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Orbital and Medial Prefrontal Cortex Functional Connectivity of Major Depression Vulnerability and Disease

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ABSTRACT

BACKGROUND: Pathophysiology models of major depression (MD) center on the dysfunction of various cortical areas within the orbital and medial prefrontal cortex. While independent structural and functional abnormalities in these areas are consistent findings in MD, the complex interactions among them and the rest of the cortex remain largely unexplored.

METHODS: We used resting-state functional magnetic resonance imaging connectivity to systematically map alterations in the communication between orbital and medial prefrontal cortex fields and the rest of the brain in MD. Functional connectivity (FC) maps from participants with current MD ($n = 35$), unaffected first-degree relatives ($n = 36$), and healthy control subjects ($n = 38$) were subjected to conjunction analyses to distinguish FC markers of MD vulnerability and FC markers of MD disease.

RESULTS: FC abnormalities in MD vulnerability were found for dorsal medial wall regions and the anterior insula and concerned altered communication of these areas with the inferior parietal cortex and dorsal posterior cingulate, occipital areas and the brainstem. FC aberrations in current MD included the anterior insula, rostral and dorsal anterior cingulate cortex, and lateral orbitofrontal areas and concerned altered communication with the dorsal striatum, the cerebellum, the precuneus, the anterior prefrontal cortex, somatomotor cortex, dorsolateral prefrontal cortex, and visual areas in the occipital and inferior temporal lobes.

CONCLUSIONS: Functionally delineated parcellation maps can be used to identify putative connectivity markers in extended cortical regions such as the orbital and medial prefrontal cortex. The anterior insula and the rostral anterior cingulate cortex play a central role in the pathophysiology of MD, being consistently implicated both in the MD vulnerability and MD disease states.

Keywords: Family history, Functional connectivity, Major depression, MRI, Prefrontal, Vulnerability

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Major depression (MD) is a debilitating syndrome presenting with various symptoms in mood, reward, and decision making (1). The efficacy of MD neuromodulation therapies such as transcranial magnetic stimulation (2) and deep brain stimulation (3) with various targets demonstrates in a “proof of concept” manner that MD is a systems-level disorder involving a complex pattern of altered interactions between several brain areas. Convergent neuroimaging findings suggest that, together with limbic and autonomic centers, subregions within the orbital and medial prefrontal cortex (OMPFC) (4–6) play a central role in MD’s aberrant networks. Understanding of the neurocircuitry pathways underlying MD symptoms and treatment response remains elusive, despite the large body of evidence documenting abnormalities in various OMPFC subregions and the efficacy of connectivity-based treatments with OMPFC targets.

The elucidation of MD-related changes, if any, in the functional wiring between the OMPFC subregions and key brain

areas for autonomic, cognitive, and affective control is critical for generating new hypotheses on MD disease mechanisms and for identifying connectivity biomarkers to guide diagnosis and treatment. On the theoretical side, neurocircuit models of MD propose altered pathways based only on tracer or lesion findings in animals and rare postmortem human reports (7). Thus far, magnetic resonance imaging (MRI) studies of MD have examined functional wiring of the OMPFC for select coordinates derived from activation studies, either as part of the anterior default mode network or coarsely with predefined general anatomical labels [see (8–11) and reviews in (12,13)].

Recent neuroimaging advances on MRI connectivity analysis tools enable us to study the cortical organization systematically for a specified area or the cerebral cortex as a whole [see review in (14)]. These tools use homogeneity in functional connectivity (FC) in an attempt to delineate cortical fields, which are anatomically defined as architectonic and

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connectional homogeneous patches of cortex (15,16). While it is still undetermined how these fields correspond to anatomically defined cytoarchitectonic areas, at the group level these data-driven methods yield a systematic parcellation of cortex in subregions (17) that are neuroanatomically plausible in general terms of location, spatial extent, and whole brain FC (14,18–24).

In the current study, we make use of such a parcellation of the OMPFC in the left hemisphere of 34 healthy adults. That study delineated 19 functional subregions in the left hemisphere cortex covering the anterior medial PFC, orbital surface, and ventral anterior insula (white outlines in Figures 1–3). Their spatial organization and intrinsic cortical and subcortical FC characteristics were generally in accordance with current knowledge of the anatomical organization of this part of the cerebral cortex from cytoarchitectonic and tracer studies in the macaque monkey and cytoarchitectonic and diffusion MRI studies in humans [for a detailed discussion see Samara *et al.* (17) and their Supplement]. Here, we used this parcellation map as a layout to identify FC changes associated with OMPFC in MD.

We focused on the left OMPFC because only this hemisphere was extensively studied (17). Pathophysiology studies of MD and repetitive transcranial magnetic stimulation interventions (i.e., excitatory left dorsolateral PFC vs. inhibitory right) in patients with MD suggest that left and right PFC might be differentially involved, while transcranial magnetic stimulation treatment centered on the left dorsolateral PFC is the most widely used (25). We sought specifically to test the hypotheses that OMPFC subregions show altered connectivity patterns that are 1) common to MD patients and at-risk individuals compared to healthy control subjects (connectivity markers of MD vulnerability) and 2) unique to the MD group compared with at-risk individuals and control subjects (connectivity markers of acute MD or MD disease). With this design, we aimed to uncover FC abnormalities that might confer susceptibility to MD by giving rise to emotional and cognitive symptoms observed in unaffected at-familial MD risk individuals and in MD patients in remission. At the same time, we specifically aimed to dissociate these abnormalities from the FC aberrations that characterize the acute MD state and that may underlie the cognitive, affective, and somatic symptoms observed during depressive episodes.

METHODS AND MATERIALS

Clinical Assessments

Thirty-five participants experiencing a major depressive episode (cutoff Beck Depression Inventory-II score >20 ; mean age $\pm$ SD, 38.9 ± 11.6 years; 71% female) (MD group), 36 unaffected first-degree relatives (mean age $\pm$ SD, 34 ± 14.6 years; 72% female) (family history [FH] group), and 38 nonpsychiatric control subjects (mean age $\pm$ SD, 36 ± 16.4 years; 68% female) (healthy control [HC] group) participated after providing informed consent. Patients were included if they met DSM-IV-TR criteria for MD and excluded if they were diagnosed with bipolar disorder I or II or substance dependence or were taking benzodiazepines. Participants in the other two groups were excluded in the presence of any Axis I diagnosis. Screening procedures and diagnostic and medication histories are reported in the Supplement. The study was approved by the Medical

Ethical Committee of Maastricht University. Participants completed the Beck Depression Inventory-II, the Brief Symptom Inventory, and the Quick Inventory of Depressive Symptomatology Self-Report (26–28). They also completed Raven's Standard Progressive Matrices, a 60-item test of nonverbal IQ (29).

MRI Acquisition and Preprocessing

MRI data included a resting state scan of minimally 6.4 minutes (repetition time = 2.5 seconds, $2 \times 2 \times 3$ mm voxels, 153 or 203 volumes, equally spread across the three groups), a high-resolution T1-weighted anatomical scan, and a field map. The echo-planar imaging sequence was optimized to reduce susceptibility artifacts in the orbital cortex: low echo time (25 ms), thinner slices (2 mm) oriented with the orbital surface ($\pm 30^\circ$), and field map distortion correction [see Samara *et al.* (17) for quantifications and discussion of the orbital signal quality with this sequence and scanner]. Data preprocessing with SPM 5 software (Wellcome Trust Centre for Neuroimaging, London, UK) included correction for slice timing, head motion, and spatial distortion; normalization to the Montreal Neurological Institute 152 template; 6-mm full width at half maximum smoothing; removal of linear trends, white matter, cerebrospinal fluid signals, and affine head motion parameters; and finally 0.1 to 0.01 Hz bandpass filtering. To further eliminate detrimental effects of head motion (30,31), volumes with a framewise displacement exceeding 10% of the slice thickness were removed and groups were equated on the mean framewise displacement ($p = .57$). Acquisition parameters and preprocessing are detailed in the Supplement.

Statistical Analyses

We sought to identify FC abnormalities in 19 OMPFC fields of the left hemisphere parcellation map (17). For ease of comprehension, we refer to these fields by their presumed anatomical interpretations, as discussed in Samara *et al.* (17). The locations of the fields are indicated as outlines in Figures 1, 2, and 3 [for details, see Samara *et al.* (17)]. A set of 19 seed time courses was created for each participant by selecting voxels within a sphere of a 4-mm radius around the center of mass of each field. The focus on the field centers ensured that only voxels that were representative of each field's functional dynamic were included, despite individual variation in the exact location of the fields in each individual data set. To further increase the field specificity of the connectivity profiles, we computed for each field the first Eigen vector of the low frequency (0.01–0.1 Hz) signal in the time courses of the selected voxels. Per seed, whole-brain FC profiles were calculated as the Fisher Z transformed Pearson's correlation between each seed's time course and the time course of each voxel in that participant's brain. These field- and participant-specific FC maps were subjected to a random effects general linear model analysis to estimate differences between the three groups, with age, gender, and IQ Raven score as covariates.

To test for connectivity abnormalities of MD vulnerability, we created conjunction maps of the F contrasts between 1) the HC and the MD groups and 2) the HC and the FH groups. These maps highlighted voxels whose FC with the seed differed both between control subjects and patients and

between control subjects and at-risk participants. Further, to ensure in our vulnerability measure that FH participants were not different from MD patients, we removed from the conjunction maps all voxels significant at a lenient threshold (.001 uncorrected) in the F contrast between MD versus FH groups. This eliminated as markers of vulnerability all voxels in which the FC change in the at-risk participants was intermediate between the HCs and the MD patients.

To test for connectivity abnormalities associated with acute MD, we created new conjunction maps, now of the F contrasts between 1) the MD and HC groups and 2) the MD and FH groups. These conjunction maps now highlighted voxels whose FC with the seed differed both between MD patients and control subjects and between patients and at-risk participants. Further, to ensure in our disease manifestation measure that at-risk participants were not different from the HCs, we removed from the conjunction maps all voxels significant at a lenient threshold (.001 uncorrected) in the F contrast between FH versus HC. This excluded all voxels with an FC change in the at-risk participants that was intermediate between the HCs and the MD patients so that the final maps contained voxels whose FC was exclusively altered in the disease state.

All conjunction maps were tested for significance with Monte Carlo simulations (10,000 iterations; voxel level $p = .01$, cluster level $p = .0025$, Bonferroni-adjusted for 19 independent

comparisons). We ensured that the connectivity differences reported here were not driven by antidepressant medication use or comorbidity (MD group) or self-reported symptoms (both depression and other psychiatric complaints in the FH group) by regressing the influence of these variables from the MD and FH individual maps before the final across-groups analysis and using the residual cleaned maps for these groups in the next step. Gray matter differences between the three groups were controlled by removing from our results maps all voxels which their probability of being gray matter was significantly different (.001 uncorrected) among the groups.

We determined the direction of FC differences in MD vulnerability and in disease manifestation with region of interest-based pairwise t tests using the r to Z transformed values in the conjunction maps. Correlation analyses for the MD group between the FC changes in the acute phase and our clinical measures were also performed (details of all analyses can be found in the [Supplement](#)).

RESULTS

Demographic and Clinical Characteristics

MD patients had their first episode on average at 29.3 years of age (SD = 11.4 years) and had a mean of 2.9 episodes (SD = 3

Figure 1. Functional connectivity changes associated with major depression (MD) vulnerability. Region nomenclature corresponds to Samara *et al.* (17). Voxel clusters of MD vulnerability-related functional connectivity changes (MD, at-risk family history group [FH] $\neq$ healthy control subjects [HC]) are colored in the same color as the region that provided the seed for the functional connectivity map. **(A)** Lateral view of the left hemisphere. **(C)** Lateral view of the right hemisphere. **(D)** Posterior view of both hemispheres. **(E)** Bar plots showing connectivity strength ($Z[r]$) in the three groups for the anterior insula (al) and the rostral perigenual cingulate (p32) (see [Supplement](#) for all plots). Error bars represent 95% confidence intervals. a, periaqueductal gray; b, posterior cingulate cortex; BA, Brodmann area; c, dorsal inferior parietal cortex; d, intraparietal sulcus; d32, paracingulate region 32 dorsal; e, intraparietal sulcus/occipital.

Figure 2. Functional connectivity abnormalities of major depression (MD) disease. Region nomenclature corresponds to Samara *et al.* (17). Voxel clusters of MD disease-related functional connectivity changes (MD $\neq$ at-risk family history group [FH], healthy control subjects [HC]) are color-coded according to the orbital or medial region that provided the seed for the functional connectivity map. (A) Lateral view of the left hemisphere (LH). (B) Posterior dorsal view of the left hemisphere. (C) Medial view of the left hemisphere. (D) Slices through the cerebellum and basal ganglia to show cluster of altered connectivity with the anterior insula (al) region and the lateral orbital 47/12 region. (E) Ventral view of both hemispheres. (F) Bar plots showing connectivity strength ($Z(r)$) in the three groups for the anterior insula and the rostral perigenual cingulate region 32 (p32) (see Supplement for all plots). Error bars represent 95% confidence intervals. a, cerebellum; a24', midcingulate field a24; b, putamen; c, caudate; d, fusiform; e, occipital; f, precuneus; g, precuneus; h, paracentral lobule; i, occipital; j, inferior temporal; k, caudate body; l, paracentral lobule; m, dorsolateral prefrontal cortex; n, superior frontal gyrus; p24, rostral perigenual cingulate region 24; RH, right hemisphere.

episodes). Comorbidity (having at least one additional Axis I diagnosis), and the use of antidepressants at the time of the scan was reported by 51% and 48% of the MD group, respectively. The most prevalent comorbid diagnosis was social phobia, and most participants were taking selective serotonin reuptake inhibitors (Supplemental Table S1). Average Beck Depression Inventory-II and Quick Inventory of Depressive Symptomatology Self-Report scores at the time of the scan in the MD group were 32.74 and 16.57, respectively. At-risk participants had clinically and statistically significantly lower scores of depressive and general psychiatric symptomatology compared with the MD group (Table 1). Their

symptom scores were somewhat elevated compared with HCs (Table 1), but none scored near the cutoff for clinical symptomatology. Groups were matched in age, gender, and IQ (all p values $> .2$).

Neuroimaging Analysis

FC Abnormalities of MD Vulnerability. In our analysis for markers of MD vulnerability we found that MD patients and at-risk individuals share various FC abnormalities in the OMPFC compared with control subjects. The general linear model analysis revealed changes in the FC of four OMPFC regions: the

Figure 3. Summary representation of all connectivity findings. Regions in orange were found to have altered functional connectivity in major depression vulnerability, while regions in red were found to have altered functional connectivity in the acute major depression phase. The anterior insula and the rostral cingulate (marked with asterisks) were found to have changed connectivity with various areas in the rest of the cortex both in major depression vulnerability and during depressive episodes.

anterior insula, the paracingulate regions 32 pregenual (p32) and 32 dorsal (d32) [see (20) for area homology, nomenclature, and relevant references], and the dorsomedial frontal Brodmann area 9 (BA 9) (Figure 1). Region of interest-based post hoc analysis indicated that MD vulnerability is characterized by decreased coupling between BA 9 and an area of the ventral intraparietal sulcus and between area p32 and the dorsal posterior cingulate and contralateral inferior parietal cortex (see Table 2 for *p* values

of post hoc tests). In contrast, increased FC was observed between the anterior insula and the brainstem and between medial region d32 and the contralateral dorsal occipital cortex. It should be noted that in MD vulnerability no significant changes in the functional coupling among any of the 19 OMPFC fields with each other were observed.

FC Abnormalities of MD Disease. In our analysis for aberrations in MD disease, we found that MD patients, in addition to the FC changes that they share with the at-risk group, also show unique impairments in the communication of the OMPFC with several other brain areas in the rest of the cortex. The random effects general linear model analyses revealed additional changes for six OMPFC fields, summarized in Figure 2 and Table 2. Two of the OMPFC fields implicated in vulnerability also show abnormalities associated with MD disease: the anterior insula and the dorsomedial prefrontal cortex (p32). The anterior insula had changed coupling ipsilaterally with the lateral occipital cortex, fusiform gyrus, cerebellum, and putamen, and contralaterally with the caudate nucleus. Field p32 had altered coupling with the ipsilateral precuneus. Four additional fields had changed functional coupling in MD patients compared with the other two groups. On the medial side, p24 had changed coupling with the anterior superior frontal gyrus (SFG), while midcingulate field a24' had changed coupling with the dorsolateral PFC and the left paracentral lobule. At the orbital side, changed coupling was found between lateral orbital area 47/12 and the dorsal occipital cortex bilaterally, the left inferior temporal lobe and the parietal paracentral lobule, and subcortically with the contralateral body of the caudate nucleus. Also, central orbital area 11 had changed coupling with the dorsal precuneus. Region of interest-based post hoc analysis indicated that MD patients had decreased FC between area p32 and the precuneus compared with both at-risk individuals and control subjects. In contrast, the MD group had increased FC compared to the other two groups between all the other OMPFC cortical fields and the cortical and subcortical regions reported. Similar to the MD vulnerability results, no functional coupling changes between the 19 OMPFC fields were observed in this analysis.

Table 1. Sample Characteristics and Clinical Measures

	MD		FH		HC		$F_{2,106}$	<i>p</i> Value	
	Mean	SD	Mean	SD	Mean	SD			
BDI-II	32.74	7.66	5.78	5.04	2.24	2.97	328.68	.000 ^a	.020 ^b
BSI GSI	1.67	0.55	0.34	0.38	0.14	0.17	159.24	.000 ^a	.098
BSI PST	38.66	7.67	12.42	10.16	6.5	7.27	147.18	.000 ^a	.010 ^b
BSI PSDI	2.26	0.46	1.18	0.39	0.89	0.41	108.07	.000 ^a	.009 ^b
QIDS	16.57	3.38	3.91	3.46	2.1	1.84	252.58	.000 ^a	.030 ^b
Age, Years	38.88	11.8	34.03	14.77	36.21	16.65	0.98	.377	–
Female, %	71	–	72	–	68	–	$\chi^2_{(2)} = 0.14$	.930	–
Raven IQ	45.2	8.99	48.28	6.5	46.03	7.46	1.53	.221	–

BDI-II, Beck Depression Inventory-II; BSI, Brief Symptom Inventory; FH, at-risk family history group; GSI, global severity index; HC, healthy control subjects; MD, major depression group; PSDI, positive symptom distress index; PST, positive symptom total; QIDS, Quick Inventory of Depressive Symptomatology.

^aThe MD group differs significantly from relatives and control subjects in the *F* test.

^bThe FH group differs significantly from control subjects in post hoc comparisons. In the post hoc tests between MD vs. HC and MD vs. FH, all post hoc *p* values are < .000.

Table 2. Summary of Magnetic Resonance Imaging Results

OMPFC Area	Anatomy	Average MNI	Voxel Extent	p Value
MD Vulnerability				
al	Brainstem	3, -26, -15	73	.000005
p32	Posterior cingulate	1, -30, 30	61	.000048
p32	BA 40/39	44, -50, 45	61	.000027
BA 9	Intraparietal sulcus	-30, -72, 32	69	.000001
d32	Occipital	23, -91, 20	82	.000001
MD Disease				
47/12 (OFC)	Inferior temporal	48, -46, -18	53	.000001
47/12 (OFC)	Occipital (RH)	26, -92, 20	61	.000003
47/12 (OFC)	Occipital (LH)	-25, -87, 21	90	.000001
47/12 (OFC)	Paracentral lobule	2, -47, 73	62	.000003
47/12 (OFC)	Caudate body (RH)	12, 3, 15	55	.000014
al	Cerebellum	29, -61, -36	76	.0000001
al	Fusiform (medial)	34, -72, -18	93	.000006
al	Putamen	-23, 5, 5	68	.000002
al	Caudate	13, 25, 2	61	.000538
al	Occipital (LH)	-34, -85, 3	54	.000003
p32	Precuneus (LH)	-8, -72, 33	60	.000000
p32	Precuneus (RH)	11, -71, 41	69	.000130
p24	Superior frontal gyrus	-27, 58, 15	72	.000269
a24'	DLPFC	-10, 42, 47	68	.000037
a24'	Paracentral lobule	-7, -25, 63	58	.000008
11 (OFC)	Precuneus	4, -66, 52	58	.000929

Anatomy labels are given according to automated anatomical labeling as seen in Tzourio-Mazoyer *et al.* (89). *p* Values concern *F* tests (see Supplement for all *p* values).

a24', midcingulate field a24; al, anterior insula; BA, Brodmann area; d32, paracingulate region 32 dorsal; DLPFC, dorsolateral prefrontal cortex; LH, left hemisphere; MD, major depression group; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; OMPFC, orbital and medial prefrontal cortex; p24, paracingulate region 24 pregenual; p32, paracingulate region 32 pregenual; RH, right hemisphere.

Correlation Analyses

MD patients and FH participants share a set of FC indicators and show increased self-reported measures of depressive symptomatology compared with HC participants. Within neither group, however, did correlation analyses between the self-report measures of depressive symptomatology and the connectivity aberrations reveal significant relationships.

DISCUSSION

We examined changes in the FC of the OMPFC associated with MD. By starting from a previously established parcellation scheme (17), we delineated the specific subregions of OMPFC involved in the disease. By including a group of participants at familial risk for MD alongside MD patients and HCs, we distinguished between the FC alterations that confer vulnerability to MD (i.e., [MD = FH] ≠ HC) and the FC correlates of the current MD episode (i.e., MD ≠ [FH = HC]). Our results suggest that individuals with familial risk for MD, in the absence of clinically significant symptoms, share with patients aberrations in the FC of OMPFC fields that center on two foci, one in the dorsomedial prefrontal cortex and one in the anterior insula. Acute MD patients, in addition to these vulnerability changes, exhibit unique FC alterations originating from these same two foci and from one

additional focus in the orbital frontal cortex. This suggests that neurobiologically MD starts off with confined predisposing FC abnormalities and progresses to a disease state with more extensive OMPFC alterations (Figure 3).

FC in MD Vulnerability

The first of the two foci of FC abnormality associated with MD vulnerability concerns an increased functional coupling between the anterior insula and the periaqueductal grey (PAG). The PAG is a brainstem control center for survival-related responses during stress and threat (32). Insula–PAG coupling strength has been shown to increase with perceived painfulness of a stimulus (33), experienced versus observed pain (34,35), stressfulness of cognitive tasks (36), and proximity of a virtual predator (37). Against this background, the increased insula–PAG coupling observed here may suggest a proclivity in at-risk individuals to interpret anticipated events as more emotionally threatening or generally negative. In line with this, behavioral studies of vulnerability for MD show anticipatory affect biases, including increased threat reactivity (38,39).

An affective bias hypothesis could also make sense of the second focus of vulnerability-related alterations in functional coupling between regions of the dorsal medial PFC and the posterior, “receptive” brain. The involved dorsal medial PFC region extends from the cingulate sulcus to the dorsal convexity of the SFG at around the intersection of the cognitive

and affective part of the medial PFC (40). This region has dense anatomical connections to autonomic centers (41,42) and has been implicated in the assessment salience and affective value of emotional information (43), conflict monitoring in the presence of emotional distractors (40,44–49), and in awareness and regulation of emotional responses (40,50–52). This affective bias hypothesis is further in agreement with behavioral characteristics observed in people with genetic MD susceptibility and those with remitted depression (53,54), such as difficulty directing attention away from negative stimuli (54), reappraising (55), and suppressing negative distractors (56).

The altered FC of medial regions associated with this second focus fits this pattern. On the one hand, BA 9 and d32 showed changed coupling with the posterior intraparietal sulcus, which is part of the dorsal visual attention network (57). On the other hand, area p32 was uncoupled from the dorsal inferior parietal cortex implicated in the computation of priorities for attentional allocation (58,59), the re-evaluation of conflicting choices between options (60,61), and the reappraisal/suppression of emotion (55). Interestingly, the inferior parietal lobule has been found to respond to cognitive behavioral therapy (62,63), a treatment aimed at modifying attentional biases and reinforcing emotion regulation strategies. Area p32 also lost functional coupling with the posterior cingulate cortex, which may relate to areas p32's role in memory consolidation (64). The dorsal posterior cingulate cortex has a mixed pattern of anatomical connectivity linking frontal default mode regions with parietal attention areas (65,66) and is thought to balance internal and external attentional foci to retrieve and update behavioral strategies (67). In line with this, posterior cingulate cortex lesions result in deficits in implementing new strategies and changing cognitive set (67).

Taken together, the observed pattern of FC dysregulation between these OMPFC areas and the brainstem, dorsal attention areas, the inferior parietal lobule, and the posterior cingulate cortex might be the manifestation of a predisposition in MD-vulnerable individuals for anticipating or perceiving environmental events as threatening, painful, and overall negative. Increased occurrence of (perceived) negative experiences combined with a diminished ability to cognitively regulate the resulting emotional arousal might make at-risk individuals more prone to stress, chronic negative affect, and a dysregulated hypothalamic-pituitary-adrenal axis.

FC in MD Disease

In addition to the changes associated with MD vulnerability, patients with acute MD exhibited an extension of changes in the coupling of the two foci marking MD vulnerability (i.e., the anterior insula and the rostral cingulate) and an emergence of a new focus in the orbital frontal cortex. The cerebral targets of FC aberrations across these foci tend to aggregate in two functional zones. The first of these zones comprises areas of higher-order vision and attention in the posterior brain, which is already prominent in the vulnerability markers, while the second, in the SFG, seems specific to disease manifestation.

All three medial OMPFC foci show changed coupling with higher visual cortex, in both the ventral (loci d, e, and j in

Figure 2) and the dorsal (loci f–i in Figure 2) streams. The insular (al) and orbital (47/12) foci have changed coupling with the anterior ventral stream, responsible for the analysis and representation of visual objects and their identity (68). The orbital area 47/12 had changed coupling with the dorsal visual stream, namely the ventral intraparietal sulcus (69), already highlighted as an MD vulnerability indicator. The additional loss of coupling of this area with the contralateral oculomotor/attentional part of the caudate nucleus further confirms the functional involvement of visual attentional processes. Finally, medial (area p32) and orbital foci (area 11 and 47/12) had changed coupling with parts of the nonlimbic precuneus also implicated in visual processing (66,69). This part of the precuneus has previously been linked to MD, with patients showing increased node centrality (70) and abnormal activation to attentional targets and emotional distractors (71). This pattern of FC disturbances originating from all three OMPFC foci of MD-related FC change strengthens the earlier suggestion that changed affective modulation of information processing is a core aspect of MD. In MD patients, the dorsal medial focus of FC change indicative of MD vulnerability gets an important extension into the cingulate gyrus (Figure 3), with two additional areas (p24 and a24') showing changed functional coupling. The cingulate extension spans the transition from the anterior to the midcingulate section of the cingulate cortex (72), with a24' being the rostral part of the midcingulate cortex, including the rostral cingulate motor area in the cingulate sulcus. This, together with the action selection/monitoring function attributed to the midcingulate cortex (73), might explain the changed coupling of a24' with the motor-related paracentral gyrus. Both of these areas show changed functional coupling with the SFG. The function of this part of SFG is not well studied, but it shows consistent functional coupling with nodes of the default mode network (18,74–76). Moreover, introspective tasks increase activity specifically in this part of SFG, with activity extending medially into BA 32 (77), while damage to SFG and BA 32 correlates with impairment in reappraising the personal relevance of negative events (78). Interestingly, this part of the SFG has also been implicated in expressions of positive affect, such as laughter (79) and humor (80), which are important for self-centered reappraisal.

Limitations

While our results provide the first insightful dissociation of FC abnormalities in MD vulnerability and disease, replication is needed, particularly given the heterogeneity of clinical populations. Although we corrected rigorously for medication and Axis I comorbidity effects, replication should ideally be sought in a large independent sample of unmedicated MD participants. Second, while the FC abnormalities described here reflect significant group differences related to MD vulnerability and disease, we could not examine whether they are specific to MD. Future studies should examine whether these FC changes could differentiate between unipolar depression and other psychiatric syndromes. Lastly, our focus on OMPFC prevents drawing conclusions regarding other brain areas. For instance, executive dysfunctions often manifest in MD, which would predict FC abnormalities associated with more cognition-centered networks.

Conclusions

The current study systematically delineated FC alterations of cortical units in the OMPFC in MD using a published parcellation map. This enabled a more fine-grained localization of the pathogenetically relevant subregions within the affective cortex. We also used conjunction analyses on groups of HCs, MD-susceptible individuals, and patients during MD episodes and dissociated the patterns of connectivity aberrations in MD vulnerability from aberrations in MD manifestation. Our results complement previous evidence that the OMPFC, anatomically and functionally linked to autonomic and affective centers, shows connectivity aberrations in both MD states. Moreover, we provide evidence that these functional aberrations concern primarily the relationship of specific OMPFC subparts and the posterior receptive cortex and various regions specifically within the dorsal and ventral visual processing streams. This is in line with the increasingly recognized relationship between emotion and visual perception: visual stimuli and experiences trigger and shape emotions and affect, as well as being shaped by mood states (81,82).

Further, our results highlight two OMPFC regions—both of which are implicated in MD vulnerability and disease manifestation—as being central to depression's pathophysiology: the anterior insula and the rostral anterior cingulate area p32. Both areas have been previously shown to have altered activity and connectivity in MD (83–86). More importantly, they are both central nodes within two extended neural networks, the salience network and the default mode network, that have also been implicated in MD (87,88). We provide evidence that the connectivity of these central nodes or hubs is altered not only in the MD disease state but also long before any clinical symptoms appear in individuals with familial MD vulnerability.

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