	–48	48	0.001549
Left superior frontal gyrus (BA 8)	2	–4	41	53	0.002442

YBOCS, Yale Brown Obsessive–Compulsive Scale; BOLD, blood oxygen level-dependent; BDI, Beck Depression Inventory; BA, Brodmann area.

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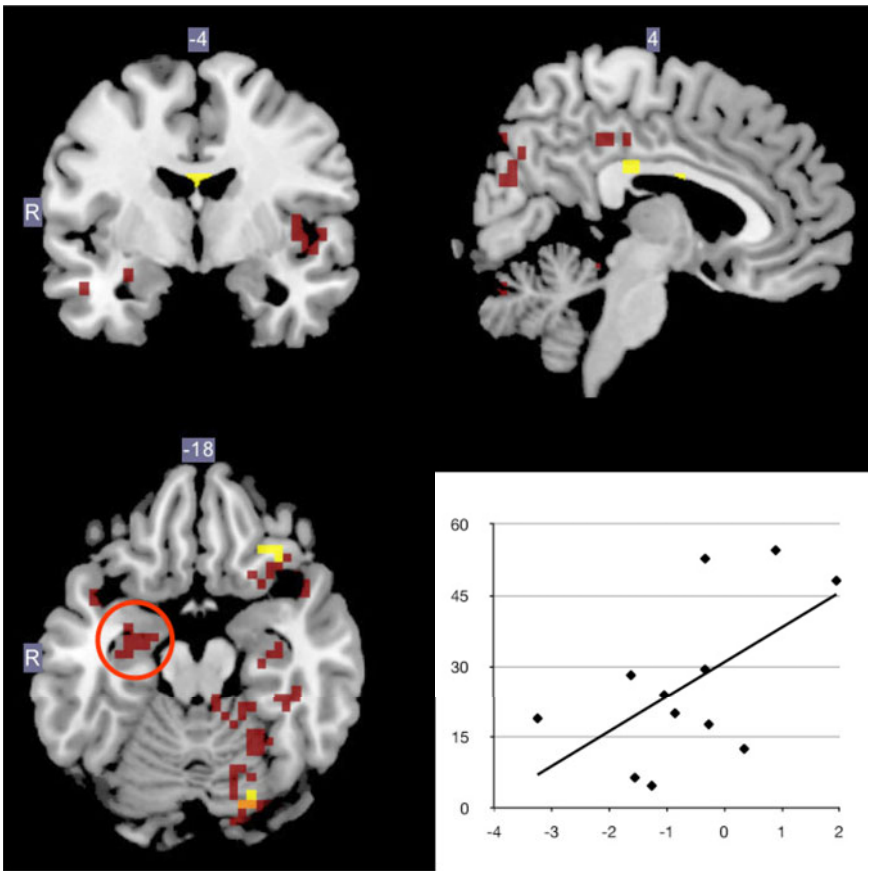


Fig. 1. Significant positive correlations between percentage improvement on the Yale–Brown Obsessive Compulsive Scale (YBOCS) and the blood oxygen level-dependent (BOLD) signal during the early (yellow) and late (red) phases of the exposure blocks, controlling for pretreatment Beck Depression Inventory (BDI) and YBOCS scores and percentage improvement in BDI score. The scatterplot in the shows the correlation between the BOLD signal in the right amygdala during the late phase of exposure and percentage improvement on the YBOCS.

the visual cortex (Mourão-Miranda *et al*. 2003), and changes in higher-order visual areas have been found to correlate with the effects of behavioral treatment on other anxiety disorders (Doehrmann *et al*. 2013). Activation in visual areas during symptom provocation may index greater fear activation and processing, which facilitates better treatment outcomes with CBT.

The present study also found that activation in areas such as the anterior prefrontal cortex and anterior cingulate during symptom provocation with contamination images was negatively correlated with improvement in OCD severity during CBT. These findings are also in line with prior research showing that dysregulation in brain regions such as the medial prefrontal cortex and the anterior cingulate may interfere with extinction learning and its retention (Milad & Quirk, 2002; Phelps *et al*. 2004; Milad *et al*. 2005). Activation in the prefrontal cortex and anterior cingulate may also inhibit negative emotional processing in the amygdala (Etkin *et al*. 2011), thus dampening subsequent treatment response. A significant negative correlation between activation in the left dorsolateral prefrontal cortex in the 'late', but not 'early', phase of symptom provocation and improvement in OCD severity was also observed. Activation in these brain regions has been implicated in the appraisal and regulation of negative emotion (Phillips *et al*. 2008) and prior research suggests that greater dorsolateral prefrontal cortex during emotional processing reflects engagement of cognitive control networks that are beneficial for emotional and cognitive functioning (Aupperle *et al*. 2012). Although a replicable finding in the literature is that more prefrontal cortex activation may reduce anxiety by moderating amygdala activity (Hariri *et al*. 2003), the present findings suggest that excessive activation in frontal brain regions may reflect inflexible and maladaptive attempts at emotion regulation during symptom provocation that correspondingly make extinction learning difficult during CBT. One interpretation of such findings is that too much affect regulation may interfere with the mechanism of action

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Table 3. *Significant negative correlations between percentage improvement on the YBOCS and the BOLD signal during the early and late parts of the blocks, controlling for pretreatment BDI and YBOCS scores and percentage improvement in the BDI*

Cerebral region	Size	Talaraich coordinates			Cluster probability
		x	y	z	
Early					
Cerebellum	26	22	–52	–40	0.000081
Cerebellum	10	–18	–52	–40	0.000081
Cerebellum	7	40	–63	–29	0.000647
Right parahippocampal gyrus (BA 34)	2	7	–4	–24	0.004124
Right middle temporal gyrus (BA 21)	5	65	–11	–13	0.000081
Right fusiform gyrus (BA 19)	5	54	–67	–13	0.000404
Right medial gyri (BA 10)	10	7	59	9	0.000081
Right middle occipital gyrus (BA 18)	2	11	–96	15	0.003315
Right anterior cingulate (BA 32)	13	7	37	9	0.000081
Left cingulate gyrus (BA 32)	6	–22	15	31	0.000081
Late					
Cerebellum	23	22	–56	–40	0.000058
Right superior frontal gyrus (BA 10)	8	4	63	–2	0.000058
Right middle frontal gyrus (BA 46)	6	32	41	9	0.000117
Right anterior cingulate (BA 24)	4	4	37	9	0.000175
Right middle frontal gyrus (BA 10)	7	21	48	4	0.000058
Right cuneus (BA 17)	6	14	–89	9	0.003438
Left superior temporal gyrus (BA 41)	6	–43	–37	15	0.000058
Left dorsolateral prefrontal cortex (BA 46)	39	–29	26	15	0.000058
Right thalamus (pulvinar)	7	22	–26	15	0.001981
Left caudate body	6	–22	–22	26	0.000991
Right postcentral gyrus (BA 3)	4	58	–19	37	0.000524
Right precentral gyrus (BA 6)	7	47	–11	37	0.000058
Right superior frontal gyrus (BA 8)	8	14	48	49	0.001282
Left precentral gyrus (BA 6)	9	–40	–11	53	0.000058

YBOCS, Yale Brown Obsessive–Compulsive Scale; BOLD, blood oxygen level-dependent; BDI, Beck Depression Inventory; BA, Brodmann area.

of ERP by dampening physiological arousal during exposure.

Excessive cognitive control may be the psychological process that underlies activation of the anterior prefrontal cortex and anterior cingulate during symptom provocation. Such control may include avoiding or suppressing anxiety that arises from exposure to contamination cues. Prior research has shown that suppression, relative to reappraisal, produces later activation in the prefrontal cortex (Goldin *et al.* 2008). Given that the dorsolateral prefrontal cortex has been implicated in the conscious regulation of emotion to reduce fear responses (Ochsner *et al.* 2002), sustained emotional suppression may partially account for the negative correlation between activation in the left dorsolateral prefrontal cortex in the 'late' phase of symptom provocation and improvement in OCD symptoms. Excessive suppression may interfere with CBT by producing a paradoxical 'rebound' of intrusive thoughts (Abramowitz *et al.* 2001).

The present study also suggests that the time course of activation in different brain regions may have some prognostic value in predicting the effects of CBT for OCD. Indeed, prior research has highlighted the value of the temporal features of brain activation in better characterizing affective disorders (Larson *et al.* 2006; Fu *et al.* 2008). Prior research has also shown that patients with major depressive disorder who showed sustained amygdala reactivity to emotional words had a better response to CBT (Siegle *et al.* 2006). Such research is consistent with the view that the neural timing of brain–behavioral associations may elucidate biomarkers for various interventions (Goldin *et al.* 2009). In line with this view, activation in the right amygdala and the left dorsolateral prefrontal cortex during the 'late' phase of symptom provocation was found to be highly correlated with a drop in YBOCS scores after CBT. These findings suggest that, for patients with OCD, prolonged activation of areas involved in the processing of aversive stimuli

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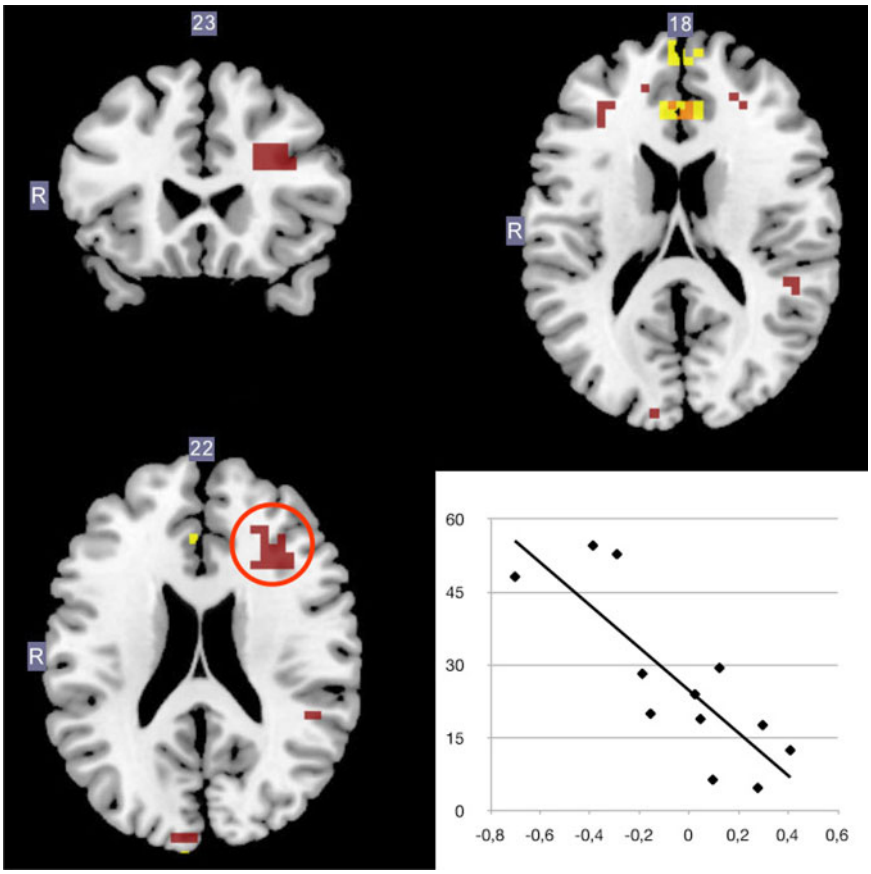


Fig. 2. Significant negative correlations between percentage improvement on the Yale–Brown Obsessive Compulsive Scale (YBOCS) and the blood oxygen level-dependent (BOLD) signal during the early (yellow) and late (red) phases of the exposure blocks, controlling for pretreatment Beck Depression Inventory (BDI) and YBOCS scores and percentage improvement in the BDI score. The scatterplot shows the negative correlation between the BOLD signal in the left dorsolateral prefrontal cortex during the late phase of exposure and percentage improvement on the YBOCS.

(without activation in dorsal 'emotion regulation' areas) prior to treatment may be a valuable biomarker for predicting responsiveness to CBT.

These findings highlight neural biomarkers that seem to be uniquely informative in determining who will benefit best from CBT as anxiety ratings of neither contamination nor neutral images predicted treatment response among patients with contamination-based OCD. However, these findings must be considered within the context of the study limitations. One important limitation is the relatively small sample size of the OCD patients and of those with predominantly contamination obsessions and washing compulsions. Replication of these findings in a larger sample is clearly needed before more definitive inferences can be made. Another limitation is the absence of a treatment control group, which makes it difficult to delineate the extent to which the therapeutic effects and their neural correlates are specific to CBT. Despite the study's limitations, these findings suggest that activation in brain areas involved in emotional processing and regulation has prognostic value in the treatment of contamination-based OCD. Prior research does suggest that different OCD symptom dimensions are mediated by distinct neural processes (Mataix-Cols *et al*. 2004). Thus, it will be valuable to see if the pattern of findings observed among OCD patients with predominantly contamination obsessions and washing compulsions generalize to other OCD symptom dimensions. Future programmatic research using randomized trial designs comparing various treatment modalities for different OCD symptom dimensions can build on these findings to identify neural correlates that may help to guide treatment selection.

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Declaration of Interest

None.

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