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The Subgenual Anterior Cingulate Cortex in Mood Disorders

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Abstract

INTRODUCTION—In the latest edition of our series of neuroanatomical areas of importance for neuropsychiatry, Wayne Drevets, MD, and Jonathan Savitz, PhD, have outlined the clinical importance of the ventral anterior cingulate structures for the regulation of mood. This area was an early target for interventional neurosurgery for depression some half a century ago, and today has become one of the key sites of deep brain stimulation for affective disorders. The anterior cingulate cortex was a part of the initial circuit of Papez thought to be related to the regulation of emotion. However, since then, much experimental work has outlined different cingulate regions with differing anatomical connectivity and functions. Drevets and Savitz draw attention to the subgenual area and describe the local and distant anatomical connectivities that emphasize its relevance for several neuropsychiatric disorders.

ABSTRACT—The anterior cingulate cortex (ACC) ventral to the genu of the corpus callosum has been implicated in the modulation of emotional behavior on the basis of neuroimaging studies in humans and lesion analyses in experimental animals. In a combined positron emission tomography/magnetic resonance imaging study of mood disorders, we demonstrated that the mean gray matter volume of this "subgenual" ACC (sgACC) cortex is abnormally reduced in subjects with major depressive disorder (MDD) and bipolar disorder, irrespective of mood state. Neuropathological assessments of sgACC tissue acquired postmortem from subjects with MDD or bipolar disorder confirmed the decrement in gray matter volume, and revealed that this abnormality was associated with a reduction in glia, with no equivalent loss of neurons. In positron emission tomography studies, the metabolic activity was elevated in this region in the depressed relative to the remitted phases of the same MDD subjects, and effective antidepressant treatment was associated with a reduction in sgACC activity. Other laboratories replicated and extended these findings, and the clinical importance of this treatment effect was underscored by a study showing that deep brain stimulation of the sgACC ameliorates depressive symptoms in treatment-resistant MDD. This article discusses the functional significance of these findings within the context of the preclinical literature that implicates the putative homologue of this region in the regulation of emotional behavior and stress response. In experimental animals, this region participates in an extended "visceromotor network" of structures that modulates autonomic/neuroendocrine responses and neurotransmitter transmission during the neural processing of reward, fear, and stress. These data thus hold important implications

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for the development of neural models of depression that can account for the abnormal motivational, neuroendocrine, autonomic, and emotional manifestations evident in human mood disorders.

INTRODUCTION

The ventral anterior cingulate cortex (ACC) increasingly has been implicated in the modulation of emotional behavior on the basis of neuroimaging studies in humans and lesion analyses in experimental animals. In a neuroimaging study of mood disorders,[1] it was discovered that this region's gray matter volume was abnormally reduced in familial bipolar disorder and major depressive disorder (MDD). The magnetic resonance imaging- (MRI) based morphometric measures acquired to demonstrate this abnormality were guided by positron emission tomography (PET) images showing an abnormal reduction of cerebral blood flow (CBF) and glucose metabolism in the prefrontal cortex (PFC) ventral to the corpus callosum genu (ie, "subgenual") in depression (Figure 1).[1] Voxel-by-voxel analyses of neurophysiological data from independent depressed samples versus controls localized the peak difference in activity more specifically to the subgenual ACC (sgACC). Because antidepressant treatment did not reverse these physiological abnormalities, MRI measures of gray matter volume of the sgACC were obtained to determine whether the decrements in regional CBF and metabolism might be accounted for by a corresponding reduction in cortex.[2] This hypothesis was confirmed, as the mean gray matter volume of the left sgACC was reduced in bipolar disorder and MDD compared with healthy control samples.[1]

In pursuing the nature of these neuroimaging abnormalities, Ongür and colleagues[3] undertook postmortem assessments of brain tissue taken from the sgACC of subjects diagnosed as having bipolar disorder, MDD, schizophrenia, or no psychiatric disorder. The sgACC implicated by the neuroimaging data consisted of Brodmann area (BA) 24b and, to a lesser extent, BA 24a anteriorly, and area 25 posteriorly (Figure 2).4 Although the PET data showed that the posterior and anterior sgACC were affected, the peak difference between groups localized to the anterior sgACC. Thus, initial histopathological assessments targeted the section of BA 24 located ventral and posterior to the corpus callosum genu (Figure 3). These assessments confirmed the reduction in mean sgACC gray matter volume in bipolar disorder and MDD versus healthy controls, and associated this deficit with a reduction in glia and no equivalent loss of neurons.[3] The neuronal density appeared increased, as would be expected in association with a reduction in neuropil (moss-like layer of gray matter containing axons and dendrites that occupies most of the cortex volume).

SPECIFICITY OF STRUCTURAL NEUROIMAGING ABNORMALITIES IN THE SUBGENUAL ANTERIOR CINGULATE CORTEX

Other studies have shown that this volumetric reduction existed early in the illness course of MDD and bipolar disorder[5,6] and was also evident in young adults at high familial risk for MDD[7,8] Furthermore, this abnormality persisted during antidepressant treatment and was present in the manic and depressed phases of bipolar disorder.[1] The volumetric deficit applied to males[8,9] and females,[5] to psychotic unipolar and bipolar depression,[6,10,11] and to bipolar-spectrum illness.[12]

The variability of the volumetric measures of gray matter volume in the sgACC across subjects was high, the ranges of values in ill and normative groups overlapped substantially, and not all studies replicated these findings (Tables 1–4). Such variability is typical of neurobiological data acquired from mood disordered samples, partly because MDD and bipolar disorder appear heterogenous with respect to etiology, and studies generally find that subsets, rather than entire samples, of subjects meeting criteria for these disorders manifest biological markers for affective disease. For example, elderly MDD subjects with late-onset depression show an

increased prevalence of neuroimaging correlates of cerebrovascular disease, including nonspecific signs of atrophy, but did not show evidence of focal reductions.[7] Research by Drevets and colleagues[13] limited the sample selection to early-onset MDD and bipolar disorder cases, who have shown volumetric abnormalities that are localized more specifically to some PFC and temporal lobe structures.

In unipolar depressives, to further enhance the sensitivity for identifying neurobiological markers for affective illness, Drevets and colleagues[1] initially selected cases according to criteria for "familial pure depressive disease," a condition defined by having an MDD subject with a first-degree relative with MDD, but no first-degree relative with mania, alcoholism, or sociopathy.[21] In contrast to MDD samples with familial pure depressive disease or familial bipolar disorder, subjects who met criteria for depression spectrum disease (MDD subjects who have a first-degree relative with alcoholism or sociopathy[21] did not differ significantly from healthy controls with respect to the mean sgACC glucose metabolism[29] or volume) (J. Savitz, PhD, et al, unpublished data, 2008).

Drevets and colleagues[1] also enhanced the likelihood of identifying biological markers in bipolar disorder by selecting subjects who had first-degree relatives with bipolar disorder. The extent to which the neuroimaging abnormalities in the sgACC also extend to non-familial cases, thus, remained unclear. An MRI study from an independent laboratory[6] found that the mean sgACC gray matter volume (defined using the same anatomical landmarks we used) was reduced significantly versus controls in bipolar disorder subjects with mood disordered first-degree relatives, but not in bipolar disorder subjects without mood disordered first-degree relatives. Consistent with these data, McDonald and colleagues[42] showed that reduced volume of a right "perigenual" ACC region that included both the sgACC and the ACC situated anterior to the corpus callosum genu (ie, "pregenual"; pgACC) was associated with increasing genetic risk for bipolar disorder (based upon the numbers of affected relatives). Boes and colleagues[8] found that the left pgACC (sgACC plus pgACC) volume was smaller in boys with sub-clinical depressive symptoms, and that the negative correlation between left sgACC volume and depression symptoms was particularly robust in boys with a family history of depression.

In more recent research, morphometric MRI studies[4] divided this region into anterior and posterior sgACC regions, which corresponded approximately to BAs 24 and 25, respectively (Figure 2). The posterior sgACC appears homologous with the infralimbic cortex (BA 25) of the rodent and monkey on the basis of cytoarchitectonic and connectional features.[4] The posterior sgACC volume was reduced in MDD cases with psychotic features, but not in a psychiatric control group with schizophrenia.[10] Only the MDD group showed an increase in posterior sgACC gray matter after a 2-year follow-up period (of naturalistic treatment). For the MDD subjects, but not for the subjects with schizophrenia, the Global Assessment Scale scores during follow-up correlated positively with cortical depth at baseline and with volume increases during follow-up. Thus, the volumetric abnormalities in this region may predict and reflect the course of depressive illness.

The finding that the posterior sgACC volume may increase in association with prolonged clinical improvement is noteworthy based upon cross-sectional studies (Neumeister et al, unpublished data, 2008) of MDD cases studied during long-term remission. Despite the finding that the sgACC volume deficit in MDD showed no significant change during antidepressant treatment for a mean of 4 months,[36] subjects with a history of MDD who were selected for their capacity to remain in remission while unmedicated for at least 3 months (and a mean of several years) showed sgACC volumes that were significantly higher than those of controls. These cross-sectional data did not allow determination of whether such subjects had manifested reduced sgACC volume during depression that then had increased during prolonged remission,

or whether these subjects were instead resilient to the pathophysiologcal process that led to the reduction in sgACC volume during MDD. Longitudinal studies are needed to elucidate this issue, but the possibility that such individuals possess (a) resilience factor(s) that allows them to recover from major depressive episodes without the development of chronic illness would hold great potential clinical importance in mood disorders research.

However, chronic lithium treatment, which exerts robust neurotrophic effects in animal models, has been associated with increasing gray matter volume toward normal in treatment responders in the sgACC and other PFC areas (Figure 3).[50]

Partly compatible with these data, Bearden and colleagues[47] reported that the volumes of the left ACC, including of the sgACC, were greater in lithium-treated bipolar disorder subjects than both healthy controls and bipolar disorder subjects not receiving lithium. In magnetic resonance spectroscopy studies of bipolar disorder, chronic lithium treatment also was associated with increased concentrations of *N*-acetyl-aspartate (NAA), a marker of neuronal integrity.[52]

ANATOMICAL SPECIFICITY OF SUBGENUAL ANTERIOR CINGULATE CORTEX ABNORMALITIES

Most neuroimaging studies have not identified significant differences between mood disordered and healthy control groups in the volumes of the whole brain, although several groups have reported gray matter loss in other portions of anterior or posterior cingulate cortex.[62] In the ACC, abnormalities in CBF/metabolism, tissue volume, and glial cells have been demonstrated in the ACC situated anterior to the corpus callosum genu (ie, pgACC}. This region includes portions of BAs 24 and 32, an area that also forms an integral part of the ventral "emotion" circuit implicated in affective illness.[63]

The sgACC shares similarities with the pgACC area situated immediately adjacent to the sgACC, such that distinctions of the cortex at the actual sgACC/pgACC interface seem arbitrary. The anterior sgACC and the adjacent ventral pgACC both are cytoarchitectonically BA 24 (Figure 4), and they share similar anatomical connectivity.[4] Moreover, the abnormal reductions of glia in MDD extend to the pgACC (BA 24)[64] as well as to the orbitofrontal and dorsal anterolateral PFC (BA 9)[65–67] and the amygdala.[68,69] Hence, the term "perigenual" ACC is often applied to the ACC near the genu, and for comparison we listed findings in the pgACC together with those in the adjacent sgACC in Tables 1–4.

NEUROPHYSIOLOGICAL IMAGING STUDIES OF SUBGENUAL ANTERIOR CINGULATE CORTEX ACTIVITY

Nevertheless, the functions of the anterior sgACC and more dorsal regions of the pgACC appear distinct with respect to some neuroimaging studies of emotional behavior. The tissue near the sgACC/pgACC junction shows increased hemodynamic activity during a variety of emotional-behavioral tasks, including tasks involving sadness induction[70,71]; exposure to traumatic reminders[72]; selecting sad or happy targets in an emotional go-no-go study[73]; monitoring of internal states in individuals with attachment avoidant personality styles[74]; and extinction learning to previously fear-conditioned stimuli.[75] These findings suggest in humans roles the ACC in the automatic regulation of emotional behavior. In contrast, more dorsal regions of the pgACC show physiological responses to more diverse types of emotionally valenced or autonomically arousing stimuli.[76–78] In mood disorders, the sgACC activity frequently has been shown to correlate positively with the severity of depressive symptoms,[79] whereas the pgACC activity has more consistently been linked to treatment outcome.[80]

The reduction in resting sgACC CBF and metabolism that we initially observed in depressed bipolar disorder and MDD subjects has been replicated by other studies of MDD[20,26,38] and bipolar disorder (Tables 1 and 2).[24,37–39] These findings also were extended by data showing that metabolic reductions predate the onset of clinical symptoms, as Kumano and colleagues[31] found that cancer patients who went on to develop depression had lower baseline metabolic rates of the sgACC compared with cancer controls who did not become depressed. However, other studies reported increased metabolic activity in the sgACC in primary[15,16,19,28,30,41,45,81] or secondary depression.[82]

These apparently discrepant results may be explained by the interrelationships between deficits in gray matter volume and physiological imaging data. The reduction in sgACC volume is sufficiently prominent (ranging in magnitude from 15% to 50% across positive studies [Tables 3 and 4]) to produce partial volume effects in functional brain images due to their relatively low spatial resolution. Therefore, although relative to controls, the depressed MDD and bipolar disorder subjects showed metabolic activity that appeared reduced in the sgACC,[1] when this volumetric deficit was taken into account by correcting the metabolic data for the partial volume averaging effect associated with the corresponding gray matter reduction, metabolism instead appeared increased in the sgACC in the unmedicated-depressed phase and normal in the medicated-remitted phase.[83]

Consistent with the conclusions of these partial volume corrections, researchers consistently show that the sgACC metabolism is elevated in the depressed phase relative to the remitted phase of the same MDD subjects. For example, in studies of remitted MDD subjects, the sgACC metabolism increases during depressive relapse induced during either tryptophan depletion[84] or catecholamine depletion.[85] Moreover, the sgACC metabolism decreases during effective antide-pressant treatment. For example, Drevets and colleagues,[1] Drevets and colleagues,[38] Holthoff and colleagues,[25] and Mayberg and colleagues[16] reported a remission-associated decrease in the activity of this region during antidepressant treatment, Nobler and colleagues[86] obtained analogous results after ECT administration, and Mayberg and colleagues[28] showed that CBF decreased in the sgACC and other ventromedial PFC regions during improvement associated with deep brain stimulation of the sgACC. Also consistent with these data, several studies have shown that in MDD the depression severity correlates positively with blood flow or metabolism in the sgACC[79] compatible with evidence that blood flow increases in the sgACC in healthy humans during experimentally induced sadness.[70,71]

Finally, the abnormal elevation of sgACC metabolism that Mah and colleagues[43] and others[39] observed in depressed bipolar disorder subjects were limited to cases who were medicated chronically with lithium or divalproex. Chronic lithium treatment resulted in increased gray matter volume in the sgACC (Figure 3),[3] consistent with evidence from preclinical studies[87] indicating that lithium and divalproex exert neurotrophic and neuroprotective effects in the frontal cortex of experimental animals. If the increase in sgACC tissue is sufficient to reduce the partial volume averaging effect in PET images, then metabolic activity would be imaged as being elevated in such depressed subjects versus controls (Table 5), Longitudinal imaging studies acquired both pre- and post-mood stabilizer therapy are needed to characterize relationships between volume and metabolism.

NEUROPATHOLOGICAL MEASURES: CORRELATIONS WITH RODENT MODELS OF REPEATED STRESS

Although it remains unclear whether they reflect a neurodevelopmental abnormality or an acquired effect of recurrent illness, it is noteworthy that in regions that appear homologous to areas where gray matter reductions are evident in depressed humans (ie, medial PFC, hippocampus), repeated stress results in dendritic atrophy and reductions in glial cells in

rodents.[88–92] Dendritic atrophy putatively would be reflected by a decrease the volume of the neuropil. These data suggest that impaired emotion regulation may contribute to the volumetric abnormalities found in these structures in MDD, by permitting stress responses that are exaggerated in magnitude or duration.[92] Such changes could, in turn, exacerbate the emotion dysregulation associated with bipolar disorder, as in rodents dendritic atrophy arising in the medial PFC during repeated stress resulted in impaired modulation (ie, extinction) of behavioral responses to fear-conditioned stimuli.[91] Notably, when rats were subjected to repeated stress, the dendritic atrophy could be reversed by lithium administration,[90] resembling the effects of lithium on the gray matter reductions in bipolar disorder (Figure 3).

The stress-induced dendritic remodeling process depends upon interactions between the increased *N*/-methyl-D-aspartate receptor stimulation and glucocorticoid secretion associated with repeated stress.[92] The depressive subtypes (eg, bipolar disorder, familial pure depressive disease) who show regional reductions in gray matter volume also show evidence of increased cortisol secretion during stress[94] and glutamatergic transmission (eg, elevated glucose metabolism predominantly reflects corresponding increases in glutamatergic transmission.[95] Notably, impaired sgACC function in mood disorders may conceivably contribute to cortisol hypersecretion in depression.[96] Diorio and colleagues[97] showed that glucocorticoid receptors expressed in the ventral ACC play a major role in the negative feedback effect of glucocorticoid secretion during stress, and that lesions of the prelimbic and infralimbic portions of the ACC increase the adrenocorticotropic hormone and corticosterone (CORT) responses to restraint stress. Conversely, CORT implants in these regions decreased the adrenocorticotropic hormone and CORT responses to restraint stress.

Another potential predisposition for undergoing excessive remodeling in the sgACC may be the “short” allele of the serotonin transporter promoter length polymorphism. This polymorphism was associated with reduced gray matter in the sgACC, reduced functional connectivity between the amygdala and the sgACC, and higher temperamental anxiety in otherwise healthy *s*-carriers.[97] Conceivably, this effect may prove maladaptive under severe stress, potentially underlying the increased risk the *s*-allele confers for developing depression within the context of stress.[98]

RELATIONSHIP BETWEEN STRUCTURAL ABNORMALITIES IN THE SUBGENUAL ANTERIOR CINGULATE CORTEX AND OTHER REGIONS

The sgACC shares substantial, predominantly ipsilateral anatomical connections with the amygdala and subiculum, and it is possible that the left-lateralized volumetric reductions in these structures are related. In the amygdala, left-lateralized reductions in glia have been demonstrated in MDD,[68,69] although the literature disagrees about the direction and existence of volumetric changes in mood disorders. In the hippocampus, MDD subjects showed greater decrements in volume following fixation (implying a deficit in the neuropil),[99] while, more specifically, in the hippocampal subiculum/ventral CA1 region, bipolar disorder subjects had reductions in synapses and synaptic proteins[100,101] and left-lateralized reductions in gray matter[102] compared with controls.

The sgACC also projects to the ventromedial striatum and the accumbens area,[4] which were reported to be abnormally small in a postmortem volumetric study of mood disorders,[103] and to the periventricular and mediodorsal nuclei of the thalamus that line the third ventricle wall. Although, third ventricle enlargement is consistently found in bipolar disorder, the specific tissue where volume loss resulted in ex vaccuo changes in third ventricle size has remained unclear.[7,13] Nevertheless, taken together, these data suggest that mood disorders are associated with a neuropathological process affecting circuits that involve the sgACC together with

anatomically related parts of the orbitomedial PFC, amygdala, hippocampus, striatum, and thalamus.

POTENTIAL CLINICAL CORRELATES OF SUBGENUAL PREFRONTAL CORTEX DYSFUNCTION

In monkeys and other experimental animals, the putatively homologous cortex to the sgACC shares extensive anatomical connections with the amygdala; subiculum; hypothalamus; accumbens; ventral tegmental area (VTA); substantia nigra; raphe; locus ceruleus; periaqueductal gray and brainstem autonomic nuclei; and other areas of the orbitomedial PFC.[4,76] These structures are implicated in the modulation of emotional behavior, raising the possibility that abnormal synaptic interactions between these areas and the sgACC may contribute to disturbances in emotional processing or regulation.[3]

Rats with bilateral lesions of the ACC and dorsal prelimbic cortex show exaggerated freezing behavior and heart rate increases during exposure to fear-conditioned sensory and/or contextual stimuli.[104,105] In contrast, bilateral lesions involving the infralimbic and the ventral prelimbic cortices result in reduced heart rate responses to fear-conditioned stimuli.[105] Sullivan and Gratton[106] more specifically showed that rats with lesions involving the left infralimbic, prelimbic, and anterior cingulate cortices demonstrated heightened sympathetic autonomic arousal and exaggerated CORT responses to restraint stress relative both to control animals and to animals with right-sided lesions of the same areas. In contrast, right-lesioned animals showed attenuation of the CORT rise and the autonomically mediated gastric stress pathology associated with restraint stress. From these data, Sullivan and Grattan[106] concluded that left ventromedial PFC lesions disinhibit the function of the right ventromedial PFC, which mediates the heightened sympathetic autonomic, affective, and hypothalamic-pituitary-adrenal axis arousal seen in the left-lesioned animals. In mood disorders, an altered balance between left and right sgACC function conceivably may contribute to the heightened affective, neuroendocrine, and sympathetic autonomic arousal seen in depression.

For example, depression has been associated with a reduction in the parasympathetic-to-sympathetic tone that is hypothesized to contribute to the elevated risks for developing ventricular tachycardia, myocardial infarction, and sudden death in depressed patients with cardiovascular disease.[107] The extensive interconnections between the posterior sgACC (BA 25) and the nucleus tractus solitarious of the vagus nerve that mediate parasympathetic function led to this region initially being termed “visceromotor cortex.”[105] The anterior sgACC and pgACC share more prominent projections with the PAG columns that mediate sympathetic autonomic expression.[108] Lesions of the ventromedial PFC also alter parasympathetic autonomic function in rats in a manner that shows an intriguing parallel with autonomic abnormalities reported in humans with MDD.[105] Together, these data suggest the hypothesis that dysfunction of the sgACC results in understimulation of parasympathetic tone in mood disorders.

Humans with lesions that include the sgACC demonstrate abnormal autonomic responses to emotional experiences, inability to experience emotion related to concepts that ordinarily evoke emotion, and inability to use information regarding the likelihood of punishment versus reward in guiding social behavior.[109] Based partly upon these observations[110] proposed that the ability to evaluate the consequences of social behavior depends upon visceral feedback mediated through interactions between the ventromedial PFC, hypothalamic autonomic centers, and brain-stem monoaminergic neurotransmitter systems. Although the ventromedial PFC lesions under consideration affected such a large region that it was not possible to draw specific conclusions regarding the sgACC from such cases, these observations, combined with the known connectivity of the sgACC, suggest the hypothesis that pathological modulation of

visceral feedback may underlie the oversensitivity to failure and pathological guilt in depression and the insensitivity to the negative outcome of pleasurable or violent behavior in mania.

Finally, the role of the ventral ACC in modulating the electrophysiological responses of VTA dopamine neurons suggests this cortex may also participate in evaluating the salience of rewards. Of the PFC areas that receive dopaminergic inputs, BA 24 of the ACC receives the most dense dopamine innervation (principally from the VTA), and in rats, electrical or glutamatergic stimulation of ventral ACC elicits burst-firing patterns of dopaminergic cells in the VTA and dopamine release in the nucleus accumbens.[76] The phasic, burst firing of dopamine neurons and accompanying rise in dopamine release normally occur in response to primary rewards and reward-predicting stimuli.[111] The findings that glucose metabolism in the sgACC is abnormally decreased in the depressed but increased in the manic phases of bipolar disorder[1] suggests the hypothesis that, in depression, reduced sgACC activity is associated with diminished stimulation of mesolimbic dopamine release, resulting in the absence of behavioral incentive, apathy, and anhedonia, whereas in mania increased sgACC activity results in excessive stimulation of mesolimbic dopamine release, manifested by exaggerated hedonic responses and elevated motivational drive.[76]

CONCLUSION: ROLE IN NEURAL CIRCUITS AFFECTED BY MOOD DISORDERS

Neuroimaging, neuropathological, and lesion analysis data implicate an extended anatomical network formed by the neural projections of the sgACC and other areas of the orbitomedial PFC with the amygdala; hippocampus; superior and medial temporal gyri; ventral striatum; mid- and posterior cingulate cortex; thalamus; hypothalamus; periaqueductal gray; and habenula,[4] in the regulation of the evaluative, expressive, and experiential aspects of emotion.[55] Impaired function within this network could conceivably dys-regulate emotional expression and experience, conceivably giving rise to the clinical signs and symptoms of depression or mania.[7] ***CNS***

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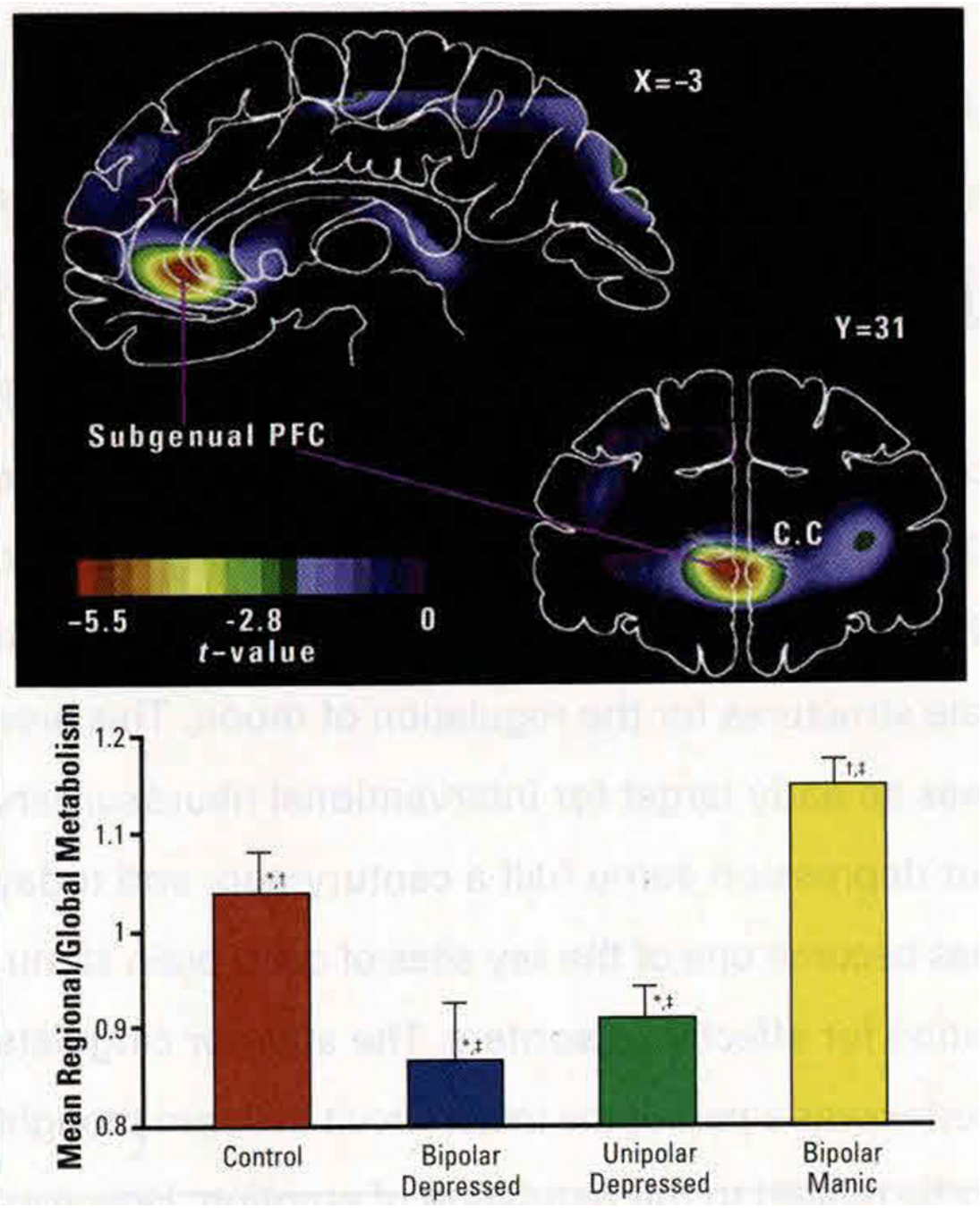

FIGURE 1. The area of reduced glucose metabolism in the subgenual PFC is illustrated in images composed of voxel *t*-values that compare depressives and controls, shown in sagittal (left) and coronal (right) sections[1,2]

This image was produced by a voxel-by-voxel computation of the unpaired *t*-statistic[2] to identify inherent differences in metabolism between samples of familial bipolar and unipolar depressives relative to healthy controls.[1] The *t*-images shown were generated to provide optimal localization of a regional metabolic abnormality identified using other techniques, which included comparisons involving independent subject samples,[1] The negative *t*-values, shown in a coronal section at 31 mm anterior to the anterior commissure (y=31 mm) and a sagittal section at 3 mm left of the midline (x=−3 mm), correspond to areas where metabolism

is decreased in the depressives relative to the controls. Both the stereotaxic center-of-mass of the peak metabolic difference shown here (x=−2, y=32, z=−2; interpreted as in Table 1) and that of the peak blood flow difference computed in an independent subject set(x=1, y=25, z=−6) localized to the agranular region of the anterior cingulate gyrus ventral to the corpus callosum. The mean normalized metabolism for each group is shown from Drevets and colleagues.[1] However, the area of reduced metabolism in the sgACC was at least partly accounted for by a corresponding reduction in cortex in both the bipolar disordered and the unipolar depressed groups relative to the control group (Figure 3). While the spatial resolution of PET precludes clear laterality distinctions in midline structures, the MRI-based neuromorphometric measures showed the grey matter volume reduction to be left-lateralized. Anterior is to the left and dorsal toward the top.

* $P<.025$, control versus depressed.

† $P<.05$, control versus manic.

‡ $P<.01$, depressed versus manic.

PFC=prefrontal cortex; CC=corpus callosum; SgACC=subgenual anterior cingulate cortex; PET=positron emission tomography; MRI=magnetic resonance imaging

Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature.* 1997;386:824–827.

Mazziotta JC, Phelps ME, Plummer D, Kuhl DE. Quantitation in positron emission computed tomography, 5. Physical—anatomical effects. *J Comput Assist Tomogr.* 1981;5:734–743.

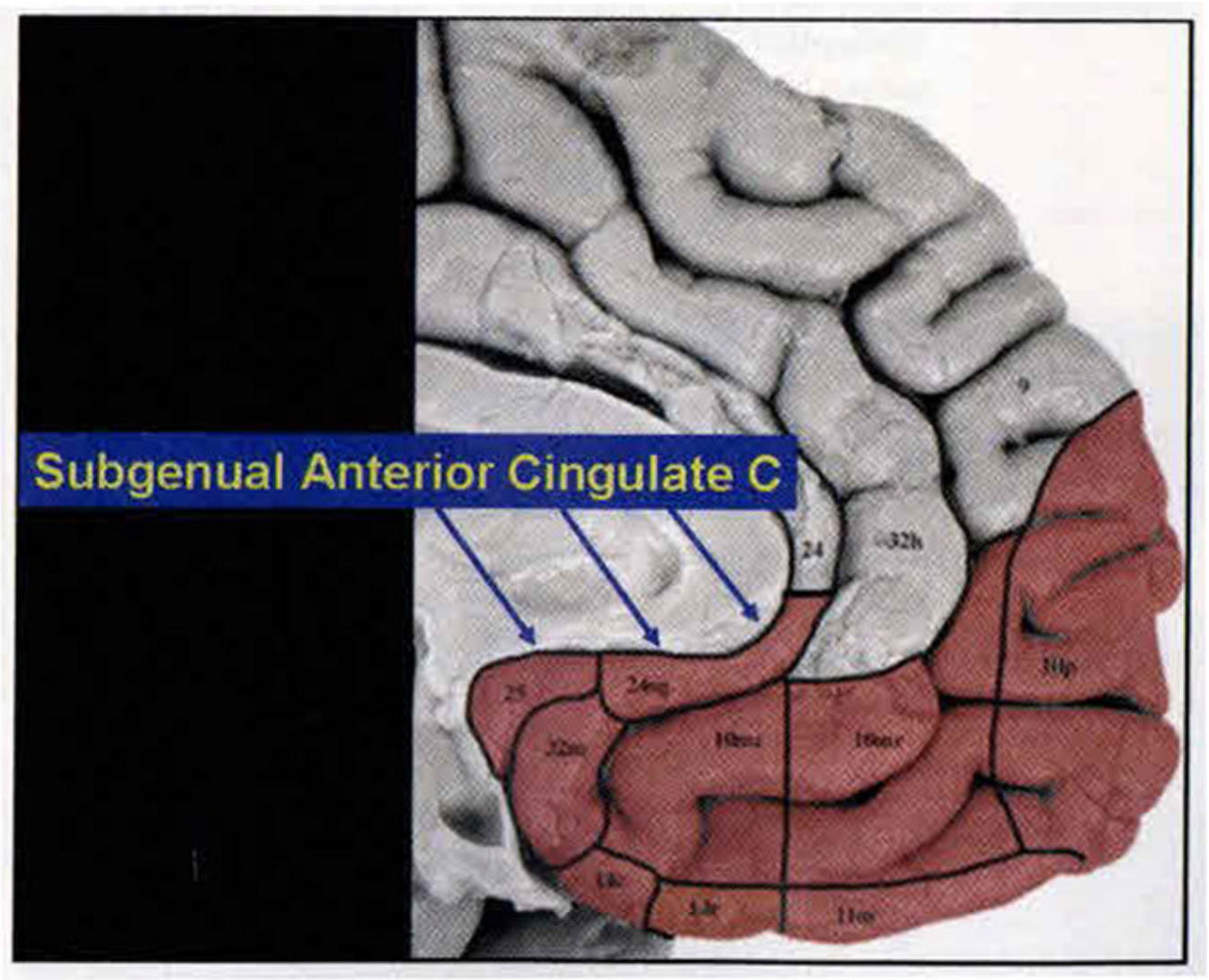

FIGURE 2. Sagittal section through the midline of a human brain photographed postmortem and marked to show the cytoarchitectonic areas established by dissection and histological characterization of other human brain specimens[*3]

[*]The human subgenual (or "subcallosal") anterior cingulate gyrus consists of agranular cortex characterized as BA 24 anteriorly and BA 25 posteriorly.

C=cotex; BA=Brodmann area.

Ongür D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol. 2003;460:425–449.*

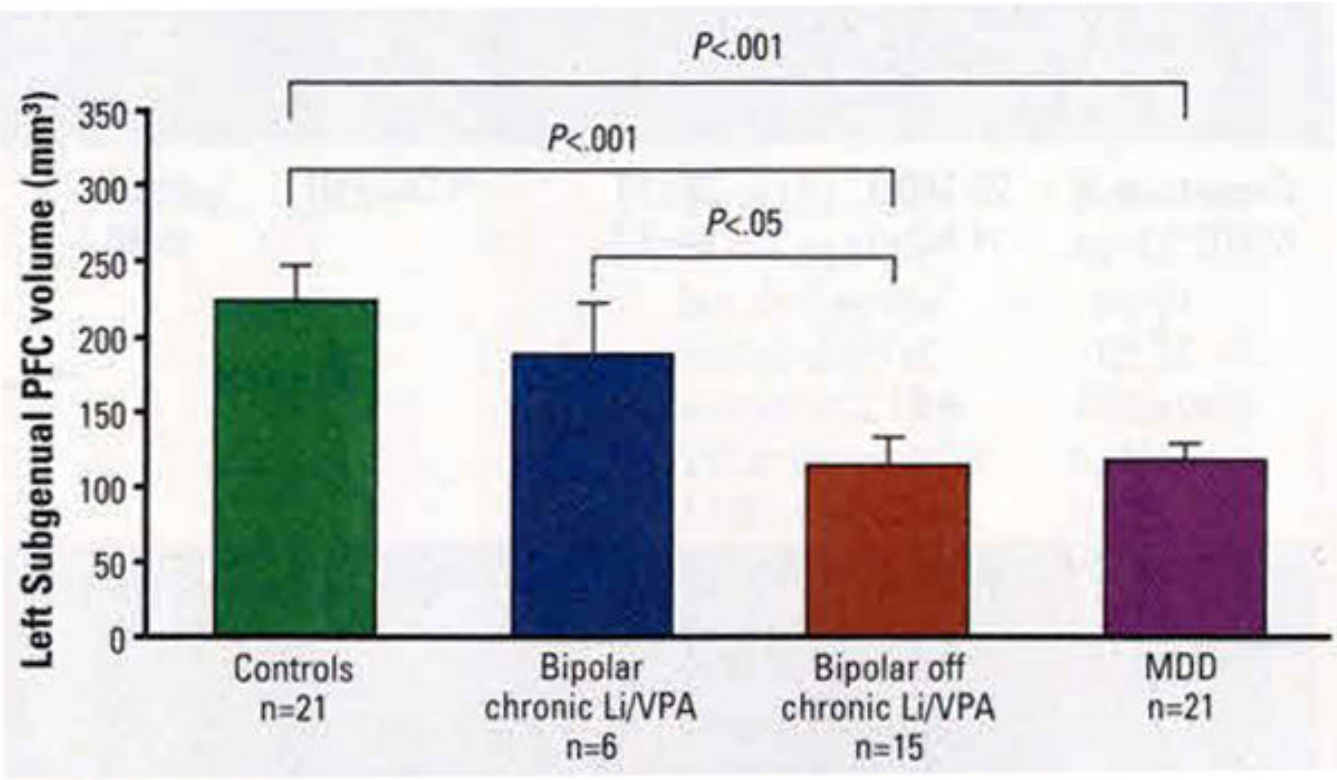

FIGURE 3. Mean (±SEM) MRI-based volumes of the left sgACC gray matter differed between the bipolar disordered, unipolar depressed, and control groups[4]

The left subgenual PFC/whole brain volume ratio also was reduced in the bipolar and unipolar groups relative to the control group. Although the bipolar subjects who underwent PET imaging had been unmedicated prior to scanning, additional bipolar subjects were included in the MRI portion of the study who had been chronically medicated with lithium (n=4) or divalproex (n=2). The mean volume for this medicated subsample is shown separately, and differed significantly (P<.05) from both the unmedicated bipolar disorder and MDD groups, but did not differ significantly from the healthy control group.

SEM=standard error of the mean; MRI=magnetic resonance imaging; sgACC=subgenual anterior cingulate cortex; PFC=prefrental cortex, Li/VPA=lithium/divalproex; MDD=major depressive disorder; PET=positron emission tomography.

Drevets WC, Price JL, Simpson JR Jr. et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature.* 1997;386:824–827.

TABLE 1

Neurophysiological Imaging Studies of the Perigenual Anterior Cingulate Cortex (ie, sgACC and pgACC) in MDD ("unipolar" depression)* [14–35]

Study (year)	Sample	Age (years)	PET Method	Age of Onset (years)	Family History of Illness	Clinical Status Testing	Medication Status	Findings	Brodmann Area†/ Stereotaxic Coordinates‡
Drevets et al (1992)[14]	13 depressed MDD 10 remitted MDD 33 HC	36.2±8.9 33.6±10.0 30.1±7.8	^{15}O-H_2O and ^{18}FDG-PET	Prior to 40 years	Yes	Depressed or euthymic	Depressed sample unmediated ≥3 weeks; remitted sample unmedicated for ≥4 months	Depressed patients showed increased rCBF of L pgACC§; effects not seen in remitted group	pgACC BA 24/32 7; 43//; 6
Drevets et al (1997)†	10 MDD 21 HC	39±7.3 34±8.2	^{18}FDG-PET	Prior to 40 years	Yes	Depressed	Cohort not treated for 4 weeks prior to scans	Decreased metabolism of L sgACC in MDD group	sgACC BA 24 −2; 32; −2
Wu et al (1999)[15]	12 MDD responders 24MDD non-responders 26 HC	28.8±9.2 30.8±9.9 29.4±9.5	^{18}FDG-PET	NR	NR	Depressed	No medication for ≥2 weeks	Responders had higher metabolic rates in medial PFC, sgACC at baseline; severity of depression correlated with metabolism of L medial PFC; positive response associated with decreased metabolism of medial PFC	sgACC BA 24; 25 3; 25; −4 8; 27; −4 7; 17; −4
Mayberg et al (2000)[16]	17 MDD	49±9	^{18}FDG-PET	NR	NR	Depressed	Scanned before and after fluoxetine treatment	Improvement associated with decreased activity of sgACC, no sgACC changes in non-responders to fluoxetine	sgACC BA 25 4;2; −4 BA 24 2; 26; −8
Kennedy et al(2001)[17]	13 MDD 24 HC	36±10 31.7±6.7	^{18}FDG-PET	NR	NR	Depressed	Scanned off medication ≥4 weeks before and again after paroxetine	Depresssd group had higher activity in R pgACC, which increased further with treatment	pgACC BA 24 8; 36; −4
Drevets et al (2002)[18]	20 MDD 14 HC	36±10 34±9.1	^{18}FDG-PET	Prior to 40	NR	Depressed	Scanned off medication ≥3 weeks before and again after sertraline	In sgACC depressed group had lower baseline metabolism in sgACC; activity decreased further with treatment	sgACC BA 24 3;31; −10
Dunn et al (2002)[19]	31 MDD	42.4±13.6	^{18}FDG-PET	15.9±13.1	NR	Mildly to severely depressed	Unmedicated ≥2 weeks	Anhedonia associated with greater activity of the L and R pgACC	pgACC BA 24/32 −16; 44; 4; 41; 42; −4
Liotti et al (2002)[20]	10 remitted MDD, 7 ill MDD 8 HC	37±9 42±15 36±6	^{15}O-H_2O-PET	NR	NR	Euthymic	Medicated with AD	Decreased rCBF in pgACC in remitted MDD group	pgACC BA 24 12; 38; 16

Study (year)	Sample	Age (years)	PET Method	Age of Onset (years)	Family History of Illness	Clinical Status Testing	Medication Status	Findings	Brodmann Area[†]/ Stereotaxic Coordinates[‡]
Smith et al (2002)[22]	12 MDD	70.1±6.3	^{18}FDG-PET	9 patients with illness onset after 60 years of age	Patients prior to study	Depressed	No medication for ≥2 weeks	Decreased glucose metabolism of R cingulate gyrus (BA 24) associated with symptom improvement following treatment as shown	pgACC BA 4; 42; 6; 14; 40; 6
Davidson et al (2003)[23]	12 MDD 5 HC	38.17±9.3 27.8±10.4	1.5T fMRI viewing negatively valenced stimuli	NR	NR	Depressed	NR for baseline	Less activation of the L ACC at baseline, which improved with treatment	NR
Kegeles et al(2003)[24]	19 (14 MDD, 5BD) 10 HC	36±11 39±19	^{18}FDG-PET	NR	Yes	Depressed	BZ discontinued 24 hours before study in 12 cases; 7 subjects on BZ. Patients free of other medication for ≥2 weeks	Reduced metabolism in depressed subjects vs controls under placebo baseline condition	sgACC BA 24/32 4; 34, −12
Holthoff et al (2004)[25]	41 MDD Controls? (most of whom were in first episode)	45.1±15.66	^{18}FDG-PET	NR	NR	Depressed	Treated with AD; BZ discontinued 3 days before baseline scan	Remission associated with decreased metabolism of L ventromedial PFC	pgACC −16; 40; −2
Pizzagalli et al (2004)[26]	38 MDD (20 melancholic) 18 non-melancholic 18 HC	33.1±8.8 36.5±12.9 38.1±13.6	^{18}FDG-PET MRI 1.5T VBM	NR	Yes: in 12 melancholic and 7 non-melancholic subjects	Depressed	Free of medication ≥2 months	Decreased (16%) metabolism of sgACC in melancholic patients only	sgACC BA 25 −3; 9; −6
Gotlib et al (2005)[27]	18 MDD 18 HC	35.2 30.8	3T fMRI	NR	NR	Depressed	9 on AD	Greater BOLD response to sad faces in L sgACC (BA 25) in MDD; also greater perfusion of L BA 24 in response to happy faces	BA 25 BA 24
Mayberg et al (2005)[28]	6 MDD	46±8	^{15}O-H_2O PET	29.5±12	Yes: in 5 out of 6 subjects	Depressed	NR	Elevated CBF to the sgACC but decreased metabolism of dorsal ACC (BA 24) at baseline in MDD; treatment with DBS associated with reduced activity of BA 25 and elevated metabolism of BA 24	***Baseline:*** sgACC ~BA 24 −10; 28; −12 ***Treatment:*** sgACC BA25 −2; 8; −10 BA 24 10; 20; −4
Clark et al (2006)[30]	5 MDD responders 17 MDD non-responders 8 HC	43.4±6.1 42.0±10.8 35.0±9.5	1.5T fMRI ASL	NR	NR	Depressed	Patients medication free ≥2 weeks prior to study; rescanned after sleep deprivation	At baseline, responders had higher activity of L ventral ACC (including sgACC) that correlated with depressed mood; after sleep deprivation	NR

Study (year)	Sample	Age (years)	PET Method	Age of Onset (years)	Family History of Illness	Clinical Status Testing	Medication Status	Findings	Brodmann Area† / Stereotaxic Coordinates‡
								perfusion decreased in L ventral ACC cingulate in responders	
Kumano et al (2006)[31]	19 cancer patients followed longitudinally	58.4 ± 15.7 (group developing depression) 57.9±16.4 (group without depression)	^{18}FDG-PET	NR	No	Depressed + euthymic	Anti-cancer medication	Patients who became more depressed over time showed prodromal hyper-metabolism of sgACC	sgACC BA 25 −4; 9; −12 2; 11; −7
Chen et al (2007)[32]	17 MDD	44.1 ± 8.36	1.5T fMRI Viewing sadface stimuli	NR	NR	Depressed	Patients scanned off medication ≥4 weeks and again after fluoxetine	Increased functional activation of pgACC associated with decreased symptom severity at baseline	pgACC BA 24/32 −2; 40; 15
Nahas et al (2007)[33]	17 MDD Chronic (current episode 71.2 ±57.3 mos)	46.8±6.3	1.5T fMRI	NR	NR	Depressed	Yes: not specified	VNS decreased activity of the R sgACC	sgACC BA 25 0; 8; −16

*Only the results of these studies that pertained to the pgACC are reviewed here; many of these studies also reported neurophysiological abnormalities in other medial PFC regions that are reviewed elsewhere.[34]

†Stereotaxic coordinates corresponding to the spatial array of Talairach and Tournoux[35] such that positive x=right of the midline, positive y=anterior to the anterior commissure, and positive z=dorsal to the horizontal plane containing the anterior and posterior commissures.

‡BAs approximated from the human cytoarchitectonic maps of Ongür and colleagues.[4] In some cases, these BA designations differed from those reported in the primary articles.

§The sgACC additionally showed a nonsignificant trend toward reduced blood flow in the depressives versus controls in this study. The Drevets and colleagues[14] study was performed using an earlier generation—and lower spatial resolution—PET camera than that used by Drevets and colleagues,[1] which may account for the higher sensitivity in this latter study compared with the former study for detecting differences in the relatively small sgACC.

//This y-coordinate from the Drevets and colleagues[14] study was based upon the stereotaxic array of Talairach and colleagues,[35] in which the origin was the midpoint of the segment connecting the anterior and posterior commissures. In the current Table, this coordinate has been translated to the stereotaxic array of Talairach and Tournoux (1988), in which the origin was the anterior commissure.

¶Coordinates were obtained from a statistical parametric map computed post hoc by combining the 10 unipolar depressives with bipolar depressives scanned using the same technique.[1]

sgACC=subgenual anterior cingulate cortex; pgACC=pregenual anterior cingulate cortex; MDD=major depressive disorder; PET=positron emission tomogrpahy; HC=healthy control; ^{15}O-H_2O=^{15}O-water; ^{18}FDG-PET=18fluorodeoxyglucose-positron emission tomography; rCBF=regional cerebral blood flow; L=left; BA=Brodmann area; NR-not reported; PFC=prefrontal cortex; R=right; fMRI=functional magnetic resonance imaging; ACC=anterior cingulate cortex; BD=bipolar disorder; BZ=benzodiazepines; AD=antidepressants; VBM=voxel-based morphometry; BOLD=blood-oxygen-level dependent; DBS=deep brain stimulation; ASL=arterial spin labelling; VNS=vagal nerve stimulation; MOS=months.

TABLE 2

Neurophysiological Imaging Studies in the Perigenual ACC in Bipolar Disorder[1,19,24,36–45]

Study (year)	Sample	Age (years)	Method	Family History of Illness	Clinical Status at Testing	Medication Status	Findings	Brodmann Map/Stereotaxic Coordinates*
Drevets et al (1997)[1]	21 BD 21 HC	35±8.2 34±8.2	^{15}O-H_2O and ^{18}FDG-PET	Yes	17 depressed 4 manic/ hypomanic	Untreated ≥4 weeks	Depressed BD vs HC showed decreased CBF and metabolism in sgACC; manic BD vs HC showed greater metabolism in sgACC	sgACC BA 24 1;25;−6
Blumberg et al (2000)[36]	11 BD	33.4±11.6	^{15}O-H_2O-PET	NR	5 manic BD; 6 euthymic	Subjects receiving MS, AP, AD, or BZ	Manic BD had greater rCBF in sgACC than remitted BD	sgACC BA 24 10; 26; −8
Ketter et al (2001)[37]	43 BD-I + BD-II (treatment resistant) 43 HC	37.5±10.6 38.1±10.4	^{18}FDG-PET	NR	Depressed, mildly depressed + euthymic	Unmedicated ≥2 weeks	Decreased metabolism of sgACC, L middle frontal and inferior frontal gyri in depressed BD patients only	BA9 + 44
Drevets et al (2002) [38]	20 MDD 14 HC	36±10 34±9.1	^{18}F-FDG	NR	Depressed	Patients medication free ≥3 weeks prior to study	Reduced baseline metabolism of L sgACC PFC in MDD	NR
Dunn et al (2002)[19]	27 BD	36.7± 11.3	^{18}F-FDG	NR	Mildly to severely depressed	Unmedicated for ≥2 weeks	Anhedonia associated with greater metabolism of R sgACC	pgACC BA 24/32 10; 42; −4
Kegeles et al (2003) [24]	19 (14 MDD, 5 BD) 10 HC	36±11 39±19	^{18}FDG-PET	Yes	Depressed	BZ discontinued 24 hours before study in 12 cases; 7 subjects on BZ	Lower metabolic activity of the R pgACC in MDD	BA 32 4; 34; −12
Kruger et al (2003) [39]	11 depressed BD 9 remitted BD	43±9 38±12	^{15}O-H_2O-PET	NR	Depressed/Remitted	MS	BL decreases in rCBF to ventral medial PFC after sadness	BA 10 20; 62; −4 −18; 54; 10 −14; 64; 0 4; 58; 9

Study (year)	Sample	Age (years)	Method	Family History of Illness	Clinical Status at Testing	Medication Status	Findings	Brodmann Map/Stereotaxic Coordinates*
							induction in both BD groups	No significant change in perigenual ACC
Lennox et al (2004)[40]	10 BD 12 HC	37.3±12.8 32.6±10.7	3T fMRI	NR	Manic	BD subjects receiving MS, AP	BD vs HC showed attenuated response to to sad faces in subgenual PFC	−2; 20; −14 ~BA 24sg[4]
Bauer et al (2005)[41]	10 BD-I 10 HC	39.3±7.8 35.0±9.3	^{18}FDG-PET	NR	Depressed	BD subjects receiving AD, MS	Higher metabolism in sgACC, which decreased with treatment	sgACC BA 24 8; 24; −6
Rich et al (2006)[42]	22 BD 21 HC	14.2±3.1 14.5±2.5	voxel-wise	NR	Half euthymic, half depressed or hypomanic	80% medicated	In L orbital cortex BD patients showed greater activation to neutral face stimuli	−32; 20; −16 No significant change in perigenual ACC
Haldane et al (2007)[43]	8 BD-I	42.1±11.8	1.5T fMRI	NR	Mildly depressed	Lamotrigine	Greater activation of pgACC in response to angry faces after lamotrigine therapy relative to baseline	pgACC BA 24/32 −4; 46; 10 pgACC BA 24 10; 36; 6
Mah et al (2007)[44]	13 BD-II 18 HC	43.0±8.4 39.0±8.0	^{18}FDG-PFT	NR	Depressed	BD subjects on lithium monotherapy	Increased metabolism of R pgACC in BD vs HC	pgACC BA 24/32 12; 47; 5
Fales et al (2007)[45]	27 MDD 24 HC	33.4±8 36.4±9	3T fMRI 3T	NR	Depressed	No medication for ≥4 weeks	Elevated activity of sgACC in MDD	−6; −13; −13 This is not sgACC check coordinate

*Only the results of these studies that pertained to the pgACC are reviewed here; many of these studies also reported neurophysiological abnormalities in other medial PFC regions that are reviewed elsewhere.[34]

pgACC=pregenual anterior cingulate cortex; BD=bipolar disorder; HC=healthy control; ^{15}O-H_2O=^{15}O-water; ^{18}FDG-PET=18 fluorodeoxyglucose-positron emission tomography; CBF=regional cerebral blood flow; sgACC=subgenual anterior cingulate cortex; BA=Broadmann area; NR=not reported; MS=mood stabilizers; AP=antipsychotics; AD=antidepressents; BZ=benzodiazepines;

rCBF=regional cerebral blood flow; BD-I=bipolar I disorder; BD-II=bipolar II disorder; L=left; MDD=major depressive disorder; fMRI=functional magnetic resonance imaging; PFC=prefrontal cortex; R=right; BL=bilateral.

TABLE 3

Volumetric MRI Studies of the Perigenual ACC in MDD[1,5,8–10,24,32,46–49]

Study (year)	Sample	Age (years)	Method*	Age of Onset (years)	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings†
Drevets et al (1997)†	10 MDD 21 HC	39±7.3 34±8.2	1 mm ROI	NR	NR	Yes	Depressed	Cohort not treated for 4 weeks prior to scanning	NR	Decreased volume of L sgACC in MDD groupb
Shah et al (1998)[46]	20 MDD (chronic) 20 MDD (remitted) 20 HC	21–65	VBM	NR	NR	NR	Depressed and remitted	Subjects receiving AD	No mania, significant substance abuse, organic pathology, or neurological illness	Reduced GM volume of L inferior lateral frontal gyrus in chronic MDD
Botteron et al (2002)[5]	30 MDD 8 HC	20.2±1.6	1 mm ROI	15.2±2.3	NR	Yes	Depressed	<10% of MDD sample on medication	NR	Decreased volume of L sgACC in MDD
Bremner et al (2002)[47]	15 MDD 20 HC	43±8 45±11	3 mm ROI	NR	2±3 (episodes)	NR	Remitted	Subjects receiving AD	Current substance abusers excluded. No history of SCZ, PTSD; ~20% of sample had past history of substance abuse	No volumetric changes of pericallosal tissue
Kegeles et al (2003)[24]	19 (14 MDD, 5 BD) 10 HC	36±11 39±19	1.5 mm ROI	NR	NR	Yes	Depressed	BZ discontinued 24 hours before study in 12 cases; 7 subjects on BZ. Patients free of other medication for ≥2 weeks.	3 panic disorder, 2 dysthymia, 1 each with social phobia, simple phobia, anorexia + PTSD; no medical illness	No significant differences in sgACC volume across groups
Hastings et al(2004)[9]	18 MDD 18 HC	38.9±11.4 34.8±13.6	1.5 mm ROI	23±12.3	4.7±4.4	Mixed	Depressed	Unmedicated at scanning	No other Axis I disorders; no current drug abuse	Volume reduction in L sgACC in males only
Coryell et al (2005)[10]	10 MDD 10 SCZ 10 HC	22±4.9 22±6.0	1 mm ROI	NR	4.7±5.7	NR	Depressed	NR	Psychosis in the MDD group	Volume reductions in L posterior sgACC but

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Study (year)	Sample	Age (years)	Method*	Age of Onset (years)	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings†
										not anterior sgACC in MDD with psychotic features
Caetano et al (2006)[48]	31 MDD 31 HC	39.2±11.9 36.7±10.7	1.5 mm ROI	27.9±11.7	11±11 5.1±6.1 (episodes)	NR	21 depressed, 10 remitted	Unmedicated	No comorbid disorders except substance abuse in remission for ≥6 months	Currently depressed MDD group had smaller BL ACC volume‡; remitted group had smaller L ACC volume than HC
Boes et al (2007)[8]	31 HC: no family history 28 HC: + family history	12.0±2.72 12.1±2.13	1.5 mm ROI	NA	No *DSM-IV*-defined episodes	Mixed	Mixed	NR	No serious medial or neurological illness, psychiatric illness, learning disorder (but no clinical interview)	In boys (but not girls) with subclinical depression smaller L perigenual (sgACC + pgACC) volumes; association most robust in family history + group
Chen et al (2007)[32]	17 MDD	44.1 ±8.36	3 mm VBM	NR	NR	NR	Depressed	Scanned before and after treatment with fluoxetine; patients off medication ≥4 Weeks before study	No current Axis I comorbidity or substance abuse within 2 months of study; personality disorders not assessed	Increased GM volume of pgACC (0,41,2) and sgACC (0, −31, −2) associated with faster improvement to fluoxetine; increased GM in pgACC (5,44, 1) associated with lower symptom severity at baseline
Tang et al (2007)[49]	14 MDD 13 HC	29.5±6.84 29.5±6.86	1.6 mm ROI	first episode	5.4±5.2 months	NR	Depressed	Medication naive	No medical or neurological disorder, head injury, substance	Decreased volume of sgACC in MDD at x=2; y=30; z=−2

Study (year)	Sample	Age (years)	Method*	Age of Onset (years)	Duration of Illness/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings†
									abuse; 4 with GAD	

*All of these studies were performed using 1.5T MRI scanners. Differences between groups were identified using either the more sensitive ROI approach or VBM. The image slice thickness is listed.

†The ROI approach does not generate a set of stereotaxic coordinates that indicates the peak difference between groups.

‡The ROI applied for the outcome measures in this study included the perigenual ACC, but also included the more dorsal supragenual ACC.

MRI=magnetic resonance imaging; pgACC=pregenual anterior cingulate cortex; MDD=major depressive disorder, HC=healthy control; ROI=region of interest; NR=not reported; L=left; sgACC=subgenual anterior cingulate cortex; VBM=voxel-based morphometry, AD=antidepressants; GM=gray matter; SCZ=schizophrenia; PTSD=posttraumatic stress disorder; BZ=benzodiazepines; BD=bipolar disorder; BL=bilateral; ACC=anterior cingulate cortex; NA=not available; *DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* GAD=general anxiety disorder.

TABLE 4

Volumetric MRI Studies in the Perigenual ACC in Bipolar Disorder[1,6,47,53–61]

Study (year)	Sample	Age (years)	Method	Age of Onset (years)	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings*
Drevets et al (1997)[1]	21 BD 21 HC	35±8.2 34±8.2	1.5T 1 mm ROI	NR	NR	Yes	Depressed	Cohort not treated for 4 weeks prior to scans	NR	Decreased volume of L sgACC in BD group
Hirayasu et al (1999)[6]	21 BD 17 SCZ 20 HC	23.7±5.1 24.0±4.3	1.5T 1.5mm ROI	23.7±5.1	First hospital	14 familial subjects	First episode affective psychosis	AP	No substance abuse within last 5 years	Decreased volume of L sgACC in familial patients
Brambilla et al (2002)[53]	27 BD 38 HC	35±11 37±10	1.5T 1.5mm ROI	NR	NR	12 familial, 12 non-familial	11 mildly depressed, 1 hypomanic, 15 euthymic	No medication for ≥2 weeks in 11 subjects, other 16 on lithium alone	No comorbid psychiatric conditions; no current medical problems	No difference in sgACC volumes§; No difference between familial and non-familial subjects
Sharma et al (2003)[54]	12 BD 8HC	38±6 38±7	4T 3.3mm ROI	21.1±6.4	12±17.2	6 with family history. 6 without	Euthymic	MS, AD	No substance abuse in last 5 years	Decreased volume of R sgACC in BD
Bruno et al (2004)[55]	39 BD (28 BD-I, 11 BD-II) 35 HC	39.1 34.8	1.5T VBM MTI		13.2 yrs	9 with family history of BD, 10 with family history of other mood disorders	NR	MS, AD, AP	No comorbid conditions	Reduced magnetization transfer ratio in R sgACC and adjacent white matter in BD group; no difference in regional gray matter
Doris et al (2004)[56]	11 BD-I 11 HC	40.5±11.6 38.1 ±10.8	2T 1 mm VBM	24.3±5.1	16.2±11.1 7.8±3.4 (hospital)	NR	Euthymic	MS, AD, AP	No comorbid conditions	Decreases in gray matter density of R pgACC/ medial frontal gyri (peak at 9; 52; −2; BA 10/32)
Lochhead et al (2004)[57]	11 BD (7 BD-I, 4 BD-II) 31 HC	38±11 36±14	1.5T 1.5 mm VBM	24±9.2	9.0±6.4 episodes	NR	Depressed	2 weeks off meds for 10 subjects	1 with eating disorder, 5 with personality disorder	pgACC smaller bilaterally in BD group
Kaur et al (2005)[58]	16 BD 21 HC	15.5±3.4 16.9±3.8	1.5T 1.5mm ROI	NR	NR	Yes	2 depressed, 14 euthymic	10 lithium, 3 AD, 1 AP, 1 stimulant, 1 BZ	No substance abuse; 5 ADHD, 1 ODD, 1 CD	Decreased volume of L ACC‡

Study (year)	Sample	Age (years)	Method	Age of Onset (years)	Illness Duration/# Episodes	Family History of Illness	Clinical Status at Testing	Medication Status	Comorbidity	Findings*
Sanches et al (2005)[59]	15 BD(3 BD-II, 1 BD NOS) 21 HC	15.5±3.5 16.9±3.8	1.5T 1.5 mm ROI	NR	3.8±2.4	Yes	13 euthymic, 2 mildly depressed	13 on MS	No substance abuse; 5 ADHD, 1 ODD, 1 CD	No group differences in sgACC volumes; no differences between patients on and off medication
Zimmerman et al (2006)[60]	27 BD 22 HC	24.0±6.4 23.5±6.5	1.5T 1.5mm ROI	NR	NR	NR	Manic or mixed episode	28 MS, 3 AD, 18 AP, 7 BZ	NR	No volume differences between groups in the combined R and L ACC subregions
Bearden et al (2007}[47]	28 BD (70% on lithium) 28 HC	36.1±10.5 35.9±8.5	1.5T VBM	18.6±6.1	15.1±18.2	NR	30% depressed 70% euthymic	Lithium for ≥ 2 weeks (treated group); no lithium for ≥1 month (untreated group)	No neurological, medical problems; no substance abuse, other psychiatric disorders	Greater volumes of the LACC, including the sgACC in lithium treated group compared to HC and lithium negative BD
Chiu et al (2007)[61]	16 BP 24 autism spectrum 15 HC	10.6±4.6 10.5±1.9 10.9±1.7	1.5T 1.5mm	NR	NR	NR	NR	12 AD, 9 MS, 8 AP, 3 adrenergic agents	No CNS disease, serious medical problems, IQ<70	Smaller L sgACC in BD vs both healthy and autism control groups

*The magnetic field strength for the MRI scanner employed is listed for each study. Differences between groups were identified using either the more sensitive ROI approach or VBM. The image slice thickness is listed.

†The ROI approach does not generate a set of stereotaxic coordinates that indicates the peak difference between groups, therefore coordinates are listed only where relevant for the studies that assessed regional grey matter using the VBM approach.

‡The ROI applied for the outcome measures in this study included the perigenual ACC, but also included the more dorsal supragenual ACC.

§Although this article aimed at defining the sgACC ROI using the same landmarks as Drevets and colleagues, [1] Botteron and colleagues, [5] and Hirayasu and colleagues, [8] the volumes obtained in the healthy control subjects in the Brambilla and colleagues[53] study were almost two-fold greater than those obtained in these other studies, suggesting that differences existed in the application of these methods in the latter relative to the former studies.

pgACC=pregenual anterior cingulate cortex; BD=biploar disorder; HC=healthy control, ROI=region of interest; NR=not reported; L=left, sgACC=subgenual anterior cingulate cortex; SCZ=schizophrenia; AP=antipsychotics; MS=mood stabilizers; R=right; BD-I=bipolar I disorder; BD-II=bipolar II disorder, VBM=voxel-based morphometry; MTI=magnetization transfer imaging; AD=antidepressants; BA=Brodmann area; BZ=benzodiazepines; NOS=not otherwise specified; ADHD=attention-deficit/hyperactivity disorder; ODD=oppositional defiant disorder; CD=conduct disorder; CNS=central nervous system; IQ=intelligence quotient; MRI=magnetic resonance imaging.

TABLE 5

Neuroimaging and Histopathological Abnormalities Evident in the Visceromotor Network[4] in Early-Onset, Recurrent MDD, and/or Bipolar Disorder[*,93]

	Gray matter volume	Cell counts, cell markers	Glucose metabolism	CBF
Brain Regions	**Dep vs Con**		**Dep vs Rem**	
Dorsal medical/anterolateral PFC(BA 9)	↓	↓	↓	↑
Frontal polar cortex (BA 10)	↓	↓	↑	↑
sgACC	↓	↓	↓/↑[†]	↑
pgACC	↓	↓	↑	↑
Orbital cortex/Ventrolateral PFC	↓	↓	↑	↑
Posterior cingulate	↓		↑	↑
Parahippocampal cortex	↓	↓ BD	↑	↑
Amygdala	↓/↑[‡]	↓MDD	↑	↑
Ventromedial Striatum	↓	↓	↑	↑
Hippocampus	↓	↓ BD	NS	NS
Superior temporal gyrus/Temporopolar cortex	↓			↑
Medial thalamus			↑	↑

[*] Empty cells indicate insufficient data.

[†] In the sgACC the apparent reduction in CBF and metabolism in PET images of depressed subjects is thought to be accounted for by the reduction in tissue volume in the corresponding cortex, as after partial volume correction for the reduction in grey matter the metabolism appears increased relative to controls.

[‡] The literature is in disagreement with respect to the amygdala volume in mood disorders.

MDD=major depressive disorder; CBF=cerebral blood flow; Dep vs Con=unmedicated depressives vs healthy controls, Dep vs Rem=unmedicated depressives vs themselves in either the medicated or unmedicated remitted phases; PFC=prefrontal cortex; sgACC=subgenual anterior cingulate cortex; pgACC=pregenual anterior cingulate cortex; BD=bipolar disorder; NS=differences generally not significant.

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