Functional Connectivity Bias of the Orbitofrontal Cortex in Drug-Free Patients with Major Depression

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Background: The orbitofrontal cortex (OFC) plays a crucial role in emotion-processing circuits and should therefore also be included in models of the pathophysiology of major depression. The aim of this study was to compare the functional connectivity of the OFC during emotion processing in patients with major depression and healthy control subjects.

Methods: Twenty-five untreated patients with major depression and 15 healthy control subjects were investigated using a functional magnetic resonance imaging face-matching task.

Results: Dorsal anterior cingulate cortex, precuneus, and cerebellum activity showed less connectivity with the OFC in patients than in control subjects. In contrast, functional connectivity between the OFC and the right dorsolateral prefrontal cortex (DLPFC), right inferior frontal operculum, and left motor areas was increased in patients compared with healthy control subjects.

Conclusions: The OFC plays a key role in the pathophysiology of major depression. The observed imbalance of OFC connectivity seems to represent a neural mechanism of the processing bias. From a neurobiological point of view, the uncoupling of precuneus and gyrus cinguli activity from the OFC might be associated with problems in the regulation of self-schemas, whereas the increased connectivity of the DLPFC to the OFC might represent a higher neural response to negative stimuli.

Key Words: Functional connectivity, functional magnetic resonance imaging, major depression, orbitofrontal cortex

The orbitofrontal cortex (OFC) is known to be a key player in emotion, but its exact role in emotion processing is still under investigation. In humans, damage to the OFC causes major changes in emotion, personality, behavior, and social conduct (1). Bechara *et al.* (2) reported that subjects with OFC lesions were unable to anticipate future outcomes. Researchers assume that the OFC is involved in emotion because it appears to be crucially involved in representing and altering the reward value of primary and secondary reinforcers (1). Interestingly, OFC volume was found to be smaller in patients with major depression than in healthy control subjects (3–5), suggesting a role of the OFC in the pathophysiology of major depression. With respect to the part of the OFC that is altered, different functional consequences might arise, because corticocortical connections provide the basis for a medial and an orbital network within the orbital and medial prefrontal cortex. The orbital prefrontal network seems to play a role in integration of visual, somatosensory, visceral, olfactory, and gustatory stimuli as well as in merging together with limbic influences, whereas the medial prefrontal network is the origin for projections to the hypothalamus and brainstem (6). A disturbance of the integrative function of the orbital network might result in mood, visceromotor, eating, and sleep disturbances as seen in major depression.

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Previous functional magnetic resonance imaging (fMRI) studies examining neural responses to emotional stimuli in patients with major depression indicated increased responses in the amygdala, anterior cingulum (ACC), fusiform gyrus, putamen, and prefrontal cortical regions (7–9). Although many researchers assume that the depressive syndrome might arise from abnormal interactions between brain regions, relatively few functional neuroimaging studies have examined the connectivity of the neural network. With respect to connectivity, a study in 15 unmedicated patients with major depression and 15 healthy volunteers found decreased correlation between ACC and limbic regions, which is consistent with the hypothesis that decreased cortical regulation of limbic activation in response to negative stimuli may be present in depression (10). Again the amygdala was negatively coupled with the ACC, but also positively coupled bilaterally with medial temporal and ventral occipital regions in 19 unmedicated patients with major depression and 19 healthy volunteers (11). Studies on functional connectivity in patients with major depression receiving antidepressant medication have achieved varied results. The results have indicated that a neural network consisting of the cingulate region, prefrontal cortical regions, amygdala, and subcortical regions may play key roles in major depression: compared with healthy control subjects, patients with depression showed increased functional connectivity among the amygdala, hippocampus, and caudate-putamen regions during emotion processing (12) but significantly reduced amygdala–prefrontal connectivity (13). Uncoupling of the prefrontal cortex and gyrus cinguli was found in 14 patients with major depression and 14 healthy control subjects during a verbal working memory task (14). Resting-state fMRI showed that subgenual cingulate and thalamic functional connectivity were significantly increased in 20 patients with major depression compared with 20 healthy control subjects (15).

Until now, no study has investigated alterations of functional connectivity between the OFC and the other brain regions involved in emotion processing in drug-naive patients with major depression, although the OFC is involved in the integration of limbic and sensory influences. The aim of this study was

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Table 1. Demographic Characteristics of Healthy Controls and Patients Shown as Mean (SD) Values

	Healthy Control Subjects ($n = 15$)	Patients ($n = 25$)	p Value
Age (Years)	35.5 (10.8)	39.4 (10.4)	.27
Sex (Female/Male)	5/10	9/16	.86[a]
Weight (kg)	70.0 (10.5)	75.0 (12.6)	.19
Hamilton Depression Rating Scale		20.6 (5.2)	
Illness Duration (Months)		51.8 (63.9)	
Number of Episodes		1.52 (.6)	

[a]Chi-Square Test.

therefore to investigate whether such patients show a dysfunction, in terms of decrease or increase, of functional connectivity between the OFC and these brain regions during an emotion processing task.

Methods and Materials

Subjects

Twenty-five patients with major depression were recruited from the Department of Psychiatry of the Ludwig-Maximilian University, Munich (Table 1). Psychiatric diagnoses were based on DSM-IV criteria and the Structured Clinical Interview for DSM-IV and determined by a consensus of at least two psychiatrists. All patients were antidepressant free: 16 patients had never received antidepressant medication; nine patients had received antidepressant medications during a previous episode but not within the year before the fMRI investigation. Patients were allowed to have benzodiazepines. Ten patients did not need any benzodiazepines, whereas the rest of the patients had in the mean 1.7 (.56) mg of lorazepam. Clinical variables were documented using the Hamilton Depression Rating Scale (HDRS).

For comparison, 15 healthy control subjects, matched for age, sex, and handedness, were enrolled. Each group included one left-handed subject. A structured interview was used to assess medical history and exclusion criteria. Exclusion criteria for patients and control subjects were previous head injury with loss of consciousness; cortisol medication in the medical history; previous alcohol or substance abuse; previous neurological diseases; age under 18 or over 65; pregnancy; and comorbidity with other mental or neurological illnesses or with personality disorders. No subject had received electroconvulsive therapy. Neither the healthy control subjects nor their first-degree relatives had a history of neurological or mental illness. Handedness of all participants was determined using the Edinburgh Inventory (16). After an extensive description of the study, written informed consent was obtained from all study participants. The study protocol was approved by the local ethics committee of the Ludwig-Maximilian University and prepared in accordance to the ethical standards laid down in the Declaration of Helsinki.

Emotional Paradigm

Stimuli consisted of faces taken from a database (17). The facial recognition task was adapted from Hariri *et al.* (18); we made changes with respect to the kind of emotion and used explicit as well as implicit conditions. Instead of using sad and anxious faces, we included sad and angry faces, because we wanted to focus on clear major depression without comorbidity of anxiety. With respect to the explicit task, each picture that was presented consisted of one face at the top (presented in the middle) and two faces (left and right) at the bottom. There were 48 of these kinds of pictures (triplets) of emotional faces (sad or angry), arranged in a block design, resulting in eight blocks of six triplets each, interspersed with nine control blocks. Control blocks consisted of six triplets each, presenting simple geometric, black figures (squares, triangles, circles, ellipses). For the explicit task, each triplet contained either three female or three male faces. Participants were instructed to choose which faces at the bottom (left or right) had the same emotional expression as the face at the top. Responses were given with an fMRI-compatible LumiTouchsystem (Photon Control Inc., Burnaby, Canada) using two keys for choosing the right or left face. For the implicit task, each triplet contained one male or female face as the target at the top and two other faces of both sexes at the bottom (left and right). Participants were asked to determine the sex of the individual at the bottom (left or right) that matched the target face. The target faces alternately showed angry and sad emotions. Again subjects had to respond with the LumiTouchsystem. Each triplet was presented for 5.3 sec, resulting in a total length of about 9 min for each task (eight blocks with emotional faces, nine control blocks with geometric figures). The order of tasks (explicit, implicit) and of target stimuli was randomized.

Image Acquisition

Functional images were acquired on a 3-T MRT-Scanner (Signa HDx, GE Healthcare, Milwaukee, Wisconsin), using a T2*-weighted gradient echo-planar imaging sequence (repetition time [TR] 2100 msec, echo time [TE] 35 msec, flip angle 90°, matrix 64 × 64, field of view [FOV] 256 × 256 mm). Two functional runs, one for explicit and one for implicit processing, of 265 contiguous volumes were acquired. Volumes comprised 37 axial slices of 4-mm thickness, covering the whole brain; slices were positioned parallel to the axial plane defined by the line between anterior and posterior commissure.

Structural T1-weighted MRI were acquired within the same session using a three-dimensional fast spoiled gradient echo sequence (TR 6.9 msec, TE 3.2 msec, flip angle 15°, matrix 256 × 256, FOV 220 mm, slice thickness 1.4 mm, number of slices 248).

Behavioral Data Analysis

Behavioral performance differences between healthy control subjects and depressive patients were calculated separately for the implicit and explicit trials by using two-sample t tests for reaction time and errors.

fMRI Data Analysis

For data analysis, Statistical Parametric Mapping (SPM5, Wellcome Trust Centre for Neuroimaging, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software/spm5) was used with the following preprocessing steps: removal of the first five volumes because of T1 equilibration effects; realignment of all volumes from the sixth scan to correct for subject motion (exclusion criteria: more than 3 mm); coregistration of the functional and structural data sets; spatial normalizing into a standard stereotactic space, using a template from the Montreal Neurological Institute (MNI); and smoothing of the data with an 8-mm Gaussian kernel. A general linear model was used to calculate statistical parametric maps (19).

A standard analysis of the fMRI data of all 40 subjects was conducted to determine the regions of the orbitofrontal cortex involved in emotion processing. For each subject, the MaRsBar Toolbox (http://marsbar.sourceforge.net) (20) was then used to extract the mean voxel time series (160 time points) of the OFC

region of interest for a 10-mm radius region around the maximum area of activation within the OFC.

Functional Coupling

First Level Analysis. To map OFC coupling in the whole brain, we used a method previously introduced by our group (21). The time series representing the right and left lateral OFC (explicit: 34, 28, −8 and −34, 26, −6; implicit: 34, 30, −6, −34, 24, −6) were regressed separately on all fMRI time series in each individual's data set (without prior convolution by a model of the hemodynamic response function). This resulted in four maps (left and right OFC connectivity for the implicit and left and right OFC connectivity for the explicit task) of the regression coefficients for the effect of right and left OFC activity on all other brain regions for each study participant.

Second Level Analysis. To identify the locations of significant group, side, task, group-by-task, and group-by-side effects on OFC coupling, we performed a 2 × 2 × 2 mixed effects analysis of covariance (ANCOVA) using the OFC coupling as the dependent variable and age and sex as covariates. We had 25 drug-free patients but only 15 healthy volunteers, so the group sizes were not balanced, which requires the use of sex as a covariate in the SPM5 analysis. Age was also entered as a covariate, because we feel that small age differences also might influence the results. The ANCOVA model included a main effect of group (with two levels: depressed patients and healthy volunteers), task (with two levels: implicit and explicit), and side (with two levels: left and right). Statistical significance was based on a threshold of $p < .05$ (family-wise error [FWE], voxel-level corrected). Moreover, cluster-level statistical analyses were performed and are also reported in the tables (cluster level, $p < .05$, FWE corrected with a primary threshold of $p < .001$). However, voxel FWE correction is the more conservative statistical approach, and so we focus mainly on these findings, which are also indicated bold in the result tables. The anatomic localization of

Table 2. Brain Regions Showing Lower Orbitofrontal Cortex Connectivity in Patients Compared with Control Subjects

	k	Cluster (FWE)	Region	FWE	*T* Value	MNI Coordinates
Overall Effect						
Patients < control subjects	1184	<.001	**Precuneus Right**	.004	5.55	2, −58, 70
	731	<.001	**Cerebellum Left**	.006	5.43	−8, −28, −14
	349	.013	Thalamus Right	.051	4.89	2, −6, −4
Implicit > explicit	2428	<.001	**Precuneus Right**	<.001	6.22	2, −58, 70
and			**Occipital Sup Left**	.003	5.62	−2, −86, 52
Patients < control subjects			**Middle Cingulum Left**	.024	5.09	0, −38, 52
	509	.002	**Cerebellum Left**	.015	4.99	−6, −40, −6
			Lingual Right	.840	3.84	6, −42, 4
	305	.022	**Crus Cerebelli Right**	.023	5.09	52, −68, −44
			Crus Cerebelli Right	.177	4.53	50, −58, −50
	183	.127	**Middle Temporal Right**	.040	4.95	68, −54, −8
	253	.046	Thalamus Right	.069	4.8	2, −6, −4
Explicit > implicit	988	<.001	**Cerebellum Left**	.001	5.77	−8, −26, −14
and			**Cerebellum Right**	.046	4.91	6, −28, −16
Patients < control subjects			Hippocampus Right	.200	4.49	18, −26, −6
	122	.111	**Superior Parietal Left**	.029	5.04	−28, −52, 50
	406	.006	Fusiform Right	.052	4.88	38, −22, −34
	626	<.001	Superior Parietal Right	.090	4.73	26, −62, 76
			Postcentral Left	.135	4.61	−22, −46, 82
	386	.008	Thalamus Right	.106	4.68	4, −6, −4
			Hippocampus Left	.894	3.77	−8, −6, −12
	267	.038	Fusiform Left	.503	4.15	−32, −94, −16
			Calcarine Left	.586	4.08	−20, −104, −6
Explicit	492	<.001	**Middle Temporal Right**	.032	5.01	48, −26, −14
Patients < control subjects			Superior Temporal Right	.780	3.90	56, −30, 10
	361	.011	Parahippocampal Left	.077	4.77	−10, −24, −14
			Cerebellum Left	.789	3.89	−4, −38, −8
	304	.023	Fusiform Left	.106	4.68	−28, −16, −42
			Inferior Temporal Left	.772	3.91	−46, −32, −28
	444	.004	Precuneus Right	.213	4.47	2, −58, 70
			Paracentral Left	.761	3.92	−2, −40, 76
Implicit	449	.004	**Thalamus Right**	.019	5.14	2, −4, −4
Patients < control subjects			Caudate Right	.932	3.71	8, 2, −14
	773	<.001	**Precuneus Right**	.047	4.91	0, −58, 70
			Superior Parietal Right	.144	4.59	26, −62, 74
	559	.001	Cerebellum Left	.088	4.74	−8, −28, −14
			Precuneus Right	.139	4.6	12, −38, 6
	248	.049	Lingual Left	.251	4.41	−34, −90, −16
			Crus Cerebral Left	.391	4.25	−36, −88, −30

Bold type indicates regions for which the difference was significant on the voxel level (FWE, $p < .05$ for multiple correction). Regions not in bold type were significant at the cluster level (FWE, $p < .05$), Cluster (FWE) and voxel (FWE) *p* values are indicated.

FWE, family-wise error.

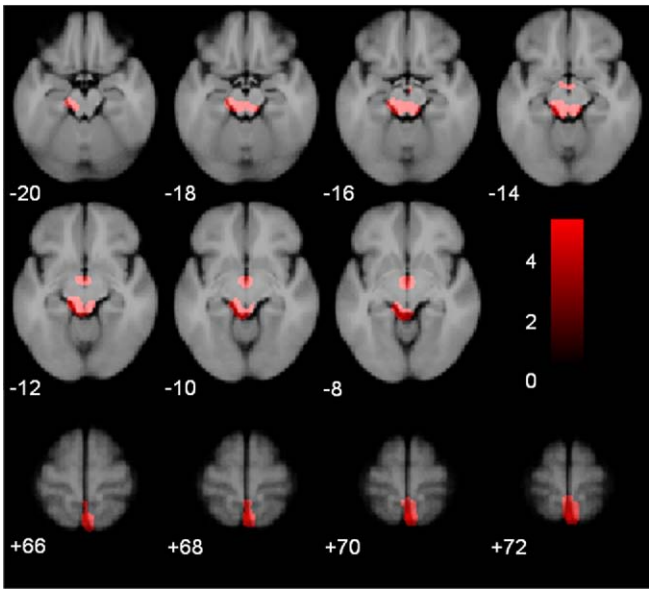

Figure 1. Functional connectivity between the orbitofrontal cortex and the right precuneus, left cerebellum, and right thalamus was significantly lower in patients than in control subjects (cluster level statistics, family-wise error $< .05$). These brain regions are indicated by the colored areas.

significant clusters was identified using the SPM5 toolbox automated anatomic labeling (22).

Results

There were no significant differences in age, sex, or weight between the patients and healthy control subjects (Table 1). Patients and control subjects showed no differences in the number of correct responses or reaction time in the explicit, implicit or comparison conditions. No significant differences were detected between connectivity of the left and right OFC.

Disruptions of Functional Coupling in Patients

Table 2 shows the regions in which patients had weaker OFC connectivity than healthy control subjects. There was a significant overall group effect, with patients having significantly lower functional connectivity between the OFC and both the right precuneus and the left cerebellum ($p < .05$, FWE voxel level). The lower connectivity with the right thalamus was only significant after a cluster level correction (Figure 1). In the explicit task, patients showed less connectivity than control subjects between the OFC and the right middle temporal cortex, right precuneus, and left parahippocampal, left fusiform, and left paracentral cortices; in the implicit task, they showed less OFC connectivity with the right thalamus, right precuneus, left cerebellum, and left lingual cortex.

Moreover, when the implicit and explicit tasks were compared, significantly more functional OFC connectivity with the left middle cingulum, right precuneus, right and left cerebellum, and superior occipital left and right middle temporal gyrus was detected in the healthy control subjects than in the patients (Table 2). Patients showed fewer differences than healthy control subjects between implicit and explicit processing; healthy control subjects had significantly increased functional connectivity between the OFC and the left middle cingulum, anterior cingulum, left dorsolateral prefrontal cortex, left and right superior medial prefrontal cortex, olfactory region, and left paracentral lobule in the implicit condition than in the explicit condition.

Enhanced Functional Connectivity in Patients

Table 3 shows that the connectivity between the OFC and the left angular gyrus, left middle occipital cortex, left supplementary motor area, left precentral, right frontal inferior operculum, right middle frontal gyrus, and right inferior parietal cortex was significantly increased in patients than in control subjects (Figure 2). OFC connectivity was higher in the implicit than in the explicit condition; it was also higher in patients than in control subjects in the left angular cortex, left and right supplementary motor area, right inferior parietal area, and left precentral cortex.

In the explicit task, compared with control subjects, patients showed higher connectivity between the OFC and the left inferior frontal operculum and left middle occipital cortex, whereas in the implicit task patients showed increased OFC connectivity than control subjects between the OFC and the right inferior parietal cortex, left angular cortex, left supplementary motor area, and left precentral cortex.

Discussion

Our study demonstrates an altered connectivity between the OFC and other brain regions of the emotion-processing circuit in untreated patients with major depression. In particular, we found that connectivity between the OFC and right dorsolateral prefrontal cortex, right inferior frontal operculum, left motor regions, and left angular cortex was increased in patients than in

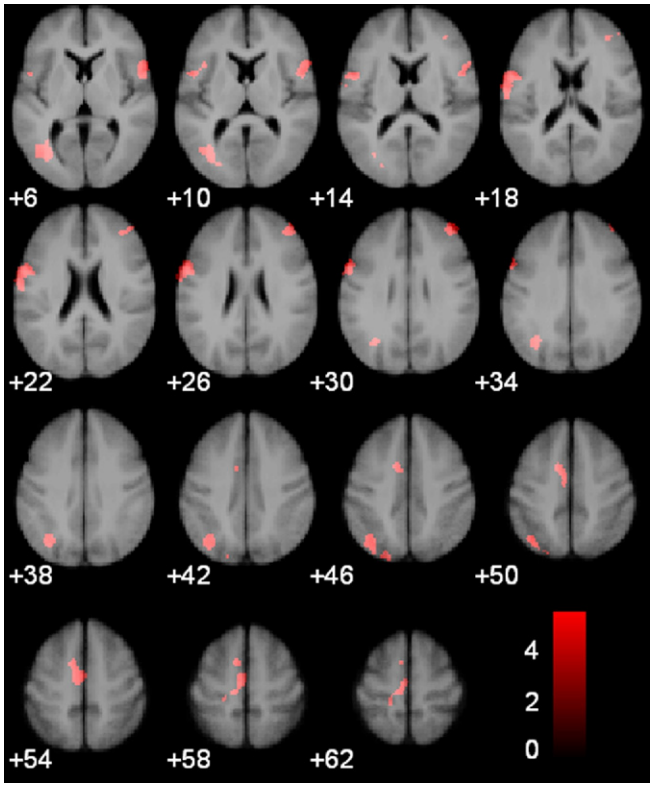

Figure 2. Significantly enhanced functional connectivity of the right dorsolateral prefrontal cortex (right middle frontal cortex), right inferior frontal operculum, right inferior parietal cortex, left angular cortex, left supplementary motor area, and left precentral cortex with the orbitofrontal cortex (cluster level statistics, family-wise error $< .05$). These brain regions are indicated by the colored areas.

Table 3. Brain Regions Showing Increased Orbitofrontal Cortex Connectivity in Patients Compared with Control Subjects

	k	Cluster (FWE)	Region	Voxel (FWE)	*T* Value	MNI Coordinates
Overall Effect						
Patients > control subjects	793	<.001	**Angular Left**	.001	5.93	−38, −74, 54
			Superior Occipital Left	.61	4.06	−22, −84, 48
	220	.074	**Inferior Parietal Right**	.006	5.45	62, −56, 46
	234	.06	**Middle Frontal Right**	.006	5.42	40, 46, 30
	464	.003	**Supplementary Motor Left**	.006	5.41	−6, −8, 54
	735	<.001	**Precentral Left**	.007	5.14	−58, 16, 38
	291	.027	**Inferior Frontal Operculum Right**	.028	5.05	56, 12, 4
	277	.033	Middle Occipital Left	.174	4.53	−36, −68, 8
Implicit > explicit	830	<.001	**Angular Left**	<.001	6.11	−38, −72, 52
and			Superior Occipital Left	.310	4.34	−22, −84, 46
Patients > control subjects	294	.026	**Supplementary Motor Left**	.002	5.71	−4, −8, 54
	642	<.001	**Inferior Parietal Right**	.003	5.62	58, −58, 52
			Supramarginal Right	.525	4.13	68, −46, 36
			Inferior Parietal Right	.845	3.74	66, −42, 48
	185	.128	**Middle Frontal Right**	.004	5.54	40, 46, 30
	216	.078	**Inferior Frontal Operculum Right**	.023	5.10	56, 12, 4
Explicit > implicit	819	<.001	**Precentral Left**	<.001	6.02	−58, 16, 38
and	1303	<.001	**Angular Left**	.007	5.39	−36, −74, 54
Patients > control subjects			**Inferior Parietal Left**	.022	5.11	−32, −64, 38
			Middle Occipital Left	.031	5.02	−36, −66, 8
	113	.368	**Inferior Frontal Operculum Right**	.036	4.98	62, 16, 32
	146	.223	**Supplementary Motor Left**	.044	4.93	−6, 22, 46
Explicit	518	.002	**Inferior Frontal Operculum Left**	.002	5.68	−54, 6, 18
Patients > control subjects			Postcentral Left	.58	4.08	−60, −6, 18
			Precentral Left	.63	4.04	−58, 16, 38
	473	.003	**Middle Occipital Left**	.009	5.34	−34, −64, 36
			Inferior Parietal Left	.073	4.79	−36, −76, 52
	394	.007	Supplementary Motor Left	.318	4.33	−10, 0, 54
			Precentral Left	.411	4.23	−24, −18, 60
Implicit	410	.006	**Inferior Parietal Right**	<.001	6.41	62, −56, 46
Patients > control subjects			Angular Right	.085	4.75	56, −62, 52
			Supramarginal Right	.125	4.63	70, −42, 36
	591	.001	**Angular Left**	.002	5.74	−38, −72, 54
			Superior Occipital Left	.712	3.97	−24, −84, 48
	160	.181	**Supplementary Motor Left**	.007	5.38	−4, −10, 54
	428	.005	**Precentral Left**	.028	5.04	−58, 16, 38

Bold type indicates are regions for which the difference was significant on a voxel level FWE, $p < .05$, for multiple correction). Regions not in bold type were significant only at the cluster level (FWE, $p < .05$). Cluster (FWE) and voxel (FWE) *p* values are indicated.

FWE, family-wise error.

control subjects but lower in patients in the middle ACC, precuneus, cerebellum, and right thalamus.

Structural connections with the OFC have been described for the amygdala, anterior and posterior cingulum, prefrontal areas 9 and 46, and the premotor area (1). Therefore, it is reasonable to assume that functional connectivity between the OFC and prefrontal, ACC, and left motor areas is based on these direct structural connections. However, functional connectivity does not necessarily require direct structural connections; it could also be an indirect effect of similar activation in two brain regions. Interestingly, the OFC projects to the striatum, which is connected with the ventral pallidum, which, in turn, projects to the mediodorsal thalamic nucleus and then back to the OFC (6); these connections could explain why alterations were detected in functional connectivity between the OFC and the thalamus.

Interestingly, the premotor area contains the representation of distal arm movement, with neurons responding to goal-related motor acts and motivational visual stimuli (23) and has reciprocal connections with the lateral and caudal OFC (24). In the fMRI tasks in our study, to indicate whether the left or right picture at the bottom was the same as the picture at the top, subjects had to press a button with their right hands, a movement that involved the left motor areas. Patients with depression overactivate a neural OFC-prefrontal motor system that is involved in processing of negative affective faces.

Another important question is, whether the processing of negative emotions is related to the emotion-processing bias seen in patients with major depression. Cognitive theories of depression (25) posit that negative cognitions, derived from dysfunctional self-schemas, play a central role in the etiology and course of depression. These dysfunctional schemas are hypothesized to bias information-processing in depression, with depressed individuals selectively attending to and remembering affectively negative material. Neuropsychologic studies support the hypothesis that patients with major depression (MD) preferentially attend to sad emotions (26). Moreover, they interpret emotionally neutral faces as sad (27) and are unable to ignore negative emotional distractor stimuli while performing a word classification task (28). Patients with MD also tend to misperceive happy faces as being neutral and neutral faces as being sad (29). Thus,

patients with MD seem to have an enhanced memory for negative material and seem to overactivate a neural system that subserves encoding of affective material. This is supported by the fMRI finding that during encoding of subsequently remembered negative stimuli the right amygdala is more active and shows increased functional connectivity with the hippocampus and caudate–putamen regions in depressed patients compared with healthy subjects (12).

Antidepressant-free patients with major depression had less connectivity among the OFC and ACC, precuneus, and cerebellum. The ACC is thought to have a crucial role in the model of affect regulation in patients with major depression (30). It includes specific processing modules for a rostral–ventral emotional and a dorsal cognitive division (31). Functional MRI findings in healthy volunteers provide direct evidence for differential engagement of ACC subdivisions in cognitive and emotion processing and for differential functional connectivity in the implementation of cognitive control and emotion regulation (32). In our study, uncoupling of the OFC was seen in the dorsal ACC of patients with major depression, which may be related to a dysfunction in cognitive control of emotion processing and may then result in or enhance the negative processing bias in major depression.

Another region that showed reduced functional coupling with OFC was the precuneus. The precuneus belongs to a medial prefrontal–midparietal neural network supporting the mental representation of the self. Various tasks such as visuospatial imagery, episodic memory retrieval, and self-processing operations—namely, first-person perspective taking and an experience of agency, have been related to the precuneus. Some of the visuospatial imagery studies suggest involvement in internally guided attention to and manipulation of mental images, while those directed at mental imagery more directly draw upon internal self-representation, which is also implicated in most episodic memory retrieval and first person perspective-taking tasks. All of these findings were brought together to form the hypothesis that the precuneus plays a central role in the modulation of conscious processes (33). Although no direct structural connections between the OFC and the precuneus have been described, they are functionally connected; a disruption of functional connectivity between the OFC and the precuneus may be the neural correlate of an alteration in the mental representation of the self and disturbances of self-processing operations in patients with major depression. This disruption of functional connectivity may result in the negative self-view of patients with major depression and in their lack of energy for self-related interests, but this hypothesis needs to be confirmed with special psychopathologic and neuropsychologic ratings and also with a specific fMRI task that involves self-representation.

The cerebellum is critical for motor learning (34), is involved in affect processing, and shows volume decline in patients with major depression (35). For a long time, the cerebellum was not considered in neurobiological studies; however, recent findings indicate that it seems to be more important than previously thought.

Because our patients were antidepressant-free, it can be concluded that the imbalance in OFC connectivity was associated with the disease process and not with medication effects. Other studies have shown functional disconnections between brain regions in patients already treated with antidepressants; however, it was not clear whether an effect of the antidepressant could have been responsible for this alteration. The antidepressant-free patient sample is relatively large for neuroimaging studies; however, the sample of healthy control subjects included fewer subjects and is not balanced, which is a limitation. However, both patients and control subjects did not differ with respect to age and gender distribution. Moreover, earlier studies differed with respect to the kind of task used (e.g., cognitive tasks, and thus the brain regions involved). The task is relevant to the areas that will be activated and can then show connectivity, for example, with the OFC. Therefore, a limitation of these kinds of studies is that conclusions can only be drawn on brain regions that are involved in the task processing. One other study focused on the frontal cortex connectivity using a cognitive task and found that, compared with 14 healthy control subjects, 14 patients with major depression who received antidepressants showed an altered connectivity of dissociable prefrontal and cingulate regions (14). Amygdala–prefrontal connectivity was significantly lower in 34 depressed patients receiving antidepressant treatment than in the healthy control subjects (13). Sixteen unmedicated patients with major depression showed a higher connectivity for the dorsal to rostral ACC than healthy control subjects (36). Interestingly, a study in healthy volunteers did show that inflammation-associated changes in total mood, which were experimentally received by typhoid vaccination, modulated the connectivity of the ACC and nucleus accumbens with reduction in effective interconnectivity predicting greater deterioration in total mood (37). Therefore, in the future, it will be interesting to link other neurobiological findings like changes in neurochemistry to functional brain changes in major depression.

In conclusion, functional connectivity between the OFC and regions of the emotion circuit plays a considerable role in the pathophysiology of major depression. Patients with depression seem to overactivate the neural orbitofrontal–prefrontal system during negative emotion processing. Whether this is related to the negative processing bias is speculative and needs further exploration. Moreover, we showed underactivation in the neural orbitofrontal–cingulate system, which may be related to the failure to balance or regulate positive and negative processing. Interestingly, disruptive connectivity was also found between the OFC and the precuneus, which could hypothetically explain the negative self-view of patients with major depression. A further step is to connectivity analysis of fMRI for therapy evaluation, which may be advanced compared with standard fMRI analysis. It is hoped that this could facilitate the development of new therapeutics.

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