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Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression

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The first brain-wide voxel-level resting state functional connectivity neuroimaging analysis of depression is reported, with 421 patients with major depressive disorder and 488 control subjects. Resting state functional connectivity between different voxels reflects correlations of activity between those voxels and is a fundamental tool in helping to understand the brain regions with altered connectivity and function in depression. One major circuit with altered functional connectivity involved the medial orbitofrontal cortex Brodmann area 13, which is implicated in reward, and which had reduced functional connectivity in depression with memory systems in the parahippocampal gyrus and medial temporal lobe, especially involving the perirhinal cortex Brodmann area 36 and entorhinal cortex Brodmann area 28. The Hamilton Depression Rating Scale scores were correlated with weakened functional connectivity of the medial orbitofrontal cortex Brodmann area 13. Thus in depression there is decreased reward-related and memory system functional connectivity, and this is related to the depressed symptoms. The lateral orbitofrontal cortex Brodmann area 47/12, involved in non-reward and punishing events, did not have this reduced functional connectivity with memory systems. Second, the lateral orbitofrontal cortex Brodmann area 47/12 had increased functional connectivity with the precuneus, the angular gyrus, and the temporal visual cortex Brodmann area 21. This enhanced functional connectivity of the non-reward/punishment system (Brodmann area 47/12) with the precuneus (involved in the sense of self and agency), and the angular gyrus (involved in language) is thus related to the explicit affectively negative sense of the self, and of self-esteem, in depression. A comparison of the functional connectivity in 185 depressed patients not receiving medication and 182 patients receiving medication showed that the functional connectivity of the lateral orbitofrontal cortex Brodmann area 47/12 with these three brain areas was lower in the medicated than the unmedicated patients. This is consistent with the hypothesis that the increased functional connectivity of the lateral orbitofrontal cortex Brodmann area 47/12 is related to depression. Relating the changes in cortical connectivity to our understanding of the functions of different parts of the orbitofrontal cortex in emotion helps to provide new insight into the brain changes related to depression.

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Abbreviations: BWAS = brain-wide association study; HAMD = Hamilton Depression Rating Scale; OFC = orbitofrontal cortex; MDD = major depressive disorder

Introduction

Major depressive disorder (MDD) is ranked by the World Health Organization as the leading cause of years-of-life lived with disability (Drevets, 2007; Gotlib and Hammen, 2009; Hamilton *et al.*, 2013). Major depressive episodes, found in both MDD and bipolar disorder are pathological mood states characterized by persistently sad or depressed mood. MDDs are generally accompanied by: (i) altered incentive and reward processing, evidenced by amotivation, apathy, and anhedonia; (ii) impaired modulation of anxiety and worry, manifested by generalized, social and panic anxiety, and oversensitivity to negative feedback; (iii) inflexibility of thought and behaviour in association with changing reinforcement contingencies, apparent as ruminative thoughts of self-reproach, pessimism, and guilt, and inertia toward initiating goal-directed behaviour; (iv) altered integration of sensory and social information, as evidenced by mood-congruent processing biases; (v) impaired attention and memory, shown as performance deficits on tests of attention set-shifting and maintenance, and autobiographical and short-term memory; and (vi) visceral disturbances, including altered weight, appetite, sleep, and endocrine and autonomic function (Drevets, 2007; Gotlib and Hammen, 2009).

The ability to measure brain function using non-invasive neuroimaging techniques has greatly enhanced our understanding of this illness (Rigucci *et al.*, 2010). Patients with depression show impairments in the coordinated activity of several brain regions considered to be important for several domains of mental functioning such as emotional processing (amygdala, subgenual anterior cingulate and pallidum) (Sheline *et al.*, 2010; Disner *et al.*, 2011), self-referential processes (medial prefrontal cortex, precuneus and posterior cingulate cortex) (Price and Drevets, 2010; Sheline *et al.*, 2010; Kuhn and Gallinat, 2013), cognitive functions such as memory (hippocampus, parahippocampal cortex) (Lorenzetti *et al.*, 2009), visual processing (fusiform gyrus, lingual gyrus and lateral temporal cortex) (Veer *et al.*, 2010), and attention processing (dorsolateral prefrontal cortex, anterior cingulate cortex, thalamus and insula) (Hamilton *et al.*, 2012).

Research into the pathophysiology of depression has included the analysis of possible differences in the functional connectivity of different brain areas to elucidate some of the brain changes that may relate to depression. Resting-state functional MRI provides a task-free approach that removes some performance-related confounds, and provides a reliable measure of 'baseline' brain activity and connectivity (Gusnard *et al.*, 2001). The functional

Table 1 A summary of the demographic information and the psychiatric diagnosis in the present study

Sites	Group	Age (years)	Sex (male/female)	Education (years)	Medication (yes / no)	HAMD	Duration of illness	Mean FD
Taiwan	Healthy	49.18 ± 8.58	60 / 36	15.04 ± 3.83				0.133 ± 0.054
	Patient	52.64 ± 14.86	33 / 21	12.66 ± 3.95	54 / 0	9.34 ± 6.99	8.63 ± 6.92	0.116 ± 0.056
	Statistic (*t* / *P*)	−1.810 / 0.072	0.028 / 0.866	3.60 / 4.3×10^{-4}				1.833 / 0.0687
Dongbei	Healthy	29.90 ± 11.89	87 / 51	14.22 ± 3.40				0.101 ± 0.040
	Patient	29.02 ± 10.49	61 / 24	11.80 ± 3.18	25 / 60	20.9 ± 8.79	1.04 ± 1.67	0.098 ± 0.039
	Statistic (*t* / *P*)	0.554 / 0.580	1.611 / 0.204	5.25 / 3.7×10^{-7}				0.591 / 0.555
Xinan	Healthy	39.65 ± 15.80	166 / 88	13.01 ± 3.89				0.133 ± 0.063
	Patient	38.74 ± 13.65	183 / 99	11.91 ± 3.58	157 / 125	20.8 ± 5.87	4.16 ± 5.51	0.125 ± 0.054
	Statistic (*t* / *P*)	0.719 / 0.472	0.013 / 0.911	3.41 / 6.9×10^{-4}				1.729 / 0.084

FD = framewise displacement.

connectivity is measured by the correlation between the functional MRI blood oxygen level-dependent signals in different brain areas when in the resting state, that is when no task is being performed. The concept is that the correlations may reveal evidence about which brain systems may interact differently in neuropsychiatric disorders (Deco and Kringelbach, 2014). There have been a number of resting state functional connectivity studies on depression (Wang *et al.*, 2012; Iwabuchi *et al.*, 2015). Most studies do not include large numbers of participants, and therefore there are insufficient data to allow voxel-level analysis, though this can be very important in helping to reveal exactly which cortical systems may be connected differently in mental disorders (Cheng *et al.*, 2015). There is an urgent need to use methods that will allow large-scale pooling of data to increase the statistical power to obtain voxel-level analysis, as well as to reduce the impact of heterogeneity in the patient population. A meta-analysis of previous investigations of resting state functional connectivity in depression was based on seed-based studies each with tens of participants, and concluded as follows (Kaiser *et al.*, 2015):

> 'Major depressive disorder was characterized by hypoconnectivity within the frontoparietal network, a set of regions involved in cognitive control of attention and emotion regulation, and hypoconnectivity between frontoparietal systems and parietal regions of the dorsal attention network involved in attending to the external environment. Major depressive disorder was also associated with hyperconnectivity within the default network, a network believed to support internally oriented and self-referential thought, and hyperconnectivity between frontoparietal control systems and regions of the default network. Finally, the MDD groups exhibited hypoconnectivity between neural systems involved in processing emotion or salience and midline cortical regions that may mediate top-down regulation of such functions.'

For comparison, the present study included almost as many participants as this meta-analysis, was not forced, because of small numbers of participants, to rely on *a priori*, seed-based analyses, and was able—given the voxel-based approach—to focus on particular brain regions, rather than brain systems identified, for example as the 'default mode network' or 'fronto-parietal control systems'.

Given this background, the objective of this investigation was to perform the first investigation using a voxel-based unbiased brain-wide association study (BWAS) approach on resting state functional MRI data in patients with MDD. The BWAS approach is modelled along the lines of genome-wide association studies where large genetic datasets are pooled to identify significant genetic variations in specific disorders. We aimed to include a large number of participants in this neuroimaging research to enable voxel-level accuracy and robustness of the findings (Button *et al.*, 2013). In this investigation, the voxel-level resolution of the functional connectivity enabled differences of functional connectivity to be measured in nearby but functionally different parts of the orbitofrontal cortex (OFC), and to reveal with which voxels in other brain areas there was altered functional connectivity. The voxel-level analysis enabled this advance to be made. The value of the unbiased approach was that it enabled the functional connectivity between every pair of voxels in the brain to be measured, so that the findings were not limited by prior hypotheses.

Materials and methods

Participants

There were 421 patients with a diagnosis of major depression, and 488 control subjects. The patients were from Taiwan (Veteran General Hospital, Taipei), Dongbei (Department of Psychiatry, First Affiliated Hospital of China Medical University and the Mental Health Center of Shenyang, China) and Xinan (First Affiliated Hospital of Chongqing Medical School in Chongqing, China). All participants were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorder-IV criteria for MDD. Depression severity and symptomatology were evaluated by the Hamilton Depression Rating Scale (HAMD, 17 items) (Hamilton,

1960) and the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974). One hundred and eighty-five of the patients were not receiving medication at the time of neuroimaging. Table 1 provides a summary of the demographic information and the psychiatric diagnosis (showing how they were diagnosed) of the participants. Further details are provided in the Supplementary material.

Image acquisition and preprocessing

Data for resting state functional connectivity analysis were collected in 3 T MRI scanners in an 8-min period in which the participants were awake in the scanner not performing a task, using standard protocols described in the Supplementary material.

Data preprocessing was performed using DPARSF (Chao-Gan and Yu-Feng, 2010) (http://restfMRI.net), which is a toolbox based on the SPM8 software package. The first 10 echo planar imaging (EPI) scans were discarded to suppress equilibration effects. The remaining scans of each subject underwent slice timing correction by sinc interpolating volume slices, motion correction for volume to volume displacement, spatial normalization to standard Montreal Neurological Institute (MNI) space using affine transformation and non-linear deformation with a voxel size of $3 \times 3 \times 3$ mm^3 followed by spatial smoothing (8 mm full-width at half-maximum). To remove the sources of spurious correlations present in resting state blood oxygen level-dependent data, all functional MRI time series underwent band-pass temporal filtering (0.01–0.1 Hz), nuisance signal removal from the ventricles, and deep white matter, and regressing out any effects of head motion using the Friston *et al.* (1996) 24 head motion parameters procedure. Finally, we implemented additional careful volume censoring ('scrubbing') movement correction as reported by Power *et al.* (2014) to ensure that head-motion artefacts are not driving observed effects. The mean framewise displacement was computed with framewise displacement threshold for displacement being 0.5 mm. In addition to the frame corresponding to the displaced time point, one preceding and two succeeding time points were also deleted to reduce the 'spill-over' effect of head movements. Subjects with $>10\%$ displaced frames flagged were completely excluded from the analysis as it is likely that such high-level of movement would have had an influence on several volumes. Global signals were not regressed out (see Supplementary material, where the results with global signal removal are referred to for completeness).

Any effects of gender ratio, years of education, and age between the patient and control groups were regressed out in the analysis. In fact, there were no differences in the gender ratios, though the number of years of education was lower in the patients than controls. Additional analyses showed for males versus females that the overall pattern of functional connectivity differences for patients versus controls were similar, and that the correlation of the functional connectivity changes between males and females was high (0.89, $P < 0.0001$). Further, none of the functional connectivity link differences found between patients and controls was correlated significantly [false discovery rate (FDR) $P < 0.05$] with the number of years of education. We also note that the Taiwanese sample included patients with depression in remission while under antidepressant treatment, and thus their scores on the HAMD assessment were in the low range.

Voxel-wise brain-wide association studies

Step 1: Analysis within each imaging centre

In the present study, each resting state functional MRI image included 47 619 voxels, which is based on the automated anatomical labelling (AAL2) atlas (Rolls *et al.*, 2015). For each pair of voxels, the time series were extracted and their correlation was calculated for each subject followed by z-transformation. Two-tailed, two-sample t-tests were performed on the 1 133 760 771 ($47\,619 \times 47\,618/2$) Fisher's z-transformed correlation coefficients to identify significantly altered functional links in patients with depression compared to controls within each imaging centre. The effect of age, gender ratios, education and head motion (mean framewise displacement) were regressed within each dataset in this step.

Step 2: Combination of results from all imaging centres

The Liptak-Stouffer z-score method (Liptak, 1958), which is a well-validated method for multi-site datasets and has previously been used widely in multi-site MRI data analysis (Glahn *et al.*, 2008; Yu *et al.*, 2011) was then used to combine the results from the individual datasets. Specifically, the P-value of each functional connectivity result from the two-sample t-test in Step 1 was converted to its corresponding z-score. This was calculated firstly as in equation:

$$z_i = \Phi^{-1}(1 - p_i) \quad (1)$$

where Φ is the standard normal cumulative distribution function and i represents the i site. Next, a combined z-score for a functional connectivity was calculated using the Liptak-Stouffer formula:

$$Z = \frac{\sum_{i=1}^{k} w_i z_i}{\sqrt{\sum_{i=1}^{k} w_i^2}} \quad (2)$$

which follows a standard normal distribution under the null hypothesis; where $w_i = \sqrt{samplesize}$ is the weight of the i dataset. Finally, The Z is transformed into its corresponding P-value and a FDR procedure was used to correct for multiple comparisons.

Step 3: Calculating a measure for the association of voxels

A measure for the association (MA) between a voxel i and the brain disorder was then defined as: $MA = N_\alpha$, where N_α is the number of links between voxel i and every other voxel in the brain that have a P-value of less than α (which in the present study with FDR correction was $P < 0.01$, corresponding to a P threshold of 2.52×10^{-7} in t-tests). A larger value of MA implies a more significant difference in functional connectivity.

For the functional connectivity of a voxel to be treated as significantly different ($P < 0.01$) after FDR correction from another voxel, the significance level uncorrected had to be

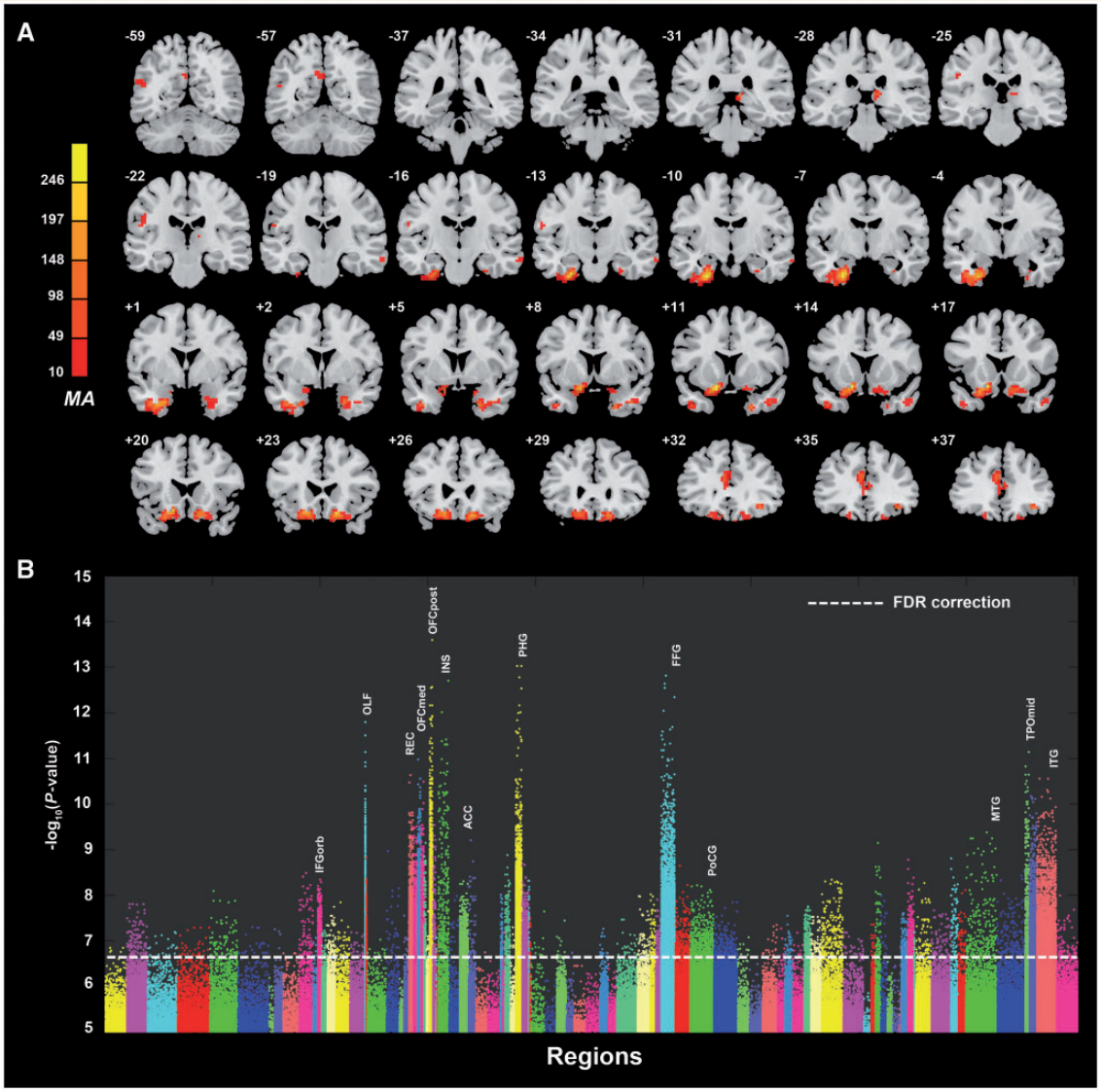

Figure 1 Anatomical location of consistently different functional connectivity in depression obtained from voxel-based BWAS. (**A**) Voxels showing the largest number of whole brain voxel-level functional connectivity differences in patients with depression. Clusters of voxels containing more than 10 significant voxels are shown. The colour bar represents the measure of association (*MA*) given by the number of significantly different functional connectivity links relating to each voxel. The right of the brain is on the right of each slice. Some of the different clusters are in the following range of *y*-values for the slices shown: MedOFC13 +37 to +8; LatOFC47/12_R +37 to +32; medial temporal lobe MTL_L +17 to −16; thalamus −25 to −31; precuneus −57 to −59; angular gyrus −57 to −59. (**B**) Manhattan plot of voxel-based BWAS results with voxels grouped in accordance with the AAL2 atlas labels (Rolls *et al.*, 2015). The order of the bars is as shown in Supplementary Table 1, and the width of each bar reflects the number of voxels in each AAL2 region. ACC = anterior cingulate cortex; FFG = fusiform gyrus; IFGorb = inferior frontal gyrus (pars orbitalis); INS = insula; ITG = inferior temporal gyrus; MTG = Temporal pole: middle temporal gyrus; OFCmed = medial OFC; OFCpost = posterior OFC; OLF = olfactory; PHG = parahippocampal gyrus; PoCG = postcentral gyrus; REC = rectus; TPOmid = middle temporal pole.

$P < 2.52 \times 10^{-7}$. The smallest *P*-value found was $\sim 10^{-13}$. Clusters with less than 10 voxels were not included to reduce the possibility of false positive results and to ensure that only consistent differences in functional connectivity were considered, following earlier practice (Wittmann *et al.*, 2005; Konrad *et al.*, 2006; Hart *et al.*, 2012).

Although the voxel-level BWAS identifies all altered voxel-wise different functional connectivities in patients with depression, it is difficult to describe and show all of these changed links. Accordingly, to facilitate the description of the voxel-wise results, we conducted *post hoc* clusterwise analyses from each cluster of voxels returned by BWAS. It

Table 2 Coordinates of the peaks of the voxel clusters with different functional connectivity in patients with depression

Areas	Abbreviation	# Voxels	Peak *MA* value	MNI coordinates (Peak)		
Hippocampus_L, ParaHippocampal_L, Fusiform_L, Temporal_Mid_L, Temporal_Pole_Mid_L, Temporal_Inf_L	MedTL_L	274	284	−27	−9	−36
ParaHippocampal_R, Fusiform_R, Temporal_Pole_Mid_R	MedTL_R	115	141	24	12	−39
Olfactory_R, Rectus_R, OFCmed_R, OFCpost_R (BA 13)	OFC13_R	140	209	15	24	−18
Olfactory_L, Rectus_L, OFCmed_L, OFCant_L, OFCpost_L, Insula_L (BA 13)	OFC13_L	206	296	−15	12	−15
OFCmed_R (BA 13)	OFC13_R_2	12	50	12	60	−21
Temporal_Mid_R (BA 21)	MidTG21_R	14	43	66	−15	−18
Frontal_Inf_Orb_2_R (BA 47/12)	OFC47/12_R	11	136	36	36	−12
Thalamus_R	Thal_R	17	82	9	−27	9
Cingulate_Ant_L (BA 24)	ACC_L	43	86	−6	36	21
Angular_L, Temporal_Mid_L (BA 39)	Angular_L	15	18	−48	−60	21
Postcentral_L	Postcentral_L	20	21	−60	−12	18
Cingulate_Post_L, Precuneus_L	Precuneus_L	24	15	−6	−54	30
Angular_L (BA 39)	Angular_L_2	22	36	−48	−69	42

Brodmann areas (BA) are provided where useful.

should be noted that all cluster-wise analyses are based on the findings of BWAS, and that it is the BWAS statistics only on which we rely. The cluster analyses just simplify the description of the different functional connectivities in depression.

Clinical correlates

We also investigated whether the differences in functional connectivity between patients and controls were correlated with clinical variables HAMD (Hamilton, 1960), BDI (Beck and Beamesderfer, 1974), and illness duration (Bell-McGinty *et al.*, 2002; de Diego-Adelino *et al.*, 2014). We used the Liptak-Stouffer *z*-score method (Liptak, 1958) to combine the data from the different neuroimaging sites for this analysis, for this provides a principled way to take into consideration possible differences in these measures between sites. Specifically, we calculated the partial correlation between the strength of each altered functional connection with HAMD, BDI score, and with illness duration after removing the effect of sex and age, in each individual centre, then we used the Liptak-Stouffer *z*-score method to combine the results from the individual datasets.

Results

The functional MRI resting state functional connectivity analyses were performed with 421 patients with a diagnosis of major depression, and 488 control subjects, and this large population was sufficient to allow voxel-level analysis with fully corrected statistics.

A brain-wide association study of voxels with different functional connectivity in depressed patients

As shown in Fig. 1 and Table 2, there were a number of voxel clusters with different functional connectivity in patients with depression compared to controls.

A large cluster of voxels ($n = 274$) was in the left medial temporal lobe with peak at (x y z −27 −9 −36). This cluster was in the parahippocampal gyrus, extending into the fusiform gyrus and inferior temporal and temporal pole areas, and indeed these voxels were classified as in areas in the AAL2 atlas (Rolls *et al.*, 2015) that included left hippocampus, parahippocampal gyrus, fusiform gyrus, middle temporal gyrus, temporal pole (middle temporal gyrus), and inferior temporal gyrus (Table 2). The voxel with the highest measure of association [*MA*, the number of voxels with which a voxel has a functional connectivity difference significant at $P < 0.01$ (FDR correction)] was 284 (Table 2). It is clear from Fig. 1 that the majority of these voxels were in the perirhinal cortex Brodmann area (BA) 36, and the entorhinal cortex BA 28. There was a corresponding cluster on the right [with peak at (24 12 −39)] (Table 2).

A second large cluster of voxels was in the medial OFC BA 13 with peak at (−15 12 −15) (Table 2 and Fig. 1). In the AAL2 atlas this included left olfactory, rectus, medial OFC, anterior OFC, posterior OFC, insula, but the locations of these voxels as shown in Fig. 1 was in BA 13 just extending anteriorly in area 11, according to the cytoarchitectonic designation (Öngür *et al.*, 2003)

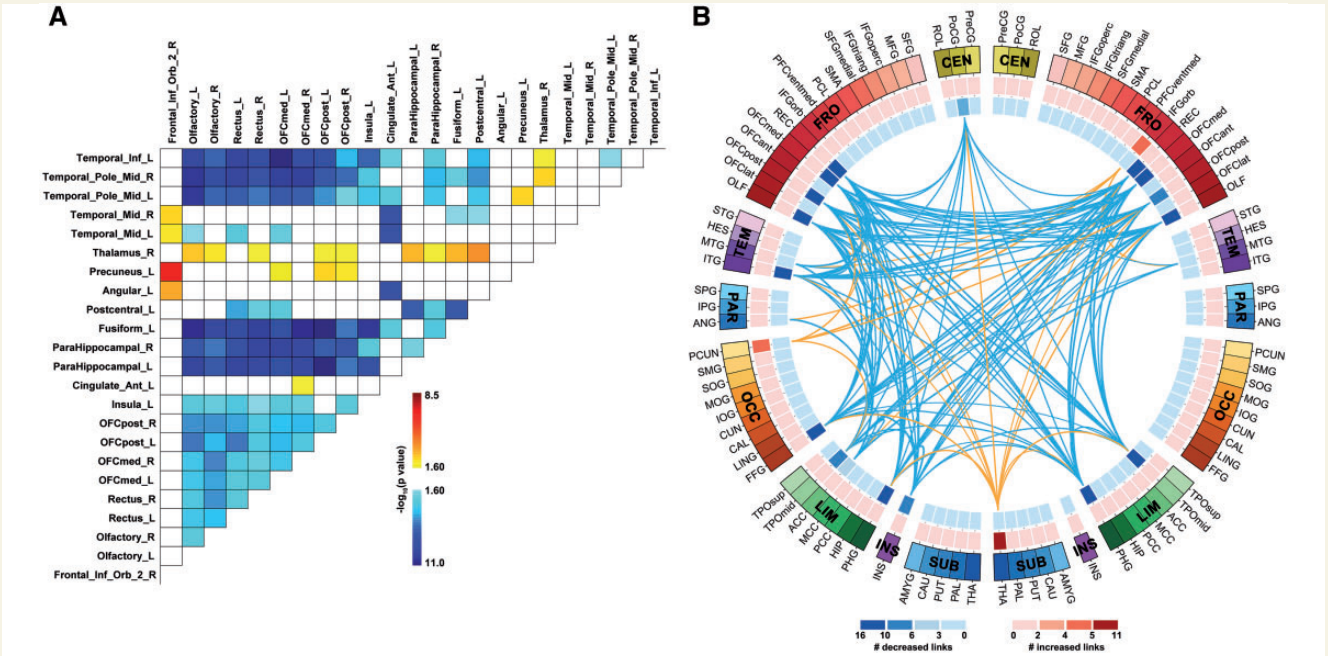

Figure 2 Functional connectivity differences between the voxels that are significantly different in the depressed and the control group, separated by the AAL2 region in which the significant voxels were located. (**A**) Links with increased functional connectivities in patients are shown in yellow-red, and decreased connectivities are in blue. The colour bar shows the $-\log_{10}$ of the *P*-value for the difference of the functional connectivity. Entries in the matrix are provided where $P < 0.05$ (FDR correction). The matrix itself contains rows and columns for all cases in which there were 10 or more significant voxels within an AAL2 region. (**B**) The links are shown in red if they are significantly stronger in the patient group, and in blue if they are significantly weaker in the patient group. The thickness of the lines indicates the degree of alteration of the functional connectivity. The anatomical abbreviations are for the areas in the automated anatomical atlas, with abbreviations shown in Supplementary Table 1. The brain regions in the left hemisphere are in the left semicircle of the diagram.

[see Figure 4 in Öngür *et al.* (2003), which shows that area 13 extends quite far posterior towards what topologically is close to the anterior ventral insula]. There was a corresponding cluster on the right [with peak at (15 24 −18)].

A third cluster, with a high peak *MA* value of 136, was in lateral OFC area 47/12 (Öngür *et al.*, 2003) with peak at (36 36 −12). In Fig. 1 it can be seen in slices at $y = 32$, 35 and 37. It was in AAL2 region Frontal_Inf_Orb_2_R.

A fourth cluster was in the anterior cingulate cortex in the just supracallosal part with peak at (−6 36 21) (Fig. 1 and Table 2).

A fifth cluster was in the precuneus and adjoining posterior cingulate cortex with peak at (−6 −54 30) (Fig. 1 and Table 2).

A sixth cluster was in the left angular gyrus, with peaks at (−48 −60 21) and (−48 −69 42).

A seventh cluster was in the middle temporal gyrus, in a part that is BA 21 and is a high order temporal cortical visual area involved in processing objects and faces.

Other minor clusters in the thalamus and postcentral cortex are indicated in Table 2.

Analysis of the functional connectivity links that were different in patients with depression

To investigate the brain areas between which there was different functional connectivity in depression, and whether it was increased or decreased, the functional connectivity of the voxels with significant differences of functional connectivity (after FDR correction at $P < 0.05$, and within the voxel clusters shown in Table 2) were measured for each of the AAL2 regions within which the voxels were located. In this way, 23 regions of interest were identified, and the functional connectivity differences between the significantly different voxels in these regions are shown in Fig. 2 as a connectivity matrix.

First the altered functional connectivity of the medial OFC, area 13, brain region is considered. The relevant voxels are in regions such as medial OFC, anterior OFC, posterior OFC, olfactory, rectus, and insula in the AAL2 atlas on the left and the right (Table 2). The voxels within this area 13 cluster have high positive

Table 3 Correlations between the functional connectivity links and the depression symptom severity scores

Functional connectivity		Clinical variable	*P*-value	Correlation value
Olfactory_R	OFCpost_R	BDI	0.022249	−0.14572
Olfactory_R	Temporal_Pole_Mid_R	BDI	0.041603	−0.13001
OFCmed_R	ParaHippocampal_R	BDI	0.044183	−0.12843
OFCpost_R	ParaHippocampal_R	BDI	0.044118	−0.12846
OFCpost_R	Temporal_Pole_Mid_R	BDI	0.048206	−0.12610
Fusiform_L	Temporal_Mid_R	BDI	0.030704	−0.13782
Postcentral_L	Temporal_Mid_R	BDI	0.0027053	−0.14063
Temporal_Pole_Mid_L	Temporal_Inf_L	BDI	0.027426	−0.11088
Olfactory_L	Rectus_L	HAMD	0.0094015	−0.13148
Olfactory_L	Rectus_R	HAMD	0.026386	−0.11273
Olfactory_L	OFCmed_L	HAMD	0.0046205	−0.14343
Rectus_R	OFCmed_L	HAMD	0.038747	−0.10504
Frontal_Inf_Orb_2_R	Angular_L	Illness duration	0.01825	−0.12418
Frontal_Inf_Orb_2_R	Temporal_Mid_L	Illness duration	0.00077913	−0.17688
Insula_L	ParaHippocampal_R	Illness duration	0.016651	−0.12658
Insula_L	Fusiform_L	Illness duration	0.021031	−0.12198
Insula_L	Temporal_Inf_L	Illness duration	0.046867	−0.10538
Cingulate_Ant_L	Angular_L	Illness duration	0.046772	−0.10438
Postcentral_L	Temporal_Pole_Mid_L	Illness duration	0.036223	−0.11027

BDI = Beck Depression Inventory.

correlations between them, and have generally the same pattern of altered functional connectivity in depression, and so is described in the remainder of this paper as OFC13. As shown in Fig. 2, OFC13 has very significantly reduced functional connectivity with the parahippocampal, fusiform, temporal pole and temporal_Inf areas (and many of the voxels in these areas are in the perirhinal cortex area 36 and the entorhinal cortex area 28, as shown in Fig. 1), which again act similarly in this investigation, so are referred to as the medial temporal lobe (MedTL) cluster in the remainder of this paper. OFC13 also has reduced functional connectivity between the voxels in its different AAL2 regions (Fig. 2). Some parts of OFC13, in particular posterior OFC, has increased functional connectivity with the precuneus.

Second, OFC47/12 on the right (Frontal_Inf_Orb_2_R in the AAL2 atlas) has increased functional connectivity with the left angular gyrus, left precuneus, and left and right Temporal_Mid [e.g. (66 −15 −18) which is BA 21, temporal visual cortex]. OFC47/12 does not have reduced functional connectivity with the parahippocampal areas (Fig. 2). This lateral OFC network is therefore very different in its change in functional connectivity in depression from the OFC13 network in the medial OFC.

Third, the anterior cingulate cortex (in which the voxels are just supracallosal) has reduced functional connectivity in depressed patients with some temporal cortex areas including the fusiform gyrus, with the angular cortex, and no difference in functional connectivity with most medial orbitofrontal areas (OFC13) (apart from a small increase with OFC_Med_R).

Other functional connectivity changes include increased thalamic connectivity with some medial orbitofrontal, and parahippocampal/temporal cortex regions, and the postcentral gyrus (Fig. 2).

Clinical symptom correlates of the altered circuits

As can be seen from Table 3, there were significant correlations ($P < 0.05$ uncorrected) between some of the region of interest-wise functional links and the symptom severity scores and illness duration. Specifically, the HAMD (Hamilton, 1960) score was correlated with weakened functional connectivity between some of the areas within the medial OFC (OFC13). Analysis of the subscores of the HAMD showed that links involving OFC13 were correlated with most of the 17 subscores apart from 10 and 15. Interestingly, links involving OFC47/12 were negatively correlated with H6 Insomnia (waking up early), and with H17 Insight.

The BDI score (available only for the Xinan dataset of 183 patients) was also correlated with decreased functional connectivity between several of the medial OFC13 subregions and several of the parahippocampal/temporal subregions; and also with decreased functional connectivity of the temporal areas (Temporal_Inf_L and Temporal_Pole_L), and of Temporal_Mid-R with the postcentral gyrus (Table 3). For the Xinan dataset, which includes both HAMD and BDI scores, the Pearson correlation coefficient between each region of

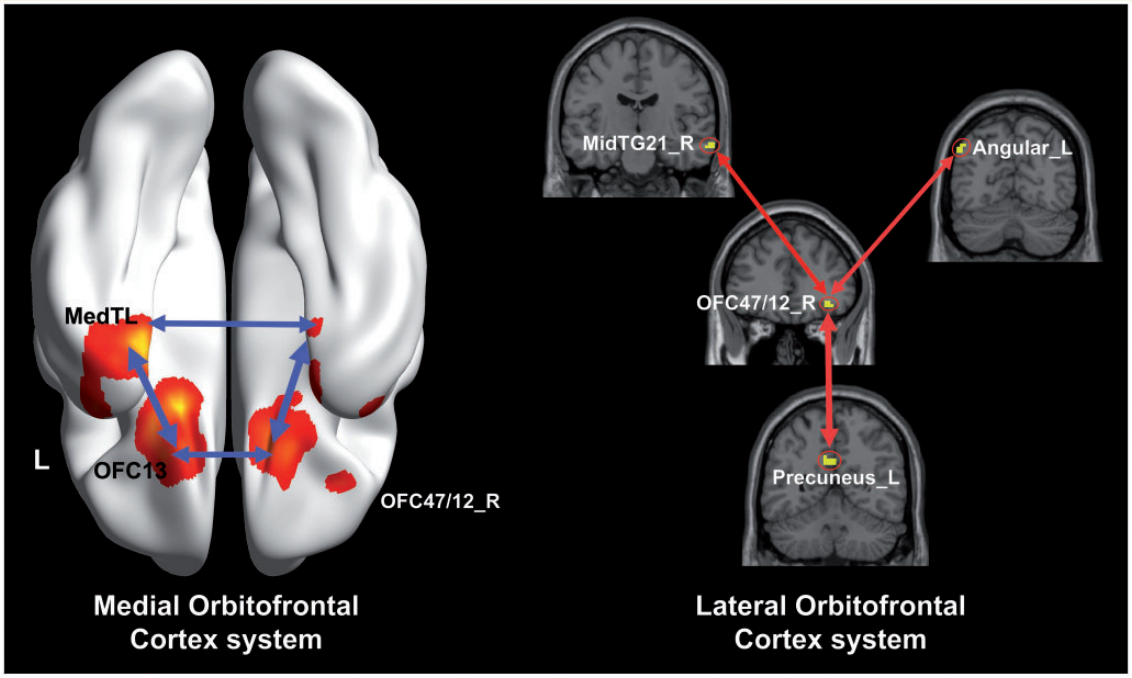

Figure 3 The medial and lateral OFC networks that show different functional connectivity in patients with depression. A decrease in functional connectivity is shown in blue, and an increase in red. MedTL = medial temporal lobe from the parahippocampal gyrus to the temporal pole; MidTG21_R = middle temporal gyrus area 21 right; OFC13 = medial orbitofrontal cortex area 13; OFC47/12_R = lateral orbitofrontal cortex area 47/12 right. The lateral orbitofrontal cortex cluster in OFC47/12 is visible on the ventral view of the brain anterior and lateral to the OFC13 clusters.

interest-wise functional connectivity and either the HAMD or the BDI reached 0.41 ($P = 1.6 \times 10^{-11}$).

The illness duration (Table 3) was negatively correlated with functional connectivity between the lateral OFC47/12 voxels and the left angular gyrus and Temporal-Mid_L cluster of Table 3. The illness duration was also correlated with weaker functional connectivity between the posterior part of the medial OFC13 cluster (specifically the part within Insula_L in the AAL2 atlas) and some parahippocampal/temporal areas (Table 3). Illness duration was also correlated with weaker functional connectivity between the left angular gyrus and the (supracallosal) anterior cingulate cortex. These correlations strengthen the interpretation of the changes in functional connectivity in these regions found in patients with depression, in that these functional connectivities were related to the depression that was measured in these patients.

Comparison of functional connectivity in medicated and unmedicated patients with depression

Within the depressed group, 185 were not receiving medication, and 236 patients were receiving medication. Although it was not a primary aim of this investigation, and following a suggestion, the effects of medication were assessed by comparing the functional connectivity in 185 patients not receiving medication, and 182 patients receiving medication, from the Dongbei and Xinan datasets (see Supplementary material for details including demographic and clinical details, and limitations). The medication consisted in most cases of selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, paroxetine, sertraline, citalopram and escitalopram; or serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venflaxine, or a tetracyclic antidepressant such as mirtazepine. The overall pattern of functional connectivity differences between patients and controls is similar for the unmedicated (Supplementary Fig. 1A) and the medicated (Supplementary Fig. 1B) subgroups of patients, providing evidence that the main differences between patients and controls shown in Figs 1–3 were found in depressed patients whether or not they were receiving medication.

Although the overall pattern of functional connectivity is similar in the subgroup without medication (Supplementary Fig. 1A) and with medication (Supplementary Fig. 1B), to test for significant differences, a *t*-test was performed between these two functional connectivity matrices, with the results shown in Supplementary Fig. 1C. As one of the main findings for differences of functional connectivity between patients and controls was increased functional connectivity of the lateral OFC BA 47/12 with the precuneus, angular gyrus and mid-temporal gyrus (Figs 2 and 3), and to relieve the burden of multiple comparisons, we tested in a pre-planned comparison whether these three functional

connectivity links were weaker in medicated than in unmedicated patients. For the Frontal_Inf_Orb_2R with precuneus link there is a significantly smaller functional connectivity in the medicated than the unmedicated group ($t = 2.17$, $P = 0.015$, one-tailed test of the specific prediction in all three cases). For the Frontal_Inf_Orb_2R with angular gyrus link there is a significantly smaller functional connectivity in the medicated than the unmedicated group ($t = 2.55$, $P = 0.005$). For the Frontal_Inf_Orb_2R with temporal_Mid_L link there is a significantly smaller functional connectivity in the medicated than the unmedicated group ($t = 1.76$, $P = 0.039$). The results overall are thus consistent with the hypothesis that the increased functional connectivity of the lateral OFC BA 47/12 with the precuneus, angular gyrus, and mid-temporal gyrus is related to depression, and that treatment with medication reduces the functional connectivity of these three links.

Discussion

The main findings are first that one major circuit with altered functional connectivity in depression involves the medial OFC BA 13, which is implicated in reward, and which had reduced functional connectivity in depression with memory systems in the parahippocampal gyrus and medial temporal lobe, involving especially the perirhinal cortex BA 36 and entorhinal cortex BA 28. The lateral OFC BA 47/12, involved in non-reward and punishing events, did not have this reduced functional connectivity with memory systems, so that there is an imbalance in depression towards decreased reward-related memory system functionality. Second, BA 47/12 had increased functional connectivity with the precuneus, the angular gyrus, and the temporal visual cortex BA 21. This enhanced functional connectivity of the non-reward/punishment system (BA 47/12) with the precuneus (involved in the sense of self and agency), and the angular gyrus (involved in language) is thus related to the explicit affectively negative sense of the self, and of self-esteem, in depression.

In a further analysis, it was shown that the overall pattern of functional connectivity differences between patients and controls is similar for the unmedicated (Supplementary Fig. 1A) and the medicated (Supplementary Fig. 1B) subgroups of patients, providing evidence that the main differences between patients and controls shown in Figs 1–3 were found in depressed patients whether or not they were receiving medication. In preplanned comparisons, it was further shown that the functional connectivities of the right lateral OFC BA 47/12 (Frontal_Inf_Orb_2R) with the precuneus, angular gyrus, and mid-temporal gyrus, the links highlighted in Fig. 3B, were reduced in the medicated patients compared to the unmedicated patients (Supplementary Fig. 1C, with the statistics in the Supplementary material). The results overall are thus consistent with the hypothesis that the increased functional connectivity of the lateral OFC BA 47/12 with the precuneus, angular gyrus, and mid-temporal gyrus is related to depression, and that treatment with medication reduces the functional connectivity of these three links. In addition to these preplanned tests, it is notable that the medicated patients had a lower functional connectivity between the lateral OFC and the medial OFC (Supplementary material). These parts of the OFC have a reciprocal relation with respect to their activations by rewards (medially) and by non-reward or loss laterally, and the smaller functional connectivity in medicated patients than unmedicated patients may be related to a change in this reciprocal relation. It is noted that limitations of this analysis of the effects of medication are that this was not a main aim of this investigation, that this is a cross-sectional not longitudinal comparison, and that the mean illness duration was 28.5 months in the unmedicated group and 58.6 months in the medicated group.

We now place these findings on functional connectivity differences in depression in the context of the known functions of the brain regions implicated in this investigation, which include emotion-related, non-reward and punishment-related regions of the OFC (Rolls, 2014, 2016*b*), and of previous investigations into depression. The theory that depression is associated with the maladaptive responses to non-reward and punishment and hyposensitivity to reward has been extensively investigated (Eshel and Roiser, 2010; Russo and Nestler, 2013; Whitton *et al.*, 2015; Rolls, 2016*b*). At the psychological level, Beck's psychological theory of depression (Beck, 1979) and Seligman's learned helplessness model (Seligman, 1972), both focused around punishment and reward, and brain areas related to punishment and reward have become primary targets in psychotherapy (Beck, 2008). At the neural level, networks related to punishment and reward have been related to depression, and in some cases to monoamines (McCabe *et al.*, 2012; Harmer and Cowen, 2013; Felger *et al.*, 2015; Huys *et al.*, 2015).

Given this background, we first consider voxels in the medial parts of the OFC shown in Fig. 1 that are within the OFC13 cluster. Figure 2 shows that in depression the voxels with altered functional connectivity in these areas have reduced functional connectivity with the parahippocampal/temporal lobe/fusiform cortical left and right clusters, especially involving the perirhinal cortex BA 36 and entorhinal cortex BA 28 as shown in Fig. 1. These parahippocampal areas are involved in memory, and *inter alia* provide a gateway to and from the hippocampal memory system (Kesner and Rolls, 2015). Indeed, the medial and mid OFC BA13 has direct reciprocal connections with the perirhinal cortex BA 36 (Kondo *et al.*, 2005), which in turn connects via the entorhinal cortex BA 28 to the hippocampus (Kesner and Rolls, 2015). There is extensive evidence that the human medial OFC areas, including OFC13, is activated by rewarding stimuli that are subjectively pleasant (including pleasant odours, pleasant touch, pleasant flavour, and monetary reward) (O'Doherty *et al.*, 2001;

Grabenhorst and Rolls, 2011; Rolls, 2014). The connections between the medial and mid OFC BA 13 and the perirhinal cortex BA 36 (which in turn connects to the entorhinal cortex and thus to the hippocampus) provides a route for reward/emotion-related information to reach the hippocampus to become part of an episodic memory; and during later recall for the reward/emotion-related part of an episodic memory to be recalled to the OFC (Rolls, 2014, 2016*a*; Kesner and Rolls, 2015). It has therefore been suggested that there are weaker functional connectivity links in depression between brain areas involved in pleasant feelings and rewards with memory systems, and that this may be part of the mechanism of depression (Rolls, 2016*b*). This hypothesis is strengthened by the correlation between the symptoms of depression and the weakening of links between the medial OFC13 system and the parahippocampal/medial temporal lobe memory system areas as shown in Table 3. Consistent with the hypothesis, the anhedonia of depression can be related to decreased effects of pleasant rewarding stimuli in the medial OFC during depression, effects that can be restored by antidepressants (Ma, 2015). Consistent with the importance of the OFC in depression, grey matter volume reductions are found in this area in patients with depression (Ballmaier *et al.*, 2004).

Second, the lateral OFC cluster OFC47/12 is in a region that is activated by many types of non-reward and unpleasant stimuli (Grabenhorst and Rolls, 2011; Rolls, 2014), including losing money (O'Doherty *et al.*, 2001), not receiving an expected social reward (Kringelbach and Rolls, 2003), and unpleasant odours. This region has very different changed functional connectivity in depression, with increased functional connectivity with the precuneus, angular gyrus, and middle temporal gyrus BA 21. The precuneus is a parietal region implicated in the sense of self and agency (Cavanna and Trimble, 2006), and the left (not right) angular gyrus/middle temporal gyrus is implicated in language processing (Cabeza and Nyberg, 2000). This has led to the hypothesis that this lateral non-reward/punishment system in OFC47/12 with its increased functional connectivity with self- and language-related systems relates to some of the symptoms of depression (Rolls, 2016*b*). The BA 21 region is high order visual cortex corresponding to the macaque inferior temporal visual cortex where faces and objects are represented (Rolls, 2012), and the increased functional connectivity of OFC47/12 with BA 21 may result in more affectively negative processing of visual inputs (Rolls, 2016*b*). Indeed, this increased functional connectivity between the inferior temporal visual cortex area 21 and the lateral OFC OFC47/12 non-reward/punishment system may lead to depressed patients having difficulty in categorizing happy face stimuli as happy (Harmer and Cowen, 2013).

Consistent with the hypothesis of disturbed function of the OFC in depression, there is increased regional cerebral blood flow in the ventrolateral OFC area 47/12 in depression (Drevets *et al.*, 1992, 2004; Price and Drevets, 2010). In addition, over-general autobiographical memory manifests in individuals with MDD tested during depressed (dMDD) or remitted phases (rMDD), and healthy individuals at high risk for developing MDD. During specific autobiographical memory recall, high risk individuals have increased activity relative to rMDDs and healthy controls in the ventrolateral prefrontal cortex (VLPFC) and lateral OFC (Young *et al.*, 2015). The increased functional connectivity of the lateral OFC (involved in non-reward and aversive processing), the precuneus (involved in the sense of self), and the angular gyrus (involved in language) in depression is of interest, for a sign of the start of a depressive episode may be negative thoughts about the self and low self-esteem, all expressed explicitly in language (Wegener *et al.*, 2015). It is notable that OFC47/12, the non-reward punishment area, has increased functional connectivity with each of these areas, but that they do not have increased connectivity with each other. The common hub to this system is the lateral OFC47/12.

In comparing the medial OFC13 (reward) and lateral OFC47/12 (non-reward) systems, there is evidence that they are very different systems, for the correlation between the functional connectivities within the different AAL2 regions of OFC13 was typically high (r = 0.6–0.9), and the functional connectivities of each of these areas with OFC47/12 were typically low (r = 0.23–0.37) ($P < 10^{-14}$). Both systems though may contribute to the lack of motivation that is frequent in depression. The medial OFC/medial temporal lobe memory system reduced functional connectivity may contribute by making remembered rewards, the goals for action, less rewarding, and therefore less motivating (Rolls, 2014, 2016*b*). The lateral orbitofrontal non-reward system with its increased functional connectivity may make non-reward more potent, and this facilitation would also be expected to check motivation by enhancing the inhibiting effects on behaviour of non-reward and expected non-reward (Rolls, 2014, 2016*b*).

The anterior cingulate cortex (in which the voxel clusters are just supracallosal) had reduced functional connectivity in depressed patients with some temporal cortex areas including the fusiform gyrus, and with the angular cortex (Figs 2A and 3A), and no difference in functional connectivity with most medial orbitofrontal areas (OFC13) (apart from a small increase with OFC_Med_R). This supracallosal part of the far anterior cingulate cortex is at the anterior end of a supracallosal cingulate region in which many unpleasant stimuli are represented (Grabenhorst and Rolls, 2011; Rolls, 2014), and is therefore implicated in mood (Rolls, 2014). This region is just above and behind the pregenual cingulate cortex area in which a few additional voxels with significantly different functional connectivity were found in the depressed group, and this pregenual cingulate region has representations of pleasant and rewarding stimuli (Grabenhorst and Rolls, 2011; Rolls, 2014), and is thereby also implicated in mood (Rolls, 2014). Interestingly, functional connectivity changes were not found in the subcallosal cingulate cortex including the subgenual cingulate cortex (with the area found here more

ventral, in OFC13), though a few voxels with altered functional connectivity were found in the amygdala, with both these regions showing increased cerebral blood flow in depression (Drevets *et al.*, 1997; Price and Drevets, 2010).

We now consider the changes in functional connectivity in depression in other brain areas not typically associated with mood and emotion. The thalamus had increased functional connectivity with a number of cortical areas, as shown in Fig. 2, with the coordinate (9 −27 9) indicating that this is part of the medial pulvinar, which has temporal lobe connections including visual temporal cortex areas (Johansen-Berg *et al.*, 2005). The medial thalamus has increased cerebral blood flow in depression (Price and Drevets, 2010).

It is interesting to relate these changes in functional connectivity to the level of activity in these different brain areas in patients with depression. Hyperactivation during affective processing tasks has been described in the thalamus and parahippocampal gyrus (Miller *et al.*, 2015), and increased cerebral blood flow in patients with MDD has been found in the medial as well as the lateral OFC (Drevets *et al.*, 1992; Price and Drevets, 2010).

Although changes have been found in some of these regions in previous studies in depression including the precuneus, angular gyrus, and hippocampal system (Sundermann *et al.*, 2014), the present study is statistically more powerful because of the large number of participants involved (421 patients with a diagnosis of major depression, and 488 controls), and therefore allows analysis at the voxel level, which as we have seen greatly facilitates the interpretation of the findings by enabling the functional connectivity to be related to the different functions of even nearby brain regions such as the medial and lateral OFC.

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Supplementary material

Supplementary material is available at *Brain* online.

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