

Prefrontal brain responsiveness to negative stimuli distinguishes familial risk for major depression from acute disorder

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Background: Identifying reliable trait markers of familial risk for major depressive disorder (MDD) is a challenge in translational psychiatric research. In individuals with acute MDD, dysfunctional connectivity patterns of prefrontal areas have been shown repeatedly. However, it has been unclear in which neuronal networks functional alterations in individuals at familial risk for MDD might be present and to what extent they resemble findings previously reported in those with acute MDD. **Methods:** We investigated differences in blood oxygen level-dependent (BOLD) response of the medial orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) to aversive stimuli between acute MDD and familial risk for the disorder in healthy first-degree relatives of acutely depressed patients with MDD (HC-FH+), healthy age- and sex-matched controls without any family history of depression (HC-FH-), and acutely depressed patients with MDD with (MDD-FH+) and without a family history of depression (MDD-FH-) during a frequently used emotional face-matching paradigm. Analyses of task-specific network connectivity were conducted in terms of psychophysiological interactions (PPI). **Results:** The present analysis included a total of 100 participants: 25 HC-FH+, 25 HC-FH-, 25 MDD-FH+ and 25 MDD-FH-. Patients with MDD exhibited significantly increased activation in the medial OFC to negative stimuli irrespective of familial risk status, whereas healthy participants at familial risk and patients with MDD alike showed significant hypoactivation in the DLPFC compared with healthy participants without familial risk. The PPI analyses revealed significantly enhanced task-specific coupling between the medial OFC and differing cortical areas in individuals with acute MDD and those with familial risk for the disorder. **Limitations:** The main limitation of our study is its cross-sectional design. **Conclusion:** Whereas hypoactivation during negative emotion processing in the DLPFC appears as a common feature in both healthy high-risk individuals and acutely depressed patients, activation patterns of the medial OFC and its underlying connectivity seem to distinguish familial risk from acute disorder.

Introduction

Major depressive disorder (MDD) ranks among the most disabling and thus most cost-producing health care issues in developed countries.¹ Enhanced prevention of this disorder is one of the principal long-term objectives of translational psychiatric research. For this purpose, it is essential to gain a better understanding of the underlying etiological processes leading the way from disease risk to disease onset. As genetic liability for MDD remains one of the best known risk factors for the disorder, the precise delineation of trait markers of familial risk for MDD has frequently been suggested as an important requirement in achieving this aim.^{2,3}

In recent years neuroimaging studies have described overlapping structural alterations in individuals with MDD and corresponding risk factors, whereas evidence for reliable functional biomarkers of different MDD risk factors is still widely absent.⁴

Acute MDD is frequently reported to be characterized by overactive bottom-up signalling during emotion processing, probably combined with decreased top-down or regulatory mechanisms in cortical brain areas. More precisely, over the last decade enhanced neural response in a ventromedial neural circuit, including the medial orbitofrontal cortex (OFC), the amygdala and the insula, and decreased neural response in a dorsal network, predominantly involving the

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dorsolateral prefrontal cortex (DLPFC), have been shown to be the most consistent functional imaging findings in studies of acute MDD.^{5,6}

However, the few existing studies focusing on functional alterations associated with familial risk for MDD have reported differing results.⁴ For example, Joorman and colleagues⁷ found reduced DLPFC activation in female participants at high familial risk for MDD during automatic mood regulation. These findings were confirmed by a study reporting reduced DLPFC activation in individuals at familial risk for MDD during presentation of fearful faces.⁸ A study by Lévesque and colleagues⁹ reported associations between more severe depressive symptomatology in parents and higher activation levels in the insula and the cingulate cortex in their corresponding offspring. Although the notion of overactivation in the cingulate cortex during emotion processing associated with familial risk for MDD was corroborated by Lisiecka and colleagues,¹⁰ a more recent study showed deactivation of the subgenual cingulate cortex associated with future diagnosis of MDD in high-risk individuals.¹¹

These differences might be explained by the heterogeneity of experimental procedures, but also by vast differences in the inclusion and exclusion criteria of previous studies, particularly regarding the assessment of risk factors for MDD. Moreover, most studies investigating functional correlates of familial risk for MDD did not include both healthy and patient samples. One of the few functional MRI (fMRI) studies including both patients and healthy individuals stratified for familial risk status pointed to aberrant executive control functioning during emotional processing in unaffected first-degree relatives of patients with MDD.¹²

It remains unclear in which neuronal networks functional alterations in individuals at familial risk for MDD might be present and to what degree they might resemble aberrant neural signalling in acute MDD. Hence, with this study we aimed to compare alterations in the 2 most commonly reported MDD-related neuronal circuits in familial risk and in acute disorder. We thus investigated functional alterations in the medial OFC as a key structure of the ventromedial/bottom-up signalling circuit and the DLPFC for the dorsolateral/top-down network during presentation of negative stimuli in acute disorder and in familial risk for MDD, using a 2-factorial design with familial risk (presence *v.* absence) and disease status (MDD *v.* healthy controls). We hypothesized that acute MDD would be associated with overactivation in the medial OFC, whereas familial risk would be characterized by decreased signalling in the DLPFC.

Methods

Participants

We recruited healthy relatives of patients with MDD (HC-FH+), sex- and age-matched healthy controls with no family history of MDD (HC-FH-), acutely depressed patients with a positive family history of MDD (MDD-FH+) and acutely depressed patients without a family history of MDD (MDD-FH-) to participate in this study.

Among the controls, the HC-FH+ group consisted of healthy first-degree relatives of patients with MDD under current or former inpatient treatment at the University Hospital of Münster, Germany. Clinical diagnoses in all depressed relatives of the HC-FH+ group were obtained using the DSM-IV Structured Clinical Interview (SCID-I).¹³ Participants of the HC-FH- group were recruited via public notices and newspaper announcements. To be included in either the HC-FH+ or the HC-FH- group, participants had to be free from any history of psychiatric disorders according to the SCID interview, as conducted by a clinically experienced interviewer.

The patients included in the present study were under current inpatient treatment at the University Hospital of Münster. To assess the influence of psychopharmacological therapy in the MDD sample, medication load was coded in terms of dose and treatment durations into levels 1–4 according to the suggestions of Sackeim¹⁴ and as conducted previously by our group and others.^{15–17} To be included, patients with MDD had to be free from psychotic symptoms according to the SCID-I.¹³

We assessed family history of depression in the MDD-FH+, the MDD-FH- and the HC-FH- samples via familial anamnesis. We included individuals in the HC-FH- and MDD-FH- samples only if absence of any affective disorder, including unipolar and bipolar disorder in all first-degree relatives, could be ascertained via familial anamnesis.

To assess the current level of depressive symptoms we administered the Hamilton Rating Scale for Depression (HAM-D)¹⁸ and the Beck Depression Inventory (BDI).¹⁹ In all samples, exclusion criteria were any history of neurologic (e.g., concussion, stroke, tumour, neuroinflammatory diseases) and medical (e.g., cancer, chronic inflammatory or autoimmune diseases, heart diseases, diabetes mellitus, infections) conditions, and for the HC-FH+ and the HC-FH- samples we excluded individuals regularly taking medication. All participants had to have normal or corrected-to-normal vision as well as adequate knowledge of German and cognitive abilities (verbal IQ > 80; multiple-choice vocabulary intelligence test MWT-B²⁰). We evaluated presence and level of childhood maltreatment with the Childhood Trauma Questionnaire (CTQ), which assesses 5 types of adverse early life experiences by means of a 25-item retrospective self-report questionnaire.²¹ All participants received financial compensation. The study was approved by the ethics committee of the University of Münster, and written informed consent was obtained from all participants before their inclusion in the study.

Stimulus materials and procedure

We applied an fMRI paradigm that has repeatedly been shown to robustly elicit neural responsiveness during processing of emotional faces.^{22–24} To activate brain regions associated with emotional processing, we used a series of negative (angry and fearful) faces. More precisely, the paradigm comprised 5 blocks of a sensorimotor control task alternating with 4 blocks of a face-processing task. During the face-processing task, participants viewed a trio of faces and selected 1 of the 2 faces (bottom) that was identical to the target

face (top). Each face-processing block consisted of 6 images, balanced for target sex. Trios of geometric shapes (circles and ellipses) were presented during the sensorimotor control blocks, in which participants viewed and selected 1 of the 2 shapes (bottom) that was identical to the target shape (top). Each sensorimotor control block consisted of 6 shape trios. Each single block was preceded by an instruction (“match faces” or “match shapes” in German) that lasted 2 seconds. In the face-processing blocks, each of the 6 face trios was presented for 4 seconds with a variable interstimulus interval of 1.5–5.5 seconds (mean 3.5 seconds), for a total block length of 47 seconds. In the sensorimotor control blocks, each of the 6 shape trios was presented for 4 seconds with a fixed interstimulus interval of 1.5 seconds, for a total block length of 35 seconds. The total task time was 363 seconds. Participant performance (accuracy and reaction time) was recorded.

We acquired T_2^* functional data using a 3 T scanner (Gyrosan Intera 3T, Philips Medical Systems) and a single-shot echoplanar sequence, with parameters selected to minimize distortion in the region of central interest while retaining adequate signal-to-noise ratio and T_2^* sensitivity. Volumes consisting of 34 slices were acquired (matrix 64×64 , resolution 3.6 mm^3 , repetition time [TR] 2.1 s, echo time [TE] 30 ms, flip angle 90°). The slices were tilted 25° from the anterior–posterior commissure line in order to minimize drop-out artifacts in the mediotemporal and orbitofrontal region.

The paradigm presentation was projected to the rear end of the scanner (Sharp XG-PC10XE with additional high-frequency shielding). During the experiment, participants lay supine in the MRI scanner with the response box in their right hand. The head position was stabilized with a vacuum head cushion.

Statistical analysis

Data were analyzed using statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm). Functional data were pre-processed, including realignment using a set of 6 rigid-body transformations determined for each image as well as unwarping and normalization of each participant’s functional images to the Montreal Neurological Institute International Consortium for Brain Mapping (MNI) template. Images were smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

Following published protocols,^{25,26} 1 participant from the HC-FH+ and 1 participant from the HC-FH– group had to be excluded from the fMRI analyses owing to excessive head movement (exclusion criterion $3 \text{ mm}/3^\circ$). No significant differences in head movement could be detected between groups ($p > 0.87$).

The onsets and durations of the experimental conditions (faces and shapes) were modelled using a canonical hemodynamic response function in the context of the general linear model, and the model was corrected for serial correlations. We used a high-pass filter of 128 seconds to remove low-frequency noise. For each participant, 1 contrast image (contrasting negative faces with the shapes baseline) was

generated in each individual first-level analysis. Analyses of group differences were subsequently carried out on the second level based on the resulting contrast images using a full factorial design.

Second-level analyses

At first, in order to address our hypothesis regarding differing functional alterations in lateral and medial prefrontal brain areas associated with acute MDD and familial risk for MDD, region of interest (ROI) analyses of blood oxygen level–dependent (BOLD) response were performed for the bilateral medial OFC and the bilateral DLPFC. The bilateral medial OFC mask was created by means of the Wake Forest University (WFU) PickAtlas²⁷ by dilating the bilateral mask of the orbital part of the medial frontal gyrus according to the automated anatomical labelling atlas²⁸ by 1 mm. The mask for the bilateral DLPFC included the entire bilateral Brodmann areas 9 and 46, again dilated by 1 mm, while leaving out all voxels medial of $x = 20/-20$ in order to solely comprise voxels of lateral parts of the prefrontal cortex. In order to control for multiple statistical testing, we maintained a cluster-level corrected false-positive detection rate at $p < 0.05$, which, since all hypotheses were tested in 2 ROIs (medial OFC and bilateral DLPFC), was again adjusted using Bonferroni correction ($p = 0.05 \div 2$), resulting in a final false-positive threshold of $p = 0.025$ using a voxel-level threshold of $p < 0.01$ for each mask with a cluster extent (k) empirically determined by Monte Carlo simulations ($n = 5000$ iterations). This was performed by means of the AlphaSim procedure, which accounted for spatial correlations between grey matter values in neighbouring voxels, implemented in the REST toolbox (<http://restfmri.net/forum/index.php>).^{16,29–31} The cluster threshold calculation was based on a residual smoothness value of 10 mm FWHM, as estimated with SPM8. The empirically determined cluster threshold was $k = 26$ voxels for the medial OFC and $k = 40$ voxels for the bilateral DLPFC.

The following steps were carried out to address our hypotheses:

- 1) We conducted a group (HC, MDD) \times family history (FH+, FH–) analysis of variance (ANOVA) of BOLD contrasts to investigate corresponding main and interaction effects.
- 2) To test our hypothesis of hyperactivation during presentation of negative stimuli in the OFC in acute disorder, we carried out 2-sided t tests between the MDD and control participants.
- 3) To test our hypothesis of decreased signalling in the DLPFC being associated with familial risk for the disorder, we conducted 2-sided t tests between the HC-FH+ and HC-FH– groups and between the MDD and HC-FH– groups.

Additionally, we conducted analyses of psychophysiological interactions (PPI) to detect possibly altered network connectivity associated with the faces versus shapes condition, as performed previously.^{26,32,33} Therefore, the clusters of the DLPFC and OFC yielding significant effects in the preceding fMRI analyses were defined as seed regions. The signal time courses of these seeds were extracted, and the faces versus shapes contrast served as a psychological factor. The individual contrast images of the PPI terms reflecting the

influence of task condition on network connectivity were modelled into 2 new group \times family history ANOVAs (DLPFC and medial OFC).

For analyses of psychophysiological interactions as well as for additional whole brain analyses, we controlled for multiple statistical testing by maintaining a cluster level-corrected false-positive detection rate at $p < 0.05$ by using the AlphaSim procedure for a mask comprising the entire cerebrum, yielding a cluster level-corrected false-positive detection rate at $p < 0.05$ using a voxel-level threshold of $p < 0.001$ with a cluster threshold of $k = 89$ voxels ($n = 5000$ iterations; residual smoothness value of 10 mm FWHM, as estimated by SPM8).

Results

Participants

Our initial study sample comprised 26 participants in the HC-FH+ group, 26 in the HC-FH- group, 25 in the MDD-FH+ group and 25 in the MDD-FH- group; however, owing to excessive movements, 1 HC-FH+ participant and 1 HC-FH- participant had to be excluded, leaving a final study sample of 25 participants per group (Table 1).

Functional MRI analyses of group differences in the OFC and the DLPFC

With regard to our first analysis step, the group (HC, MDD) \times family history (FH+, FH-) ANOVA of BOLD contrasts revealed no significant main effect of family history and no

significant interaction effect of diagnostic group \times family history in the DLPFC or OFC. A significant main effect of diagnostic group (HC, MDD) was exclusively found in the medial OFC (MNI coordinates: $x, y, z = 6, 52, -12$, $F_{1,96} = 14.60$, z -score = 3.50, $p < 0.001$, $k = 58$ voxels; Fig. 1 and Fig. 2).

In accordance with our second analysis step, independent t tests revealed that depressed patients showed significantly enhanced BOLD response to negative stimuli in the medial OFC compared with healthy controls, irrespective of family history (MNI coordinates: $x, y, z = 6, 52, -12$, $t_{1,96} = 3.82$, z -score = 3.68, $p < 0.001$, $k = 128$ voxels).

Finally, in the right DLPFC significantly reduced BOLD response to negative stimuli emerged in the HC-FH+ compared with the HC-FH- group (MNI coordinates: $x, y, z = 48, 28, 42$, $t_{1,96} = 4.04$, z -score = 3.88, $p < 0.001$, $k = 185$ voxels) as well as in the MDD groups compared with the HC-FH- group (MDD-FH+ v. HC-FH-: MNI coordinates: $x, y, z = 48, 30, 18$, $t_{1,96} = 3.73$, z -score = 3.59, $p < 0.001$, $k = 104$ voxels; MDD-FH- v. HC-FH-: MNI coordinates: $x, y, z = 50, 32, 22$, $t_{1,96} = 3.42$, z -score = 3.31, $p < 0.001$, $k = 277$ voxels). No significant differences in BOLD contrast could be observed between the MDD-FH+ and MDD-FH- groups.

No significant interaction or main effect could be observed in additional whole brain analyses at the applied thresholds.

As the prevalence of adverse early-life experiences has been shown to be elevated in relatives of depressed patients,³⁴ we aimed to control for a possible confounding effect of childhood trauma by repeating the analysis of group differences on BOLD response, including CTQ sum scores as a covariate of no interest. The same pattern of results could be observed. Again, depressed patients exhibited significantly

Table 1: Demographic and clinical characteristics of our final study sample

Characteristic	Group; mean \pm SD*				p value†
	HC-FH+ ($n = 25$)	HC-FH- ($n = 25$)	MDD-FH+ ($n = 25$)	MDD-FH- ($n = 25$)	
Age	37.12 \pm 12.95	37.16 \pm 12.54	37.20 \pm 12.83	37.60 \pm 12.86	> 0.99
Sex, male:female	10:15	10:15	11:14	10:15	0.99
HAMD score	5.32 \pm 5.06	2.16 \pm 1.86	26.12 \pm 8.35	27.32 \pm 9.38	< 0.001
BDI score	1.08 \pm 1.66	1.04 \pm 1.23	23.20 \pm 4.12	23.72 \pm 4.73	< 0.001
CTQ total score	35.84 \pm 9.02	32.44 \pm 6.98	48.33 \pm 17.66	47.56 \pm 15.96	< 0.001
No. of depressive episodes	NA	NA	5.72 \pm 5.46	3.44 \pm 4.13	0.10
Total duration of inpatient treatment, wk	NA	NA	14.52 \pm 18.53	7.12 \pm 10.12	0.09
Medication type, no.					
SNRIs	NA	NA	8	9	0.77
SSRIs	NA	NA	7	8	0.76
NaSSAs	NA	NA	4	7	0.31
Tricyclic antidepressants	NA	NA	1	0	0.31
Melatonergic antidepressants	NA	NA	3	2	0.64
NRIs	NA	NA	0	1	0.31
Antipsychotics	NA	NA	12	10	0.57

BDI = Beck Depression Inventory; CTQ = Childhood Trauma Questionnaire; HAMD = Hamilton Rating Scale for Depression; HC-FH+ = healthy first-degree relatives of acutely depressed patients with MDD; HC-FH- = healthy age- and sex-matched controls without any family history of depression; MDD-FH+ = acutely depressed patients with major depressive disorder with a family history of depression; MDD-FH- = acutely depressed patients without a family history of depression; NA = not applicable; NaSSA = noreadrenergic and specific serotonergic antidepressants; NRI = norepinephrine reuptake inhibitor; SD = standard deviation; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

*Unless indicated otherwise.

†Group differences measured with analysis of variance or χ^2 tests.

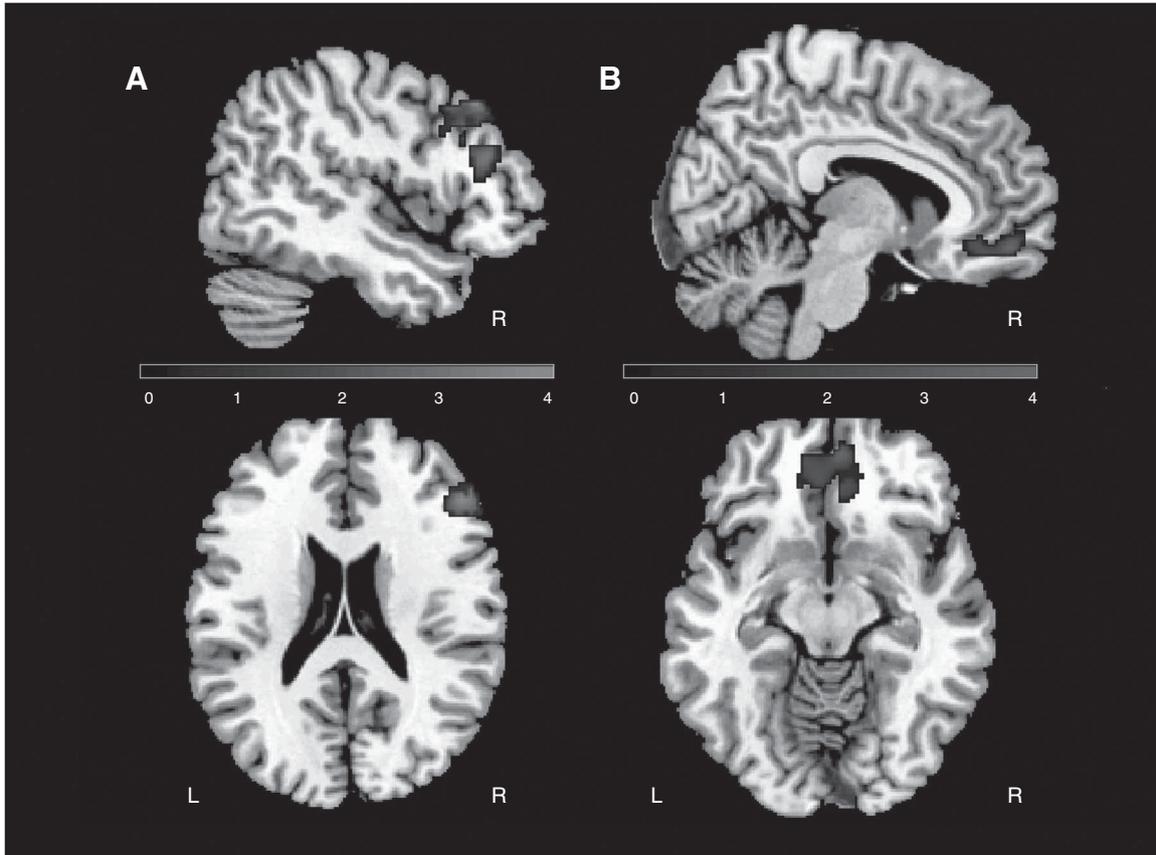


Fig. 1: A) Healthy first-degree relatives of acutely depressed patients with major depressive disorder (MDD) exhibit significantly reduced blood oxygen level-dependent (BOLD) response to negative stimuli in the right dorsolateral prefrontal cortex (DLPFC) compared with age- and sex-matched controls without any family history of depression (Montreal Neurological Institute [MNI] coordinates: $x, z = 47, 21$). **B)** Participants with MDD show increased BOLD response to negative stimuli in the medial orbitofrontal cortex (OFC) compared with healthy controls (MNI coordinates: $x, z = 8, -11$). For display reasons values are thresholded at $p = 0.05$, uncorrected. L = left hemisphere; R = right hemisphere.

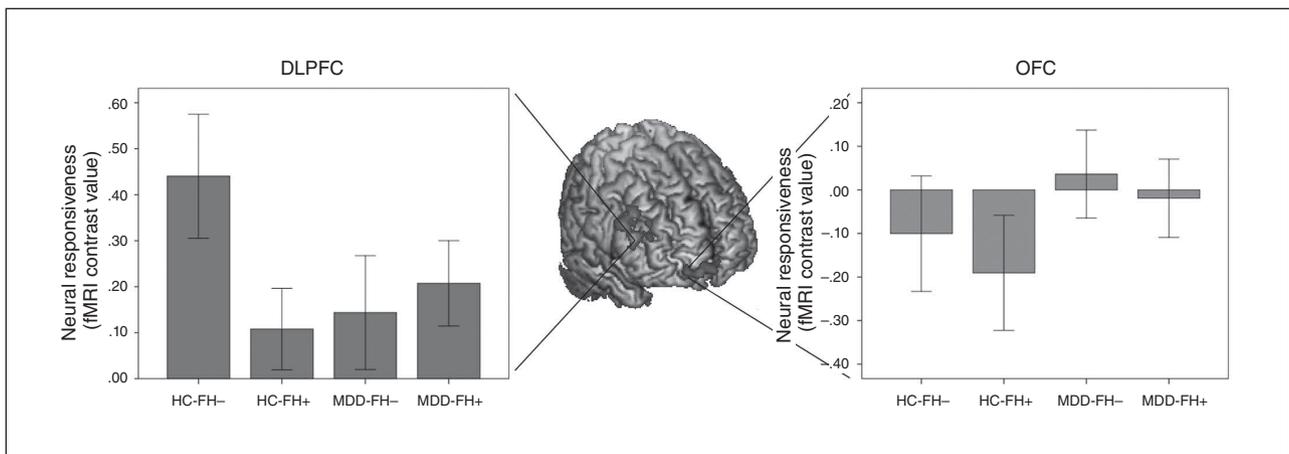


Fig. 2: Plots depicting differences in blood oxygen level-dependent (BOLD) response (mean fMRI contrast value) among the groups for the right dorsolateral prefrontal cortex (DLPFC; at Montreal Neurological Institute [MNI] coordinates $x, y, z = 48, 28, 42$) and the medial orbitofrontal cortex (OFC; at MNI coordinates $x, y, z = 6, 52, -12$). For display reasons values are thresholded at $p = 0.05$, uncorrected. Error bars depict the 95% confidence interval. HC-FH+ = healthy first-degree relatives of acutely depressed patients with MDD; HC-FH- = healthy age- and sex-matched controls without any family history of depression; MDD-FH+ = acutely depressed patients with major depressive disorder with a family history of depression; MDD-FH- = acutely depressed patients without a family history of depression.

enhanced BOLD response in the medial OFC compared with healthy individuals, irrespective of family history for MDD (MNI coordinates: $x, y, z = 6, 52, -12$, $t_{1,94} = 3.88$, $p < 0.001$, $k = 97$ voxels). Additionally, the HC-FH+ group again showed significantly reduced BOLD response in the right DLPFC compared with the HC-FH- group (MNI coordinates: $x, y, z = 48, 28, 42$, $t_{1,94} = 3.88$, $p < 0.001$, $k = 137$ voxels). No other significant main or interaction effect could be detected for this model at the applied thresholds. Additionally, no significant associations between CTQ sum scores and BOLD response could be detected in whole brain analyses at the applied thresholds, and no significant interaction effect of CTQ \times family history emerged.

To determine possible associations between depressive symptoms and BOLD response in our ROIs, regression analyses of BDI scores on BOLD response in the DLPFC and OFC were conducted for all participants ($n = 100$), controlling for age and sex as nuisance regressors. As could be expected, BDI scores were positively associated with BOLD response in the medial OFC (MNI coordinates: $x, y, z = 10, 38, -14$, $t_{1,96} = 3.25$, z -score = 3.16, $p < 0.001$, $k = 46$ voxels), whereas no positive or negative association between BDI scores and BOLD contrast in the DLPFC could be observed.

To rule out a possible influence of medication load on BOLD contrast in our ROIs, multiple regression of medication load scores (Sackeim scores) on BOLD response of the DLPFC and the medial OFC were performed for all participants with MDD ($n = 50$). No significant associations be-

tween medication load and BOLD response in the DLPFC or the medial OFC could be detected at the applied thresholds. Moreover, no association between medication load and whole brain BOLD response emerged at an exploratory threshold of $p < 0.001$ and $k > 25$ voxels.

No differences in mean reaction time or mean performance (correct v. wrong responses) in the fMRI task could be detected between groups (all $p > 0.27$).

Analyses of PPI

The ANOVA of the PPI contrasts with the medial OFC as a seed region revealed a significant interaction effect of diagnostic group \times family history in the occipital cortex (MNI coordinates: $x, y, z = 36, -88, 4$, $k = 138$ voxels; Table 2 and Fig. 3). A significant main effect of family history for MDD emerged in terms of enhanced functional coupling between the medial OFC and occipital cortical areas (MNI coordinates: $x, y, z = 28, -94, 4$, $k = 272$ voxels). Moreover, significantly enhanced task-specific neural coupling between the medial OFC and the parietal cortex (MNI coordinates: $x, y, z = 62, -24, 30$, $k = 550$ voxels), the insula (MNI coordinates: $x, y, z = 38, 12, 2$, $k = 153$ voxels) and the precuneus (MNI coordinates: $x, y, z = -16, -66, 50$, $k = 158$ voxels) occurred for a main effect of diagnostic group.

No significant interaction or main effects could be observed regarding the functional coupling of the DLPFC at the applied thresholds ($p < 0.001$, $k > 89$ voxels).

Table 2: Results of the group (MDD, HC) \times FH (FH+, FH-) analysis of variance for the analysis of psychophysiological interactions with the medial OFC as seed region ($x, y, z = 6, 52, -12$)^a

Interaction; region	Cluster size (k)	MNI (at peak)			Side	F_{96}	z-score
		x	y	z			
Group \times family history interaction							
Middle occipital gyrus/inferior occipital gyrus	138	36	-88	4	R	19.90	4.09
Main effect of group							
Supramarginal gyrus/inferior parietal gyrus/postcentral gyrus	550	62	-24	30	R	32.28	5.13
Inferior parietal gyrus	143	-40	-46	48	L	27.70	4.78
Superior frontal gyrus/middle frontal gyrus	304	-18	4	68	L	27.34	4.75
Inferior parietal gyrus/supramarginal gyrus	164	-62	-44	42	L	26.47	4.68
Insula/putamen	153	38	12	2	R	23.08	4.38
Superior frontal gyrus/middle frontal gyrus	244	26	2	60	R	22.70	4.35
Superior parietal gyrus/precuneus	158	-16	-66	50	L	21.18	4.21
Middle frontal gyrus/superior frontal gyrus	103	26	56	36	R	16.85	3.76
Main effect of family history							
Middle occipital gyrus/inferior occipital gyrus/superior occipital gyrus	272	28	-94	4	R	28.66	4.86
Supramarginal gyrus/rolandic operculum	93	52	-28	24	R	22.91	4.37

FH+ = positive family history of MDD; FH- = no family history of MDD; HC = healthy controls; MDD = major depressive disorder; MNI = Montreal Neurological Institute; OFC = orbitofrontal cortex.

^aAll whole brain analyses with a voxel threshold of $p < 0.001$, minimum cluster volume threshold of $k \geq 89$.

Discussion

With this study we provide evidence for differential activation patterns of the lateral and medial prefrontal cortex in familial risk for MDD and in acute disorder. Whereas hypoactivation in the DLPFC during negative emotion processing appears as a common feature in both healthy high-risk individuals and acutely depressed individuals, diverging signalling in the medial prefrontal cortex contrasts familial risk and acute disorder.

Our finding of a decreased DLPFC response to negative emotional stimuli in both healthy participants at familial risk for MDD as well as in acutely depressed patients is well in line with the findings of a number of previous imaging studies reporting DLPFC hypoactivation as a frequently replicated feature of acute MDD.^{35,36} The DLPFC is considered a key structure of a top-down signalling network controlling executive functioning and distractor suppression.^{5,37} In fact, reduced activation in lateral prefrontal areas also appears to be one of the most concise findings in fMRI research on familial risk for the disorder. Out of the few studies available, DLPFC hypoactivation was reported in individuals at familial risk during presentation of fearful faces,⁸ highly matching the present results, but also during

an automatic mood regulation paradigm.³⁸ Moreover, Lisiecka and colleagues¹² showed aberrant functioning in further brain areas thought to be of high relevance for executive control during emotional processing, including the inferior parietal gyrus and the postcentral gyrus in unaffected first-degree relatives of patients with MDD.

Of note, DLPFC hypoactivation to aversive stimuli in healthy individuals appeared as a function of familial risk status, whereas in acutely depressed patients DLPFC hypoactivation was present irrespective of familial risk. We thus conclude that dysfunctions in the executive control network involving the DLPFC are a common feature of both acute disorder and familial predisposition for the disorder in healthy individuals with no history of depression. This finding holds mechanistic insights into the development of mood disorders. First, both acutely depressed and never depressed individuals at familial risk for MDD exhibit DLPFC hypoactivation to negative stimuli, pointing to a possible trait characteristic of DLPFC functioning in healthy individuals at risk for the disorder. This finding is further supported by the fact that no association between depressive symptoms and DLPFC response could be detected in the present study. Second, as acutely depressed patients without familial risk shared the same pattern of dorsolateral hypoactivation,

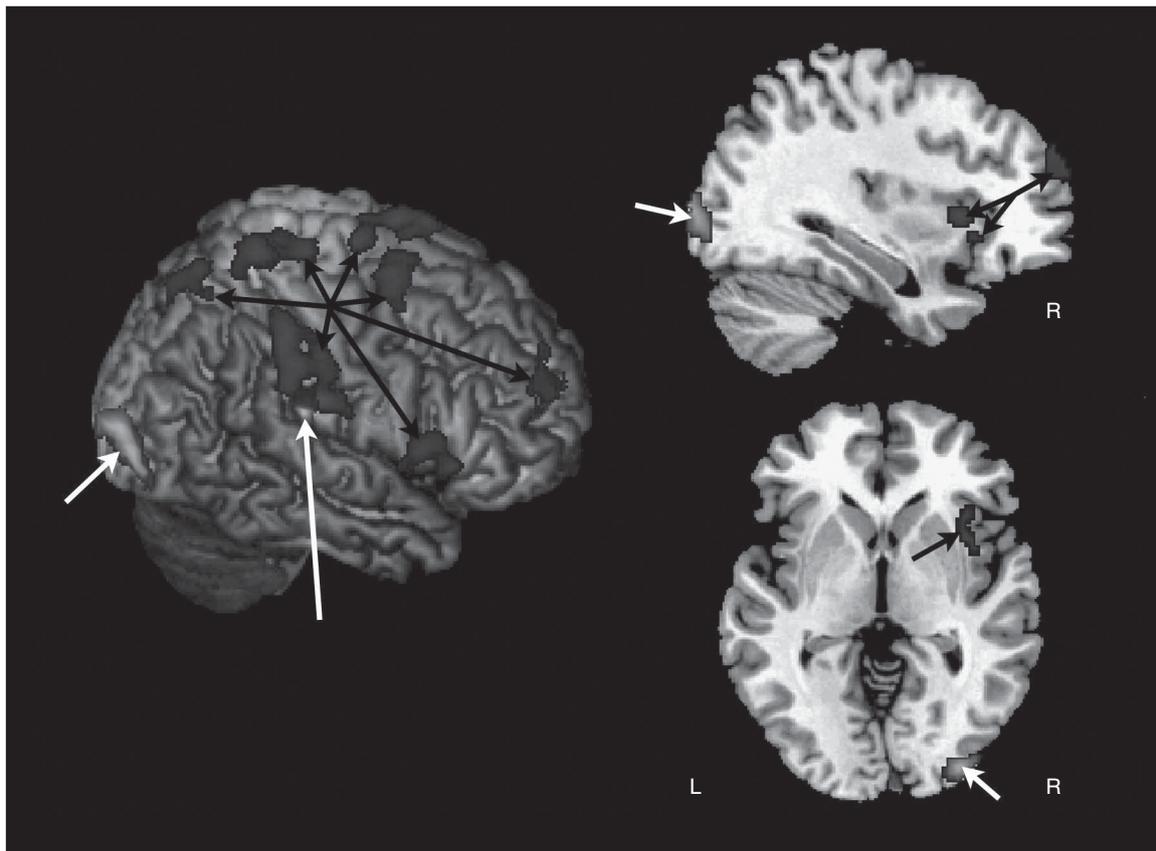


Fig. 3: Results of the analyses of psychophysiological interaction. Differential functional coupling between the medial orbitofrontal cortex (OFC; seed region) and diverging cortical areas associated with family history of major depressive disorder (MDD; white arrows) and acute disorder (black arrows) (Montreal Neurological Institute [MNI] coordinates: $x, z = 34, -1$). L = left hemisphere; R = right hemisphere.

altered DLPFC signalling cannot exclusively be regarded as a trait marker of familial risk for MDD. Rather, it appears likely that genetic liability is one of several different neurobiological pathways resulting in aberrant DLPFC signalling as a feature of acute MDD.

Unfortunately, our analysis of task-specific connectivity did not provide further evidence of the possible underlying network mechanisms associated with functional alterations in the DLPFC in this study.

Regarding our investigation of aberrant functioning of the medial prefrontal cortex as a key structure of bottom-up signalling in the ventromedial network, our findings clearly indicate increased BOLD response in the medial OFC appears to be a state characteristic of acute disorder. This finding again is well in line with those of a variety of functional imaging studies in MDD reporting overactive signalling during emotion processing in a medial network involving the OFC, the amygdala and the insula as key structures of dysfunctional emotion processing in depressed patients.^{5,39,40} Interestingly no association between familial risk for MDD and altered neural signalling in the medial OFC could be detected. These findings add to the specificity of overreactive medial OFC response as a state marker of acute MDD, which is underlined by the observed positive association between depressive symptoms and OFC response to negative faces. Hyperreactive neural responses during emotion processing in the medial bottom-up network seem to characterize acute disorder rather than pre-existing familial risk. This is in line with findings pointing to a positive correlation between signalling in the anteromedial OFC and severity of depression as well as with reduced activity in this brain area following effective antidepressant treatment.⁴¹ Furthermore, our findings are well in line with research showing hyperactivation of the medial prefrontal cortex during sad mood induction as a feature of relapse risk in individuals with remitted depression.⁴² On the other hand, altered functioning of the OFC has been shown during reward processing in first-degree relatives of patients with MDD.⁴³ However, these findings must not be regarded as contradictory to the present results; rather, they refer to the complex role of the OFC in different conditions in terms of diverging signalling during different paradigms, such as emotional face matching or reward processing.

A recent fMRI study revealed significant associations between increasing threat-related amygdala reactivity in adolescents during aging and familial risk for MDD, independent of depressive symptoms.⁴⁴ As stated earlier, the amygdala is another key structure of the ventromedial circuit during emotion processing, which is why this finding could be considered to contradict our results. It could point to a certain degree of heterogeneity between different brain regions in ventromedial functioning in individuals at risk for MDD. Also, one has to keep in mind that in contrast to the study by Swartz and colleagues,⁴³ which investigated neural responses in adolescents, participants of the present study were adults (mean age 37.12 ± 12.95 years), which generally might be regarded as an obstacle in a direct comparison of results from samples of different age groups. More in-depth research regarding this opposing

pattern of signalling in the ventromedial network is needed before firm conclusions can be drawn.

Additional analyses of task-specific neural coupling in this study revealed vast differences in the functional connectivity between the medial OFC and differing cortical areas during emotion processing associated with acute depressive state and familial risk. Our findings point to aberrant signalling during emotion processing in a series of brain areas apparently connected to the medial OFC in acutely depressed patients involving the parietal, the frontal and the insular cortex as well as the precuneus. The present findings thus underline the importance of integrated alterations in neural responses to negative stimuli in a variety of brain areas as a neurofunctional correlate of depressive symptomatology. More specifically, our results are corroborated by diverse findings from previous studies highlighting the importance of these brain regions in acute MDD, including reports on increased resting-state functional connectivity between the insula and the OFC associated with altered interoceptive awareness in depressed patients.^{45–49} As comparable alterations were not observed in individuals at familial risk for MDD in our study, the present work might highlight differential functional connectivity in this circuit as a possible state-dependent neural substrate of altered interoception and social emotional processing as core features of acute MDD.

In contrast, altered signalling in the supramarginal gyrus in familial risk for MDD as observed in our PPI analyses matches a previous report on functional alterations in familial risk¹² and might again point to altered executive functioning in individuals at risk for MDD, whereas the relevance of enhanced task-specific coupling between the OFC and the occipital cortex remains uncertain so far owing to lacking corresponding evidence from the literature. In a more general sense, the present results highlight the urgent need for a more detailed understanding of aberrant network signalling in MDD. Future fMRI studies should address this important and complex issue and, instead of targeting neural response in single brain areas, should aim to uncover the role of diverging brain circuits in the development of psychopathology.

Strengths of our study comprise the inclusion of a balanced number of healthy and depressed participants stratified for familial risk for MDD, which allowed us to separately investigate the influence of both factors (acute disorder and familial risk) as well as their interactions in terms of a full factorial design using a 2 × 2 ANOVA. Moreover, because familial risk for MDD and early adverse experiences have been shown to be positively correlated,³⁴ studies on familial risk for MDD should account for a possible confounding effect of childhood trauma. We controlled for this important factor and demonstrated that childhood trauma did not significantly bias the present findings.

Limitations

Some limitations must be acknowledged. First and foremost, because the design of the present study was cross-sectional, causality cannot be inferred, and conclusions of our work

regarding the chronology of functional alterations in MDD must thus be treated with caution. Despite the fact that we detected a positive association between depressive symptoms and OFC response in the present study, we cannot fully exclude the possibility that effects observed in acutely depressed patients are in fact not a function of acute depressive state, but a residual of preceding depressive episodes. The inclusion of a sample of patients with remitted MDD would have been desirable to clarify this issue and to further distinguish endophenotypic effects from acute disease status, which should be considered in future studies. Second, the sample size of each group was limited and might have been underpowered especially for the testing of interaction effects. Moreover, the inclusion criteria for FH+ status differed in the MDD-FH+ and the HC-FH+ samples; whereas HC-FH+ individuals were included only if the MDD diagnosis was directly confirmed in their respective first-degree relative via SCID interview, patients were assigned to the MDD-FH+ sample based on positive familial anamnesis. However, we would like to stress that patients who are receiving current inpatient treatment for a depressive episode are much less likely than healthy controls to misjudge depressive symptomatology or MDD diagnosis in their relatives. Nonetheless, we have to state that inclusion criteria were more elaborate and thus probably more accurate in the HC-FH+ sample. Moreover, given the observed age range (18–56 yr) in the HC-FH+ sample, we cannot rule out the possibility that especially older HC-FH+ participants were in fact resilient to the development of MDD, even though we did not observe differences regarding DLPFC response to negative stimuli between younger and older HC-FH+ subsamples (divided by median split) in the present study.

Conclusion

Taken together, our findings of DLPFC hypoactivation during negative emotion processing in healthy first-degree relatives much resembles findings in acute MDD, suggesting genetic liability as a possible determinant of aberrant neural signalling in the lateral prefrontal cortex in individuals with the disorder. An opposite pattern of results could be observed for the medial prefrontal cortex, with overactivation of the medial OFC as a state marker of acute MDD. Activation patterns of the medial prefrontal cortex and its underlying connectivity thus seem to distinguish familial risk from acute disorder.

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