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 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 functional connectivities. However, in 125 unmedicated patients, primarily increases of functional connectivity 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 functional connectivities were lower than in the unmedicated group. Parcellation was performed based on the functional connectivity of individual ACC voxels in healthy controls. A pregenual subdivision had high functional connectivity with medial orbitofrontal cortex areas, and a supracallosal subdivision had high functional connectivity with lateral orbitofrontal cortex and inferior frontal gyrus. The high functional connectivity 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 functional connectivity between the medial orbitofrontal cortex and supracallosal ACC in depression may also contribute to depressive symptoms.

Introduction

There is considerable evidence that the anterior cingulate cortex is involved in emotion, with a pregenual part activated by many rewards, and a supracallosal part activated by non-reward and punishers (Rolls 2009; Vogt 2009; Grabenhorst and Rolls 2011; Rolls 2014). The subcallosal anterior cingulate cortex (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; Hamani *et al.* 2011; Price and Drevets 2012; 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 functional connectivity 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 functional connectivity 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 functional connectivity differences of the anterior cingulate cortex in depression, much smaller sample sizes with typically tens of participants were studied, and voxel-to-voxel functional connectivity was not measured.

In this investigation, we performed the first voxel-level resting state functional-connectivity neuroimaging analysis of depression of voxels in the anterior cingulate cortex 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 analyse every anterior cingulate voxel for significantly different functional connectivity with every voxel throughout the rest of the brain in depressed people vs controls, in order to advance understanding of the anterior cingulate cortex and depression. In this paper we utilize what we term 'hypothesis-based voxel-level functional connectivity analysis' in which we select a brain region of interest, but then calculate for every voxel in that region whether it has functional connectivity with individual voxels in every other brain region. In the present paper, we select the anterior cingulate cortex as the region of interest, given the research on it described above implicating it in depression, and then we show exactly which anterior cingulate voxels have altered functional connectivity in depression with which individual voxels in every other brain area. Given that the anterior cingulate cortex has 822 voxels, and that there are 47619 voxels in the $3 \times 3 \times 3 \ mm$ automated anatomical atlas (AAL2) brain (Rolls et al. 2015), the number of voxel pairs in this study was approximately 822×47619. This methodology is quite different from and more statistically powerful than a whole brain voxel-to-voxel functional connectivity analysis (Cheng et al. 2016) for two reasons. First, the number of functional connectivities 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 functional connectivity analysis to correct for multiple comparisons, which utilized the spatial information from clusters of voxel-level functional connectivities (Gong et al. 2018). Further, we describe here how anterior cingulate cortex 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 anterior cingulate cortex, and are able to report significant differences in its FC in depression, and even of the subdivisions of the anterior cingulate cortex.

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

The focus here is on the anterior cingulate cortex, because not only is it 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; Grabenhorst and Rolls 2011; Rolls 2014). A highlight of the current investigation is that a connectivity-related parcellation of the anterior cingulate cortex was performed in the healthy control participants; and that these subregions had different alterations of functional connectivity in depression. We relate the discoveries described here to a new theory of depression in which areas that project to the anterior cingulate cortex, 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 2016b; Rolls 2017b; Rolls 2018).

Methods

Participants

There were 282 patients with a diagnosis of unipolar major depressive disorder, and 254 controls. The data available for this study were from Xinan (First Affiliated Hospital of Chongqing Medical School in Chongqing, China). 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 major depressive disorder. 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). 125 of the patients were not receiving medication at the time of the neuroimaging.

Image Acquisition and Preprocessing

Data for resting state functional connectivity analysis were collected in 3T 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 anterior cingulate cortex region of interest as defined in the AAL2 atlas (Rolls *et al.* 2015) had 822 voxels. The region is illustrated in Fig. 5, and almost all of it is within the anterior cingulate cortex 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 anterior cingulate cortex 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 functional connectivity, 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 functional connectivity links in patients with depression compared to controls. The effects of age, gender, head motion (mean framewise displacements (FD)) 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 anterior cingulate cortex had been predefined by prior hypothesis as the region of interest and had 822 voxels, and that there were 47619 $3 \times 3 \times 3 \ mm$ voxels in the whole automated anatomical labelling atlas (AAL2) brain (Rolls *et al.* 2015), the number of voxel pairs in this study was approximately (822×47619), which is much smaller than the 1,133,760,771 (47619×47618/2) voxel pairs in our whole-brain study (Cheng *et al.* 2016). This enabled more differences in voxel-level functional connectivity of the anterior cingulate cortex 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 functional connectivity analysis (Gong *et al.* 2018) was used to

identify significant functional connectivity 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 ($p<1.0\times10^{-4}$ in this study), and then evaluates whether the clusters formed by spatially connected FCs are 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 $p=1.0\times10^{-4}$ as the cluster-defining threshold because in our original study (Gong *et al.* 2018), we showed that z=4.5, corresponding to $p=3.4\times10^{-6}$, can be used as a valid threshold for whole-brain analysis. As fewer FCs were analyzed in this study compared to the whole brain voxel-wise analysis considered by Gong et al, we can reduce the threshold in proportion to the number of functional connectivities 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 functional connectivities analyzed between the whole-brain study and the present study ($1.0 \times 10^{-4} \approx 3.4 \times 10^{-6} \times \frac{47619\times47618/2}{47619\times822}$). 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 atlas (Rolls *et al.* 2015) was used to provide names for brain areas in which voxels were found, and to define the anterior cingulate cortex region investigated here. The definition in this atlas of the anterior cingulate cortex is shown by the regions with orange color in Fig. 1A and Fig. 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 anterior cingulate cortex', 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 functional connectivity (FC) between patients and controls were correlated with clinical variables (the Hamilton depression rating Scale (HAMD) (Hamilton 1960), Beck Depression Inventory (BDI) (Beck and Beamesderfer 1974), and illness duration (Bell-McGinty et al. 2002; de Diego-Adelino et al. 2014)). Specifically, the functional connectivity of the voxels with significant differences of functional connectivity (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 regions of interest (ROI) 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 anterior cingulate cortex. Finally, a permutation test with 1,000 randomizations of the patient labels was used to assess the statistical significance of the mean correlation.

Parcellation of the anterior cingulate cortex

To enable a more detailed comparison between patients and controls, we performed a voxel-level parcellation of the anterior cingulate cortex based on the functional connectivity of anterior cingulate voxels with all AAL2 brain regions (Rolls *et al.* 2015) in healthy controls. Specifically, for each voxel in the anterior cingulate cortex, we first calculated the functional connectivity 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 *i*th voxel of the anterior cingulate cortex with the *j*th AAL2 region. Then a parcellation was performed using k-means clustering based on the connectivity matrix (in line with previous parcellation studies (Genon et al. 2017a; Genon et al. 2017b)). 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 functional connectivity of the anterior cingulate cortex in a large group of 282 patients with depression compared to 254 controls (Figs 1 and 2 and Tables 1 and 2). 125 of these patients were not receiving medication. In this mixed group of unmedicated and medicated patients some functional connectivities were significantly higher than in controls, and some were significantly lower. Then to investigate possible subdivisions of the anterior cingulate cortex based on its functional connectivity, of interest in understanding its function is health and disease, a parcellation was performed in 254 healthy controls based on the functional connectivity of anterior cingulate cortex voxels (Figures 3-5A and 5B). Then functional connectivity differences of the two subdivisions of the anterior cingulate cortex in the whole depressed group of 284 patients with depression from controls was performed to test whether the two subdivisions had differences in their functional connectivity in depression (Fig. 5C). Then to tease out the differences of functional connectivity related to depression vs to the effects of medication, the functional connectivity of the anterior cingulate cortex was analyzed in 125 patients that were unmedicated vs the 254 controls. Interestingly, most of the significantly different functional connectivities were higher in the unmedicated patients than in controls (Figs. 6 and S2 and Table S3). These results are important for understanding the functional connectivity 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 functional connectivities that were higher in the unmedicated patients (Fig. S1). This finding helps to advance understanding of the neural effects of the medication used to treat depression.

A hypothesis-based voxel-level functional connectivity 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 functional connectivity (FC) in patients with depression compared to controls. In most cases, a reduction in functional connectivity was found in the whole group of 284 people with depression.

The largest clusters of voxels with altered (mainly reduced) functional connectivity with the anterior cingulate cortex 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 functional connectivity with anterior cingulate cortex voxels with $p < 0.05$ cluster-wise corrected.) Additional areas with voxels with different functional connectivity with the anterior cingulate cortex 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 functional connectivity links of anterior cingulate cortex voxels that were different in patients with depression.

To investigate the brain areas between which there was different functional connectivity in the whole group of 284 people with depression, and whether it was increased or decreased, the functional connectivity (FC) of the anterior cingulate cortex 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 Table S2.) The functional connectivity differences are shown in Fig. 2 at the voxel level, with the voxels shown arranged by the AAL2 areas in which they are found. Fig. 2 shows that the anterior cingulate cortex voxels with altered functional connectivity with other brain areas tend to be in different parts of the anterior cingulate cortex. This voxel-level analysis could of course not be shown by an anterior cingulate cortex whole region seed-based analysis.

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

Second, some anterior cingulate cortex voxels, mainly supracallosal, had reduced functional connectivity in depression with the hippocampus which is implicated in memory (Figs. 1 and 2 and Table 1).

Third, increased functional connectivity 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 anterior cingulate cortex voxels had increased functional connectivity with the inferior frontal gyrus (opercular and triangular parts – see Fig. 2) in depression.

Fifth, voxels in the pregenual had reduced functional connectivity in depression the posterior cingulate cortex which is involved in autobiographical memory (Cheng et al. 2018a; Rolls and Wirth 2018) (Figs. 1 and 2 and Table1).

Sixth, some voxels in the anterior cingulate cortex had reduced functional connectivity 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 functional connectivity with the anterior cingulate cortex in depression (Fig. 2 and Table 1). This reduced functional connectivity also extended posteriorly into earlier visual areas including the occipital cortex and lingual gyrus.

Clinical symptom correlates of the reduced anterior cingulate gyrus functional connectivities in depression.

As can be seen from Table 2, there were significant correlations ($P < 0.05$ uncorrected) between some of the region of interest-wise functional connectivity links involving the anterior cingulate cortex, and the symptom severity scores and illness duration in the whole group of 284 people with depression. Specifically, the BDI score was correlated with weakened connectivity between the anterior cingulate cortex and the hippocampus. Further, we found that the illness duration (Table 2) was negatively correlated with functional connectivity between the anterior cingulate cortex and the angular gyrus (BA39), temporal cortical areas, and posterior cingulate cortex. These correlations provide additional evidence closely relating the differences in functional connectivity of the anterior cingulate cortex to the depression.

Anterior cingulate cortex voxel-level functional connectivity in healthy participants, using parcellation

To enable a more detailed comparison between patients and controls, we performed a voxel level parcellation of the anterior cingulate cortex based on the functional connectivity of ACC voxels with voxels in all other brain regions in healthy controls (Figs. 3, 4 and 5A,B) using k-means, so that we could then compare the functional connectivity differences of each subregion in patients. The two subdivisions found on the left and right are shown in Fig. 5A and B. Subdivision 1 is pregenual and subgenual anterior cingulate cortex (green in Fig. 5). Subdivision 2 is supracallosal anterior cingulate cortex (red in Fig. 5). This parcellation is based on the connectivity of each voxel in the anterior cingulate cortex with the 94 areas in the AAL2 atlas. Similar parcellation was found if the functional connectivity 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.

Figs. 3-5 show the different patterns of functional connectivity 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 functional connectivity with the lateral orbitofrontal cortex area Frontal_Inf_Orb (see Fig. 3 Y=20 to Y=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 functional connectivities for different anterior cingulate cortex subregions in depression

Fig. 5C shows the functional connectivities that are different in depression (whole depressed group - healthy controls) for the 2 subdivisions (combined over left and right, as they were similar). (A negative value for t in Fig. 5C thus represents a weaker functional connectivity in patients with depression.)

The pregenual / subcallosal cingulate cortex (subdivision 1 in Fig. 5A, B, colored green) is distinguished in depression by especially strong functional connectivity 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 functional connectivity are made below based on the functional connectivity in unmedicated patients shown in Fig. S2.

The supracallosal subdivision (2, colored red) has relatively increased functional connectivity in depression with the postcentral 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.

Functional connectivity in unmedicated patients, and the effects of medication on the functional connectivity

Fig. 6 shows the functional connectivity in 125 individuals who were not receiving medication compared to 254 controls. Increased functional connectivities of the anterior cingulate cortex 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 functional connectivity in the unmedicated patients (Fig. 6). The effects found in the unmedicated patients are shown further and quantitatively in Table S3, and are further illustrated in Fig. S2. It is shown in Fig. S2 that medial orbitofrontal cortex areas have increased functional connectivity with a part of the anterior cingulate cortex that is just above the pregenual cingulate cortex, and extends posteriorly somewhat to include part of the supracallosal anterior cingulate cortex.

It is also shown in Fig. S2 that the lateral orbitofrontal cortex area 47/12 where it adjoins the most anterior ventral insula has increased functional connectivity with the subgenual / subcallosal anterior cingulate cortex.

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

Fig. S1 shows the contrast of 125 unmedicated patients – 157 medicated patients for functional connectivity. As the illness duration was longer in the medicated than the unmedicated patients ($t = 3.65$, $p = 3.2\times10^{-4}$), the effect of illness duration was regressed out in this analysis. Many functional connectivities of the anterior cingulate cortex were lower in the medicated group compared to 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 functional connectivity in depression compared to controls are increases in functional connectivity as shown in Fig. 6 and Table S3, and the decreases of functional connectivity in the whole group of both medicated and unmedicated patients that are illustrated in Figs. 1 and 2 and Table 2 are related to the effects of the medication. The elucidation that the differences in functional connectivity in depression consist in increases as shown in Fig. 6, Fig. 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 anterior cingulate cortex, and using very large neuroimaging datasets of patients with depression and controls, we were able to characterize the altered functional connectivity at the voxel level in depression of the anterior cingulate cortex with other brain regions. The new method that we used enabled identification of which voxels in the anterior cingulate cortex had different functional connectivity with particular brain areas in depression.

In the whole population which included medicated and unmedicated patients, higher functional connectivity (relative t controls) of the anterior cingulate cortex 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 functional connectivity was found with the angular gyrus, inferior and middle temporal gyri, hippocampus, and posterior cingulate cortex / precuneus (Figs. 1 and 2 and Table 1).

However, in unmedicated patients, increased functional connectivities of the anterior cingulate cortex 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 (Figs. 6 and S2 and Table S3). Further, there were few decreases in functional connectivity in the unmedicated patients (Fig. 6). It is an important feature of this investigation that functional connectivity could be measured in a substantial cohort (125) of unmedicated patients, and this helps to show which differences in functional connectivity are associated with depression per se, rather than the effects of medication.

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

A highlight of the investigation is that we were able to parcellate the anterior cingulate cortex into two parts, and show their functional connectivity with other brain regions including the orbitofrontal cortex. Subdivision 1 is pregenual and subgenual (subcallosal) anterior cingulate cortex (green in Fig. 5). Subdivision 2 is supracallosal anterior cingulate cortex (red in Fig. 5). The functional connectivities of these subdivisions are shown in Figs. 4 and 5. Of great interest in Fig. 5 is that pregenual / subcallosal medial orbitofrontal cortex areas has relatively high functional connectivity 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, 2018). In contrast, the supracallosal anterior cingulate cortex has relatively high functional connectivity 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; Deng et al. 2017; Rolls 2017a, 2018). This provides evidence to elucidate further the hypothesis that the orbitofrontal cortex sends reward and non-reward information to the anterior cingulate cortex 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, 2018). The supracallosal anterior cingulate cortex has relatively high functional connectivity also with parts of the inferior frontal gyrus illustrated in Fig. 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 divisions in this part of the anterior cingulate cortex were also found (de la Vega et al. 2016).

We were then able to measure differences in the functional connectivity of these subdivisions in depression (Fig. 5C and 2). The pregenual / subcallosal cingulate cortex is distinguished in depression by especially strong functional connectivity 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 Fig. S2 revealed the following. It is also shown in Fig. S2 that the subgenual / subcallosal anterior cingulate cortex has increased functional connectivity 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, 2018), and projects to the subcallosal anterior cingulate cortex (Vogt 2009), in which neurons that respond to unpleasant stimuli have been found in humans (Laxton *et al.* 2013). This increased functional connectivity 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 behavioural 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 PET 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 et al. 2018b).

It is also shown in Fig. S2 that an area more superiorly at the superior margin of the inferior frontal gyrus pars triangularis and pars opercularis has increased functional connectivity 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 functional connectivity of the anterior cingulate cortex with the (right) angular gyrus (Fig. 6, Y=74), contralateral to a cortical area related to language (Cheng *et al.* 2016).

Fig. 5C shows that the supracallosal division (2) of the anterior cingulate cortex (which is activated by punishers and non-reward (Grabenhorst and Rolls 2011; Rolls 2017a, 2018) has increased functional connectivity with for example some movement-related areas such as the post-central gyrus and superior parietal lobule. Further, it is shown in 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, 2018), have increased functional connectivity with a part of the anterior cingulate cortex that is just above the pregenual cingulate cortex, and extends posteriorly somewhat to include part of the supracallosal anterior cingulate cortex, a part of the anterior cingulate cortex that is activated by punishing stimuli and by non-reward (Grabenhorst and Rolls 2011; Rolls 2017a, 2018). A possible implication for understanding depression is that even pleasant, rewarding, stimuli from the medial orbitofrontal cortex are routed to wards output to a part of the anterior cingulate cortex 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 anterior cingulate cortex with the lateral orbitofrontal cortex / inferior prefrontal convexity areas.

A strength of this investigation is that we analyzed functional connectivity at the level of voxel to voxel functional connectivity. It was this that enabled us to perform a parcellation of the anterior cingulate cortex, and to examine which voxels in the anterior cingulate cortex were connected differently to which voxels in all other brain areas, as shown for example in Fig. 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 (Figs 6 and 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 functional connectivity of patients with depression back down towards the level in healthy controls (Fig. S1). The fact that the functional connectivity 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.

Contributors

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.

Declaration of interests.

All authors declare no competing interests.

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Table 1. Numbers of voxels in different AAL2 areas with significantly different functional connectivity with the anterior cingulate cortex (ACC) in patients with depression. For ACC, the table shows the number of ACC voxels that have different functional connectivity with the whole brain. The other entries in the table show the numbers of voxels in each of the specified brain regions with different functional connectivity 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 functional connectivity links relating to the voxels ($p<0.05$, corrected). The negative value means the FCs are decreased in depression patients, and vice versa.

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

Functional connectivity		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

Figure legends

Figure 1. A) Voxels of the anterior cingulate cortex defined by the AAL2 atlas. B, C) Anatomical location of voxels with significantly increased (B) and decreased (C) functional connectivity with the anterior cingulate cortex in depression in depressed patients vs healthy controls obtained from the voxel-based Association Study (vAS). Voxels with functional connectivity differences with the anterior cingulate cortex in patients with depression are shown. The color bar represents the number of significantly different functional connectivity links relating to each voxel after cluster-wise correction ($p<0.05$). Blue indicates voxels with predominantly decreased functional connectivity in depressed patients, and red/yellow indicates voxels with predominantly increased functional connectivity 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.

Figure 2. The voxel-level functional connectivity for anterior cingulate voxels that are significantly different in the depressed and the control group, separated by the AAL2 region (Rolls *et al.* 2015) in which the significant voxels were located. Conventions as in Fig. 1. Blue indicates voxels with predominantly decreased functional connectivity, and red/yellow indicates voxels with predominantly increased functional connectivity. 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).

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

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

Figure 5. A. Voxel-level parcellation of the left Anterior Cingulate Cortex (ACC) based on its functional connectivity in healthy controls with other brain areas. Subdivision 1 is pregenual and subgenual anterior cingulate cortex. Subdivision 2 is supracallosal anterior cingulate cortex. 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 2 ACC subdivisions had different functional connectivity with these orbitofrontal cortex areas. **B.** Voxel-level parcellation of the right Anterior Cingulate Cortex (ACC) based on its functional connectivity in healthy controls with other brain areas. Subdivision 1 is pregenual and subgenual anterior cingulate cortex. Subdivision 2 is supracallosal anterior cingulate cortex. 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 functional connectivity (healthy controls – patients with depression) of the links between voxels in each subdivision and the significant ROIs showed in Table 1 for the Anterior Cingulate Cortex. The t value shown is the mean t value between all voxels (not just the significant voxels) in each sub-region and each ROI. The full names of the abbreviations of ROIs are shown in Table S2.

Figure 6. Anatomical location of voxels with significantly different functional connectivity with the anterior cingulate cortex in unmedicated depression obtained from the voxel-based

Association Study (vAS). Voxels with functional connectivity differences with the anterior cingulate cortex in 125 unmedicated patients with depression are shown, compared to 254 controls. The color bar represents the number of significantly different functional connectivity links relating to each voxel after cluster wise correction ($p<0.05$). A. Higher functional connectivity in depression. B. Lower functional connectivity in depression. The MNI Y values are shown.

References

Barnes J, Ridgway GR, Bartlett J, Henley SM, Lehmann M, Hobbs N, Clarkson MJ, MacManus DG, Ourselin S, Fox NC. 2010. Head size, age and gender adjustment in MRI studies: a necessary nuisance? Neuroimage 53:1244-1255.

Beck AT, Beamesderfer A. 1974. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 7:151-169.

Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds CF, 3rd, Becker JT. 2002. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am J Psychiatry 159:1424-1427.

Bora E, Fornito A, Pantelis C, Yucel M. 2012. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J Affect Disord 138:9-18.

Cheng W, Rolls ET, Qiu J, Liu W, Tang Y, Huang CC, Wang X, Zhang J, Lin W, Zheng L, Pu J, Tsai SJ, Yang AC, Lin CP, Wang F, Xie P, Feng J. 2016. Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. Brain 139:3296-3309.

Cheng W, Rolls ET, Qiu J, Xie X, Wei D, Huang C-C, Yang AC, Tsai S-J, Li Q, Meng J, Lin CP, Xie P, Feng J. 2018a. Increased functional connectivity of the posterior cingulate cortex with the lateral orbitofrontal cortex in depression. Translational Psychiatry 8:90.

Cheng W, Rolls ET, Ruan H, Feng J. 2018b. Functional connectivities in the brain that mediate the association between depressive problems and sleep quality. JAMA Psychiatry:doi: 10.1001/jamapsychiatry.2018.1941.

Connolly CG, Wu J, Ho TC, Hoeft F, Wolkowitz O, Eisendrath S, Frank G, Hendren R, Max JE, Paulus MP, Tapert SF, Banerjee D, Simmons AN, Yang TT. 2013. Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. Biol Psychiatry 74:898-907.

Critchley HD, Nagai Y, Gray MA, Mathias CJ. 2011. Dissecting axes of autonomic control in humans: Insights from neuroimaging. Auton Neurosci 161:34-42.

de Diego-Adelino J, Pires P, Gomez-Anson B, Serra-Blasco M, Vives-Gilabert Y, Puigdemont D, Martin-Blanco A, Alvarez E, Perez V, Portella MJ. 2014. Microstructural white-matter abnormalities associated with treatment resistance, severity and duration of illness in major depression. Psychol Med 44:1171-1182.

de la Vega A, Chang LJ, Banich MT, Wager TD, Yarkoni T. 2016. Large-Scale Meta-Analysis of Human Medial Frontal Cortex Reveals Tripartite Functional Organization. J Neurosci 36:6553-6562.

Deco G, Kringelbach ML. 2014. Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron 84:892-905.

Deng WL, Rolls ET, Ji X, Robbins TW, Banaschewski T, Bokde ALW, Bromberg U, Buechel C, Desrivieres S, Conrod P, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Ittermann B, Martinot J-L, Lemaitre H, Nees F, Papadoulos Orfanos D, Poustka L, Smolka MN, Walter H, Whelan R, Schumann G, Feng J. 2017. Separate neural systems for behavioral change and for emotional responses to failure during behavioral inhibition. Hum Brain Mapp 38:3527-3537.

Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, Anderson JS, Assaf M, Bookheimer

SY, Dapretto M, Deen B, Delmonte S, Dinstein I, Ertl-Wagner B, Fair DA, Gallagher L, Kennedy DP, Keown CL, Keysers C, Lainhart JE, Lord C, Luna B, Menon V, Minshew NJ, Monk CS, Mueller S, Muller RA, Nebel MB, Nigg JT, O'Hearn K, Pelphrey KA, Peltier SJ, Rudie JD, Sunaert S, Thioux M, Tyszka JM, Uddin LQ, Verhoeven JS, Wenderoth N, Wiggins JL, Mostofsky SH, Milham MP. 2014. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 19:659-667.

Dougherty DD, Weiss AP, Cosgrove GR, Alpert NM, Cassem EH, Nierenberg AA, Price BH, Mayberg HS, Fischman AJ, Rauch SL. 2003. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. J Neurosurg 99:1010-1017.

Drevets WC, Price JL, Simpson JRJ, Todd RD, Reich T, Vannier M, Raichle ME. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386:824-827.

Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, Schatzberg AF, Sudheimer K, Keller J, Mayberg HS, Gunning FM, Alexopoulos GS, Fox MD, Pascual-Leone A, Voss HU, Casey BJ, Dubin MJ, Liston C. 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 23:28-38.

Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, Kinkead B, Nemeroff CB, Mayberg HS. 2017. Functional Connectivity of the Subcallosal Cingulate Cortex And Differential Outcomes to Treatment With Cognitive-Behavioral Therapy or Antidepressant Medication for Major Depressive Disorder. Am J Psychiatry 174:533-545.

Gabbott PL, Rolls ET. 2013. Increased neuronal firing in resting and sleep in areas of the macaque medial prefrontal cortex (mPFC) that are part of the default mode network. Eur J Neurosci 37:1737-1746.

Gabbott PL, Warner TA, Jays PR, Bacon SJ. 2003. Areal and synaptic interconnectivity of prelimbic (area 32), infralimbic (area 25) and insular cortices in the rat. Brain Res 993:59-71.

Genon S, Li H, Fan L, Muller VI, Cieslik EC, Hoffstaedter F, Reid AT, Langner R, Grefkes C, Fox PT, Moebus S, Caspers S, Amunts K, Jiang T, Eickhoff SB. 2017a. The Right Dorsal Premotor Mosaic: Organization, Functions, and Connectivity. Cereb Cortex 27:2095-2110.

Genon S, Reid A, Li H, Fan L, Muller VI, Cieslik EC, Hoffstaedter F, Langner R, Grefkes C, Laird AR, Fox PT, Jiang T, Amunts K, Eickhoff SB. 2017b. The heterogeneity of the left dorsal premotor cortex evidenced by multimodal connectivity-based parcellation and functional characterization. Neuroimage.

Gong W, Wan L, Lu W, Ma L, Cheng F, Cheng W, Grunewald S, Feng J. 2018. Statistical testing and power analysis for brain-wide association study. Med Image Anal 47:15-30.

Grabenhorst F, Rolls ET. 2011. Value, pleasure, and choice in the ventral prefrontal cortex. Trends Cogn Sci 15:56-67.

Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, Reiss AL, Schatzberg AF. 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 62:429-437.

Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. 2011. The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry 69:301-308.

Hamilton M. 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56-62.

Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E, Lozano AM, Mayberg HS. 2008. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex 18:1374-1383.

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. 2015. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry 72:603-611.
Kang J, Bowman FD, Mayberg H, Liu H. 2016. A depression network of functionally connected regions discovered via multi-attribute canonical correlation graphs. Neuroimage 141:431-441.
Konarski JZ, Kennedy SH, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, Mayberg HS. 2009. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. J Psychiatry Neurosci 34:175-180.
Kumar V, Croxson PL, Simonyan K. 2016. Structural Organization of the Laryngeal Motor Cortical Network and Its Implication for Evolution of Speech Production. J Neurosci 36:4170-4181.
Laxton AW, Neimat JS, Davis KD, Womelsdorf T, Hutchison WD, Dostrovsky JO, Hamani C, Mayberg HS, Lozano AM. 2013. Neuronal coding of implicit emotion categories in the subcallosal cortex in patients with depression. Biol Psychiatry 74:714-719.
Lichenstein SD, Verstynen T, Forbes EE. 2016. Adolescent brain development and depression: A case for the importance of connectivity of the anterior cingulate cortex. Neurosci Biobehav Rev 70:271-287.
Lujan JL, Chaturvedi A, Choi KS, Holtzheimer PE, Gross RE, Mayberg HS, McIntyre CC. 2013. Tractography-activation models applied to subcallosal cingulate deep brain stimulation. Brain Stimul 6:737-739.
Mayberg HS. 2003. Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging Clin N Am 13:805-815.
Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 156:675-682.
Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45:651-660.
Mayberg HS, Riva-Posse P, Crowell AL. 2016. Deep Brain Stimulation for Depression: Keeping an Eye on a Moving Target. JAMA Psychiatry 73:439-440.
McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, Craddock RC, Mayberg HS. 2013. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry 70:821-829.
McInerney SJ, McNeely HE, Geraci J, Giacobbe P, Rizvi SJ, Ceniti AK, Cyriac A, Mayberg HS, Lozano AM, Kennedy SH. 2017. Neurocognitive Predictors of Response in Treatment Resistant Depression to Subcallosal Cingulate Gyrus Deep Brain Stimulation. Front Hum Neurosci 11:74.
Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. 2015. Resting-state functional connectivity in major depressive disorder: A review. Neurosci Biobehav Rev 56:330-344.
Price JL, Drevets WC. 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology 35:192-216.
Price JL, Drevets WC. 2012. Neural circuits underlying the pathophysiology of mood disorders. Trends Cogn Sci 16:61-71.
Ramirez-Mahaluf JP, Roxin A, Mayberg HS, Compte A. 2017. A Computational Model of Major Depression: the Role of Glutamate Dysfunction on Cingulo-Frontal Network Dynamics. Cereb Cortex 27:660-679.
Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK, McIntyre CC, Gross

RE, Mayberg HS. 2018. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry 23:843-849.
Rolls ET. 2009. The anterior and midcingulate cortices and reward. In: Vogt BA, editor. Cingulate Neurobiology and Disease Oxford: Oxford University Press p 191-206.
Rolls ET. 2012. Invariant visual object and face recognition: neural and computational bases, and a model, VisNet. Front Comput Neurosci 6, 35:1-70.
Rolls ET. 2014. Emotion and Decision-Making Explained. Oxford: Oxford University Press.
Rolls ET. 2016a. Cerebral Cortex: Principles of Operation. Oxford: Oxford University Press.
Rolls ET. 2016b. A non-reward attractor theory of depression. Neurosci Biobehav Rev 68:47-58.
Rolls ET. 2017a. The orbitofrontal cortex and emotion in health and disease, including depression. Neuropsychologia doi: 10.1016/j.neuropsychologia.2017.1009.1021.
Rolls ET. 2017b. The roles of the orbitofrontal cortex via the habenula in non-reward and depression, and in the responses of serotonin and dopamine neurons. Neurosci Biobehav Rev 75:331-334.
Rolls ET. 2018. The Brain, Emotion, and Depression. Oxford: Oxford University Press.
Rolls ET, Inoue K, Browning AS. 2003. Activity of primate subgenual cingulate cortex neurons is related to sleep. J Neurophysiol 90:134-142.
Rolls ET, Joliot M, Tzourio-Mazoyer N. 2015. Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. Neuroimage 122:1-5.
Rolls ET, Wirth S. 2018. Spatial representations in the primate hippocampus, and their functions in memory and navigation. Prog Neurobiol:in press.
Rushworth MF, Kolling N, Sallet J, Mars RB. 2012. Valuation and decision-making in frontal cortex: one or many serial or parallel systems? Curr Opin Neurobiol 22:946-955.
Samara Z, Evers EAT, Goulas A, Uylings HBM, Rajkowska G, Ramaekers JG, Stiers P. 2017. Human orbital and anterior medial prefrontal cortex: Intrinsic connectivity parcellation and functional organization. Brain Struct Funct 222:2941-2960.
Vogt BA editor. 2009. Cingulate Neurobiology and Disease. City: Oxford University Press.