CHAPTER 24

The Role of the Cingulate Gyrus in Depression: Review and Synthesis of Imaging Data

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Chapter contents

Depression presents as a multi-dimensional disorder involving disruption of mood, cognition, motor function, and homeostatic/drive processes, including sleep, appetite, and libido. A striking feature of depressive disorders is that nearly all patients share at least some primary symptoms (e.g., depressed mood and anhedonia) while other symptoms can be highly variable from patient to patient. For example, some patients have severe insomnia, flattened affective response, and appetite loss while others have profound hypersomnia, increased mood reactivity, and significantly increased appetite; still other patients within each of these groups may have more or less disturbance of cognition, psychomotor function, libido, and anxiety. Beyond these symptomatic differences, patients with depression also show a highly variable response to available treatments. It is well established that up to 40% of patients will have an inadequate response to medications affecting the monoaminergic systems (serotonin, norepinephrine, and dopamine) which remain the mainstay first-line pharmcacologic treatment options for depression. Similarly, certain psychotherapies (such as cognitive behavioral therapy and interpersonal psychotherapy) are clearly effective in many, but not all, depressed patients. Even electroconvulsive therapy (ECT), which remains the most effective acute treatment for depression, fails in up to 20% of patients. Research efforts over the past several decades have attempted to define how the neurobiology of depression may differ

between patients who, while all clearly "depressed", show distinct and sometimes profound differences in symptom presentation and treatment response. The goals of these efforts are obvious: if successful, a more precise neurobiology of depression will be provided and treatment strategies can be optimized. Unfortunately, such efforts to date have been largely unsuccessful.

Failure to more precisely define the neurobiology of depression may be due, at least in part, to the inadequacy of available models. Historically, neurobiological models of depression have been largely based on rodent and non-human primate models and human lesions. Animal models have included learned helplessness, early stress (including maternal separation), failed neurogenesis, social dominance hierarchies, and various genetic knockout systems. Human 'lesion' models have typically involved studying patients who become depressed following discrete brain lesions (through stoke, tumor, surgery, or traumatic brain injury). While these models have clearly been useful in extending our understanding of many of the core features of depression (e.g., the important role of serotonergic systems and frontal brain structures), they have been limited in their ability to help us understand the more subtle neurobiological variations between depressed patients that likely lead to different symptomatic presentations and variable treatment response. Because of this, there has been increased interest in studying the neurobiology of depression *in vivo*—that is, to directly study how the brain functions in patients who are actually depressed.

The ability to directly investigate brain function in depressed patients has been greatly advanced by developments in neuroimaging. Over the last 20–30 years, significant technical advances in neuroimaging have allowed investigators to define multiple aspects of brain structure, function, and neurochemical processes to a degree that was previously impossible. Data from these investigations have been used to further develop and redefine existing neurobiological models of depression. A major aspect of this has been the increased recognition of the role of the anterior cingulate cortex (ACC) in the pathophysiology of depression. Imaging data clearly suggest that certain subdivisions of the ACC play critical roles in the neurobiology of depression. Further, a growing database highlights the importance of the subgenual cingulate cortex (sACC) as a critical node in mood regulation networks involved in negative mood and treatment response.

One fascinating aspect of imaging research in depression is that it clearly shows the limitation of earlier animal and lesion models of depression. Despite the fact that very early models of mood regulation recognized the 'limbic system' (with the cingulate cortex as a core aspect), animal and human lesion models failed to identify the cingulate cortex as having a major role in the pathophysiology of depression. However, as reviewed in this chapter, imaging studies have clearly shown functioning of the ACC (and especially the sACC) to be primary in the neurobiology of the disease. This suggests two important, complementary conclusions regarding modeling of major depression: (1) the role of the cingulate cortex, while primary, is unlikely to fit classic 'lesion-deficit' expectations, and (2) the importance of the cingulate cortex (specifically the ACC and sACC) in depression is as a primary dynamic modulator within a larger, multi-component mood regulation system.

The importance of this shift in thinking about the biology of depression cannot be over-emphasized. This new framework changes the understanding of antidepressant treatments from interventions designed to correct a deficit to interventions that modulate function within a dynamic, dysfunctional system. The promise of such a change in thinking about depression is that a better understanding of the structure and function of this system will provide the basis for optimizing use of currently available antidepressant treatments and, importantly, for the development of novel interventions that more directly target dysfunctional components. Neuroimaging continues to offer a variety of techniques for accomplishing these goals.

Goals of This Chapter

This chapter reviews the neuroimaging basis for the role of subdivisions of the ACC in the neurobiology of depression and proposes the sACC as a critical node in neural networks involved in negative mood regulation and antidepressant treatment response. The specific goals include the following:

1. Describe in detail the anatomical imaging studies supporting the role of the ACC in depression.
2. Describe various functional imaging studies that support the role of the ACC in depression.
3. Demonstrate how the sACC is a critical node in mood regulation networks and may be critically involved in neurobiology of antidepressant treatment response.
4. Propose a dynamic neuroanatomical model of depression that incorporates the available imaging data and provides testable hypotheses for further investigating the effects of antidepressant treatments on brain function.

Anatomical Studies

Volumetric imaging studies are well established in the study of depression and have been used to help identify

which brain regions are most likely involved in the pathophysiology of the disease. Volume differences between depressed and non-depressed subjects have been reported for the prefrontal cortex, hippocampus, amygdala, and various basal ganglia structures, although findings have been inconsistent (Sheline, 2003). Several studies have also investigated the ACC in depression.

Volumetric studies of the ACC in depression have generally shown smaller sACC volume in depressed versus control subjects, although genetic and gender factors have been implicated in this difference. In an early study of patients with familial unipolar and bipolar depression, Drevets *et al.* (1997) found that the sACC was significantly reduced in volume compared with controls. A second group confirmed that patients with familial mood disorder had smaller sACC compared with controls and that mood disorder patients *without* a family history did not have this volume reduction (Hirayasu *et al.*, 1999). In a more recent study, Pezawas *et al.* (2005) showed that, in healthy subjects, volume of the sACC was smaller in subjects carrying the allele for the short version (s allele) of the gene for the promoter region of the serotonin transporter (5-HTTLPR) compared with subjects without this allele. This group also found that subjects carrying the s allele had functional 'de-coupling' of activity in the ACC from activity in the amygdala. Carrying the 5-HTTLPRs allele has been associated with trait anxiety (Lesch *et al.*, 1996; Sen *et al.*, 2004) and has been shown to increase the likelihood of developing depression in response to stressful experiences (Caspi *et al.*, 2003; Eley *et al.*, 2004; Kendler *et al.*, 2005). Hastings *et al.* (2004) found that, compared with sex-matched controls, depressed males had a 23% smaller sACC volume, while depressed females had an 11% smaller sACC volume, suggesting that gender may interact with disease in affecting cingulate structure (Hastings *et al.*, 2004). However, Botteron *et al.* (2002) found significant sACC volume decreases in a group of unipolar depressed women compared with women without depression (Botteron *et al.*, 2002). Finally, in a group of elderly depressed patients, significantly reduced ACC volume was found compared with controls—the volume of interest included both dorsal and ventral anterior cingulate regions; a number of other inferior frontal regions also showed volume reduction in these older depressed patients (Ballmaier *et al.*, 2004). Although a few studies have shown no difference in ACC volume in depressed versus non-depressed patients (Brambilla *et al.*, 2002; Bremner *et al.*, 2002; Pizzagalli *et al.*, 2004), these results suggest that the sACC may have volume loss in depressed patients, and also that gender and genetic factors may be relevant to this association. As discussed below, one difficulty in interpreting these findings is the non-standard definition of brain regions-of-interest. While some studies have looked specifically at subdivisions of the ACC, others have combined this region with other ventromedial structures when performing structural analyses.

The cellular substrate for this volume loss has not been conclusively established, although it may be related to loss of glial cells. Glial cell reductions have been identified in the sACC in patients with familial mood disorders (Ongür *et al.*, 1998), in the supracallosal ACC in patients with major depression (Cotter *et al.*, 2001), in the caudal orbitofrontal cortex in depressed patients (Rajkowska *et al.*, 1999), and in the dorsolateral prefrontal cortex in younger patients with depression (Miguel-Hidalgo *et al.*, 2000; Si *et al.*, 2004). Synaptic protein abnormalities have been identified in the pregenual ACC (pACC) in patients with mood disorders (Eastwood & Harrison, 2001).

Volumetric studies in depression suffer from a number of limitations. While they provide important information on the structure of the brain, they only indirectly inform on potential functional differences. Further, techniques for defining and measuring regions-of-interest differ among studies. Also, most studies included phenomenologically heterogeneous patients. For example, many studies combined patients with unipolar and bipolar depression as well as patients with and without familial history of mood disorder. Given their phenomenological overlap, it is indeed likely that unipolar and bipolar depression share some pathophysiological features; however, it is also likely that these two illnesses have important biological differences. Several studies have suggested that smaller anterior cingulate volumes are associated with bipolar disorder in general (Lochhead *et al.*, 2004; McDonald *et al.*, 2004; Sassi *et al.*, 2004; Wilke *et al.*, 2004), although the specific regions of the anterior cingulate investigated have differed among studies. Further, it is likely that familial mood disorders may be biologically distinct from non-familial disorders. The presence or absence of psychosis may also be a confound. Gender and other genetic factors may influence volumetric findings, especially in the ACC; however, these factors were not carefully controlled for in the majority of investigations. In particular, data in healthy subjects suggest that variance in the promoter region of the gene for the serotonin transporter may explain differences in volume of the subgenual ACC (Pezawas *et al.*, 2005). It is also possible that stage of illness and treatment history may impact brain structures in mood disorders (Sassi *et al.*, 2004; Sheline *et al.*, 2003). Finally, age and comorbid diseases (e.g., hypertension, smoking, anxiety disorders, and substance abuse) may affect the volume of brain structures.

Despite these limitations, several studies have found significant structural abnormalities in the ACC

(especially the sACC) in patients with depression and other mood disorders. Data suggest gender, genetics, and treatment history may impact these structural changes. Volume reductions in the sACC may be primarily related to loss of glial cells; however, it is unclear whether such loss is due to a reduction in astrocytes or oligodendrocytes, although data suggest oligodendrocyte abnormalities in depression (Aston *et al*., 2005; Hamidi *et al*., 2004). If loss of oligodendrocytes in the ACC is confirmed, this would suggest abnormalities in the ability to properly myelinate axons resulting in abnormal neural connectivity and interaction of sACC with other parts of the neural network involved in mood regulation.

Functional Imaging Studies

Functional neuroimaging studies in neuropsychiatry (broadly defined) include resting state investigations of blood flow and glucose metabolism (using positron emission tomography [PET] or single photon emission computed tomography [SPECT]), imaging of neurotransmitter receptors and transporters using PET or SPECT, task-activated studies of brain activity with PET, SPECT or functional magnetic resonance imaging (fMRI), and metabolic studies using magnetic resonance spectroscopy (MRS). Functional connectivity analyses using PET, SPECT, or fMRI methods attempt to correlate brain activity in different brain regions. Functional imaging investigations in depression and other mood disorders have vastly increased our understanding of the neurobiology of these illnesses and have greatly assisted the development of meaningful neural network models of mood regulation.

Across depressed patients, the most commonly identified resting state abnormality is hypometabolism or decreased blood flow in the frontal lobes, including the dorsolateral, ventrolateral, and orbitofrontal cortices (Baxter *et al*., 1989; Bench *et al*., 1992; Buchsbaum *et al*., 1986; Galynker *et al*., 1998; George *et al*., 1993; Gonul *et al*., 2004; Post *et al*., 1987; Videbech, 2000; Goldapple *et al*., 2004). However, normal and increased prefrontal function have also been reported (Brody *et al*., 2001; Drevets *et al*., 1992). Abnormalities in other brain regions (amygdala, anterior temporal, insula, basal ganglia, and thalamus) have been identified, but the findings are more variable (Buchsbaum *et al*., 1986; Drevets *et al*., 1992; Mayberg *et al*., 1997, 1994; Post *et al*., 1987). Several studies have identified ACC abnormalities in depression, typically including hypoactivity in dorsal portions of the ACC and hyperactivity in ventral regions including the sACC (Bauer *et al*., 2005; Bench *et al*., 1992; Ebert & Ebmeier, 1996; Galynker *et al*., 1998; Gonul *et al*., 2004; Kennedy *et al*., 2001; Mayberg *et al*., 1997, 1994; Oda *et al*., 2003; Videbech *et al*., 2002); however, decreased sACC activity in depressed patients has also been reported (Drevets *et al*., 2002; Pizzagalli *et al*., 2004). The most common findings (dorsal hypoactivity and ventral hyperactivity) are generally consistent with resting state imaging findings seen in patients with depression related to an underlying neurological or medical illness (Ketter *et al*., 1996; Mayberg, 1994; Tashiro *et al*., 2001). The variability in these findings may be related to a number of factors which are discussed in more detail below.

Beyond glucose metabolism and blood flow, a number of imaging studies have attempted to assess the function of various neurotransmitter systems in depressed patients. In Chapter 2, neurotransmitter receptor systems in the cingulate cortex and associated areas are discussed in detail, highlighting the importance of these systems in cingulate function. Using MRS, depressed patients have been found to have reductions in glutamate/glutamine (but not other compounds) in the dorsal (Auer *et al*., 2000) and perigenual cingulate cortices (Mirza *et al*., 2004; Rosenberg *et al*., 2004), suggesting decreased neuro-excitatory activity in these regions. Several studies have shown abnormalities in the serotonergic system specifically in the ACC in depressed patients, including altered serotonin transporter availability in the right cingulate cortex (Reivich *et al*., 2004) and decreased serotonin synthesis in the left ACC in depressed men and bilateral ACC in depressed women (Rosa-Neto *et al*., 2004). One study has suggested that, in healthy subjects, volume and functional connectivity of the sACC is affected by function of the serotonin transporter (Pezawas *et al*., 2005). Another study in healthy subjects showed higher resting glucose metabolism in the ACC (ROI included both dorsal and ventral regions) in carriers of two 5-HTTLPR s alleles (s/s) compared with individuals with no s allele (l/l) (Graff-Guerrero *et al*., 2005). Functional changes in the ACC have been associated with increased depressive symptoms in response to tryptophan depletion, a technique that temporarily decreases available serotonin in the brain and can lead to depressive symptoms in patients with a history of depression (Neumeister *et al*., 2004; Smith *et al*., 1999). Increased dopamine 2 receptor binding in the ACC has been found in depressed patients successfully treated with serotonin reuptake inhibitors (Larisch *et al*., 1997). In sum, these findings suggest that neurotransmitter system abnormalities previously implicated in depression (e.g., serotonin, norepinephrine, and dopamine) may involve effects at specific neuroanatomical locations in the ACC.

The above studies describe various neurochemical abnormalities involving the ACC in depression. A number of behavioral/symptomatic associations with cingulate cortex activity have also been found.

As above, functional changes in the ACC have been correlated with increased depressive symptoms in recovered depressed patients undergoing tryptophan depletion (Neumeister *et al.*, 2004; Smith *et al.*, 1999). Other studies have shown correlations between activity in the ACC (typically sACC) and sadness/negative emotional processing in healthy controls (George *et al.*, 1995; Kimbrell *et al.*, 1999; Liotti *et al.*, 2000).

Personality features, such as neuroticism and extroversion, may mediate this relationship (Keightley *et al.*, 2003). Abnormal function of the ACC has been found in depressed patients during response to emotional stimuli and emotional processing (Beauregard *et al.*, 1998; Kumari *et al.*, 2003; Liotti *et al.*, 2002), and severity of depression has been shown to correlate with functional abnormalities in the ACC (Ebmeier *et al.*, 1997; Ketter *et al.*, 2001; Kimbrell *et al.*, 2002; Milak *et al.*, 2005; Osuch *et al.*, 2000). A growing, but mixed, database suggests different symptom clusters may be associated with different functional responses in distinct subregions of the ACC (Brody *et al.*, 2001; Dunn *et al.*, 2002; Ketter *et al.*, 2001; Milak *et al.*, 2005; Osuch *et al.*, 2000; Skaf *et al.*, 2002). Among the strongest findings is the correlation of sadness/depressed mood with increased activity in the ventral anterior cingulate and decreased activity in the dorsal anterior cingulate (Brody *et al.*, 2001; Bench *et al.*, 1993; Mayberg *et al.*, 1999).

The anterior cingulate gyrus has been clearly implicated in normal cognitive processing, and depressed patients consistently show cognitive impairments. Decreased activation of the ACC has been shown during performance of a complex planning task (Elliott *et al.*, 1997) and the interference component of the Stroop task (George *et al.*, 1997) in depressed patients compared with healthy controls. Another study showed decreased activity in the ACC (areas 24b and 32) and increased activity in the dorsolateral prefrontal cortex during the cognitive interference portion of the Stroop task in bipolar disorder patients (Gruber *et al.*, 2004); however, these patients were stable and not depressed. Depressed patients show less ACC activation during verbal fluency tasks than controls (de Asis *et al.*, 2001; Okada *et al.*, 2003). A smaller increase in blood flow in ACC areas 24 and 32 during verbal memory encoding has been shown in depressed patients compared with controls (Bremner *et al.*, 2004). Abnormal ACC activation during memory encoding of sad stimuli has also been found (Fahim *et al.*, 2004). ACC activity may be greater in response to negative feedback in depressed patients versus controls (Tucker *et al.*, 2003); interestingly, this response may be attenuated in more severely depressed patients. Another study showed that cognitive processing involving an emotional component was associated with different patterns of anterior cingulate activity in depressed patients versus controls (Elliott *et al.*, 2002).

Thus, a number of studies implicate abnormal function within the ACC in the pathophysiology of depression. Sadness and negative emotions appear to be linked with increased activity in the sACC (and possibly decreased activity in dorsal ACC); interestingly, the sACC also has high connectivity with hypothalamic regions involved in homeostatic/drive processes that are abnormal in depression. Other regions of the ACC may be especially involved in emotional cognitive processing. Importantly, genetics (e.g., serotonin transporter promoter region polymorphisms) and personality may determine the strength of these relationships. Finally, the involvement of these regions in depression may be further mediated by the function of neurotransmitter systems such as serotonin.

Treatment Strategies

Neuroimaging studies of resting state changes in regional metabolism and blood flow with recovery from a major depressive episode consistently report normalization of many regional abnormalities identified in the pretreatment state. Changes in cortical (prefrontal and parietal), limbic-paralimbic (cingulate, amygdala, and insula), and subcortical (caudate/pallidum, thalamus, and brainstem) areas have been described with antidepressant medications, psychotherapy, sleep deprivation, ECT, repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation, deep brain stimulation (DBS), and ablative surgery (Bench *et al.*, 1995; Brody *et al.*, 2001; Buchsbaum *et al.*, 1997; Goodwin *et al.*, 1993; Kennedy *et al.*, 2001; Malizia, 1997; Martin *et al.*, 2001; Mayberg *et al.*, 2000; Nobler *et al.*, 2001; Teneback *et al.*, 1999; Chae *et al.*, 2003; Mu *et al.*, 2004; Mayberg *et al.*, 2005). Normalization of frontal hypometabolism is the best-replicated finding, although normalization of frontal hypermetabolism has been reported.

Several studies have specifically shown changes in the ACC associated with successful treatment of depression. Decreased activity in the sACC area 25 has been associated with antidepressant response to serotonergic medications (Drevets *et al.*, 2002; Kennedy *et al.*, 2001; Mayberg *et al.*, 2000), supraphysiologic doses of thyroid hormone (Bauer *et al.*, 2005), placebo (Mayberg *et al.*, 2002), ECT (Nobler *et al.*, 2001), and DBS of the white matter adjacent to area 25 (Mayberg *et al.*, 2005). Conversely, increases in dorsal cingulate area 24a have been found with antidepressant response to serotonergic medications (Kennedy *et al.*, 2001; Mayberg *et al.*, 2000; Vlassenko *et al.*, 2004), placebo (Mayberg *et al.*, 2002), and psychotherapy (Goldapple *et al.*, 2004).

A number of studies have identified baseline cingulate activity as a predictor of response to antidepressant treatment. Increased resting baseline metabolism in the ACC areas 24a/b predicts response to antidepressant medications (Mayberg *et al.*, 1997; Pizzagalli *et al.*, 2001; Saxena *et al.*, 2003) and sleep deprivation (Ebert *et al.*, 1994; Smith *et al.*, 2002; Wu *et al.*, 1999; Wu *et al.*, 2001), while increased sACC activity predicts better response to cingulotomy (Dougherty *et al.*, 2003). One group found that lower sACC activity at baseline was associated with better response to serotonergic medications (Brody *et al.*, 1999). Two groups identified changes in ACC activity in response to emotional stimuli that may predict eventual response to antidepressant medications (Davidson *et al.*, 2003; Fu *et al.*, 2004). The importance of the sACC in treatment response in depression is further suggested by data showing persistence of sACC hypometabolism combined with posterior cingulate hypermetabolism in patients in remission from depression and on maintenance selective serotonin reuptake inhibitor (SSRI) treatment (Liotti *et al.*, 2002; Fig. 24.1). Further the absence of sACC hypometabolism with treatment has been associated with lack of antidepressant response, suggesting that this change may be a necessary condition for response (Fig. 24.2).

In sum, these data show that activity of the ACC is intimately linked with not only the pathophysiology of depression but also its response to treatment. This latter relationship helps validate the critical role of the ACC in depression. More importantly, changes in sACC activity in response to treatment appear to be associated with clinical antidepressant response suggesting a critical role for the sACC specifically in response/non-response to antidepressant treatments.

Integration of Functional Imaging Findings: Limitations and Synthesis

The above observations provide a mixed picture of the pathophysiology and treatment of depression. A number of important conclusions, however, are possible. First, resting baseline patterns of brain activity in depressed patients contrasted with normal subjects are generally characterized by prefrontal and pACC hypoactivity and sACC hyperactivity. Second, different symptom clusters appear correlated with distinct patterns of frontal and cingulate activity. Sadness and severity of depressed mood are correlated with increased sACC activity. Third, successful antidepressant treatment appears to correct abnormal brain activity patterns at baseline in most patients; these patterns of change tend to involve increased prefrontal and ACC activity and decreased sACC activity. Importantly, different treatments may be associated with unique change patterns, although differences in imaging findings may also be related to different patient populations (e.g., treatment-resistant patients are more likely to be treated with ECT and are more likely to volunteer for trials involving novel treatments such as TMS, vagal nerve stimulation [VNS], and DBS). Fourth, some data suggest pre-treatment brain activity patterns may predict response/non-response to specific treatments: higher pre-treatment rostral anterior cingulate activity predicts response to several biological treatments, while higher subgenual anterior cingulate activity predicted response to cingulotomy (and possibly DBS of the subgenual cingulate white matter). Taken together, the available data strongly support a key role for various divisions of the ACC in the pathophysiology of depression, with an emphasis on the sACC in negative mood and treatment response.

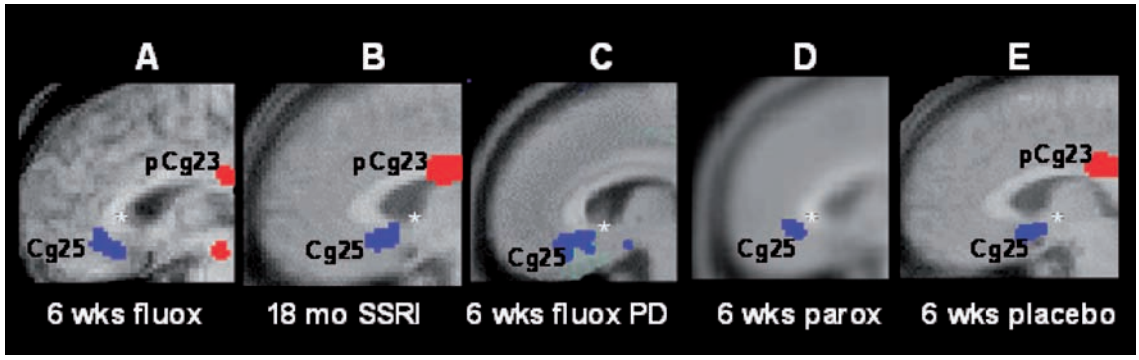

Fig. 24.1 Cerebral metabolic positron emission tomography imaging of patients with an antidepressant response following treatment showing areas of increased (red) and decreased (blue) metabolic activity compared with baseline imaging. A. Patients treated with 6 weeks of fluoxetine. B. Patients treated with 18 months of various serotonin reuptake inhibitors (SSRIs). C. Parkinson's Disease patients with depression who responded to 6 weeks of fluoxetine. D. Patients treated with 6 weeks of paroxetine. E. Patients who had an antidepressant response to placebo. *Indicates the sACC (Cg25 > Cg24/32) activity decrease seen across all of these subgroups.

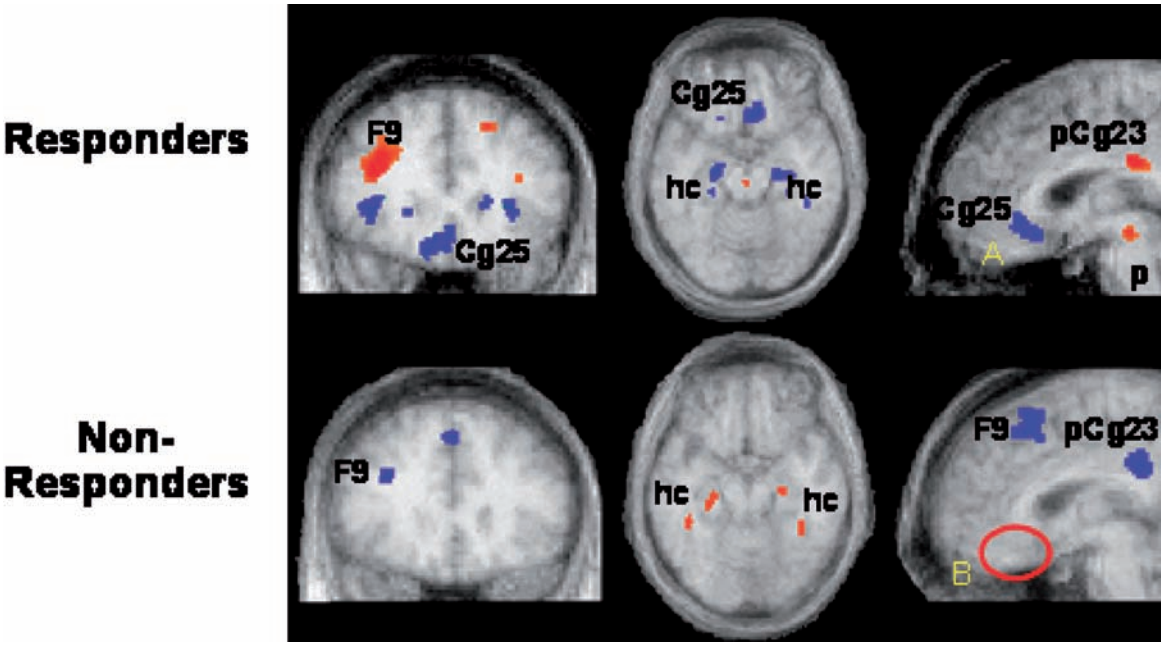

Fig. 24.2 Cerebral metabolic positron emission tomography imaging of patients following antidepressant treatment (responders and non-responders) showing areas of increased (red) and decreased (blue) metabolic activity compared with baseline imaging. Data show subgenual cingulate cortex (Cg25) hypometabolism in treatment responders (A) and absence of this finding in non-responders (B).

Despite this, there are inconsistencies in the literature that complicate interpreting and integrating these data. Some inconsistencies are likely related to limitations of imaging studies to date. Importantly, the use of different analytic strategies (e.g., voxel-wise versus regions-of-interest analyses of PET and SPECT data) is considered a major factor contributing to apparent inconsistencies (Videbech 2000; Videbech *et al.*, 2002). As well, various definitions of 'anterior cingulate' across imaging studies may contribute to variability in findings. Many of these definitions have lumped together several different subdivisions of the anterior cingulate which likely serve different functions within neural networks underlying mood regulation. Additionally, functional imaging studies suffer from the same limitations as volumetric studies in terms of the heterogeneity of patients included (e.g., different patient subgroups [familial, bipolar, unipolar, and neurological], as well as patient samples with variable illness phenomenology [e.g., illness severity, cognitive impairment, psychosis, anxiety, and psychomotor slowing]); this clinical variability likely adds to variance in imaging results (Bench *et al.*, 1993; Dunn *et al.*, 2002; Oquendo *et al.*, 2005).

Even with these limitations, the variability in group effects between imaging studies is not fully explained. Studies using similar methods in similar groups have still found very different patterns of brain activity in depressed patients at baseline and with response to treatment. Importantly, this variability has so far limited the ability to use baseline imaging to help determine an appropriate course of treatment for an individual patient—one of the main clinical goals of neuroimaging research in depression. Therefore, alternative explanations for the variability in imaging data are needed, particularly if functional imaging techniques are ever to have clinical relevance.

One approach to explaining variability in the imaging data assumes there are subtypes of depression each defined by an individual pattern of brain activity. This approach is not novel and many investigators have attempted to explain imaging variability by the use of depressive subtypes. Most commonly, these subtypes have been based on different symptomatology (e.g., presence or absence of anxiety or cognitive disturbance). This approach is not unreasonable given the association of specific imaging patterns with certain symptoms or symptom clusters. However, this purely symptom-based approach has yet to fully explain variability among imaging studies.

Another approach to defining depressive subtypes relies to a lesser degree on symptomatic phenomenology and instead views depression as a dynamic neurological illness where brain activity at any one time point represents a combination of 'functional lesions' (i.e., abnormal, disease-related functioning within a brain region or group of regions) and an ongoing

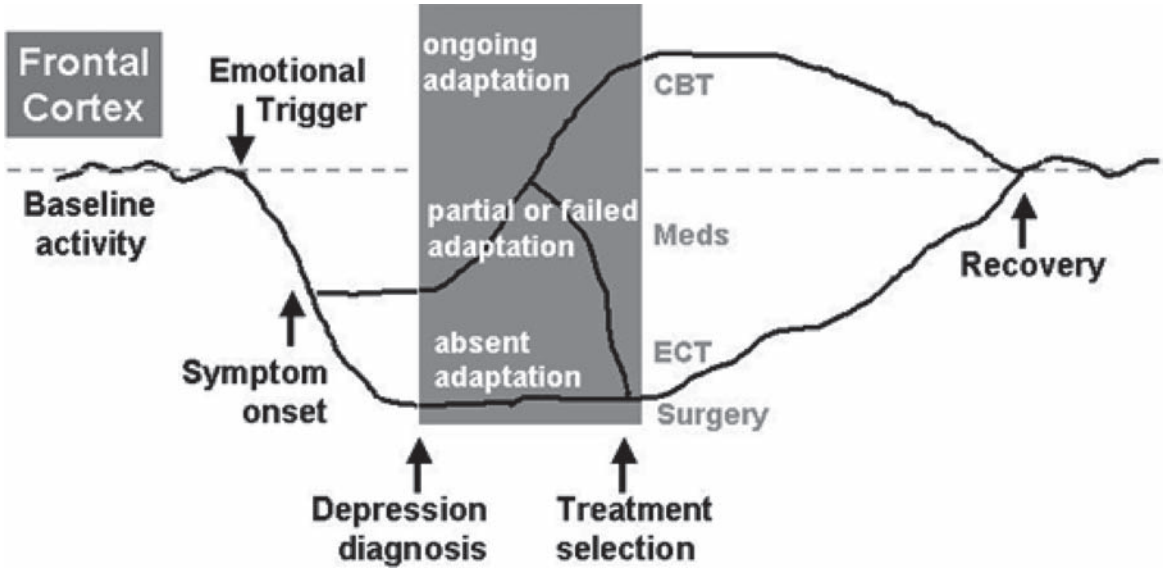

Fig. 24.3 A lesion-adaptation model for different patterns of depressive illness. Mood state is related to effects of primary 'lesions,' intrinsic adaptation, and adaptation in the context of treatment.

attempt at compensation and/or adaptation (e.g., throughout those same brain regions and/or other brain regions within the network). Figure 24.3 shows this lesion-adaptation model suggesting that there can be different patterns of illness course based on variable ability to compensate for deficits and/or adapt appropriately in the context of treatment.

From this perspective, the net regional brain activity (metabolic signal) of a particular patient represents the sum total of various synergistic and competing inputs (likely influenced by factors including heredity, temperament, early-life experiences, and previous depressive episodes) which may account for observed clinical symptoms and may characterize different illness-compensatory states. For instance, frontal hyperactivity may represent an exaggerated or maladaptive compensatory process resulting in psychomotor agitation and rumination, serving to override a persistent negative mood generated by abnormal chronic activity of limbic-subcortical structures (such as the subgenual anterior cingulate). In contrast, frontal hypometabolism seen with increasing depression severity is interpreted as failure to initiate or maintain such a compensatory state, with resulting apathy, psychomotor slowness, and impaired executive functioning. Therefore, differential functionality of an intrinsic adaptive-compensatory system may represent another important variable that explains differences in imaging findings between otherwise similar groups of patients; however, this differential activity may or may not correlate with observable differences in symptoms.

This way of conceptualizing brain function in depression may help explain differences in imaging findings to date. Further, this method also suggests a novel way of modeling brain function in depression based on a complex neural network system. In the next section, we describe a proposed neural network model of depression and discuss how this model may be used to better define and predict the effects of specific antidepressant treatments.

Multi-Nodal Network Model of Mood Regulation

Figure 24.4 shows a multi-modal network model for mood regulation and depression largely based on the neuroimaging research described above. Within this model, distinct brain regions are associated with specific systems implicated in the depressive syndrome. Cognitive and sensorimotor processing are associated with prefrontal, parietal, midcingulate, and posterior cingulate cortices. Overt cognitive processing of emotional stimuli (as well as emotional processing of cognitive stimuli) is most associated with medial frontal and orbitofrontal cortices and pACC. Covert aspects of cognitive-emotional processing are associated with amygdala, basal ganglia, thalamic, and midbrain structures. Finally, autonomic/circadian/homeostatic/drive processes are associated with ventral structures including the sACC, insula, hypothalamus, and brain stem nuclei. Given these overall divisions, it is then recognized that a specific behavioral and/or emotional

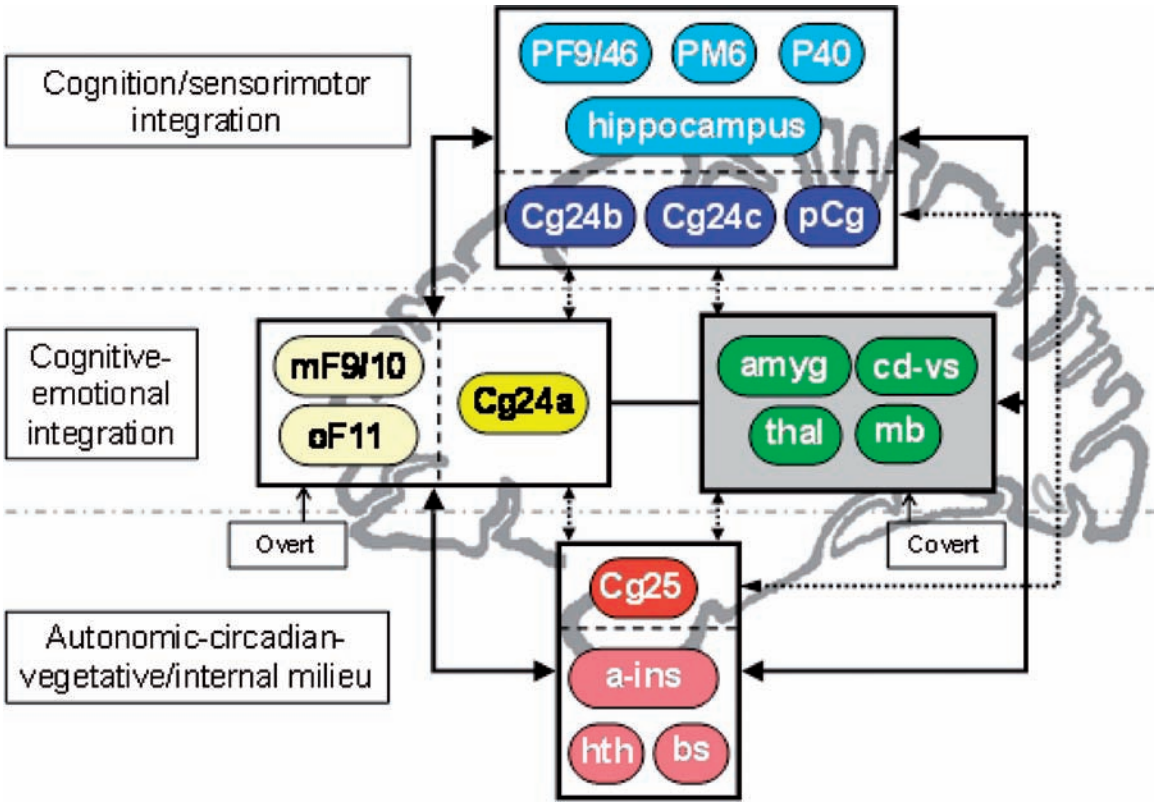

Fig. 24.4 Proposed multi-nodal network model of mood regulation. Each part of the cingulate gyrus plays a different role in brain function as shown in boxes to the left and color coded in the cingulate gyrus.

state involves the integrated activity of *all* of these regions—that is, behavioral response to an acute stressor (e.g., appearance of a rattlesnake) involves a cognitive, cognitive-emotional (both overt and covert), and autonomic response. Thus, while dysfunction may rarely occur because of an abnormality within a single region within this network, it most typically occurs due to abnormal functional connectivity between several of these regions. This is likely to be especially true in depression where single lesion models have rarely generated good models of the depressive syndrome—in other words, all brain regions may be functioning (e.g., there is no lesion), but they are not functioning *together* in a functional way.

Within this model, it is apparent that different subdivisions of the cingulate gyrus serve distinct roles. The pACC and midcingulate cortex (MCC) regions are involved in cognitive processes, pACC is involved in overt cognitive-emotional processing and the sACC is involved in autonomic/circadian/drive processes. An interesting implication of this division is suggested by data showing sACC activity to also be linked to negative mood and sadness. Thus, the model may also be conceptualized in three divisions: top (dorsal) involved in purely cognitive processing, bottom (ventral) involved in purely emotional/autonomic experience, and middle involved in mediating the interaction of the other two. The various regions of the ACC (and some portion of the MCC) play a critical role within each of these divisions and likely help mediate the interaction between regions. From this, one can predict that different 'types' of depression may involve differential activity within and across these different subdivisions and involve differential activity of the ACC.

Based on this, it is further hypothesized that treatments with different primary mechanisms of action likely act at different points within the circuit and should be equally effective if there is preserved compensatory capacity in the obligatory depression circuit overall (Fig. 24.5). For example, certain 'first-line' treatments, such as serotonergic antidepressant medications and cognitive-behavioral therapy (CBT), may have different primary sites of action within the network (frontal cortex for CBT and midbrain-subcortical regions for medications) but rely on intact connections between various regions of the circuit and the ability

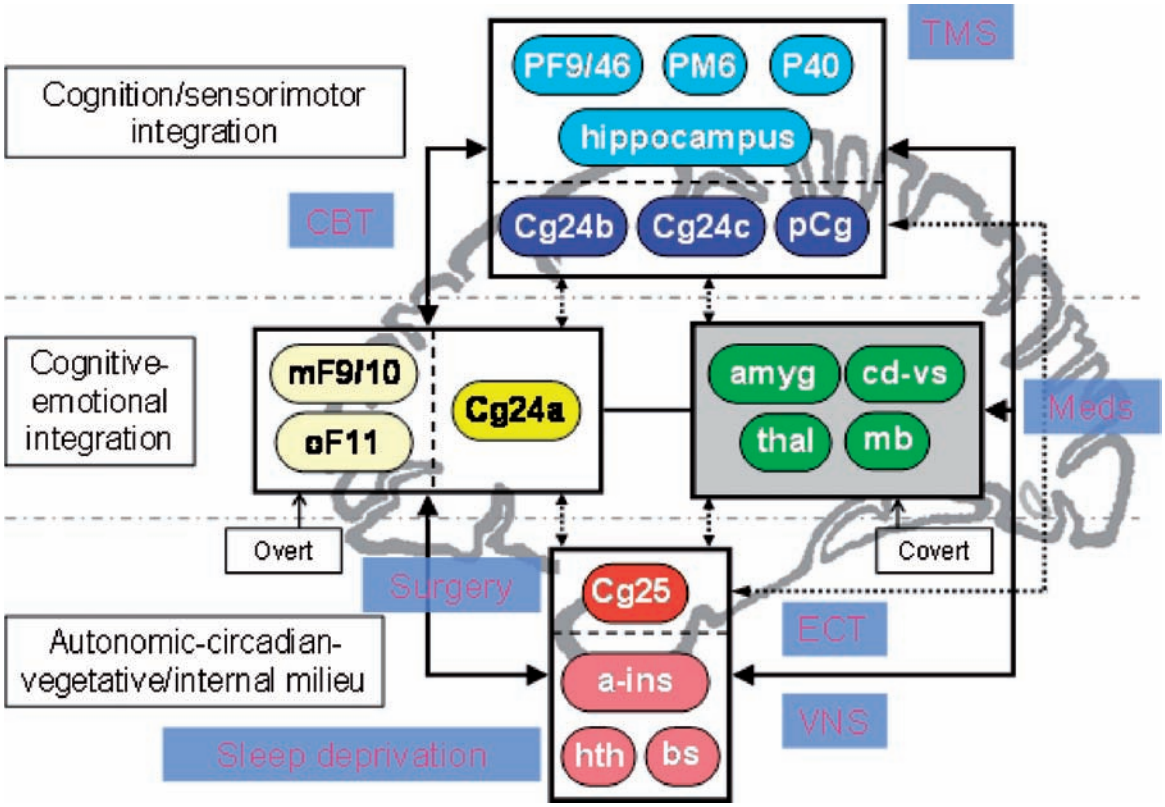

Fig. 24.5 Proposed sites of action for antidepressant treatments (identified with pink letters on blue background).

of these connected regions to respond appropriately (i.e., changes in midbrain-subcortical regions with medications must be able to result in downstream functional changes in frontal cortex; vice versa for CBT). Similarly, poor adaptive capacity within the network may underlie lack of response to common treatments and explain why progressively more aggressive treatments (such as ECT and surgery) are needed to ameliorate symptoms.

This model has been confirmed in principle using structural equation modeling (SEM) of data from prior combined imaging-treatment studies (Seminowicz *et al*., 2004). SEM is a powerful modeling technique that can be used to test the goodness-of-fit for a proposed model. Based on SEM analyses, independent groups of depressed patients can be characterized by a neural network model that includes: sACC area 25 (Cg25) and pregenual area 24 (Cg24); orbital (BA 11), medial (BA10) and dorsolateral prefrontal cortex (BA9); and the anterior thalamus and hippocampus (Fig. 24.6). Variability in the model across different patient groups was related to differences in the strength of interactions between Cg25 and other model constituents with differences across groups best explained by treatment response outcomes rather than any symptom, severity or classification variable. Patients who responded to medications were distinguished by a dominant Cg25–BA9–hippocampal connectivity pattern, while CBT responders where defined by a Cg25–Cg24–BA11–BA10 connectivity pattern. Importantly, medication non-responders showed a distinct third connectivity pattern involving Cg25, Cg24, and ventral-subcortical regions (BA11, anterior thalamus), without significant involvement of either prefrontal or medial frontal regions.

Analyses of this type suggest that it is not the absolute activity of a particular brain region that is most informative in characterizing an illness state—rather, it is the pattern of functional connectivity of multiple brain regions. Further, extrapolating from these first studies, it is hypothesized that subgroups of depressed patients (defined by differences in treatment response and non-response rather than specific symptoms or other illness features) manifest subtle but distinct differences in the functional integrity of some but not all paths within a more general mood regulation network. It is also clear that the functional connectivity of subdivisions of the anterior cingulate play a critical role in these networks. While speculative, one might

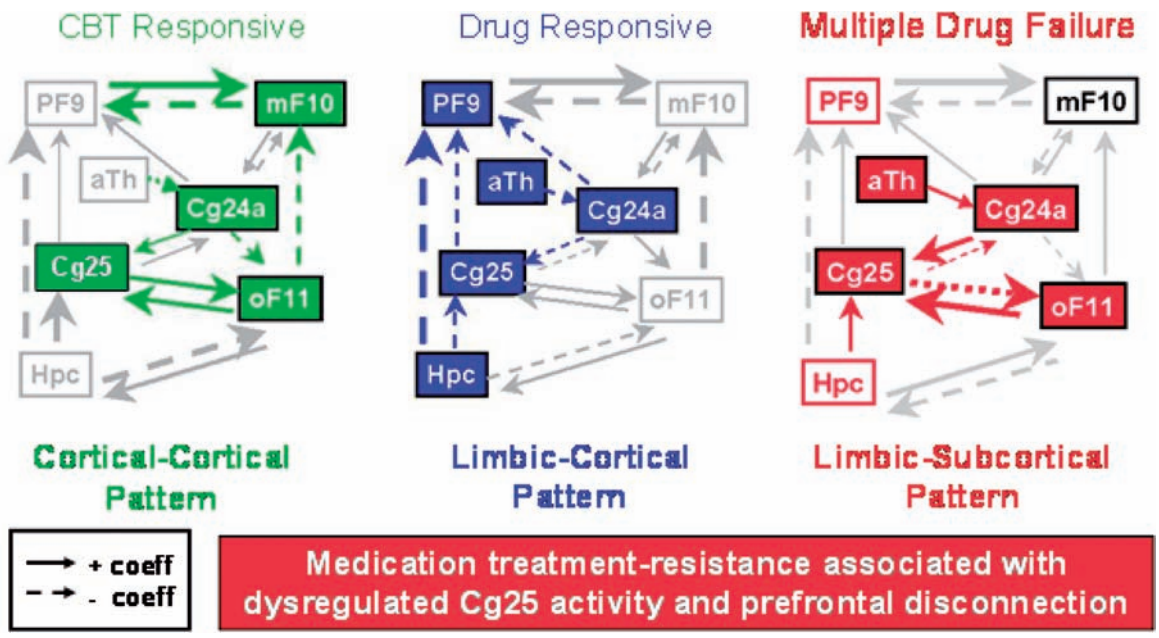

Fig. 24.6 Path modeling in different groups of treatment responders/non-responders. The different outcomes are shown in the context of different network configurations from pre-treatment baseline conditions.

then postulate that a specific functional imaging 'signature'—perhaps based on anterior cingulate connectivity—may ultimately provide a therapeutic road map for antidepressant treatment selection with specific interventions matched to ongoing ineffective adaptive responses.

Such steps are already being taken. Based on the modeling approaches described above, it was determined that the sACC (Cg25) was overactive and had abnormal connectivity with other brain regions involved in mood regulation in patients with treatment-resistant depression. From this conclusion, it was then hypothesized that high-frequency DBS of this region in such patients might help correct these abnormalities and restore normal mood regulation. In a small pilot study of this approach in six severely treatment-resistant depressed patients (five had failed ECT), four patients responded at 6 months with three in remission (Mayberg *et al.*, 2005). Associated regional cerebral blood flow (rCBF) PET imaging (Fig. 24.7) showed that, compared with healthy controls, depressed patients at baseline indeed had hyperactive sACC, hypoactive perigenual ACC (Cg24), and hypoactive dorsolateral prefrontal cortex (BA9). With 3 months of DBS, responders showed decreased sACC activity and increased Cg24 and BA9 activity; additionally, these patients showed decreased activity in medial prefrontal cortex (BA10), orbitofrontal cortex (BA11), anterior insula, and hypothalamus. At 6 months of DBS, responders continue to show this same pattern of brain activity with additional increases in activity in brainstem regions.

While these data need to be confirmed and extended, it offers a promising 'proof of principle' for the modeling approach to depression described above. It is hoped that by incorporating neuroimaging into future treatment studies, this model will be verified and revised as needed. As a long-range goal, treatment choices in depression may be optimized based on baseline neuroimaging studies that help identify the functionality of the neural networks and functional connections underlying mood regulation.

Anterior Cingulate Cortex in the Cortical Network Model

Volumetric and functional neuroimaging data clearly support a neuroanatomical basis for depression and other mood disorders. Subdivisions of the ACC have been consistently implicated in the pathophysiology of depression. However, adaptive and network models of depression do not support a simple, 'cingulocentric' explanation for depression. Instead, the ACC is better viewed as an integral part of a complex neural network involved in mood regulation, cognition, and homeostasis. A better understanding of the functional interactions of the cingulate subdivisions with other regions with this network will greatly enhance our understanding of depression and other mood disorders. More importantly,

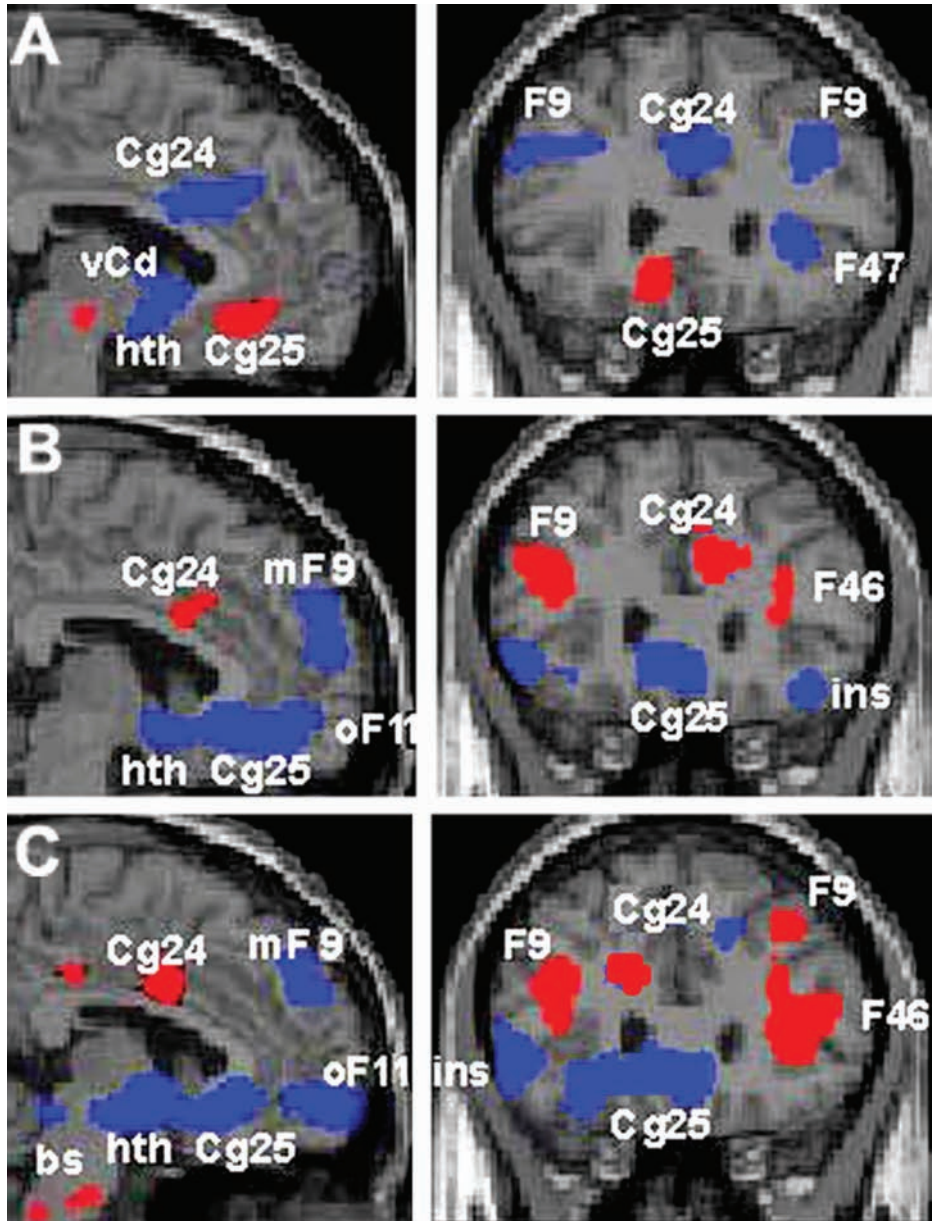

Fig. 24.7 Cerebral blood flow positron emission tomography of treatment-resistant depressed (TRD) patients undergoing high-frequency deep brain stimulation (DBS) of the white matter adjacent to subgenual cingulate cortex (sACC). A. TRD patients at baseline (prior to DBS surgery) showing areas of increased (red) and decreased (blue) blood flow in TRD patients compared with controls. B. TRD patients after 3 months of high-frequency DBS showing areas of increased (red) and decreased (blue) blood flow compared with baseline. C. TRD patients after 6 months of high-frequency DBS showing areas of increased (red) and decreased (blue) blood flow compared with baseline. bs, brainstem; Cg24, pACC; Cg25, sACC; F9/F46/F47, lateral prefrontal cortex; hth, hypothalamus; ins, insula; mF9, medial frontal cortex (BA 9); oF11, orbitofrontal cortex (BA 11); vCd, ventral caudate nucleus.

this understanding should help improve the treatment of these disabling conditions by allowing the development of rational, neurobiologically based treatment algorithms.

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