Archival Report

Functional Connectivity of the Precuneus in Unmedicated Patients With Depression

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ABSTRACT

BACKGROUND: The precuneus has connectivity with brain systems implicated in depression.

METHODS: We performed the first fully voxel-level resting-state functional connectivity (FC) neuroimaging analysis of depression of the precuneus, with 282 patients with major depressive disorder and 254 control subjects.

RESULTS: In 125 unmedicated patients, voxels in the precuneus had significantly increased FC with the lateral orbitofrontal cortex, a region implicated in nonreward that is thereby implicated in depression. FC was also increased in depression between the precuneus and the dorsolateral prefrontal cortex, temporal cortex, and angular and supramarginal areas. In patients receiving medication, the FC between the lateral orbitofrontal cortex and precuneus was decreased back toward that in the control subjects. In the 254 control subjects, parcellation revealed superior anterior, superior posterior, and inferior subdivisions, with the inferior subdivision having high connectivity with the posterior cingulate cortex, parahippocampal gyrus, angular gyrus, and prefrontal cortex. It was the ventral subdivision of the precuneus that had increased connectivity in depression with the lateral orbitofrontal cortex and adjoining inferior frontal gyrus.

CONCLUSIONS: The findings support the theory that the system in the lateral orbitofrontal cortex implicated in the response to nonreceipt of expected rewards has increased effects on areas in which the self is represented, such as the precuneus. This may result in low self-esteem in depression. The increased connectivity of the precuneus with the prefrontal cortex short-term memory system may contribute to the rumination about low self-esteem in depression. These findings provide evidence that a target to ameliorate depression is the lateral orbitofrontal cortex.

Keywords: Cingulate cortex, Depression, Functional connectivity, Hippocampus, Inferior frontal gyrus, Medial temporal lobe, Orbitofrontal cortex, Resting-state functional neuroimaging

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Major depressive disorder is ranked by the World Health Organization as the leading cause of years-of-life lived with disability, and in most countries the number of people who experience depression during their lives falls within a range of 8% to 12% (1–3). Depression is a major personal burden to individuals and their families, and is a major economic burden to society (4). Major depressive episodes, found in both major depressive disorder and bipolar disorder, are pathological mood states characterized by persistently sad or depressed mood. Major depressive disorder is generally accompanied by altered incentive and reward processing, impaired modulation of anxiety and worry, inflexibility of thought and behavior, altered integration of sensory and social information, impaired attention and memory, and visceral disturbances (1,3,5).

Resting-state functional connectivity (FC) between brain areas, which reflects correlations of activity, is a fundamental tool in helping to understand the brain regions with altered connectivity and function in mental disorders (6). Some FC differences in the precuneus have been reported in depression, making the precuneus important for understanding depression. In one study,

reduced FC of the precuneus with the fusiform gyrus, supplementary motor area, and pre- and postcentral cortex was reported, together with a correlation between the Hamilton Depression Rating Scale score and increased FC with the dorsomedial frontal cortex, middle frontal gyrus, and anterior cingulate cortex (7). In other studies, medicated patients with major depressive disorder had increased FC between the precuneus and the prefrontal cortex dorsal nexus (8,9). A meta-analysis performed on large-scale resting-state brain networks showed hypoconnectivity within the frontoparietal network, hyperconnectivity within the default mode network, and hyperconnectivity between frontoparietal control systems and regions of the default mode network (10). In previous investigations of FC differences of the precuneus in depression, much smaller sample sizes with tens of participants were studied, and voxel-to-voxel FC was not measured. More importantly, most of the patients with depression recruited in these studies were taking medication at the time of study. In one large-scale study with a very different design, areas such as the lateral orbitofrontal cortex, precuneus, and angular gyrus were found to have increased FC

with each other, but the study was performed with an analysis in which the FCs between every pair of voxels in the brain were analyzed, and although it had the advantage of being unbiased by prior hypotheses, it was somewhat insensitive to the details of the effects found in each of these regions and the effects of medication (11). Another study on a completely different group of more than 1000 people from the United States not selected to have depression showed that the Adult Self-Report Depressive Problems score was correlated with increased FC in areas that included the lateral orbitofrontal cortex and precuneus (12). That provides very useful support for the involvement of the FC of the precuneus in depression. However, that was a region-based analysis and not a voxel-based analysis, and the effects of medication could not be examined. Further background to the present investigation of FC of the precuneus in depression is that a posterior part of the default mode network that included the precuneus and other parietal areas, and the posterior cingulate cortex, had its increased FC in depression normalized by medication (13); that in a meta-analysis the precuneus was an area with different FC in depression (10); that in depression there is a reduction in the volume of the precuneus/posterior cingulate cortex region (as well as many other brain areas) (14); and that in depression there is reduced structural connectivity (measured with diffusion tensor imaging) between the precuneus and anterior cingulate cortex (15). It is with that background that the present large-scale voxel-level investigation of the FC of the precuneus and depression was performed.

The aim of the present investigation was to examine the FC of the precuneus in depression at the voxel level in a large sample of 125 nonmedicated patients with depression, 157 medicated patients with depression, and 254 matched control subjects. With this large dataset, we are able to analyze every precuneus voxel for significantly different FC with every voxel throughout the rest of the brain in depressed people versus control subjects, with this hypothesis-based voxel-level FC analysis providing evidence therefore on which parts of the precuneus have different FC in depression, and how this is different from a precuneus seed-based approach, as set out in the Supplement. Further, we analyze here the effects of medication on the FC of the precuneus in patients with depression, which also has not been performed with any large patient sample previously.

In the present investigation, we used a dataset from Xinan in Chongqing, China, as it enabled us to analyze FC in a large group of unmedicated patients with depression. We relate our discoveries regarding the precuneus to a new theory of depression, in which 1) the lateral orbitofrontal cortex has increased sensitivity of a nonreward attractor in depression; 2) the precuneus has increased FC to the lateral orbitofrontal cortex; and 3) the reciprocally related medial orbitofrontal cortex reward system is underactive in depression (5,16–18).

METHODS AND MATERIALS

Participants

There were 282 patients with a diagnosis of major depression, and 254 control subjects from Xinan (First Affiliated Hospital of Chongqing Medical School in Chongqing, China). All participants were diagnosed according to the DSM-IV criteria for major depressive disorder. Depression severity and symptomatology were evaluated by the Hamilton Depression Rating Scale (17 items) (19) and the Beck Depression Inventory (20). A total of 125

of the patients were not receiving medication at the time of the neuroimaging. Table 1 provides a summary of the demographic information and the psychiatric diagnosis of the participants, and further information is provided in the Supplement. The dataset utilized here is a subset of those described in Cheng et al.'s studies (11,21,22), for which the present different type of analysis could be performed, and the present analysis specifically analyses the precuneus, which was not the focus of any earlier investigation we have performed.

Image Acquisition and Preprocessing

All images were acquired on a 3T Siemens Trio MRI scanner using a 16-channel whole-brain coil (Siemens Medical, Erlangen, Germany) in an 8-minute period in which the participants were awake in the scanner and not performing a task, using standard protocols described in the Supplement. Data preprocessing was standard, as has been described before (11), and details are provided in the Supplement.

Hypothesis-Based Voxelwise Association Studies

In the present study, each resting-state functional magnetic resonance imaging image included 47,619 voxels. For each pair of voxels, the time series were extracted, and the Pearson correlation was calculated for each subject, to provide the measure of FC, followed by Fisher's z-transformation. Two-tailed, two-sample t tests were performed on the Fisher's z-transformed correlation coefficients to identify significantly altered voxelwise FC links in patients with depression compared with control subjects. The effect of age, sex ratio, education, and head motion (mean framewise displacement) were regressed out within each dataset in this step. Given that the precuneus had been predefined as the region of interest and had 1993 voxels, and that there were 47,619 voxels $3 \times 3 \times 3$ mm in the whole automated anatomical labeling (AAL2) atlas brain (23), the number of voxel pairs in this study was approximately $1993 \times 47,619$, which is much smaller than the 1,133,760,771 ($47,619 \times 47,618/2$) voxel pairs in our whole-brain study (11). This enabled highly significant differences in voxel-level FC of the precuneus with the rest of the brain to be identified in the present study. Finally, a false discovery rate (FDR) procedure was used to correct for multiple comparisons. In the present study, FDR correction for the FC between any pair of voxels was used, and results are presented based on this statistical test with FDR $p < .05$, corresponding to a p threshold of 1.1×10^{-5} in t tests.

Visualization of the Differences in FC for Each Voxel

To illustrate in some of the figures the extent to which voxels in different brain areas had FC differences between patients and control subjects, we used a measure for the association (MA) between a voxel i and the brain disorder. This was defined as $MA = \sum_{j=1}^{N_\alpha} T_j$, where N_α is the number of links between voxel i and every other voxel in the brain that has a p value less than α (in the present study, 1.1×10^{-5}) in t tests comparing patients with control subjects, and T_j is the t value of the jth significant link in t tests comparing patients with control subjects. To distinguish the increased and decreased FCs and avoid cancellation of positive and negative t values, we defined the MA of each voxel separately for increased FCs and decreased

Table 1. A Summary of the Demographic Information and the Psychiatric Diagnosis in the Present Study

Group	Age, Years	Male/Female	Education, Years	Medication (Yes/No)	HDRS	BDI	Duration of Illness, Years	First Episode (Yes/No)	Mean FD
Healthy Control Subjects	39.65 ± 15.80	166/88	13.01 ± 3.89	—	—	—	—	—	0.133 ± 0.063
Patients With MDD	38.74 ± 13.65	183/99	11.91 ± 3.58	157/125	20.8 ± 5.87	20.42 ± 9.33	4.16 ± 5.51	209/49	0.125 ± 0.054
Statistic	$t_{534} = 0.719$, $p = .472$	$\chi^2_1 = 0.013$, $p = .911$	$t_{534} = 3.41$, $p = 6.9 \times 10^{-4}$	—	—	—	—	—	$t_{534} = 1.729$, $p = .084$
Unmedicated Patients With MDD	37.60 ± 13.12	84/41	12.07 ± 3.72	0/125	22.22 ± 4.39	22.51 ± 8.16	2.91 ± 4.44	111/14	0.120 ± 0.053
Medicated Patients With MDD	39.64 ± 14.03	99/58	11.78 ± 3.48	157/0	19.42 ± 6.73	18.43 ± 9.95	5.33 ± 6.13	98/35	0.129 ± 0.054
Statistic	$t_{280} = -1.250$, $p = .212$	$\chi^2_1 = 0.524$, $p = .469$	$t_{280} = 0.673$, $p = .501$	—	$t_{280} = 3.907$, $p = 1.2 \times 10^{-4}$	$t_{280} = 3.520$, $p = 5.1 \times 10^{-4}$	$t_{280} = -3.539$, $p = 4.8 \times 10^{-4}$	$\chi^2_1 = 9.570$, $p = .002$	$t_{280} = -1.268$, $p = .206$

Values are n or mean ± SD. The difference between patients with MDD and control subjects for continuous variables was assessed by a two-sample t test, and the difference for the binary variable (sex) was assessed by a χ^2 test.

BDI, Beck Depression Inventory; FD, framewise displacement; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.

FCs. A larger value of *MA* implies a more significant difference in the FC of a voxel.

RESULTS

The resting-state functional magnetic resonance imaging FC analyses were performed with 282 patients with a diagnosis of major depression and 254 control subjects. This large population was sufficient to allow voxel-level analysis with FDR-corrected statistics of the FC differences of precuneus voxels with all other voxels in the brain (excluding the cerebellum) in patients versus control subjects.

Voxel-Level Differences in FC in Unmedicated Patients With Depression

Of the 282 patients with major depressive disorder, 125 patients were not receiving medication, and 157 patients were receiving antidepressant medication (Table 1). The patients with medication tended to be longer-term patients than those without medication, who were in many cases first-episode patients. When we refer to medicated versus unmedicated in what follows, the longevity of the depression may be a factor. Nevertheless, important comparisons could be made as follows, which apply to unmedicated, mainly first-episode patients with major depressive disorder.

Figure 1 shows the difference in the FCs of the 125 unmedicated patients from the 254 control subjects (after FDR correction at $p < .05$). This shows that the main differences in unmedicated patients with depression are differences in FC between the precuneus and the lateral orbitofrontal cortex, the temporal pole, the dorsolateral prefrontal cortex (AAL2 area Frontal_Inf_Tri), some occipital areas, and voxels on other parts of the precuneus. Table 2 shows the number of voxels in different AAL2 brain areas with different FC and the coordinates of the peak voxels [a list of abbreviations of the AAL2 areas (23) is provided in Supplemental Table S1]. Supplemental Table S2 shows which areas have increased FC and which areas have decreased FC with the precuneus in depression. Taken together, Table 2 and Supplemental Table S2 show that the areas with increased FC with the precuneus in depression include the lateral orbitofrontal cortex (AAL2 areas OFClat and Frontal_Inf_Orb_2), the inferior and middle gyri of the prefrontal cortex, the temporal cortex, the angular and supramarginal areas, some pre- and postcentral areas with nearby parietal areas, and the visual cortical areas. Some voxels that are mainly lateral orbitofrontal cortex in Figure 1 appear in Table 2 as medial orbitofrontal cortex AAL2 areas because they just clip these AAL2 areas. The parts of the inferior frontal gyrus shown in Figure 1 and the coordinates shown in Table 2 are close to those of the inferior frontal gyrus region with connections with the motor laryngeal area (24).

Areas with decreased FC with the precuneus in depression include the hippocampus and parahippocampal cortex, the fusiform gyrus, and the visual cortical areas.

Effect of Medication on FC Involving the Precuneus

To investigate how the medication may influence the FC, we show in Figure 2 the voxels with different FC for the 125 unmedicated patients and the 157 medicated patients. To account for the differences in severity, chronicity, and the proportion of first episode versus multiepisode patients
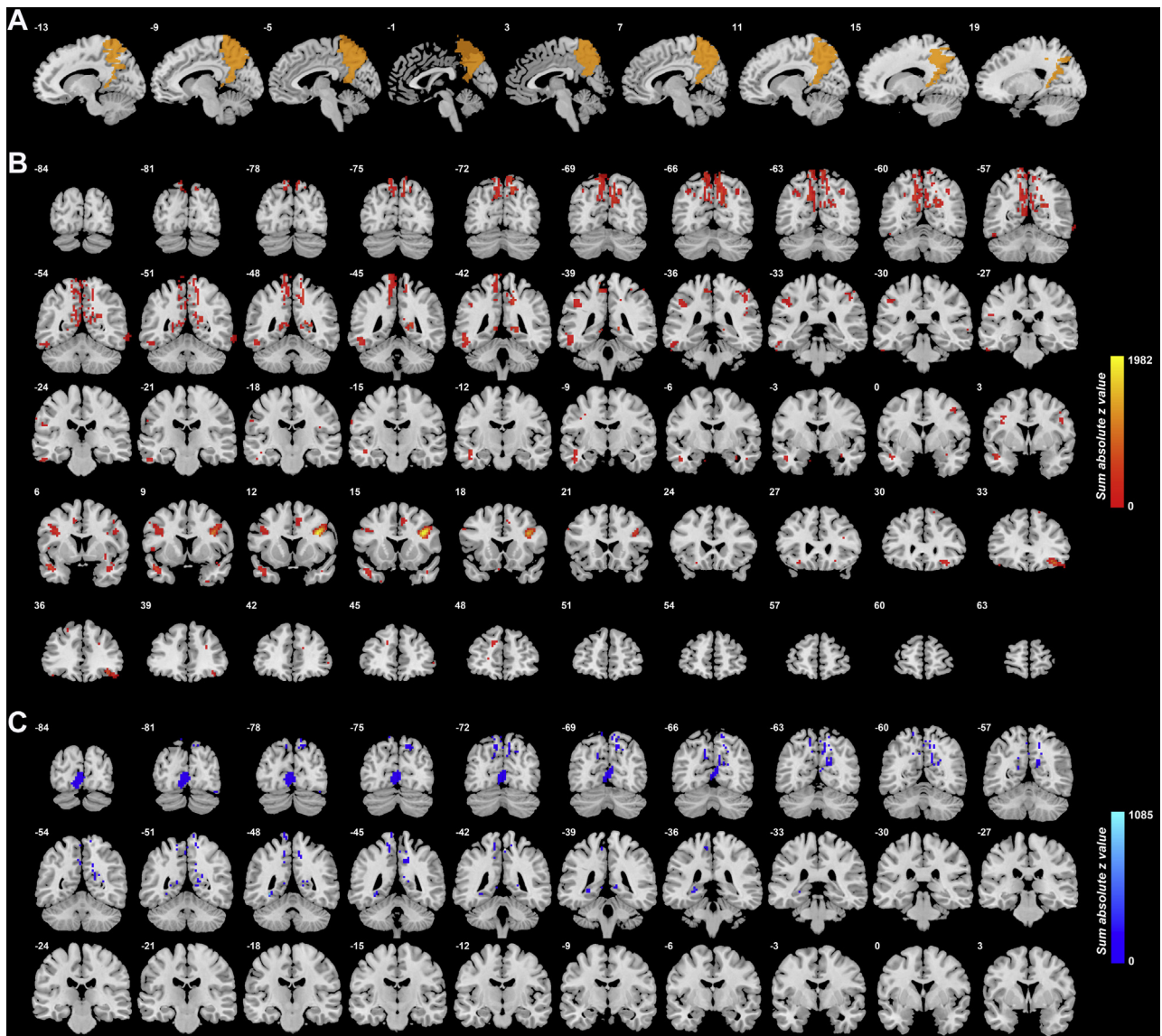
Figure 1. **(A)** Voxels of the precuneus defined by the automated anatomical labeling (AAL2) atlas. Anatomical location of voxels with significantly **(B)** increased and **(C)** decreased functional connectivity with the precuneus in depression in 125 unmedicated patients vs. 254 control subjects obtained from the voxel-based association study. z Values are shown for each voxel, showing the mean difference of functional connectivities for patients with unmedicated depression and control subjects. Red thus indicates an increase in functional connectivity in depression, and blue indicates a decrease. The right of the brain is on the right of each slice. The Y values are in Montreal Neurological Institute coordinates. This shows that the main differences in unmedicated depression for the precuneus are an increase in functional connectivity with the lateral orbitofrontal cortex (Y = 33) and with a prefrontal area in the inferior frontal gyrus that may be the prefrontal laryngeal cortex (Y = 15).

between these two groups, the Hamilton Depression Rating Scale score, illness duration, and the status of first episode versus multiepisode were regressed out in the comparison between the unmedicated patients and medicated patients. Blue in this diagram indicates a reduction in FC in the medicated group compared with the unmedicated group. The medication was associated with a reduction of FC between the lateral orbitofrontal cortex/inferior prefrontal convexity areas and the precuneus. Thus, for the lateral orbitofrontal cortex links with increased FC with the precuneus in unmedicated depression, the medication reduces those FCs. An implication

is that one way in which antidepressants work is by reducing the FC between the lateral orbitofrontal cortex and the precuneus.

In addition, the medication reduced the FC of the precuneus with the inferior/middle frontal gyrus (an area implicated in working memory), the temporal lobe cortex, the hippocampal/parahippocampal regions (involved in memory), the ventral insula (an area implicated in autonomic function), and other precuneus voxels (Figure 2). A supplementary analysis of variance–based analysis of the differences in FC between all AAL2 areas and the precuneus between control subjects and medicated and unmedicated

Table 2. Numbers of Voxels in Different AAL2 Areas With Significantly Different Functional Connectivity With the Precuneus in Unmedicated Patients With Depression

Area	Sum z Value	Voxels	MNI Coordinates (Peak)		
			X	Y	Z
Frontal_Inf_Orb_2, OFClat[a,b]	1801.3	56	36	33	−12
Precuneus_L, Precuneus_R	1084.7	974	3	−42	57
Temporal_Sup, Temporal_Pole_Sup, Temporal_Mid, Temporal_Pole_Mid, Temporal_Inf	460.1	242	−54	−42	−9
Frontal_Inf_Oper, Frontal_Inf_Tri, Frontal_Mid_2	1981.8	152	36	15	27
Angular	65.2	25	36	−63	42
Hippocampus_L, ParaHippocampal_L	386.8	19	−33	−45	−6
Calcarine, Lingual	22.8	229	−3	−99	−15
SupraMarginal_L	18.3	10	−54	−24	24
Precentral_R	9.3	12	48	6	30
Precentral_L	238.4	28	−42	9	33
Occipital_Mid_L, Parietal_Inf_L	50.4	12	−27	−63	39
Postcentral_L, Parietal_Inf_L	150.4	49	−45	−36	42
Supp_Motor_Area_R, Cingulate_Mid_R	13.9	20	9	15	45
Postcentral_R, Parietal_Inf_R	51.5	20	45	−36	45

For the precuneus, the table shows the number of precuneus voxels that have different functional connectivity with the whole brain (false discovery rate [FDR] corrected, $p < .05$). The other entries in the table show the numbers of voxels in each of the specified brain regions with different functional connectivity with precuneus voxels (FDR corrected, $p < .05$). The z value is the sum across all voxels and functional connectivity links of the absolute value of the z score for significant links between pairs of voxels. The table shows clusters with more than 10 voxels.

AAL2, automated anatomical labeling; MNI, Montreal Neurological Institute.

[a]This is a single cluster, as shown in Figure 1, which is in lateral orbitofrontal cortex area 12 (46), but some of its voxels were just in OFCpost in the AAL2 atlas.

[b]A list of abbreviations of the AAL2 areas (23) is provided in Supplemental Table S1.

patients is provided in Supplemental Figure S4 and Supplemental Table S3. The results show that patients with medication have FCs that are altered (mainly decreased) toward the values of the healthy control subjects.

Analysis of Precuneus FC in Healthy Control Subjects, and Comparison With Patients With Depression

To help interpret the differences in precuneus FC in depression, Figure 3 shows the FC of precuneus voxels with other voxels in the brain in the 254 healthy control subjects. High FC is found with the medial and lateral orbitofrontal cortex and anterior cingulate cortex, with the dorsolateral prefrontal cortex, with the olfactory tubercle/ventral striatum, with the inferior temporal gyrus, with the parahippocampal cortex and hippocampus, with the posterior cingulate cortex, and with the lateral and medial parietal cortex.

Figure 4 shows the main areas with which the precuneus has high FC in healthy control subjects, how for many areas

the connectivity is higher with the precuneus in unmedicated patients with depression, and how patients with medication have FCs that are reduced toward the values in the healthy control subjects. The clear exception is the hippocampus, which has low FC with the precuneus, which is decreased in depression. The FC value shown is the mean r (correlation) value between all significant voxels in each of the AAL2 areas indicated. This helps in understanding the FC of the precuneus in control subjects. For comparison, the mean r value for the FC of the precuneus with all other brain areas is $.143 \pm .085$ (SD). Supplemental Table S2 shows that in healthy control subjects the precuneus has moderately high FC with the dorsolateral prefrontal cortex, early cortical visual areas, angular gyrus, and temporal cortex.

Parcellation of the Precuneus

To enable a more detailed comparison between patients and control subjects, we performed a voxel-level parcellation of the precuneus based on the FC of each precuneus voxel with all 94 AAL2 brain regions (23) in the healthy control subjects (see Supplement), the results of which are shown in Supplemental Figure S1. An inferior cluster (2, yellow) had especially high FC with the nearby posterior cingulate cortex, but also, to a lesser extent, with the anterior cingulate cortex; with the parahippocampal gyrus; with prefrontal cortex areas that included Frontal_Med_Orb, the gyrus rectus, and Frontal_Sup_Medial; with the angular gyrus; and with the middle temporal gyrus (Supplemental Figure S2). The superior posterior precuneus cluster (1, blue) and the superior anterior cluster (3, red) had somewhat similar FC to each other, including high FC with visual areas (calcarine, occipital, lingual, and fusiform), the midcingulate cortex, other parts of the parietal cortex, and the supramarginal gyrus (Supplemental Figure S2). Precuneus cluster 3 (superior anterior) had higher FC than cluster 1 (superior posterior) with motor-related areas including the precentral gyrus, the paracentral lobule, the midcingulate cortex, and the postcentral gyrus. Precuneus cluster 1 (superior posterior) had higher FC with the angular gyrus and with some temporal lobe areas than cluster 3 (Supplemental Figure S2).

As shown in Supplemental Figure S3, it was cluster 2, the ventral precuneus cluster, that had increased FC in depression with the lateral orbitofrontal cortex areas such as Frontal_Inf_Orb_2 and the adjacent inferior frontal gyrus areas (opercular and triangular). Right precuneus cluster 3 (superior anterior) had increased FC in depression with some motor-related areas (precentral and postcentral gyri) and with temporal lobe cortical areas.

DISCUSSION

The main findings were as follows. Voxels in the precuneus had significantly increased FC with the lateral orbitofrontal cortex in unmedicated patients with depression. In patients receiving medication, the FC between the lateral orbitofrontal cortex and precuneus was decreased toward that in the control subjects. FC was also increased between the precuneus and prefrontal cortex areas involved in short-term working memory. In the 254 control subjects, it was shown that the precuneus has high FC with the parahippocampal and
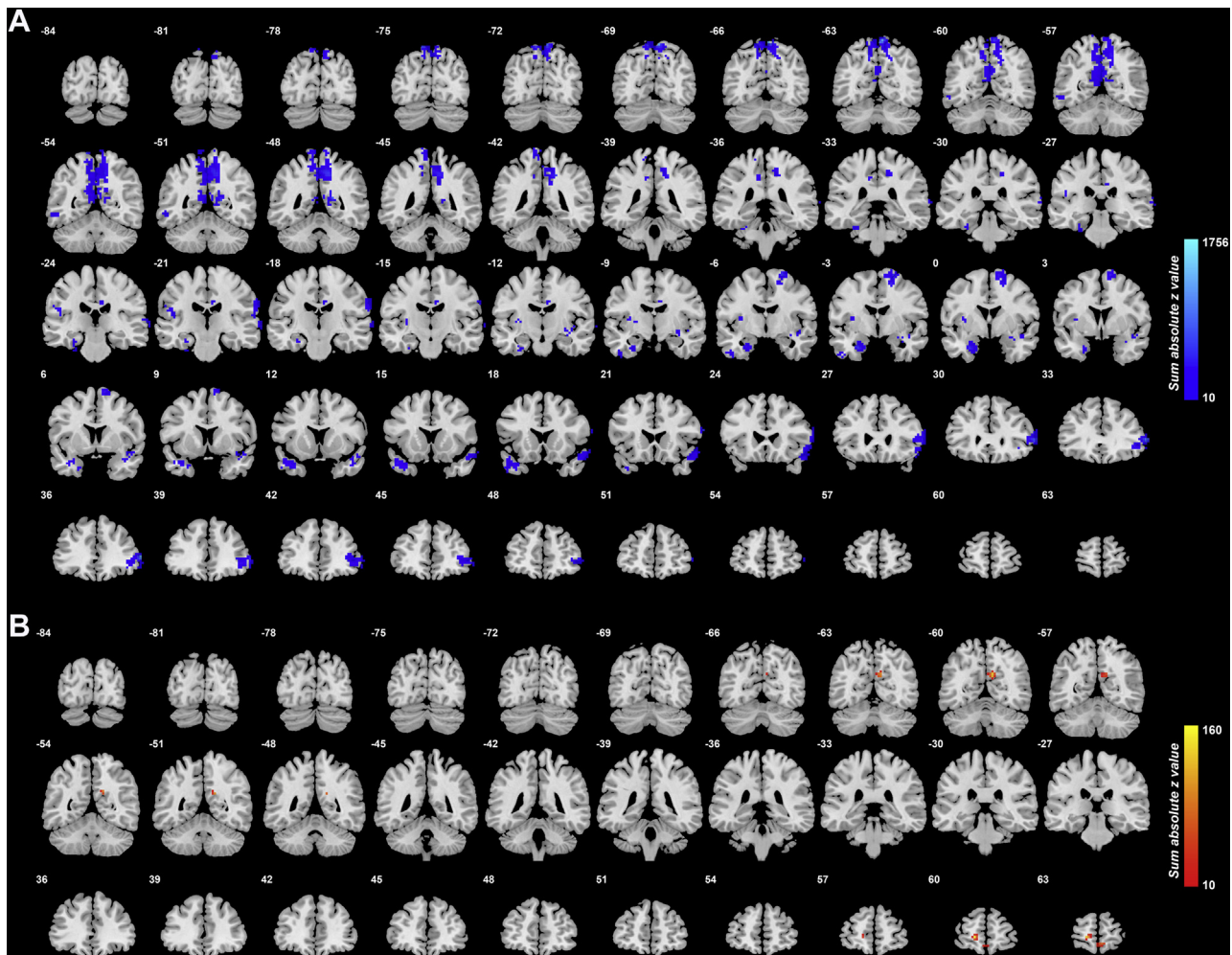
Figure 2. Anatomical location of voxels with significantly **(A)** increased and **(B)** decreased functional connectivity with the precuneus in 125 unmedicated patients vs. 157 medicated patients obtained from the voxel-based association study. z Values are shown for each voxel, showing the mean difference of functional connectivities for patients with medicated depression and patients with unmedicated depression. Blue thus indicates lower functional connectivity in patients with depression who are medicated than in those who are unmedicated. Here, we only show the voxels with sum absolute z value larger than 10 and cluster size larger than 20 voxels.

dorsolateral prefrontal regions, which are involved in memory, and with the parietal cortex. The findings support the theory that the nonreward system in the lateral orbitofrontal cortex has increased effects on memory systems, which contribute to the rumination about sad memories and events in depression (5,16–18). These new findings provide further evidence that a key target to ameliorate depression is the lateral orbitofrontal cortex (16,18,25).

The precuneus and the adjoining retrosplenial cortex (Brodmann areas 29 and 30) (26–28) [both included in the AAL2 precuneus area used here (23)] are key regions related to spatial function, memory, and navigation (29–31). The retrosplenial cortex provides connections to and receives connections from the hippocampal system, connecting especially with the parahippocampal gyrus areas TF and TH, and with the subiculum (26,27,29). The precuneus can be conceptualized as providing access to the hippocampus for spatial and related

information from the parietal cortex [given the rich connections between the precuneus and parietal cortex (26,27,32), evident in Figure 4]. Further, the precuneus has rich connectivity with the posterior cingulate cortex (32), which provides a pathway into the hippocampal memory system (33,34), and which also has increased FC with the lateral orbitofrontal cortex in depression, through which sad memories may be facilitated in depression (21). Object information from the temporal lobe connects to and from the hippocampus via the perirhinal cortex (35). This provides a basis for the hippocampus to associate an object and spatial information in the single network in the CA3 region of the hippocampus, to form an episodic memory with object and spatial components (36). However, reward-related/emotional information may also be part of an episodic memory, and connections from the orbitofrontal cortex to the hippocampal system via the perirhinal and entorhinal cortex pathway are likely
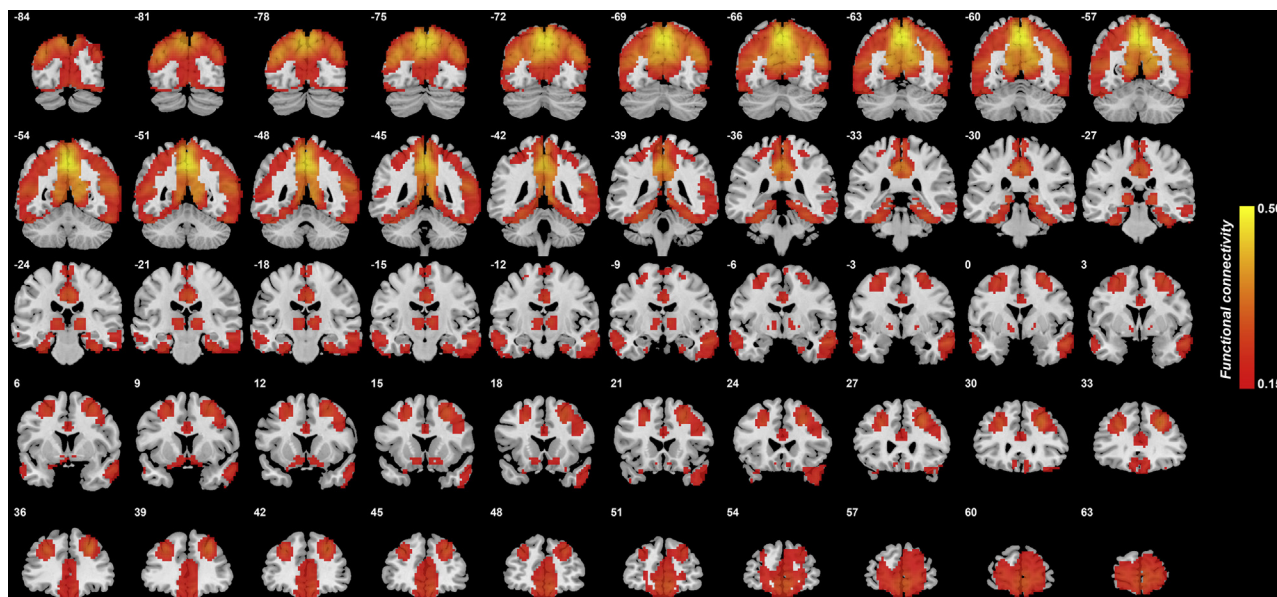
Figure 3. Functional connectivity of the precuneus in 254 healthy control subjects. The *r* values are shown (thresholded at *r* = .15).

to be one route (18,35,37,38). Interestingly, the relatively strong FC between the precuneus and the lateral orbitofrontal cortex described here indicates that reward/punishment-related information also enters this part of the system.

It was of interest that medication was associated with reduced FC between the precuneus and the lateral orbitofrontal cortex, and also with a number of other areas that have increased FC with the precuneus in depression (Figures 2 and 4).

As discussed previously (11), the precuneus is a medial parietal cortex region implicated in the sense of self, agency, autobiographical memory, and spatial function (30,31). This has led to the working hypothesis that the lateral orbitofrontal cortex nonreward/punishment system in orbitofrontal cortex 47/12 with its increased FC with the self-related precuneus system relates to some of the symptoms of depression (16). Consistent with the hypothesis of disturbed function of the orbitofrontal cortex in depression, there is increased regional

cerebral blood flow in the ventrolateral orbitofrontal cortex area 47/12 in depression (39–41). In addition, overgeneral autobiographical memory manifests in individuals with major depressive disorder tested during depressed or remitted phases and in healthy individuals at high risk for developing major depressive disorder. During specific autobiographical memory recall, high-risk individuals have increased activity relative to patients with remitted major depressive disorders and healthy control subjects in the ventrolateral prefrontal cortex and lateral orbitofrontal cortex (42). The increased FC of the lateral orbitofrontal cortex (involved in nonreward and aversive processing), with the precuneus (involved in the sense of self), is of interest, for a sign of the start of a depressive episode may be negative thoughts about the self and low self-esteem (43). It is notable that orbitofrontal cortex area 47/12, the nonreward/punishment lateral orbitofrontal cortex area, has increased FC in depression with a number of areas, including the left angular gyrus (involved in language) (11) and the posterior cingulate cortex (involved in memory) (21), but they may not have
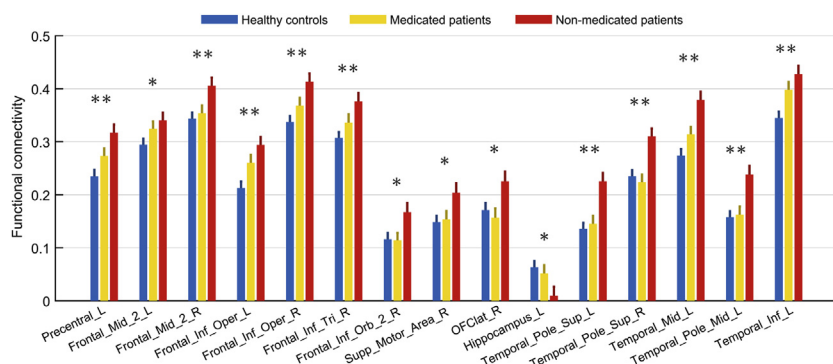

Figure 4. Comparison of the functional connectivity between the precuneus and identified significant regions of interest (27 in total) shown in Table 2 in healthy control subjects as well as medicated and unmedicated patients. The one-way analysis of variance was performed to test whether there is any difference in functional connectivity among these three groups. Here, we show only the results with *p* < .05 in the analysis of variance. For this analysis, significant voxels within each of the 27 identified regions of interest were included. The mean functional connectivity + the SEM is shown. *p* < .05; **false discovery rate correction.

increased connectivity with each other. The common hub to this system is the lateral orbitofrontal cortex area 47/12. An interesting difference to note is that in healthy control subjects the precuneus has high FC with the parahippocampal gyrus, but not with the hippocampus per se (Figure 3), whereas the posterior cingulate cortex has high FC with both the para-hippocampal gyrus and the hippocampus (21), implying that the posterior cingulate cortex is more closely related to hip-pocampal memory functions (34,36,38). The superior anterior precuneus cluster (3, red in Supplemental Figure S2) had high FC with the nearby areas anterior to it involved in motor function. The superior posterior precuneus cluster (1, blue in Supplemental Figure S2) had high FC with the visual areas posterior to it, and in depression had increased FC with some temporal lobe cortical areas and with the inferior frontal gyrus areas (Supplemental Figure S3).

The precuneus is part of the default mode network, which becomes more active when internal thoughts and processing are occurring rather than when tasks are being performed externally, and this system may have altered activity in depression (44). The increased FC between the precuneus and the prefrontal cortex described here, and noted previously in much smaller previous studies (7–9), may relate to increased internal ruminating thoughts in depression. New conceptual contributions of the present research are the links found to the lateral orbitofrontal cortex nonreward system, which links the ruminating thoughts to the negative, sad thoughts in depres-sion, as well as the hypothesis that the precuneus may make these sad ruminating thoughts refer especially to the self, and indeed be related to the low self-esteem that is found in depression.

To test some of the implications of the findings and working hypotheses described here, it would be of interest to perform a functional neuroimaging study in which activations in the precuneus and the lateral orbitofrontal cortex to sad versus happy memories are measured. The prediction is that in the precuneus and the lateral orbitofrontal cortex the activations would be higher in depressed people for sad versus happy memories.

The other link that stood out in the unmedicated patients was the increased FC between the precuneus and the inferior frontal gyrus region shown in Figure 1 and Table 2, which is probably the inferior frontal gyrus region with connections to the motor laryngeal area (24). It is suggested that this is related to the increased rumination in depression, which may produce subliminal speech-related effects. That would be consistent with the increased FC of the lateral orbitofrontal cortex with both the precuneus and the angular gyrus, a cortical area related to language (11). It is also consistent with the increased FC of the precuneus with two language-related areas, the angular and supramarginal gyri, as shown in Table 2.

Other links with increased FC in depression were between the precuneus and the temporal cortical areas (Figure 1 and Table 2). An investigation of effective (i.e., directed) connec-tivity in depression showed that it is the forward links from the middle and inferior temporal cortical areas to the precuneus that are increased in depression (45), providing evidence that perceptual and related input may have a greater influence on the precuneus in depression. The effective connectivity in the

reverse direction is 20 times smaller, making the precuneus an interesting structure with regard to its forward and reverse effective connectivities (45).

Some other links with different FC with the precuneus in depression are with motor areas, and it may be expected that a structure such as the precuneus involved in spatial and related functions has FC with motor areas. There is also some decreased FC of the precuneus with the occipital visual areas in depression, as shown in Figure 1.

The parcellation analysis revealed even more. The ventral precuneus cluster (2, yellow in Supplemental Figure S1) had high FC with areas implicated in memory such as the posterior cingulate cortex and parahippocampal gyrus, and in depres-sion it was this cluster that had increased FC with parts of the lateral orbitofrontal cortex. An implication is that this part of the precuneus may relate to the poor self-esteem and ruminating sad memories in depression.

The importance of the present study is that by focusing on the precuneus, and using very large neuroimaging datasets of patients with depression and control subjects, including a large group of unmedicated patients, we were able to characterize the altered FC at the voxel level in depression of the precuneus with other brain regions. A strength of this investigation is that we analyzed FC at the level of voxel-to-voxel FC. This was made possible by the uniquely large sample size of unmedi-cated patients with depression, which enabled us to reach the conclusions described above.

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