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Emotional processing in obsessive-compulsive disorder: A systematic review and meta-analysis of 25 functional neuroimaging studies

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Abstract

Background—Patients with obsessive-compulsive disorder (OCD) experience aversive emotions in response to obsessions, motivating avoidance and compulsive behaviors. However, there is considerable ambiguity regarding the brain circuitry involved in emotional processing in OCD, especially whether activation is altered in the amygdala.

Methods—We conducted a systematic literature review and performed a meta-analysis (Seed-based *d*-Mapping) of 25 whole-brain neuroimaging studies (including 571 patients and 564 healthy controls) using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) comparing brain activation of OCD patients and healthy controls during presentation of emotionally-valenced versus neutral stimuli. Meta-regressions were employed to investigate possible moderators.

Results—OCD patients, compared with healthy controls, showed increased activation in the bilateral amygdala, right putamen, orbitofrontal cortex extending into the anterior cingulate and ventromedial prefrontal cortex, middle temporal, and left inferior occipital cortices during emotional processing. Right amygdala hyperactivation was most pronounced in unmedicated

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patients. Symptom severity was related to increased activation in the orbitofrontal and anterior cingulate cortices and precuneus. Greater comorbidity with mood and anxiety disorders was associated with higher activation in the right amygdala, putamen, and insula, as well as lower activation in the left amygdala and right ventromedial prefrontal cortex.

Conclusions—OCD patients show increased emotional processing-related activation in limbic, frontal and temporal regions. Previous mixed evidence regarding the role of the amygdala in OCD has likely been influenced by patient characteristics (such as medication status) and low statistical power.

Keywords

Symptom provocation; emotional interference; medication; emotion; comorbidity; meta-analysis

Introduction

Patients with obsessive-compulsive disorder (OCD) often experience aversive emotions such as anxiety, fear and disgust in response to obsessive thoughts, urges or images. These aversive emotions motivate patients to avoid situations and engage in compulsive behaviors to deal with the provoked distress and to prevent the catastrophic outcomes that they anticipate (1).

The neural substrate of emotional processing in OCD has been investigated for almost three decades using a variety of experimental tasks comparing OCD patients and healthy controls. The central idea in these tasks is to experimentally elicit the negative emotions that OCD patients experience in their daily lives, thereby visualizing the brain's activation in the symptom-provoked state. During symptom provocation paradigms, participants view stimuli that resemble situations in daily life that typically elicit anxiety or an urge to ritualize in patients (e.g. potentially contaminated objects or situations where one could harm someone). The resulting brain activation patterns are contrasted to a condition with stimuli that are meant to be neutral (e.g. nature scenes or clean household objects) (2, 3). Other studies employ emotional faces (e.g. fearful, disgusted) to induce negative emotions and contrast the resulting brain activations with those of neutral facial expressions (4). Another approach is to have participants perform a cognitive task with emotional interference. In these paradigms, participants perform the cognitive task under both neutral and implicitly symptom-provoked states, for example by naming the color of disorder-related words (5, 6).

However, the results from these studies have been somewhat inconsistent and hard to reconcile, especially regarding the role of the amygdala. The largely unclear role of the amygdala in OCD contrasts with theoretical models which propose a central role of this structure in the processing of emotionally-valenced stimuli (7, 8). The amygdala is involved in the unconscious and conscious appraisal of visual stimuli in the environment (9), the acquisition and extinction of a learned response to potential threat (10), and its interference with prefrontal functioning (9). Its activation varies fast over time, under influence of bottom-up and top-down modulation, from among others the thalamus and cortical areas among others (11). Within-individual variation in amygdala responsiveness is dependent on the context (the experimental setting), contributing to inconsistencies from neuroimaging

studies. For example, studies in OCD using emotional facial stimuli showed that activation of the amygdala in response to fearful faces has been found to be increased, decreased, or neither increased nor decreased in various studies (4, 12–14). One plausible reason for these inconsistencies is the typically small sample sizes, which not only decrease the chance of finding a true effect but also increase the risk of false positive findings (15). Many studies also include patients on selective serotonin reuptake inhibitors (SSRI), which are known to influence brain activation in regions such as the amygdala or hippocampus (16). Comorbidity with anxiety or mood disorders is another source of heterogeneity, which may obscure whether alterations are specific to OCD or shared with other psychiatric disorders (17, 18).

Meta-analyses are the gold standard of evaluating quantitative findings, and work by combining information from all available studies and thereby reducing random noise from individual studies, allowing filtering out robust effects and to establish the contribution of specific factors to the variability in results. However, to our knowledge only one meta-analysis focusing on emotional processing in OCD has previously been published (19), based on eight studies using symptom provocation tasks. They found increased brain activation in OCD patients compared to healthy controls in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus, hippocampus, superior temporal gyrus, and precuneus. Though important for providing a snapshot of the literature at that time, the previous meta-analysis by Rotge et al. (19) had several limitations. The authors were not able to investigate whether contributing factors such as medication usage or comorbidity moderated their findings, both due to the limited number of included studies and the meta-analysis software available at that time, they omitted at least one available study (2), and included studies which did not compare patients to healthy controls, but only relied on within-group contrasts (20–22). The authors also included studies analyzing regions of interest with more lenient significance thresholds, which may have increased the rate for both false positive and false negative findings.

The aim of the present meta-analysis was to provide a contemporary, quantitative comparison of brain activation during emotional processing in OCD patients and healthy controls, to explore the influence of patient characteristics, and to investigate the consistency of these findings. Based on previous reviews of human and animal research on OCD (8, 23, 24) we hypothesized that OCD patients compared to healthy controls would show altered activation in limbic (amygdala), striatal (putamen), lateral temporal, and frontal (OFC, dorsal ACC) regions during emotional processing. We also hypothesized that studies with a lower proportion of patients on medication and studies with a higher proportion of patients with comorbid anxiety and mood disorders would show higher limbic (amygdala) activation during emotional processing.

Method

Study selection

Paradigms assessing emotional processing were defined as those using both stimuli intended to be neutral and those intended to elicit specific negative emotions such as fear, disgust, or more general distress, as well as urges to ritualize. The contrast of interest was the

comparison of brain activation during neutral and emotional stimuli for OCD patients and healthy controls (i.e. the group by task interaction). A systematic literature search was conducted of all whole-brain neuroimaging studies of emotional processing in OCD up to July 2017, using the PubMed, Web of Science, ScienceDirect and Google Scholar databases, as well as manual searches of relevant published articles. Corresponding authors of studies with unavailable full texts were asked to provide these. Search words were combinations of "obsessive-compulsive disorder" or "OCD", and "symptom", "provocation", "emotion*", and "neuroimaging", "fMRI", "SPECT", "PET". We defined studies of emotional processing using these specific criteria: 1) included both patients with OCD and healthy controls; 2) employed functional neuroimaging, such as fMRI, PET or SPECT; 3) included tasks with both an "emotional" condition and a "neutral" condition; 4) reported whole-brain analysis of an emotional versus neutral contrast; and 5) were written in English. MOOSE guidelines were followed (25). The systematic search and data extraction was conducted by two PhD and master students (Thorsen and Hagland), under the direct supervision of two senior authors (Radua and van den Heuvel).

Statistical analyses

Differences in activation during emotional processing between OCD patients and healthy controls were analyzed using Seed-based *d* Mapping (SDM; www.sdmproject.com), a whole-brain voxel-based meta-analytic approach (26, 27). SDM first estimated, for each study, the group by task interaction statistical parametric map (i.e. where patients show increased or decreased activation compared to healthy controls during emotional versus neutral stimuli). Hedge's g in the voxels containing a peak was calculated from the peak's t-score, and an anisotropic Gaussian kernel was used to estimate Hedge's g in their surrounding voxels (28). The estimated statistical parametric maps were then included in a random effects meta-analysis, which weighted the contribution from each study by sample size, within- and between-study heterogeneity, and ultimately resulted in a whole-brain map of the reported group differences between patients and controls. Standard permutation tests were used to estimate the statistical significance of the SDM z-scores. The comparison between OCD patients and healthy controls was thresholded at $p < 0.005$, which has been shown to be comparable to $p < 0.05$ corrected for multiple comparisons (22). Following standard criteria, significance thresholds were also set at a minimum peak voxel z-score over one, and a minimum cluster extent of 10 voxels (26, 27).

Eight studies included more than one OCD relevant condition (3, 29–35). Prior to the analysis, results from each condition were combined into one single statistical map. This was done to include all relevant contrasts without counting these studies several times, and thereby giving these studies an undue influence and violating the statistical assumption of independence.

We first performed the primary analysis assessing differences between OCD patients and healthy controls during emotional processing. We also compared the findings of studies using symptom provocation with pictures versus all other paradigms. We then performed secondary meta-regressions assessing the influence of several factors on the group by task effect. This included each study's mean symptom severity using mean Yale-Brown

Obsessive Compulsive Scale (Y-BOCS; 36), the percentage of medicated patients, and an indicator of anxiety/depression comorbidity per study. Twenty-one of the included studies reported rates of comorbidity for both anxiety and mood disorders, but these rates were highly correlated $r(18) = 0.74$, $p < 0.001$. We therefore calculated the indicator for comorbidity using the mean percentages of patients per study who also met criteria for a comorbid anxiety or mood disorder. Finally, the moderating role of percentage of males, and mean illness duration were also investigated. The moderating variables did not significantly correlate, and were therefore largely independent. Meta-regressions were thresholded at a stricter level ($p < 0.0005$) to limit the risk of false positives. A jackknife sensitivity analysis was conducted for the primary group by task meta-analysis to assess the robustness of the main findings, by iteratively repeating the analysis and excluding one data set at a time. Publication bias was assessed using Egger's tests and funnel plots for the main meta-analytical findings.

Results

Characteristics of included studies

978 studies were rejected after reading the abstract and title, as they not meet inclusion or exclusion criteria. Full texts of 39 studies were retrieved. Of these, 14 were excluded. The reasons for exclusion were as follows: ten did not report results at the whole-brain level (37–46), three did not include healthy controls (47–49), and one only reported comparisons between OCD patients and healthy controls after patients were treated using cognitive behavioral therapy (50) (see Supplemental Figure 1 for flowchart of selection process). Twenty-five studies comprising 571 OCD patients and 564 healthy controls were included in the meta-analysis. Each study included a mean of 22.84 patients (SD = 16.78) and 22.56 healthy controls (SD = 16.09). The mean age of the patients was 33.44 (SD = 5.91), and all studies included age-matched healthy controls. The mean percentage of males was 54.35% (SD = 12.10). Seventeen studies (68%) included medicated patients, and only one study included pediatric OCD patients. Two studies did not include information on medication status, and were therefore not included in the meta-regression of medication usage. The mean Y-BOCS score of the included studies was 23.46 (SD = 3.45), indicating that most patients were moderately ill (51). Thirteen studies provided the mean duration of illness, which was 12.26 years overall (SD = 4.46). Sixteen studies included participants from Europe, six from North America and three from Asia. Ten studies used symptom provocation using pictures, five used emotional faces, and ten used various other paradigms (e.g. emotional Stroop, working memory tasks combined with emotional stimuli, or symptom provocation tasks using written verbal stimuli instead of pictures, see Supplemental Table 1 for detailed information).

Comparison between OCD patients and healthy controls across all studies

Across all paradigms the main effect of group showed that OCD patients, compared with controls, show significantly increased activation in the right OFC extending into the subgenual anterior cingulate cortex (sgACC) and ventromedial prefrontal cortex (vmPFC), right putamen, bilateral amygdala, left inferior occipital gyrus and right middle temporal gyrus during emotional processing. Healthy controls did not show increased activation

compared to patients in any region (see Table 1 and Figure 1). Finally, we did not find any significant difference in the patterns of activation between studies using symptom provocation with pictures compared to other paradigms (data not shown).

Meta-regressions of factors influencing the difference between OCD patients and healthy controls

The meta-regression analyses (see Table 2 and Figure 2 for details) showed that the percentage of patients per study using psychotropic medication, primarily SSRIs, correlated negatively with activation in the right amygdala and left inferior occipital gyrus, indicating that the increased limbic and occipital activation during emotional processing in patients compared to controls is most pronounced in studies with higher percentages of unmedicated patients.

Studies including patients with higher symptom severity, as measured with Y-BOCS, showed significantly increased activation in the right rostral sgACC, the left medial prefrontal cortex and the right precuneus. Studies with a higher rate of comorbidity with anxiety and mood disorders also found more pronounced activation in the right putamen, amygdala, and insula, as well as less pronounced activation in the left amygdala and right vmPFC in patients compared to controls.

Studies with more male patients found significantly lower differences in presupplementary motor area (pre-SMA) activation. Finally, studies with longer mean duration of illness showed increased right putamen activation, and decreased left temporal pole and OFC activation in patients versus controls.

Sensitivity analysis and publication bias

The whole-brain jackknife sensitivity analysis showed that the main results were replicated in nearly all combinations of studies. Additional findings appeared, however, in some of the combinations. Activation of the left inferior frontal gyrus (IFG) was found to be significantly increased in patients versus controls when one of nine studies were removed (5, 6, 13, 31–34, 52, 53). The removal of one of three studies also resulted in significantly decreased activation in bilateral ACC in patients). Also, the removal of one of two different studies increased activation in the left angular gyrus (54) and right precuneus (13) in patients (See Supplemental Table 2 for detailed information). These jackknife analyses show that the findings of the main meta-analysis were largely robust, while hyperactivation in the left IFG and hypoactivation in the bilateral ACC in patients may have been underestimated. However, there was no apparent pattern in these studies, as these spanned all functional tasks. Also, the meta-regressions did not reveal any relations to any of the explored patient characteristics.

Inspections of Egger’s intercepts and funnel plots did not indicate significant publication bias in any region from the main results, with the lowest p value on the Egger’s test being $p = 0.175$. This indicates that there was a low risk of activation being overestimated because of studies being withheld or not being published.

Discussion

The present study is the largest meta-analysis of emotional processing in OCD to date, encompassing 25 studies using a variety of emotional tasks including symptom provocation using images or words, as well as emotional variants of typical cognitive paradigms such as the emotional Stroop task and working memory tasks with emotional distractors. The results help integrate a body of research which has often resulted in inconsistent findings that are hard to reconcile, particularly regarding the role of the amygdala in OCD. The main findings were that, compared to healthy controls, OCD patients showed increased activation in the amygdala, OFC extending into the subgenual anterior cingulate (sgACC) and ventromedial prefrontal cortex (vmPFC), putamen, and middle temporal and inferior occipital regions during emotional processing.

The meta-regression analyses showed that the findings in the amygdala are especially sensitive to a number of patient factors, such as medication status and comorbidity. In contrast, the group effects in the amygdala were independent of mean symptom severity of the patient samples. Notably, the left and right amygdala showed opposite activation patterns in the meta-regressions for medication usage and comorbidity with anxiety and mood disorders. The right amygdala showed increased activation in studies with higher percentage of unmedicated patients and in studies with more comorbid disorders. By contrast, activation in the left amygdala was less pronounced in studies with more comorbidity. Studies with more males showed lower differences in pre-SMA activation. Finally, studies with longer mean duration of illness showed increased differences in right putamen activation, and lower differences in the left temporal pole and OFC. Unfortunately, the variance in gender was low and approximately half the studies did not report duration of illness, so these effects should be interpreted with caution. These meta-regressions contribute to the understanding of the mixed findings on amygdala involvement in OCD in the literature, which has been the topic of much discussion (4, 12–14, 23). They also have implications for future research, showing factors that should be carefully considered in order to accurately measure the response in the limbic areas.

The robustly increased activation in the bilateral amygdala in OCD patients during emotional processing fits with the proposed role of the amygdala in mediating anxiety, obsessionality and urge to ritualize (2, 20, 41). It also fits the recent findings of limbic interference during cognitive processing in OCD (23, 55, 56), limbic findings in animal models of OCD (24), and current models of affected fronto-limbic and affective cortico-striato-thalamo-cortical circuits in OCD (23). Furthermore, the findings support that emotional reactivity to stimuli are important in OCD, which may have implications for the focus of psychological treatments (7, 57, 58).

Endured limbic hyper-responsiveness has been related to dysfunctional top-down control from the dorsal PFC, as shown by diminished fronto-limbic functional connectivity during emotion processing (59). However, we were not able to investigate functional connectivity in this meta-analysis, and our results did not show decreased dorsal prefrontal recruitment in OCD patients during emotional processing. Instead, we found increased activation of the OFC extending into the sgACC/vmPFC, and positive correlations between OCD symptom

severity and activation in the same region extending to the rostral ACC. Inspection of the individual studies reporting altered sgACC activation showed that this was driven by increased activation in patients during aversive emotion processing, rather than a lack of deactivation when shifting from neutral to aversive stimuli. The OFC plays a pivotal role in emotional decision making and the formation of emotional stimulus-outcome associations (60–62), but much is not known regarding the functional connectivity between cortical and subcortical areas in OCD. One hypothesis might be that both cortical (including the OFC/sgACC) and subcortical areas (such as the amygdala) excessively reinforce each other, where prefrontal emotional control does not dampen subcortical emotional responses. This would imply a failure of the top-down emotion regulation often seen in healthy controls (63). Limbic hyperactivation may also influence early recruitment of the inferior occipital gyrus, where the ventral visual stream becomes sensitive to disorder-relevant stimuli and relays their detection to the middle temporal cortex, which in turn upregulates activity in the amygdala (64, 65). Finally, we also showed increased activation of the posterior putamen, which projects to both limbic and sensorimotor areas (66, 67). This likely reflects its involvement in both the processing of aversive emotions and preparation of compulsive behaviors in OCD (23, 68). Future research on connectivity patterns during emotional processing in OCD might establish whether a positive feedback loop between cortical and subcortical areas contributes to the maintained anxiety response that OCD patients experience when they are prevented from performing compulsions.

Comparisons with findings from the largest meta-analysis of voxel-based morphometric studies comparing OCD patients and healthy controls (69) also revealed partial overlap, specifically between altered gray matter volume and increased activation in the OFC, right amygdala, and putamen in OCD patients.

Several studies have investigated whether disorder-specific stimuli elicit different neural responses compared to general aversive stimuli, with mixed results (e.g. 41, 45, 59). For instance, increased activation in the amygdala has been reported during disorder-specific stimuli in some (34, 59), but not other studies when compared to general aversive stimuli (45). Unfortunately, we were unable to compare the effects of disorder-specific and general stimuli due to the few studies with comparable paradigms. Since we were unable to differentiate between the provocations of specific symptom dimensions, we therefore assume homogeneity in our analyses, while OCD is a highly heterogeneous disorder not only in its clinical presentation, but also in its etiology (70–72). Different symptom dimensions seem to vary in their limbic involvement, being more pronounced in patients with more aggressive, sexual or religious symptoms and checking rituals (13, 73, 74).

Abnormal recruitment of the brain circuits during emotional processing in patients with OCD may represent dynamic correlates of the symptom state, and not necessarily a static trait-like marker of vulnerability to OCD. Indeed, several studies show that successful treatment with cognitive behavioral therapy or SSRIs at least partly normalizes patients' provocation-induced response in the OFC, putamen and parietal cortex (23, 75). Less is known about the effect of treatment on the limbic response. It is also possible that brain abnormalities constitute trait or risk factors for the disorder, as unaffected first degree relatives of patients with OCD also show increased activation in OFC during a reversal

learning task (76). Longitudinal, genetically informative designs, such as discordant monozygotic twin studies, are needed to shed further light on the origins of the observed emotional processing related activation patterns in OCD.

The present results show notable differences compared to the findings of the previous smaller meta-analysis (19). For instance, we were not able to replicate their findings of increased activation in medial PFC, bilateral globus pallidus, right thalamus, left OFC, or left hippocampus in patients compared to healthy controls. Since we were able to include nearly three times as many studies as in the previous meta-analysis and only selecting those using whole-brain analyses, the present results could be regarded as less sensitive to type I and type II errors.

Our study has some limitations that should be considered. We did not have access to patient-level data, which may have provided additional power. Some of the included studies were quite small (the smallest including eight patients and eight controls), and smaller studies may have an increased risk of introducing noise. The risk of undue noise was also increased as almost every study used reported foci at uncorrected p-values, which heightens the risk of false positives. Studies also varied in their use of statistical packages, as well as their use of the Montreal Neurological Institute (MNI) or Talairach coordinates, including the transformations used to convert between the coordinate systems. Although we used corrections for transforming the foci of each study into MNI using standard SDM procedures, this may have introduced additional noise in our meta-analysis. We choose to only include studies in English, which may have excluded some studies. However, we are not aware of any relevant high quality studies in other languages. Finally, though we did not find any significant differences in activation between studies using symptom provocation with pictures compared to all other paradigms, the current literature may not provide adequate power or homogeneity to find smaller differences. This could also be the case for the variables explored using meta-regressions, since the variance was limited in several of the variables. The field is currently lacking studies of emotional processing in pediatric OCD, and our findings may be seen as more generalizable to adult OCD. Studies directly comparing adults and children, or who follow developing children, are needed. The few studies employing each paradigm also meant there would not have been enough power to adequately analyze them separately. However, a recent meta-analysis of 90 studies of OC symptom induction in clinical and non-clinical samples showed similar results across a range of induction procedures (77). This provides some support for our non-significant comparison between studies using symptom provocation with pictures versus other paradigms.

Conclusions

Compared with healthy controls, OCD patients show increased activation in the fronto-limbic circuit, encompassing the amygdala, OFC/sgACC/vmPFC, occipital and middle temporal cortices and posterior/ventral putamen. Furthermore, the degree to which patients and controls differ in their limbic and striatal response is influenced by medication status, comorbidity, and symptom severity. These findings help explain some of the inconsistencies

in the literature, and highlight the importance of well-powered meta- and mega-analyses of neuroimaging data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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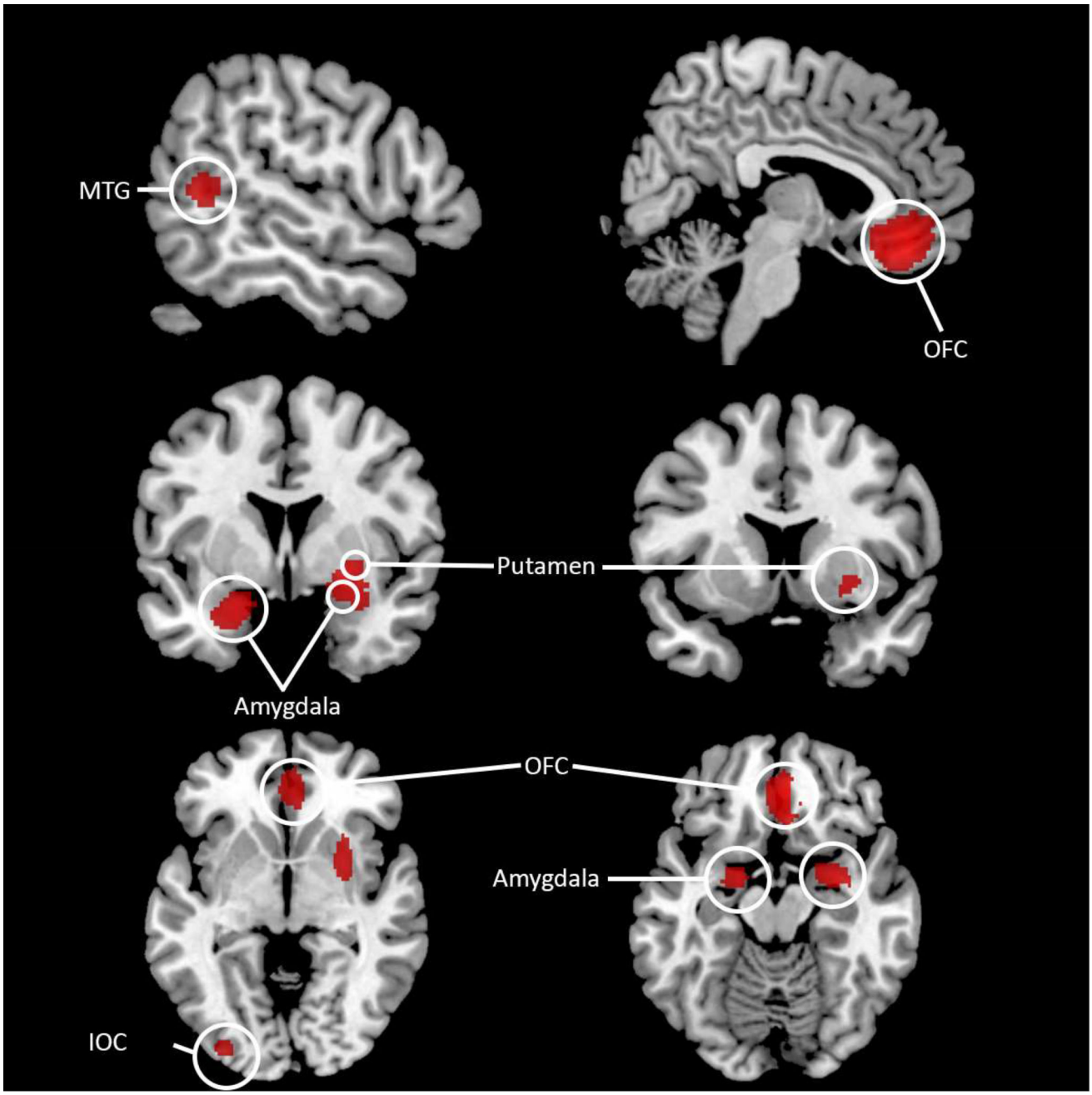

Figure 1. Main results showing increased activation in OCD patients compared to healthy controls during emotional processing

Regions of hyperactivation in OCD patients compared to healthy controls during emotional processing, showing a distributed affective circuit including frontal, limbic, striatal and ventral visual areas. Abbreviations: IOC, inferior occipital cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex.

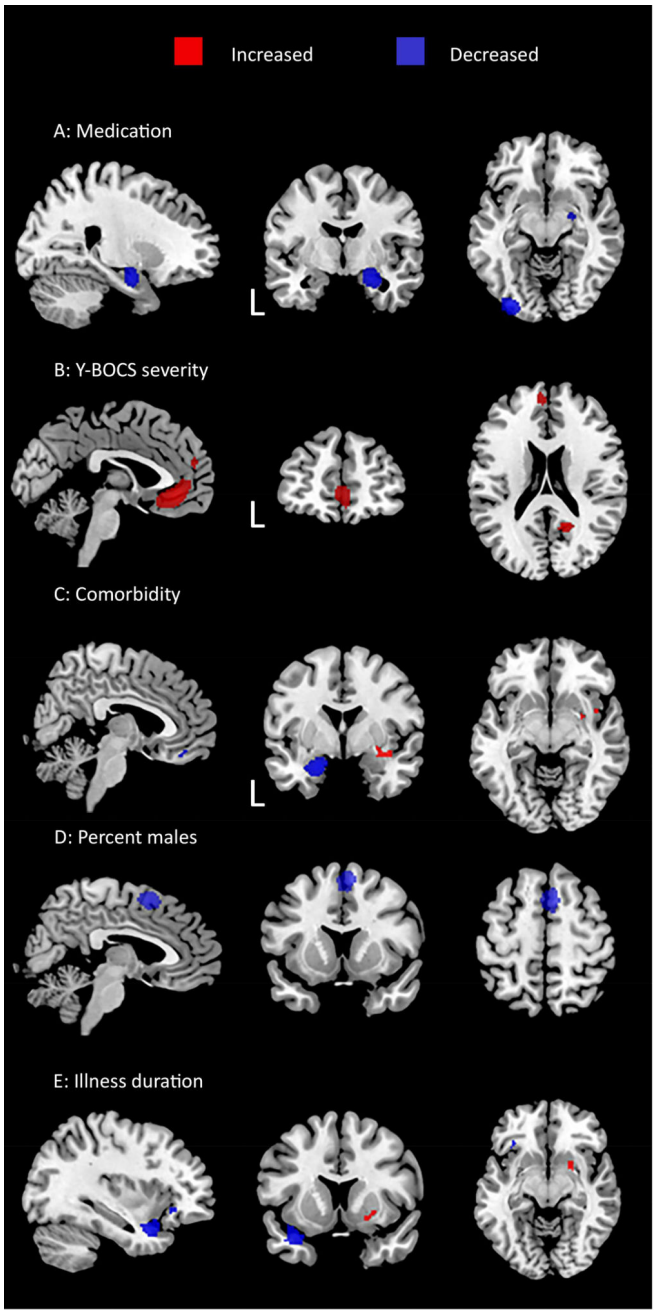

Figure 2. Meta-regressions of factors influencing the difference between OCD patients and healthy controls during emotional processing

Results of meta-regressions indicating factors that are associated with an increased (red) or decreased (blue) difference between OCD patients and healthy controls. Panel A: Patient samples with more medicated patients showed less hyperactivation in the right amygdala and left cerebellum. Panel B: Increased symptom severity correlated with increased patient hyperactivation in the subgenual/rostral ACC and medial PFC. Panel C: Patient samples with more anxiety and mood disorder comorbidity showed increased activation in the right insula, putamen, and amygdala, and decreased activation in the left amygdala and right vmPFC. Panel D: Patient samples with more males showed less activation in the presupplementary

motor area. Panel E: Patient samples with longer mean duration of illness showed increased activation in the right putamen and lower activation in the left temporal pole and orbitofrontal cortex.

Table 1

Whole-brain significant differences between comparison of OCD patients and healthy controls during emotional processing

Region	Side	MNI coordinates (X, Y, Z)	BA	SDM z-score	No. of voxels	Cluster breakdown
OCD patients > HC						
OFC	R	6, 40, −16	11	2.093	811	Bilateral OFC, sgACC, vmPFC
Amygdala	L	−20, 0, −20	N/A	1.931	437	Amygdala, parahippocampal gyrus
Amygdala	R	28, −2, −12	N/A	1.882	437	Amygdala, putamen
Inferior occipital gyrus	L	−32, −90, −10	19	1.559	95	Inferior, middle occipital gyrus
Middle temporal gyrus	R	58, −50, 8	21	1.746	85	-

Abbreviations: BA, Brodmann area; HC, healthy controls; L, Left; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; MNI, Montreal Neurological Institute; N/A, not applicable; R, right; SDM, Seed-based d mapping; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

Table 2

Meta-regressions of factors influencing the difference between OCD patients and healthy controls during emotional processing

Region	Side	MNI coordinates (X, Y, Z)	BA	SDM z-score	No. of voxels	Cluster breakdown
Medication usage – negative correlations						
Inferior occipital gyrus	L	−32, −90, −10	19	−2.8702	294	Inferior, middle occipital gyrus
Amygdala	R	24, −6, −18	N/A	−2.685	269	Amygdala, parahippocampal gyrus
Y-BOCS - positive correlations						
sgACC	R	4, 34, −8	11	2.113	634	sgACC/rACC
Medial PFC	L	−4, 54, 20	10	1.854	174	-
Precuneus	R	16, −52, 20	17	2.063	84	-
Comorbidity - positive correlation						
Insula	R	40, 4, −10	48,	1.758	64	Insula, putamen, amygdala
Comorbidity - negative correlations						
Amygdala	L	−22, 2, −22	N/A	−1.840	364	Amygdala, parahippocampal gyrus
vmPFC	R	4,42,−18	11	−1.425	13	−
Gender – negative correlation						
Pre-SMA	R	4,12,58	6	−2.268	287	-
Illness duration – positive correlation						
Putamen	R	20,6,−10	N/A	1.614	48	-
Illness duration – negative correlations						
Temporal pole	L	−36,24,−10	38	−1.464	220	Temporal pole, OFC
OFC	L	−32,30,−6	47	−1.308	15	-

Abbreviations: BA, Brodmann area; HC, healthy controls; L, left; MNI, Montreal Neurological Institute; N/A, not applicable; OFC, orbitofrontal cortex; Pre-SMA, presupplementary motor area; PFC, prefrontal cortex; R, right; rACC, rostral anterior cingulate cortex; SDM, seed-based d mapping; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.