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Original Article

ORIGINAL ARTICLE

Functional Connectivity of the Anterior Cingulate Cortex in Depression and in Health

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Abstract

The first voxel-level resting-state functional connectivity (FC) neuroimaging analysis of depression of the anterior cingulate cortex (ACC) showed in 282 patients with major depressive disorder compared with 254 controls, some higher, and some lower FCs. However, in 125 unmedicated patients, primarily increases of FC were found: of the subcallosal anterior cingulate with the lateral orbitofrontal cortex, of the pregenual/supracallosal anterior cingulate with the medial orbitofrontal cortex, and of parts of the anterior cingulate with the inferior frontal gyrus, superior parietal lobule, and with early cortical visual areas. In the 157 medicated patients, these and other FCs were lower than in the unmedicated group. Parcellation was performed based on the FC of individual ACC voxels in healthy controls. A pregenual subdivision had high FC with medial orbitofrontal cortex areas, and a supracallosal subdivision had high FC with lateral orbitofrontal cortex and inferior frontal gyrus. The high FC in depression between the lateral orbitofrontal cortex and the subcallosal parts of the ACC provides a

mechanism for more non-reward information transmission to the ACC, contributing to depression. The high FC between the medial orbitofrontal cortex and supracallosal ACC in depression may also contribute to depressive symptoms.

Key words: depression, cingulate cortex, depression, functional connectivity, medial temporal lobe, orbitofrontal cortex, precuneus, resting-state functional neuroimaging

Introduction

There is considerable evidence that the anterior cingulate cortex (ACC) is involved in emotion, with a pregenual part activated by many rewards, and a supracallosal part activated by non-reward and punishers (Rolls 2009, 2014; Vogt 2009; Grabenhorst and Rolls 2011). The subcallosal ACC (with a smaller region referred to previously as subgenual cingulate cortex) has been implicated in depression revealed in both metabolic activity (Mayberg et al. 1999; Konarski et al. 2009; Hamani et al. 2011) and gray matter volume (Bora et al. 2012). Decreased functional connectivity (FC) has been reported between the subgenual cingulate cortex and the precuneus in major depressive disorder (MDD) (Connolly et al. 2013). In addition, stimulation in the subcallosal cingulate cortex has been widely used to treat depression (Drevets et al. 1997; Mayberg 2003; Johansen-Berg et al. 2008; Price and Drevets 2010, 2012; Hamani et al. 2011; Laxton et al. 2013; Lujan et al. 2013; McGrath et al. 2013; Mayberg et al. 2016; Drysdale et al. 2017; McInerney et al. 2017; Ramirez-Mahaluf et al. 2017; Riva-Posse et al. 2018).

Resting-state 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 (Deco and Kringelbach 2014), and changes in anterior cingulate FC have been related to depression (Greicius et al. 2007; Connolly et al. 2013; Kaiser et al. 2015; Mulders et al. 2015; Lichenstein et al. 2016). However, in previous investigations of FC differences of the ACC in depression, much smaller sample sizes with typically tens of participants were studied, and voxel-to-voxel FC was not measured.

In this investigation, we performed the first voxel-level resting-state FC neuroimaging analysis of depression of voxels in the ACC with all other voxels in the brain in a large sample of 282 patients with depression and 254 matched controls. With this large dataset, we are able to analyze every anterior cingulate voxel for significantly different FC with every voxel throughout the rest of the brain in depressed people versus controls, in order to advance understanding of the ACC and depression. In this paper, we utilize what we term "hypothesis-based voxel-level FC analysis" in which we select a brain region of interest (ROI) but then calculate for every voxel in that region whether it has FC with individual voxels in every other brain region. In the present paper, we select the ACC as the ROI, given the research on it described above implicating it in depression, and then we show exactly which anterior cingulate voxels have altered FC in depression with which individual voxels in every other brain area. Given that the ACC has 822 voxels, and that there are 47 619 voxels in the $3 \times 3 \times 3\,mm$ automated anatomical labeling atlas (AAL2) brain (Rolls et al. 2015), the number of voxel pairs in this study was approximately $822 \times 47\,619$. This methodology is quite different from and more statistically powerful than a whole-brain voxel-to-voxel FC analysis (Cheng et al. 2016) for two reasons. First, the number of FCs in the present analysis was reduced considerably, reducing the burden on correction for multiple comparisons and enabling more detailed effects to be found. Second, we used a powerful approach designed specifically for voxel-based FC analysis to correct for multiple comparisons, which utilized the spatial information from clusters of voxel-level FCs (Gong et al. 2018). Further, we describe here how ACC connectivity was correlated with the depression severity and duration, which was not performed in the previous study. Part of the reason for these differences is that in the previous investigation we focused on voxel-to-voxel whole-brain connectivity, which limits the results that can be established, whereas here we focus on the ACC and are able to report significant differences in its FC in depression, and even of the subdivisions of the ACC.

In addition, we performed a parcellation of the ACC based on its FC, showed which parts of the brain each ACC subdivision was related to, and showed how the FC of each ACC subdivision was different in depression. Moreover, in healthy controls, we were able to show different connectivities of different parts of the ACC with the medial versus lateral orbitofrontal cortex.

The focus here is on the ACC, because not only it is implicated in depression as described above, but also it is implicated in emotion and processes fundamental to emotion such as the processing of rewards and non-rewards (Rolls 2009, 2014; Grabenhorst and Rolls 2011). A highlight of the current investigation is that a connectivity-related parcellation of the ACC was performed in the healthy control participants; and that these subregions had different alterations of FC in depression. We relate the discoveries described here to a new theory of depression in which an area that project to the ACC, the lateral orbitofrontal cortex, has increased sensitivity of a non-reward attractor in depression; and the medial orbitofrontal cortex reward system is underactive in depression (Rolls 2016a, 2016b, 2017a, 2017b, 2018).

Methods

Participants

There were 282 patients with a diagnosis of unipolar MDD and 254 controls. The data available for this study were from Xinan (First Affiliated Hospital of Chongqing Medical School in Chongqing, China). Supplementary Table S1 provides a summary of the demographic information and the psychiatric diagnosis (showing how they were diagnosed) of the participants, and fuller information is provided in the Supplementary Material. The data collection was approved by the local ethical review committees, was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and informed consent was obtained. 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 twenty-five of the patients were not receiving medication at the time of the neuroimaging.

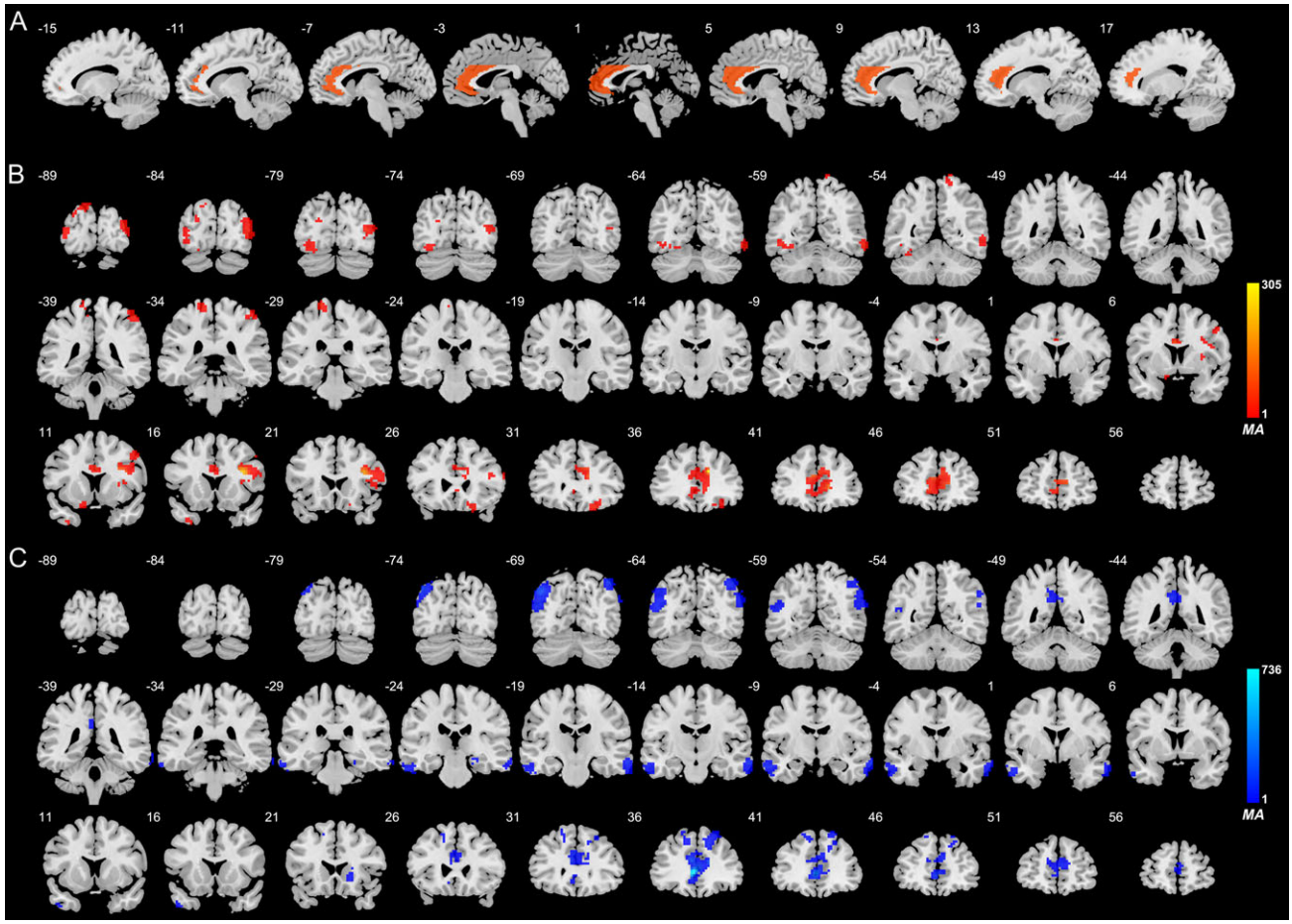

Figure 1. (A) Voxels of the ACC defined by the AAL2 atlas. (B, C) Anatomical location of voxels with significantly increased (B) and decreased (C) FC with the ACC in depression in depressed patients versus healthy controls obtained from the voxel-based Association Study (vAS). Voxels with FC differences with the ACC in patients with depression are shown. The color bar represents the number of significantly different FC links relating to each voxel after cluster-wise correction ($P < 0.05$). Blue indicates voxels with predominantly decreased FC in depressed patients, and red/yellow indicates voxels with predominantly increased FC in depressed patients. The right of the brain is on the right of each slice in all Figures. The Y values are in MNI coordinates.

Image Acquisition and Preprocessing

Data for resting-state FC 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 standard, as has been described before (Cheng et al. 2016), and details are provided in the Supplementary Material.

Hypothesis-based Voxel-wise Association Studies

In the present study, each resting-state fMRI volume included 47 619 voxels, and the ACC ROI as defined in the AAL2 atlas (Rolls et al. 2015) had 822 voxels. The region is illustrated in Figures 1A and 5, and almost all of it is within the ACC by other criteria, with perhaps a small amount of overlap posteriorly with a small part of the middle cingulate cortex (Vogt 2009). For each pair of voxels in the ACC and voxels in all other brain areas, the time series were extracted and their 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 FC links in patients with depression compared with controls. The effects of age, gender, head motion (mean framewise displacements [FDs]) and education years were regressed out by a generalized linear model (Barnes et al. 2010; Di Martino et al. 2014). To ensure that education did not account for the results, we set up subgroups with very similar education and found that the results were very similar. Given that the ACC had been predefined by prior hypothesis as the ROI and had 822 voxels, and that there were 47 619 3×3×3 mm voxels in the whole AAL2 brain (Rolls et al. 2015), the number of voxel pairs in this study was approximately (822 × 47 619), which is much smaller than the 1 133 760 771 (47 619 × 47 618/2) voxel pairs in our whole-brain study (Cheng et al. 2016). This enabled more differences in voxel-level FC of the ACC with the rest of the brain to be identified in the present study, which may not be detected in a whole-brain analysis. Finally, a cluster-level inference approach designed specifically for voxel-level FC analysis (Gong et al. 2018) was used to identify significant FC clusters. This approach shares similar concepts with traditional cluster-based tests, which first identifies all FCs with a P-value smaller than a certain cluster-defining threshold ($P < 1.0 \times 10^{-4}$ in this study) and then evaluates whether the clusters formed by spatially connected FCs are

Table 1 Numbers of voxels in different AAL2 areas with significantly different FC with the ACC in patients with depression. For ACC, the table shows the number of ACC voxels that have different FCs with the whole brain. The other entries in the table show the numbers of voxels in each of the specified brain regions with different FCs with ACC voxels

Areas	# Voxels	Peak value*		MNI coordinates (Peak)	
Fusiform_L, Fusiform_R, Temporal_Sup_R, Temporal_Mid_L, Temporal_Mid_R, Temporal_Pole_Mid_L, Temporal_Inf_L, Temporal_Inf_R	679	−101	69	−9	−18
Cingulate_Ant_L, Cingulate_Ant_R	631	−736	−3	36	6
Lingual_L, Occipital_Sup_L, Occipital_Sup_R, Occipital_Mid_L, Occipital_Mid_R, Occipital_Inf_L	371	−85	−42	−75	36
Angular_L, Angular_R	323	−200	−45	−72	42
Frontal_Sup_2_L, Frontal_Sup_2_R, Frontal_Sup_Medial_L, Frontal_Sup_Medial_R	275	−46	3	51	15
Frontal_Mid_2_R, Frontal_Inf_Oper_R, Frontal_Inf_Tri_R	255	255	36	18	24
Precentral_R, Postcentral_L, Postcentral_R, Paracentral_Lobule_L	105	38	−18	−30	75
Parietal_Sup_L, Parietal_Sup_R, Parietal_Inf_L, Parietal_Inf_R	83	−72	−36	−75	42
Rectus_R, OFCmed_L, OFCmed_R, OFCant_R, OFCpost_L, OFCpost_R, Olfactory_L	78	35	24	30	−21
Cingulate_Post_L, Cingulate_Post_R	40	−38	−6	−42	30
Caudate_R, Putamen_R	39	−27	21	24	−3
Cingulate_Mid_L, Cingulate_Mid_R	32	−49	−6	−42	33
Hippocampus_R, ParaHippocampal_R	14	−64	21	−27	−15
Precuneus_L, Precuneus_R	10	−6	−12	−48	39
Insula_R	8	21	36	12	12
Frontal_Inf_Orb_2_R	6	3	30	33	−12

*The number of significantly different FC links relating to the voxels ($P < 0.05$, corrected). The negative value means the FCs are decreased in depression patients and vice versa.

larger than expected by chance, with the analytic FWER-corrected P-value of each cluster given by random field theory. In this study, we reported all the FC clusters with FWER-corrected cluster size $P < 0.05$ (Gong et al. 2018). We selected $P = 1.0 \times 10^{-4}$ as the cluster-defining threshold because in our original study (Gong et al. 2018), we showed that $z = 4.5$, corresponding to $P = 3.4 \times 10^{-6}$, can be used as a valid threshold for whole-brain analysis. As fewer FCs were analyzed in this study compared with the whole-brain voxel-wise analysis considered by Gong et al., we can reduce the threshold in proportion to the number of FCs involved in line with the underlying random field theory. In more detail, we adjusted the cluster-defining threshold for the present study to be proportional to the number of FCs analyzed between the whole-brain study and the present study ($1.0 \times 10^{-4} \approx 3.4 \times 10^{-6} \times \frac{47\,619 \times 47\,618/2}{47\,619 \times 822}$). It should be noted that type I errors are well controlled with the cluster-level inference, irrespective of the cluster-defining threshold (Gong et al. 2018).

The AAL2 (Rolls et al. 2015) was used to provide names for brain areas in which voxels were found and to define the ACC region investigated here. The definition in this atlas of the ACC is shown by the regions with orange color in Figures 1A and 5, and we note at the outset that the posterior part of this region (part of the red area numbered 1 in Fig. 5), sometimes termed "caudal ACC", may extend into the anterior part of what has been described as middle cingulate cortex (Vogt 2009).

Clinical Correlates

We also investigated whether the differences in FC between patients and controls were correlated with clinical variables (the HAMD (Hamilton 1960), BDI (Beck and Beamesderfer 1974), and illness duration (Bell-McGinty et al. 2002; de Diego-Adelino et al. 2014)). Specifically, the FC of the voxels with significant differences of FC (after cluster-wise correction at $P < 0.05$, and within the voxel clusters shown in Table 1) was measured for each of the AAL2 regions within which the voxels were located. In this way, 29 ROIs were identified. Then for each ROI, we calculated the partial correlation between the clinical scores and the voxel-wise FCs between the significant voxels in that brain region (ROI) and the ACC, with head motion, education, sex, and age as covariates so that they did not contribute to the correlation. Then the mean correlation between the clinical scores and the voxel-wise FCs was defined as the overall correlation between the significant voxels in that brain region and the ACC. Finally, a permutation test with 1000 randomizations of the patient labels was used to assess the statistical significance of the mean correlation.

Parcellation of the ACC

To enable a more detailed comparison between patients and controls, we performed a voxel-level parcellation of the ACC based on the FC of anterior cingulate voxels with all AAL2 brain regions (Rolls et al. 2015) in healthy controls. Specifically, for each voxel in the ACC, we first calculated the FC between that voxel and all AAL2 regions (94 regions in total). This procedure was repeated for all anterior cingulate voxels (822 in total), to obtain a 822×94 connectivity matrix in which each element i, j of the vector represents the correlation between the ith voxel of the ACC with the jth AAL2 region. Then a parcellation was performed using k-means clustering based on the connectivity matrix (in line with previous parcellation studies (Genon, Li, et al. 2017; Genon, Reid, et al. 2017)). The number of subdivisions accepted (k in k-means) was selected to provide the clearest separate groups of voxels ($k = 2$).

Results

A roadmap of the results follows. The first part of the results describes the differences in FC of the ACC in a large group of 282 patients with depression compared to 254 controls (Figs 1, 2 and Tables 1, 2). 125 of these patients were not receiving

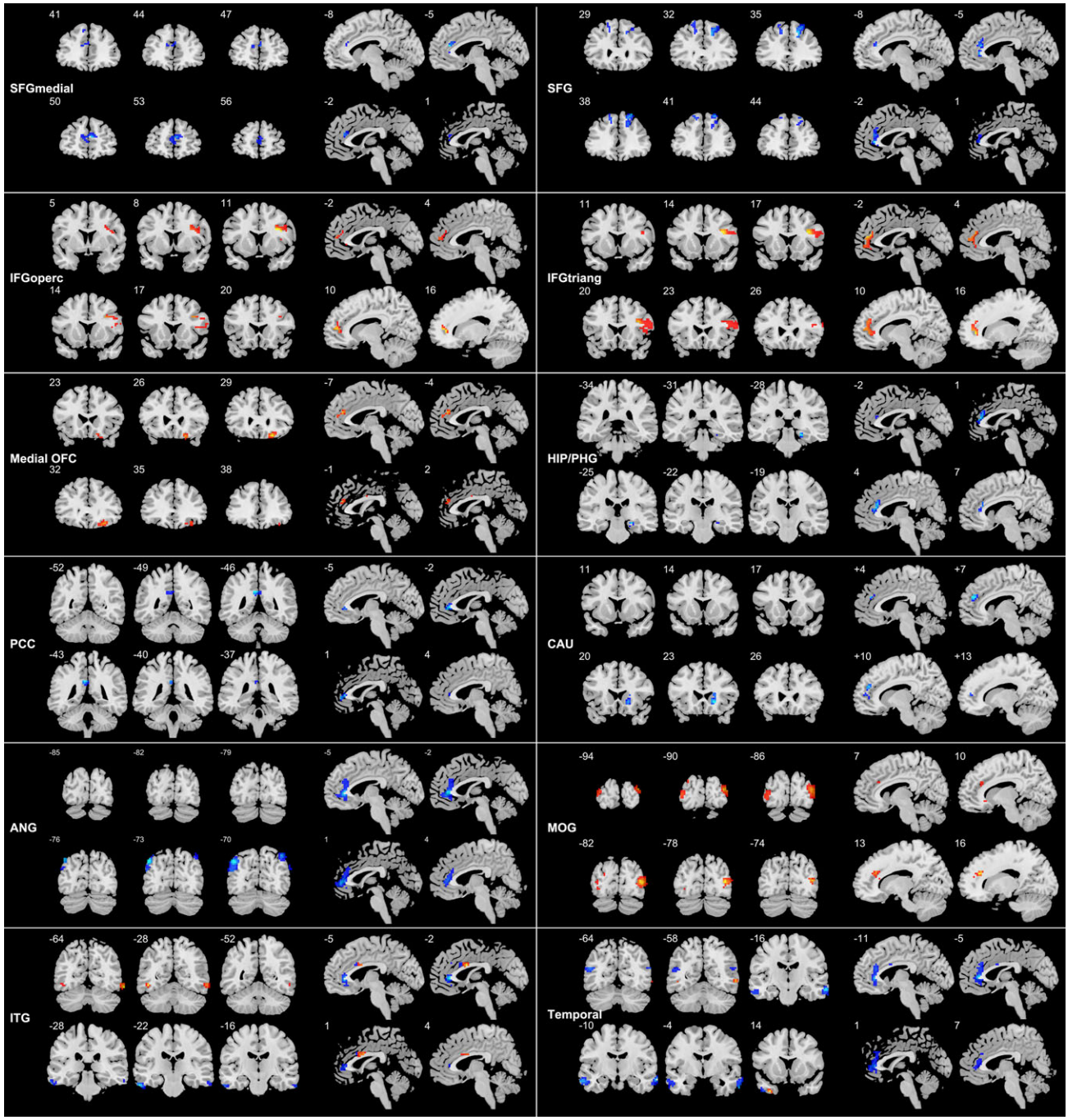

Figure 2. The voxel-level FC for anterior cingulate voxels that are significantly different in the depressed and the control groups, separated by the AAL2 region (Rolls et al. 2015) in which the significant voxels were located. Conventions as in Figure 1. Blue indicates voxels with predominantly decreased FC, and red/yellow indicates voxels with predominantly increased FC. SFGmedial: superior frontal gyrus (medial); SFG: superior frontal gyrus (dorsolateral); IFGoperc: inferior frontal gyrus (opercular part); IFGtriang: Inferior frontal gyrus (triangular part); Medial OFC: olfactory cortex + gyrus rectus + medial orbital gyrus + anterior orbital gyrus + posterior orbital gyrus; HIP/PHG: hippocampus + parahippocampal gyrus; PCC: posterior cingulate gyrus; CAU: Caudate; ANG: angular gyrus; MOG: middle occipital gyrus; ITG: inferior temporal gyrus; Temporal: superior temporal gyrus + temporal pole (superior temporal gyrus) + middle temporal gyrus + temporal pole (middle temporal gyrus).

medication. In this mixed group of unmedicated and medicated patients some FCs were significantly higher than in controls, and some were significantly lower. Then to investigate possible subdivisions of the ACC based on its FC, of interest in understanding its function in health and disease, a parcellation was performed in 254 healthy controls based on the FC of ACC voxels (Figs 3–5A,B). Then FC differences of the two subdivisions of the ACC in the whole depressed group of 282 patients with depression from controls were performed to test whether the two subdivisions had differences in their FC in depression (Fig. 5C). Then to tease out the differences of FC related to depression versus to the effects of medication, the FC of the ACC was analyzed in 125 patients that were unmedicated versus the 254 controls. Interestingly, most of the significantly different FCs were higher in the unmedicated patients than in controls (Fig. 6 and Supplementary Fig. S2 and Table S3). These

Table 2 Correlations between the FC links and the depression symptom severity scores. The effects of medication were regressed out of this analysis

FC		Clinical variable	*r* value	*P*-value
Cingulate_Ant_L	Hippocampus	BDI	−0.082	0.032
Cingulate_Ant_L	Cingulate_Ant_R	BDI	−0.083	0.016
Cingulate_Ant_R	Hippocampus	BDI	−0.090	0.012
Cingulate_Ant_L	Cingulate_Mid_L	Illness duration	−0.081	0.036
Cingulate_Ant_L	Cingulate_Post_L	Illness duration	−0.083	0.026
Cingulate_Ant_L	Parietal_Sup_R	Illness duration	0.072	0.01
Cingulate_Ant_L	Parietal_Inf	Illness duration	−0.084	0.018
Cingulate_Ant_L	Temporal_Pole_Mid_L	Illness duration	−0.076	0.036
Cingulate_Ant_R	Frontal_Sup	Illness duration	−0.052	0.044
Cingulate_Ant_R	Cingulate_Mid_L	Illness duration	−0.087	0.024
Cingulate_Ant_R	Cingulate_Post_L	Illness duration	−0.085	0.014
Cingulate_Ant_R	Frontal_Sup_R	Illness duration	0.074	0.004
Cingulate_Ant_R	Parietal_Inf	Illness duration	−0.099	0.006
Cingulate_Ant_R	Angular	Illness duration	−0.076	0.014
Cingulate_Ant_R	Temporal_Mid	Illness duration	−0.063	0.026
Cingulate_Ant_R	Temporal_Inf	Illness duration	−0.076	0.016

results are important for understanding the FC differences that are related to depression per se. Consistent with this finding, in the same section, it is also shown, using the contrast of 125 unmedicated patients—157 medicated patients, that the medication tended to reduce the FCs that were higher in the unmedicated patients (Supplementary Fig. S1). This finding helps to advance the understanding of the neural effects of the medication used to treat depression.

A Hypothesis-based Voxel-level FC Study of Anterior Cingulate Gyrus Voxels in Depression

As shown in Figures 1 and 2 and Table 1, there were a number of anterior cingulate gyrus voxels with different FCs in patients with depression compared with controls. In most cases, a reduction in FC was found in the whole group of 282 people with depression.

The largest clusters of voxels with altered (mainly reduced) FC with the ACC were in the temporal cortex including inferior, middle, and superior temporal gyrus and the temporal pole (Table 1). (These voxel numbers are those with altered FC with ACC voxels with $P < 0.05$ cluster-wise corrected.) Additional areas with voxels with different FC with the ACC in depression included the medial orbitofrontal cortex (AAL2 areas Rectus, OFCmed, OFCant, OFCpost, OLF, increased); the inferior/middle frontal gyrus (AAL2 areas Frontal_Inf etc, increased) and frontal areas (Frontal_Sup_Med and Frontal_Sup); hippocampus; posterior cingulate cortex; the precuneus; the parietal cortex; early cortical visual areas (Occipital etc); and pre- and post-central gyri (increased) (Table 1, Figs 1 and 2).

Analysis of the FC links of ACC Voxels that were Different in Patients with Depression

To investigate the brain areas between which there was a different FC in the whole group of 282 people with depression, and whether it was increased or decreased, the FC of the ACC voxels with significant differences of FC (after cluster-wise correction at $P < 0.05$, and within the voxel clusters shown in Table 1) was measured for each of the AAL2 regions within which the voxels were located. (A list of abbreviations of the AAL2 areas is provided in Supplementary Table S2.) The FC differences are shown in Figure 2 at the voxel level, with the voxels shown arranged by the AAL2 areas in which they are found. Figure 2 shows that the ACC voxels with altered FC with other brain areas tend to be in different parts of the ACC. This voxel-level analysis could of course not be shown by an ACC whole region seed-based analysis.

First, many voxels in the (mainly pregenual) ACC have mainly decreased FC with some temporal cortex areas known to be involved in visual and multimodal processing (Rolls 2012, 2016a, 2016b) (Figs 1 and 2 and Table 1).

Second, some ACC voxels, mainly supracallosal, had reduced FC in depression with the hippocampus which is implicated in memory (Figs 1 and 2 and Table 1).

Third, increased FC of pregenual and some nearby anterior supracallosal cingulate cortex voxels with the medial orbitofrontal cortex areas (gyrus rectus, OFCmed, OFCant, and OFCpost) was found (Fig. 2 and Table 1), and both are regions involved in reward and subjective pleasure (Grabenhorst and Rolls 2011; Rolls 2014).

Fourth, some mainly pregenual ACC voxels had increased FC with the inferior frontal gyrus (opercular and triangular parts—see Fig. 2) in depression.

Fifth, voxels in the pregenual had reduced FC in depression with the posterior cingulate cortex which is involved in autobiographical memory (Cheng, Rolls, Qiu, et al. 2018; Rolls and Wirth 2018) (Figs 1 and 2 and Table 1).

Sixth, some voxels in the ACC had reduced FC with voxels in the superior and middle frontal gyri, and other areas, in depression (Figs 1 and 2 and Table 1).

Seventh, the angular gyrus had reduced FC with the ACC in depression (Fig. 2 and Table 1). This reduced FC also extended posteriorly into earlier visual areas including the occipital cortex and lingual gyrus.

Clinical Symptom Correlates of the Reduced Anterior Cingulate Gyrus FCs in Depression

As can be seen from Table 2, there were significant correlations ($P < 0.05$ uncorrected) between some of the ROI-wise FC links involving the ACC, and the symptom severity scores and illness duration in the whole group of 282 people with depression. Specifically, the BDI score was correlated with weakened

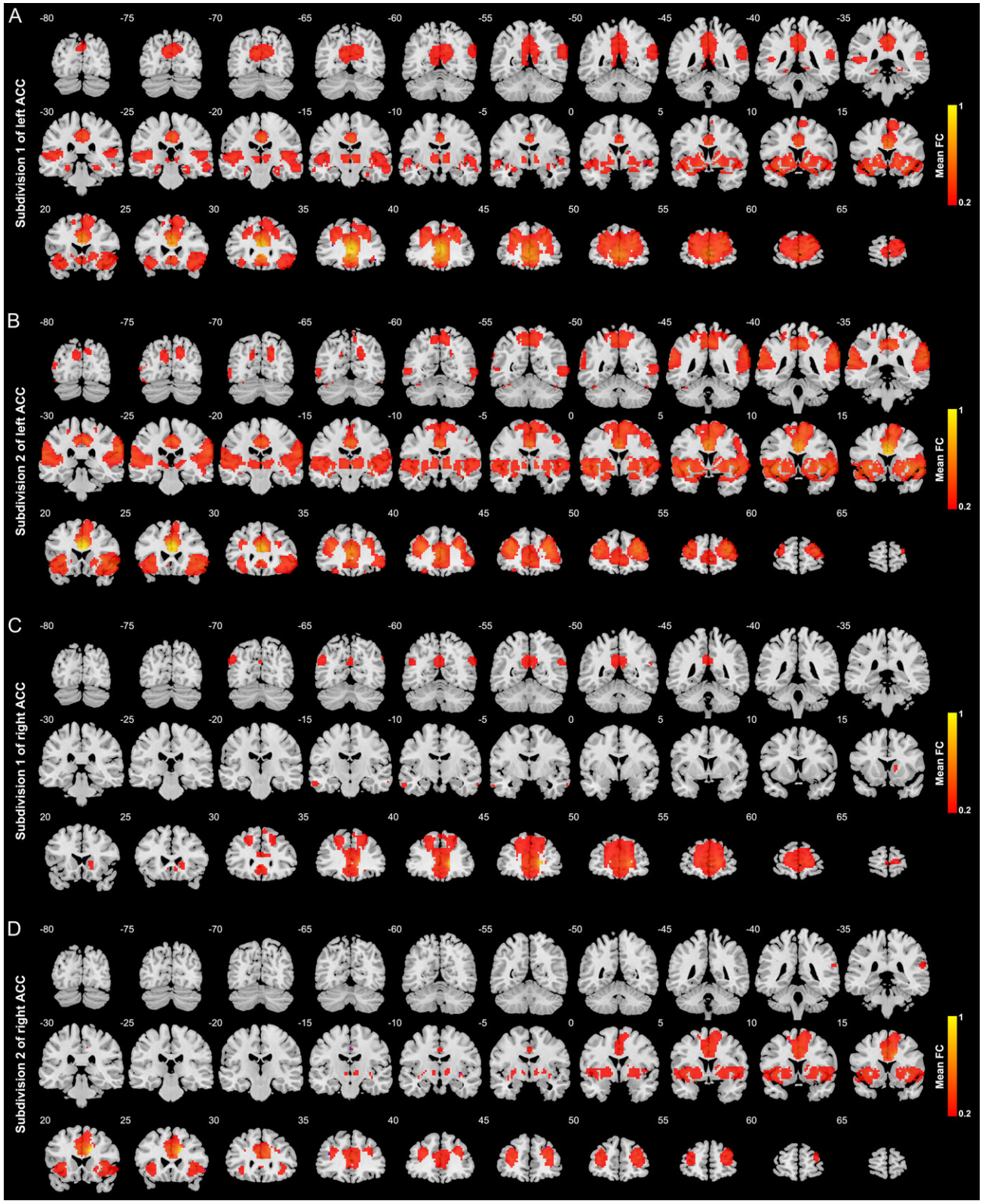

Figure 3. The voxel-wise FC pattern for each subdivision of the ACC in healthy controls. The color reflects the *r* value of the FC as shown by the calibration bar. The MNI Y coordinate is indicated for each slice. The threshold ($r > 0.2$) means that not all FCs are shown.

connectivity between the ACC and the hippocampus. Further, we found that the illness duration (Table 2) was negatively correlated with FC between the ACC and the angular gyrus (BA39), temporal cortical areas, and posterior cingulate cortex. These correlations provide additional evidence closely relating the differences in FC of the ACC to the depression.

ACC Voxel-level FC in Healthy Participants, Using Parcellation

To enable a more detailed comparison between patients and controls, we performed a voxel-level parcellation of the ACC based on the FC of ACC voxels with voxels in all other brain regions in healthy controls (Figs 3–5A,B) using *k*-means, so that we could then compare the FC differences of each subregion in patients. The two subdivisions found on the left and right are shown in Figure 5A,B. Subdivision 1 is pregenual and subgenual ACC (green in Fig. 5). Subdivision 2 is supracallosal ACC (red in Fig. 5). This parcellation is based on the connectivity of each voxel in the ACC with the 94 areas in the AAL2. Similar parcellation was found if the FC of each ACC voxel with other ACC voxels was used to perform the clustering, or if the parcellation was performed using the data from the patients with depression.

Figures 3–5 show the different patterns of FC for these two subdivisions, which can be summarized as follows.

Subdivision 1 (pregenual and subcallosal including subgenual) has relatively strong FC with medial orbitofrontal cortex areas (including Rectus and OLF, and also OFCmed, OFCant, and OFCpost, and Frontal MedOrb which is the ventromedial prefrontal cortex) and with OFClat (Fig. 5A). It also has strong FC with AAL2 areas 3,4 (superior frontal gyri laterally), and strong with 19–22 (superior frontal gyri medially) (Fig. 4). It also has relatively strong FC with 41–44 (including hippocampus, parahippocampal gyri), 39–40 posterior cingulate cortex, 69–70 (angular gyri), and with the mid-temporal cortex (Fig. 4).

Subdivision 2 (supracallosal) has relatively strong FC with the lateral orbitofrontal cortex area Frontal_Inf_Orb (see Fig. 3, *Y* = 20–30) and with other parts of the inferior frontal gyrus (Frontal_Inf_Tri, Frontal Inf_Operc). In addition, subdivision 2 has relatively strong FC with AAL2 areas 33,34 (left and right Insula), 37,38 (Middle Cingulate Gyrus), 67,68 (Supramarginal Gyrus), and motor areas (13–16 Rolandic operculum and supplementary motor area; and putamen and pallidum); and relatively weak FC with AAL2 areas 3,4,19–22 (mainly superior frontal gyri laterally and medially), 39,40 (posterior cingulate), and 69,70 (angular gyrus) (Fig. 4). (For a list of AAL2 areas see Table S2 and Rolls et al. (2015).)

Different FCs for Different ACC Subregions in Depression

Figure 5C shows the FCs that are different in depression (whole depressed group—healthy controls) for the two subdivisions (combined over left and right, as they were similar). (A negative value for *t* in Fig. 5C thus represents a weaker FC in patients with depression.)

The pregenual/subcallosal cingulate cortex (subdivision 1 in Fig. 5A,B, colored green) is distinguished in depression by especially strong FC with voxels in the right lateral orbitofrontal cortex (IFGorb), the right inferior frontal gyrus pars triangularis (BA45) and pars opercularis (BA44), the posterior orbitofrontal cortex, and also with the precentral gyrus (Fig 5C). Further distinctions in this FC are made below based on the FC in unmedicated patients shown in Supplementary Figure S2.

The supracallosal subdivision (2, colored red) has relatively increased FC in depression with the post-central gyrus, superior parietal gyrus, and the inferior temporal gyrus (Fig. 5C).

Both subdivisions have some similar differences in the whole depression group from controls, with decreased FC with FrontalSup, FrontalSupMedial, hippocampus, inferior parietal and angular gyri, middle temporal gyri, and mid- and posterior cingulate; and increased FC with some visual areas (including occipital), with the paracentral lobule, and with the putamen (Fig. 5C).

We further note that the parcellation was very similar in the depressed patients with that in the healthy controls.

FC in Unmedicated Patients, and the Effects of Medication on the FC

Figure 6 shows the FC in 125 individuals who were not receiving medication compared with 254 controls. Increased FCs of the ACC were found with the medial orbitofrontal cortex, inferior frontal gyrus, with the superior parietal lobule, and with early cortical visual areas. There were few decreases in FC in the unmedicated patients (Fig. 6). The effects found in the unmedicated patients are shown further and quantitatively in Supplementary Table S3 and are further illustrated in Supplementary Figure S2. It is shown in Supplementary Figure S2 that medial orbitofrontal cortex areas have increased FC with a part of the ACC that is just above the pregenual cingulate cortex and extend posteriorly somewhat to include a part of the supracallosal ACC.

It is also shown in Supplementary Figure S2 that the lateral orbitofrontal cortex area 47/12 where it adjoins the most anterior ventral insula has increased FC with the subgenual/subcallosal ACC.

It is also shown in Supplementary Figure S2 that an area more superiorly at the superior margin of the inferior frontal gyrus pars triangularis and pars opercularis has increased FC with the pregenual cingulate cortex.

Supplementary Figure S1 shows the contrast of 125 unmedicated patients—157 medicated patients for FC. As the illness duration was longer in the medicated than the unmedicated patients ($t = 3.65$, $P = 3.2 \times 10^{-4}$), the effect of illness duration was regressed out in this analysis. Many FCs of the ACC were lower in the medicated group compared with the unmedicated patients, including with the superior frontal gyrus, temporal lobe, posterior cingulate cortex/precuneus, and angular gyrus.

The implication of these results is that the main differences in FC in depression compared with controls are increases in FC as shown in Figure 6 and Supplementary Table S3, and the decreases of FC in the whole group of both medicated and unmedicated patients that are illustrated in Figures 1 and 2 and Table 2 are related to the effects of the medication. The elucidation that the differences in FC in depression consist in increases as shown in Figure 6, Supplementary Figure S2 and Table S3 is a new and significant finding made possible by this research on a uniquely large group of unmedicated patients with depression with resting-state fMRI scans.

Discussion

The importance of the present study is that by focusing on the ACC, and using very large neuroimaging datasets of patients with depression and controls, we were able to characterize the altered FC at the voxel level in depression of the ACC with other brain regions. The new method that we used enabled identification of which voxels in the ACC had different FC with particular brain areas in depression.

In the whole population which included medicated and unmedicated patients, higher FC (relative to controls) of the ACC with the medial orbitofrontal cortex, inferior/middle frontal gyrus, inferior temporal gyri, and early cortical visual areas was found (Figs 1 and 2 and Table 1). Decreased FC was found with the angular gyrus, inferior and middle temporal gyri, hippocampus, and posterior cingulate cortex / precuneus (Figs 1 and 2 and Table 1).

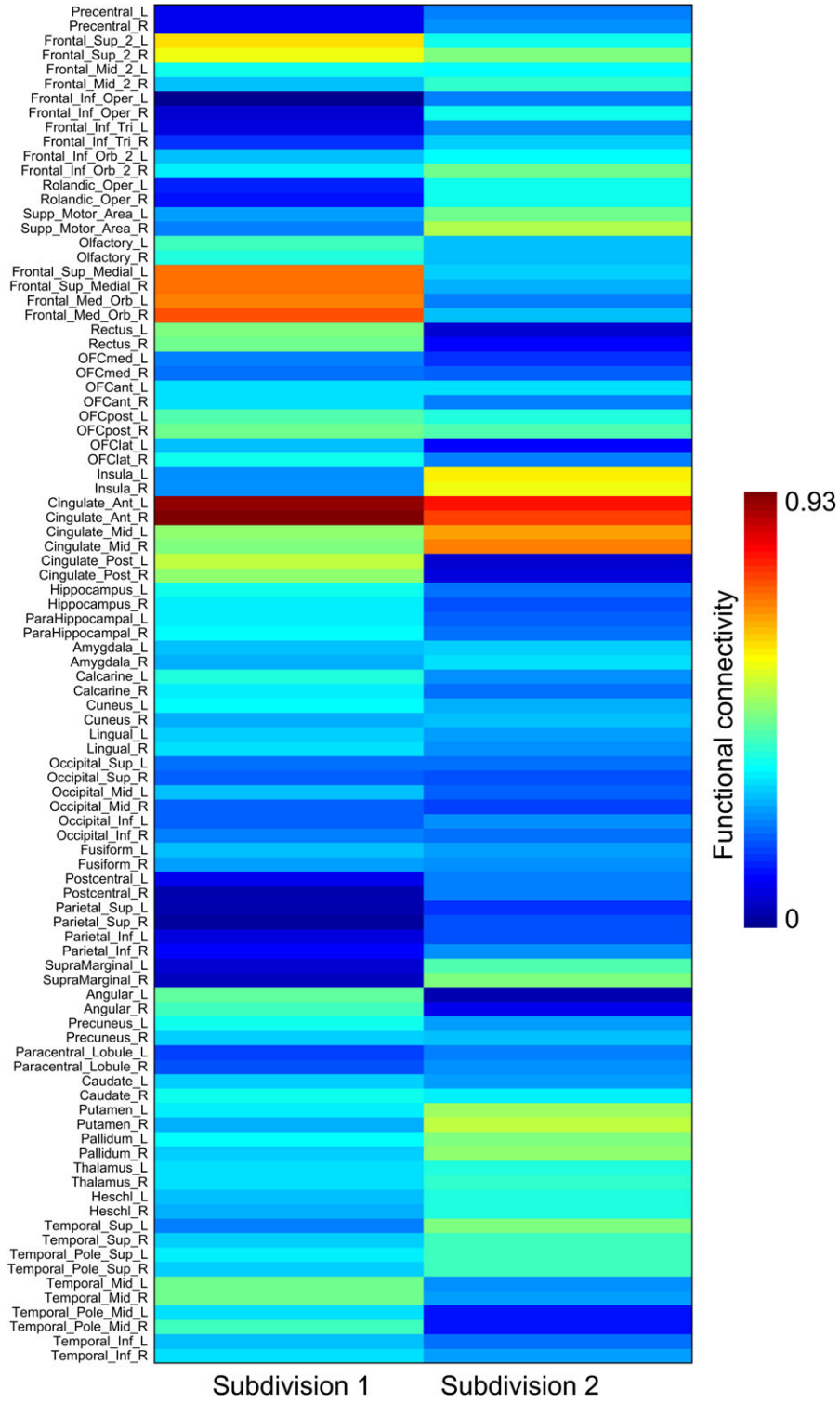

Figure 4. The ROI-wise (AAL2 regions) FC pattern for each subdivision of the ACC in healthy controls. The calibration bar shows the correlation (*r*) value for the FC. The connectivities have been combined across the two hemispheres, because they were similar.

However, in unmedicated patients, increased FCs of the ACC were found with areas that included the medial orbitofrontal cortex, temporal cortical areas, middle and inferior frontal gyri, with the angular gyrus, with parietal areas, and with early cortical visual areas (Fig. 6 and Supplementary Fig. S2 and Table S3). Further, there were few decreases in FC in the unmedicated patients (Fig. 6). It is an important feature of this investigation that FC could be measured in a substantial cohort (125) of unmedicated patients, and this helps to show which differences in FC are associated with depression per se rather than the effects of medication.

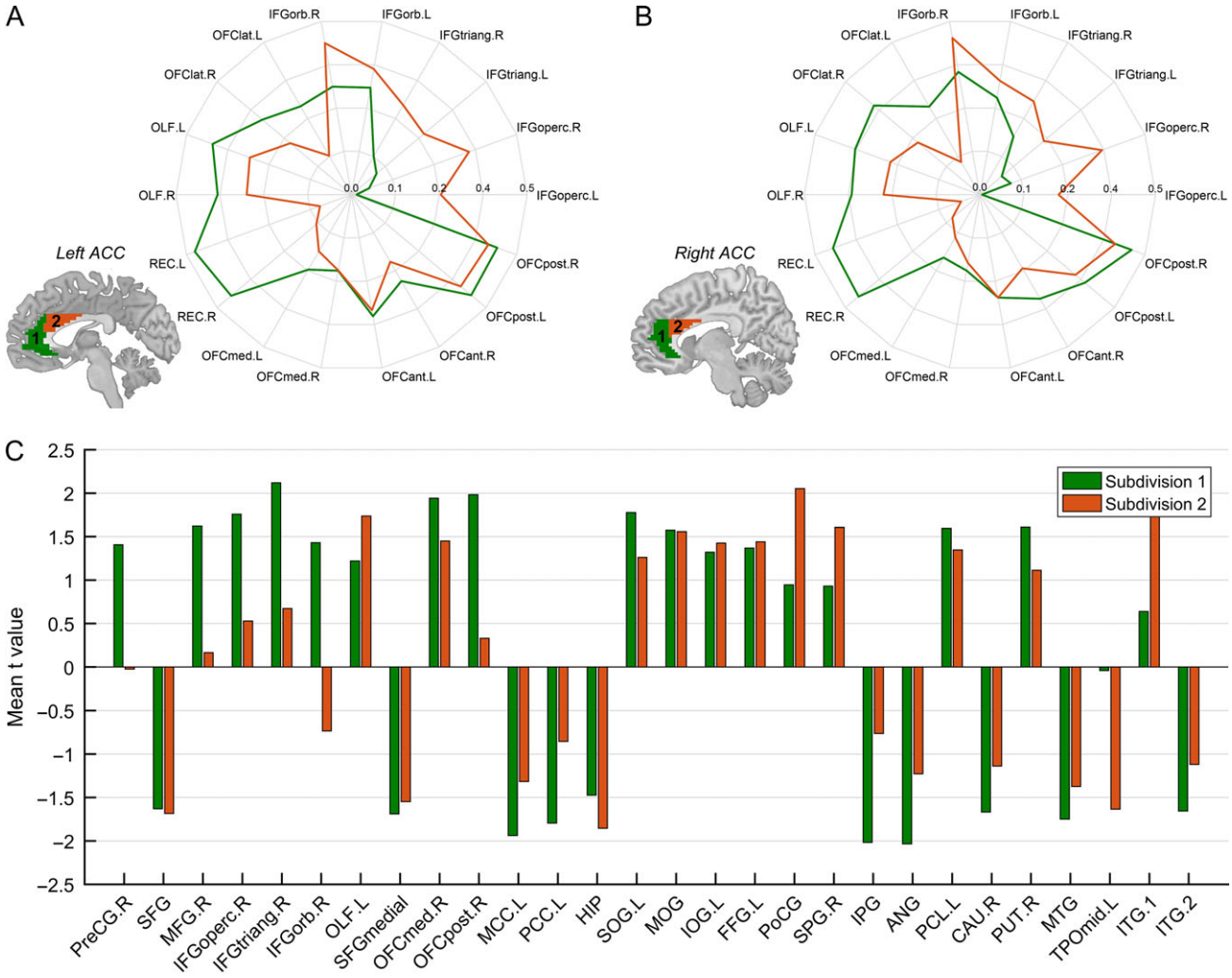

Figure 5. (A) Voxel-level parcellation of the left ACC based on its FC in healthy controls with other brain areas. Subdivision 1 is pregenual and subgenual ACC. Subdivision 2 is supracallosal ACC. The polar plot shows the correlations of the voxels in each subdivision of the ACC with the significantly different voxels in orbitofrontal cortex AAL2 areas. A two-way repeated measures analysis of variance (ANOVA) showed by the interaction term ($P < 0.0001$) that the two ACC subdivisions had different FC with these orbitofrontal cortex areas. (B) Voxel-level parcellation of the right ACC based on its FC in healthy controls with other brain areas. Subdivision 1 is pregenual and subgenual ACC. Subdivision 2 is supracallosal ACC. The polar plot shows the correlations of the voxels in each subdivision of the ACC with the significantly different voxels in orbitofrontal cortex AAL2 areas. The interaction term in the ANOVA was again significant. (C) The mean *t* value for the difference in FC (healthy controls—patients with depression) of the links between voxels in each subdivision and the significant ROIs showed in Table 1 for the ACC. The *t* value shown is the mean *t* value between all voxels (not just the significant voxels) in each subregion and each ROI. The full names of the abbreviations of ROIs are shown in Supplementary Table S2.

This analysis was supported by the effects of medication, which as shown in Supplementary Figure S1 decreased FC of the ACC with the medial orbitofrontal cortex (gyrus rectus), with the lateral orbitofrontal cortex and adjoining inferior frontal gyrus areas, with other ACC voxels, superior frontal gyrus, temporal lobe, and angular gyrus.

A highlight of the investigation is that we were able to parcellate the ACC into two parts and show their FC with other brain regions including the orbitofrontal cortex. Subdivision 1 is pregenual and subgenual (subcallosal) ACC (green in Fig. 5). Subdivision 2 is supracallosal ACC (red in Fig. 5). The FCs of these subdivisions are shown in Figures 4 and 5. Of great interest in Figure 5 is that pregenual/subcallosal medial orbitofrontal cortex areas has relatively high FC with medial orbitofrontal cortex areas (e.g., gyrus rectus and the OLF in the AAL2 atlas which is probably in part medial orbitofrontal cortex and ventral striatum), for both are implicated in representing rewards and pleasant stimuli (Grabenhorst and Rolls 2011; Rolls 2014, 2017a, 2017b, 2018). In contrast, the supracallosal ACC has relatively high FC with parts of the lateral orbitofrontal cortex (IFGorb), implicated in representing non-rewards (not obtaining expected rewards), punishers, and unpleasant stimuli (Grabenhorst and Rolls 2011; Rolls 2014, 2017a, 2017b, 2018; Deng et al. 2017). This provides evidence to elucidate further the hypothesis that the orbitofrontal cortex sends reward and non-reward information to the ACC where the reward/non-reward signals can be interfaced to cingulate systems that learn actions to obtain reward and avoid non-reward and punishers (Rushworth et al. 2012; Rolls 2014, 2017a, 2017b, 2018). The supracallosal ACC has relatively high FC also with parts of the inferior frontal gyrus illustrated in Supplementary Figure S2. The size of our sample was far larger than that in a recent study of the orbital and medial prefrontal cortex (Samara et al. 2017), and in another study two

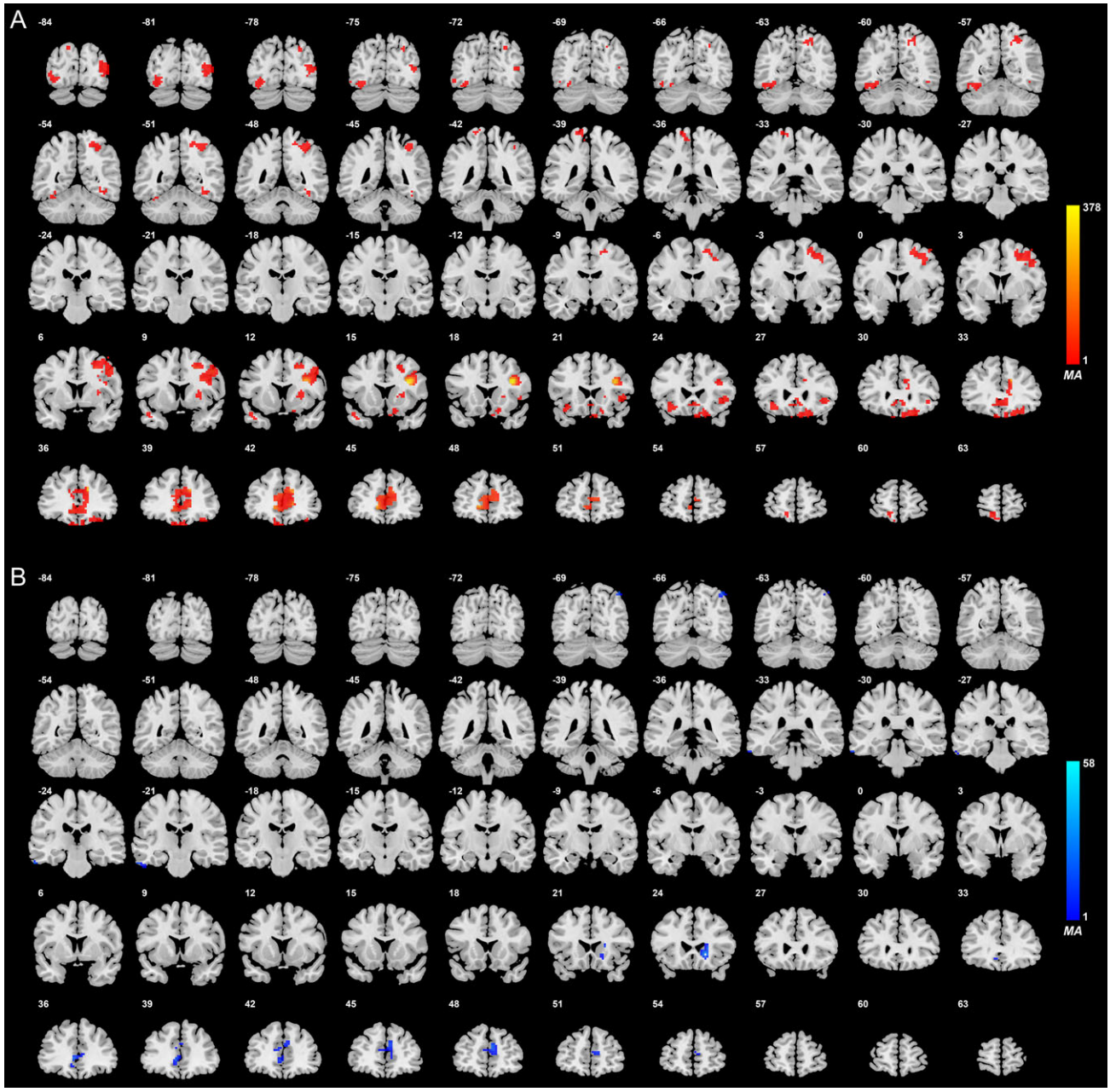

Figure 6. Anatomical location of voxels with significantly different FC with the ACC in unmedicated depression obtained from the vAS. Voxels with FC differences with the ACC in 125 unmedicated patients with depression are shown, compared with 254 controls. The color bar represents the number of significantly different FC links relating to each voxel after cluster-wise correction ($P < 0.05$). (A) Higher FC in depression. (B) Lower FC in depression. The MNI Y values are shown.

divisions in this part of the ACC were also found (de la Vega et al. 2016).

We were then able to measure differences in the FC of these subdivisions in depression (Fig. 5C and 2). The pregenual/subcallosal cingulate cortex is distinguished in depression by especially strong FC with voxels in the right lateral orbitofrontal cortex (IFGorb) and its two nearby areas, the right inferior frontal gyrus pars triangularis (BA45) and pars opercularis (BA44), and also with the precentral gyrus (Fig 5C). Analysis in the unmedicated patients shown in Supplementary Figure S2 revealed the following. It is also shown in Supplementary Figure S2 that the subgenual/subcallosal ACC has increased FC with the lateral orbitofrontal cortex area 47/12 where it adjoins the most anterior ventral insula. This is of great interest for the lateral orbitofrontal cortex has representations of many aversive, unpleasant, stimuli (Grabenhorst and Rolls 2011; Rolls 2017a, 2017b, 2018) and projects to the subcallosal ACC (Vogt 2009), in which neurons that respond to unpleasant stimuli have been found in humans (Laxton et al. 2013). This increased FC between these brain regions may produce greater influences of unpleasant, non-reward, stimuli from the orbitofrontal cortex to the subcallosal cingulate, and thus to greater effects of negative events on behavioral output, making an important contribution to depression. Indeed, the subcallosal cingulate cortex is thought to be a key area involved in depression and is a target for brain stimulation aimed to reduce depression (Lujan et al. 2013; Kang et al. 2016; Mayberg et al.

2016; Drysdale et al. 2017; Dunlop et al. 2017; Ramirez-Mahaluf et al. 2017; Riva-Posse et al. 2018). More generally, the subcallosal cingulate, especially subgenual cingulate cortex BA25 has long been implicated in autonomic output with its direct connection to the dorsal motor nucleus of the vagus (Gabbott et al. 2003; Critchley et al. 2011), and it may provide a route for unpleasant events to produce strong autonomic output in depression. Moreover, there is evidence from Positron Emission Tomography studies that this region is overactive in depression (Drevets et al. 1997; Dougherty et al. 2003; Mayberg et al. 2005; Konarski et al. 2009). Further, there are neurons in this region, BA25, and related areas in primates that increase their firing rates when a primate becomes drowsy (Rolls et al. 2003; Gabbott and Rolls 2013). This link to changes of activity relating to sleep is also of interest in relation to depression (Cheng, Rolls, Ruan, et al. 2018).

It is also shown in Supplementary Figure S2 that an area more superiorly at the superior margin of the inferior frontal gyrus pars triangularis and pars opercularis has increased FC with the pregenual cingulate cortex. This may be the inferior frontal gyrus region with connections with the motor laryngeal area (Kumar et al. 2016). 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 ACC with the (right) angular gyrus (Fig. 6, Y = 74), contralateral to a cortical area related to language (Cheng et al. 2016).

Figure 5C shows that the supracallosal division (2) of the ACC, which is activated by punishers and non-reward (Grabenhorst and Rolls 2011; Rolls 2017a, 2017b, 2018), has increased FC with, for example, some movement-related areas such as the post-central gyrus and superior parietal lobule. Further, it is shown in Supplementary Fig. S2 that in unmedicated patients the medial orbitofrontal cortex areas, which are implicated in reward and pleasant stimuli (Grabenhorst and Rolls 2011; Rolls 2017a, 2017b, 2018), have increased FC with a part of the ACC that is just above the pregenual cingulate cortex and extend posteriorly somewhat to include a part of the supracallosal ACC, a part of the ACC that is activated by punishing stimuli and by non-reward (Grabenhorst and Rolls 2011; Rolls 2017a, 2017b, 2018). A possible implication for understanding depression is that even pleasant, rewarding, stimuli from the medial orbitofrontal cortex are routed toward output to a part of the ACC that is involved in unpleasant stimuli, producing unpleasant and non-reward effects from what would normally be pleasant stimuli.

Consistent with these hypotheses, medication decreased the connectivity of the ACC with the lateral orbitofrontal cortex/inferior prefrontal convexity areas.

A strength of this investigation is that we analyzed FC at the level of voxel to voxel FC. It was this that enabled us to perform a parcellation of the ACC and to examine which voxels in the ACC were connected differently to which voxels in all other brain areas, as shown for example in Figure 2. This was made possible by the uniquely large sample size, which enabled the conclusions described above to be reached. Another unique feature was the large sample of patients with depression who were not receiving medication. We further note that the effects were of reasonable size, in that significant effects were found in the smaller group of 125 unmedicated patients (Fig. 6 and Supplementary Fig. S2), and further, we found similar effects in both of the subgroups produced by splitting the unmedicated group into two parts. Additional robustness was demonstrated by the finding that the medication decreased the FC of patients with depression back down toward the level in healthy controls (Supplementary Fig. S1). The fact that the FC of unmedicated patients with depression (Fig. 6) was quite different from a group of patients some of who received medication (Fig. 1) is important to take into account in future studies of depression.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Authors' Contribution

Edmund T. Rolls, Wei Cheng, and Jianfeng Feng contributed to the design of the study. Jiang Qiu, Zicheng Hu, Hongtao Ruan, Dongtao Wei, Jie Meng, and Peng Xie contributed to the collection of the data. Wei Cheng, Edmund T. Rolls, Weikang Gong, and Wujun Lv contributed to the analysis of the data and the preparation of the manuscript. Edmund T. Rolls and Wei Cheng participated in writing the paper. All authors had an opportunity to contribute to the interpretation of the results and to the drafting of the manuscript.

Notes

Conflict of Interest: All authors declare no competing interests.

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