Limbic-Cortical Dysregulation: A Proposed Model of Depression

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A working model of depression implicating failure of the coordinated interactions of a distributed network of limbic-cortical pathways is proposed. Resting state patterns of regional glucose metabolism in idiopathic depressed patients, changes in metabolism with antidepressant treatment, and blood flow changes with induced sadness in healthy subjects were used to test and refine this hypothesis. Dorsal neocortical decreases and ventral paralimbic increases characterize both healthy sadness and depressive illness; concurrent inhibition of overactive paralimbic regions and normalization of hypofunctioning dorsal cortical sites characterize disease remission. Normal functioning of the rostral anterior cingulate, with its direct connections to these dorsal and ventral areas, is postulated to be additionally required for the observed reciprocal compensatory changes, since pretreatment metabolism in this region uniquely predicts antidepressant treatment response. This model is offered as an adaptable framework to facilitate continued integration of clinical imaging findings with complementary neuroanatomical, neurochemical, and electrophysiological studies in the investigation of the pathogenesis of affective disorders.

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A critical role for limbic structures in the regulation of mood and affect is now considered almost axiomatic. As first articulated by Broca,[1] and later Papez,[2] Yakovlev,[3] and MacLean,[4] these regions are centrally involved in integrating exteroceptive and interoceptive inputs required for widespread motor, cognitive, and autonomic processes.[5–7] The neurobiological substrate for this integration has been further substantiated by comparative cytoarchitectural, connectivity, and neurochemical studies. These studies have delineated reciprocal pathways linking midline limbic structures (cingulate, hypothalamus, hippocampus, and amygdala) with widely distributed brainstem, striatal, paralimbic, and neocortical sites.[6–18] While there is little debate that "limbic" brain is critically involved in various aspects of motivational, affective, and emotional behaviors,[4–7,19–24] the full role of these regions in the pathogenesis of depressive illness is not known.

New strategies for testing limbic hypotheses in depressed patients have emerged with the development of in vivo structural and functional imaging techniques. To date, imaging studies have identified regional abnormalities that appear to both support and contradict the involvement of limbic structures in this disorder. Anatomical studies of patients with major depression have not demonstrated consistent changes in primary limbic

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regions, but frontal and striatal abnormalities have been repeatedly demonstrated.[25,26] Functional imaging studies, on the other hand, report involvement of limbic as well as frontal, striatal, and paralimbic sites, although there is tremendous variability among published reports.[27–30] Depression likely involves the disruption of a widely distributed and functionally interactive network of cortical-striatal and cortical-limbic pathways that is critical to the integrated regulation of mood and associated motor, cognitive, and somatic behaviors.

The working model of depression formulated in this article attempts to both consolidate these diverse experimental observations and accommodate the various symptoms that characterize the clinical syndrome (Figure 1). This model has evolved from an earlier prototype[30] developed to interpret a series of positron emission tomographic (PET) studies of patients with major depression associated with specific neurological disorders.[30–37] This current, expanded version now includes data from a more recent series of experiments examining 1) blood flow changes with induced sadness in healthy subjects, 2) resting state patterns of regional metabolism in patients with primary and secondary depression, and 3) changes in metabolism with antidepressant treatment.[38–43] The convergence of findings from these experiments and other clinical, anatomical, neurochemical, and functional imaging studies of depression is the basis for the model presented below.

For this discussion, the model will be limited to the syndrome of major depression, clinically defined as the presence of a persistent negative mood state occurring in conjunction with an array of core behavioral symptoms, including disturbances of attention, motivation, motor and mental speed, sleep, appetite, and libido as well as anhedonia, anxiety, guilt, and recurrent thoughts of death with or without suicidal ideations or attempts.[44] All clinical and biological features of this syndrome cannot be fully accounted for by this or any model at our present stage of knowledge. Rather, this formulation is offered as an evolving and adaptable framework to facilitate the integration of clinical functional imaging findings with complementary basic human and animal research in the study of the pathogenesis of primary major depression and other affective disorders.

DEPRESSION MODEL

The proposed model has three main components, each composed of brain regions previously identified in PET studies of depression.

The *dorsal compartment* (Figure 1, red boxes) includes both neocortical and midline limbic elements, and it is postulated to be principally involved with attentional and cognitive features of the illness.[45–48] Depression symptoms such as apathy, psychomotor slowing, and impaired performance on tasks of selective and directed attention and executive function are hypothesized to localize to anterior and posterior aspects of the dorsal components of the model, specifically dorsolateral prefrontal cortex (dFr 9/46), dorsal anterior cingulate (dCg 24b), inferior parietal cortex (inf Par 40), and striatum (BG). This hypothesis is based on complementary structural and functional lesion–deficit correlational studies in patients with both discrete brain lesions and other neurological syndromes (with and without depression)[18,22,24,49–51] and functional activation studies designed to specifically map these cognitive domains.[52–55] The grouping of individual regions into this dorsal compartment is based on the previous delineation of reciprocal connections of these regions with one another[5,16–18,56–59] and their communication with regions of the ventral compartment through the rostral and dorsal anterior cingulate, caudate-putamen, mediodorsal thalamus, and posterior cingulate.[6–7,10–18,59]

The *ventral compartment* (Figure 1, blue boxes) is composed of paralimbic cortical, subcortical, and brainstem regions, and it is hypothesized to mediate the vegetative and somatic aspects of the illness.[4,60,61] Sleep, appetite, libido, and endocrine disturbances reflect dysregulation of predominantly paralimbic and subcortical components of the compartment, specifically the hypothalamic-pituitary-adrenal axis (Hth), insula (vIns), subgenual cingulate (Cg 25), and brainstem (mb-p). This hypothesis is based primarily on clinical, biochemical, and electrophysiological evidence and related animal studies.[19–22,60–63] Like those in the dorsal compartment, the individual members of the ventral compartment have known reciprocal connections with one another,[4,8–12,62–64] as well as links to the dorsal compartment via the rostral cingulate, ventral striatum, anterior thalamus, hippocampus, and posterior cingulate.[7,10–15,17–19,59]

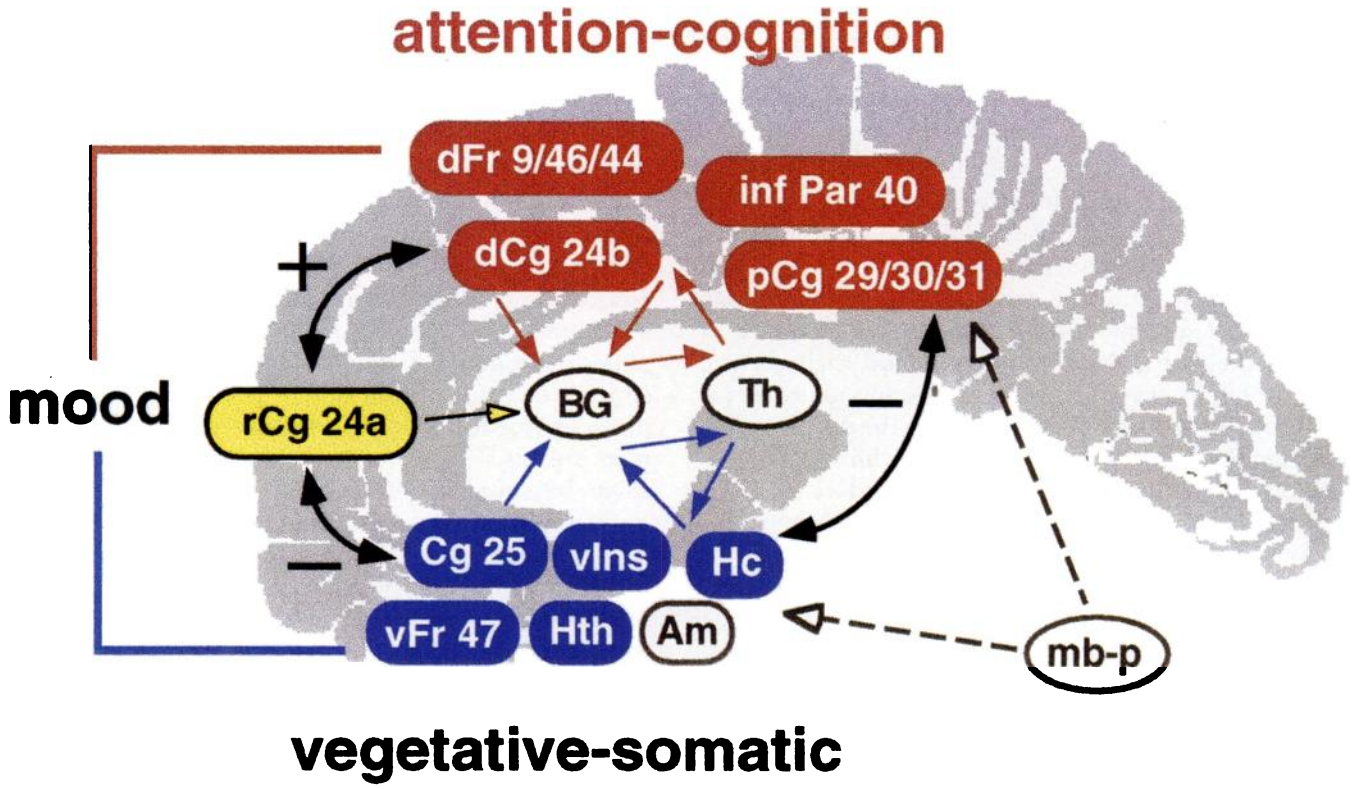
As illustrated in the model schematic, the *rostral cingulate* (Figure 1, yellow box) is isolated from both the ventral and dorsal compartments on the basis of its cytoarchitectural characteristics,[8–10,17] its reciprocal connections to both dorsal and ventral anterior cingulate,[10,12,17,59] and the recent PET finding that metabolism in this region uniquely predicts antidepressant response in acutely depressed patients.[39–40] These anatomical and clinical distinctions suggest that the rostral anterior cingulate may serve an important regulatory role in the overall network by facilitating the interactions between the dorsal and ventral compartments. Dysfunction in this area thus could have significant

impact on remote brain regions regulating a variety of behaviors, including the interaction among mood, cognitive, somatic, and autonomic responses.

It is clear that depression involves many different behaviors, none of which localizes to any single brain region. In this model, it is proposed that these behaviors are modulated by specific subsets of regions that group predominantly to either the dorsal or the ventral compartment. Interactions among these regions and compartments are necessary for the normal regulation of mood and associated motor, cognitive, and vegetative processes. Depression is not simply dysfunction of one or another of these components, but is the failure of the coordinated interactions between the subcomponents of either compartment and between the two compartments. Support for this hypothesis is presented below.

FIGURE 1. Depression model. Brain regions consistently identified in PET studies of depression are represented in this schematic model. Regions with known anatomical interconnections that also show synchronized changes (using PET) in three behavioral states—normal transient sadness (control subjects), baseline depressed (patients), and post-fluoxetine treatment (patients)—are grouped into three main compartments: dorsal *(red)*, ventral *(blue)*, and rostral *(yellow)*. The dorsal-ventral segregation additionally identifies those brain regions where an inverse relationship is seen across the different PET paradigms. Sadness and depressive illness are both associated with decreases in dorsal limbic and neocortical regions *(red areas)* and relative increases in ventral paralimbic areas *(blue areas)*; with successful treatment, there is a reversal of these findings. The model proposes that illness remission occurs when there is inhibition of the overactive ventral regions and activation of the previously hypofunctioning dorsal areas *(solid black arrows)*, an effect facilitated by fluoxetine action in dorsal raphe and its projection sites *(dotted lines)*. Integrity of the rostral cingulate *(yellow)*, with its direct anatomical connections to both the dorsal and ventral compartments, is postulated to be additionally required for the occurrence of these adaptive changes, since pretreatment metabolism in this region uniquely predicts antidepressant treatment response.

***White regions* delineate brain regions potentially critical to the evolution of the model but where changes have not been consistently identified across PET studies. *Colored arrows* identify segregated ventral and dorsal compartment afferents and efferents to and from the striatum (caudate, putamen, nucleus accumbens) and thalamus (predominantly mediodorsal and anterior thalamus), although individual cortical-striatal-thalamic pathways are not delineated. *Black arrows* indicate reciprocal connections through the anterior and posterior cingulate linking the dorsal and ventral compartments. *Dotted lines* indicate serotonergic projections to limbic, paralimbic, subcortical, and cortical regions in both compartments. *Red:* dFr = dorsolateral prefrontal; inf Par = inferior parietal; dCg = dorsal anterior cingulate; pCg = posterior cingulate. *Blue:* Cg 25 = subgenual (infralimbic) cingulate; vIns = ventral anterior insula, Hc = hippocampus; vFr = ventral frontal; Hth = hypothalamus. *Yellow:* rCg = rostral anterior cingulate. *White:* mb-p = midbrain-pons; BG = basal ganglia; Th = thalamus; Am = amygdala. Numbers are Brodmann designations.**



LITERATURE BASIS FOR MODEL

Depression in Neurological Disease

Classical lesion–deficit studies have consistently reported a strong association between frontal, temporal, and basal ganglia lesions and the development of secondary depression,[25,65–76] although the issue of lesion laterality is still debated.[66,69–70,73] It is in considering the potential common link to depression in different groups of neurological patients that the limitations of the lesion–deficit approach become most apparent. Lesion–behavior correlations fail to identify the uninjured components of the overall network that regulates mood symptoms or their functional organization. Functional imaging, on the other hand, is able to delineate the consequences of anatomic, chemical, or degenerative lesions for global and regional brain function and to identify common patterns across patient groups.

Resting state measures of brain function in secondary depressions have confirmed the anatomical observations of the lesion–deficit studies and have added the dimension of connectivity. Fluorodeoxyglucose (FDG) PET studies of depressed patients with degenerative and focal lesions have consistently identified ventral prefrontal and anterior temporal metabolic abnormalities independent of disease etiology, suggesting a critical role for these paralimbic and neocortical pathways in the regulation of mood and associated cognitive deficits.[30,33–34,77–81] Disease-specific disruption of converging pathways to these regions best explains the presence of similar depressive symptoms in patients with distinctly different disease pathologies.[30]

Proposed mechanisms for common paralimbic hypometabolism in depression associated with three basal ganglia disorders—Parkinson's disease, Huntington's disease, and caudate strokes—include anterograde or retrograde disruption of corticobasal ganglia circuits from striatal degeneration or injury, degeneration of mesencephalic monoamine neurons and their cortical projections, involvement of serotonergic neurons via disruption of orbital frontal outflow to the dorsal raphe, and remote changes in basotemporal limbic regions, with or without involvement of the amygdala.[15,48,66,76,82–84] All of these possibilities are consistent with and supportive of the model.

Primary Depression

Unlike the findings in neurological depressions, disease-specific structural changes in limbic, paralimbic, or neocortical regions have not been consistently identified in primary unipolar depressed patients, although nonspecific changes in ventricular size and T_2-weighted MRI changes in subcortical gray and periventricular white matter have been reported, particularly in late-onset patients.[26,85,86]

Resting state functional imaging studies in primary depression, on the other hand, have repeatedly reported the involvement of frontal (dorsal and ventral) and, less commonly, temporal and cingulate cortex, consistent with the general pattern seen in neurological depressions.[27–29,36,87–91] A critical issue is whether these functional regional abnormalities are disease markers or, alternatively, reflect the presence of specific depressive symptoms such as apathy, anxiety, psychomotor slowing, and executive cognitive dysfunction that are variably expressed in individual depressed patients. The latter theory might actually explain the variability in the pattern of regional changes reported in the literature. The most consistent finding is an inverse relationship between depression severity and frontal metabolism or blood flow, which has been replicated by a number of investigators (reviewed in Ketter et al.[28]). These same regions also have been found to correlate with psychomotor speed,[36,92] as well as with other unrelated cognitive measures not usually associated with depression but seen in other neurological and psychiatric diseases.[50–51,55,77,93] The presence of regional overlaps cautions against definitive conclusions regarding the role of any one brain area in regulating particular behaviors in depressive illness and suggests a more complex relationship between regional metabolic or blood flow defects and individual symptoms.

Neurochemical Markers

Evidence of neurochemical mechanisms that would account for the limbic, paralimbic, and neocortical metabolic abnormalities is compelling but circumstantial. No single neurotransmitter abnormality can fully explain the pathophysiology of depression or the associated constellation of mood, motor, cognitive, and somatic symptoms.[94] Moreover, when a peripheral chemical marker is identified, it still must be interpreted in the context of multiple neuroreceptor subtypes, second messenger effects, and regionally specific regulatory mechanisms.[95–97] Despite these caveats, a large literature exists to support changes in a number of different monoamines and peptides in depression.[98–103] However, to date there has been little direct focus on the target regions identified in published imaging studies.

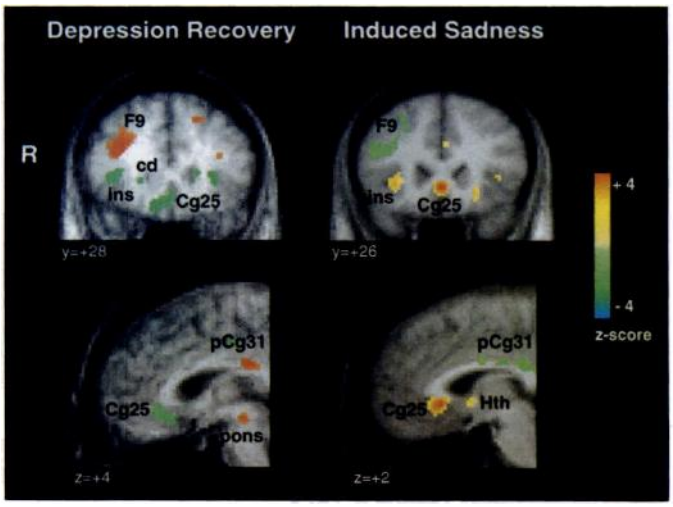
Serotonergic and noradrenergic mechanisms have dominated the neurochemical literature on depression because most typical antidepressant drugs affect synaptic concentrations of these two transmitters.[94,104] Changes in both serotonergic and noradrenergic metabolites have been reported in subsets of depressed patients, but the relationship of these peripheral mea-

sures to changes in brainstem nuclei or their cortical projections is unknown. Postmortem studies of brains of depressed suicide victims have reported changes in serotonergic and noradrenergic receptors.[105] S_2 serotonin receptor changes measured with PET have been described in the temporal cortex of depressed stroke patients,[31-32] but these measures have not yet been characterized in depressed patients who are not neurologically impaired. There is, however, clear evidence of both direct and indirect monoaminergic modulation of intrinsic cingulate, hippocampal, amygdala, thalamic, and hypothalamic neurons and their afferent and efferent projections that may have direct implications for expanding the working depression model (Figure 1, dotted lines).[106-109]

Dopaminergic projections from the ventral tegmental area (VTA) show regional specificity for the orbital/ventral prefrontal cortex and anterior cingulate,[110,111] a finding also of relevance in validating the model. A dopamine hypothesis is appealing, given the mood-enhancing properties of methylphenidate in treating some depressed patients.[48,83,102,112-114] However, dopaminergic stimulation alone is clearly inadequate in treating the full depression syndrome, and degeneration of VTA neurons or their projections has not been demonstrated.[115]

Increasing attention has focused on other transmitter and peptide systems, particularly those with known monoaminergic interactions.[61,99-100,116-119] Unfortunately, functional imaging ligands for many of the systems of greatest interest have not yet been developed. Increases in paralimbic mu-opiate receptors have been demonstrated with PET in unipolar depressed patients[37] (a finding consistent with autoradiography studies in depressed suicide victims[117]) and also in brain regions critical to the proposed depression model. The relationship of this finding to regional metabolic and perfusion changes awaits further investigation.

FIGURE 2. **Reciprocal changes in cortical and paralimbic function with manipulation of mood state. Left images: Z-score maps demonstrating changes in regional glucose metabolism (fluorodeoxyglucose PET) in depressed patients following 6 weeks of fluoxetine treatment. Right images: changes in regional blood flow (oxygen-15 water PET) in healthy volunteers 10 minutes after induction of acute sadness. Depression recovery and induced sadness involve changes in identical dorsal frontal and ventral paralimbic brain regions. Depression recovery is associated with increases in dorsal regions and decreases in ventral regions. The reverse is seen with induced sadness, where dorsal areas decrease and ventral areas increase with change in mood state. F = frontal; cd = caudate; ins = anterior insula; Cg 25 = subgenual cingulate; Hth = hypothalamus; pCg 31 = posterior cingulate. Color scale: *red* = increases, *green* = decreases in flow or metabolism.**



TESTING THE MODEL

Transient Sadness in Healthy Subjects

Mood induction experiments in healthy subjects have shown involvement of many of the same regions identified in depressed patients, but with some critical differences. Induction of transient sadness results in a combination of cortical and limbic increases and decreases in regional cerebral blood flow.[120-122,38] The exact pattern appears to be highly dependent on the provocation strategy used to elicit the mood state, the timing of the scan acquisition relative to the induction of the desired mood, and the data analysis methods used to interpret the results. However, despite technical differences among studies, the limbic, paralimbic, and neocortical components of the proposed model are repeatedly identified in all reports. Increases in the ventromedial frontal cortex and anterior cingulate are the most consistent finding.

In our experiment,[38] the goal was to separate the neural systems for dysphoria from those for attention and cognition in order to better interpret the results of our ongoing FDG studies of primary and secondary depression.[30,39-40] Surprisingly, the results of this study suggested that in healthy subjects, these behaviors were inseparable: the entire limbic-cortical depression network was simultaneously activated. Specifically, when a sad mood state was induced and maintained, blood flow increased in ventral paralimbic regions (anterior insula, subgenual cingulate) and decreased in dorsal neocortical and limbic regions (prefrontal, inferior parietal, dorsal anterior cingulate, posterior cingulate) (Figure 2). The localization of the dorsal decreases overlaps both resting state abnormalities seen in depressed

patients[27–28,30,39] and sites of increased blood flow seen in studies of normal selective and directed attention.[52–55] Of relevance to the model is the finding that the normal experience of sadness appears to affect widespread cortical systems that control selective cognitive behaviors, in a pattern similar to that seen in depressed patients.

Resting State Patterns in Depressed Patients: Unique Role of the Rostral Cingulate

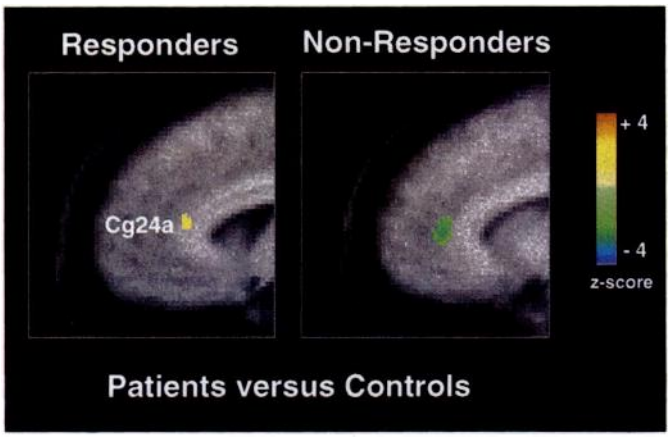
Despite the general consensus as to the regional localization of functional changes across imaging studies of depressed patients, there are some troubling discrepancies. These include contradictory reports as to whether depression is characterized by frontal and cingulate hypo- or hyperfunctioning.[28–29,90,101] One view maintains that this variability is somehow related to the heterogeneity of clinical symptoms such as inattention, apathy, psychomotor slowing, or cognitive impairment, and several studies support this argument.[92,93] Other explanations implicate medication status (drug naive versus drug washouts of varying duration), patient selection (familial versus random), severity of the illness, and transient fluctuations in mood at the time of the PET study.[28,36,90–91]

Findings from our own studies suggest an alternative explanation. We tested the hypothesis that specific metabolic patterns could predict the responsiveness of depressed patients to antidepressant medication.[39,40] In both treatment responders and nonresponders, decreases were found in frontal, parietal, dorsal cingulate, and insular cortex, consistent with previous reports. In contrast, metabolism in the rostral anterior cingulate uniquely distinguished the two groups. Patients with high pretreatment rostral anterior cingulate metabolism went on to show a good response, whereas those with low metabolism remained significantly depressed after 6 weeks of treatment (Figure 3). Metabolism in no other region discriminated the two groups, nor did associated demographic, clinical, or behavioral measures, including motor speed, cognitive performance, depression severity, or illness chronicity.

This variation in rostral anterior cingulate activity (Brodmann area 24a) is of particular relevance to the model because this region has reciprocal connections with dorsal anterior cingulate, as well as with a number of ventral paralimbic regions (insula, basal frontal, hippocampus, subgenual cingulate, amygdala).[8,10,12,17,59] These rostral cingulate projection sites are the same areas where metabolic changes were seen in this study across the entire depressed patient group.[39] The finding that metabolic activity in the rostral cingulate discriminates eventual responders from nonresponders suggests that this area may function as a bridge linking dorsal and ventral pathways necessary for the normal integrative processing of mood, motor, autonomic, and cognitive behaviors—all of which are disrupted in depression (see Figure 1).

The fact that responders and nonresponders show an inverse pattern compared with control subjects further suggests that an adaptive hypermetabolic change in the rostral cingulate may be required to facilitate response to treatment—a compensatory response not present in the nonresponder group. In this context, a central role for rostral cingulate in the depression model is reinforced because integrity of this region appears necessary for the normalization of cortical and paralimbic dysfunction that accompanies recovery from depression. Rostral cingulate function may be a marker of potential network plasticity. Functional failure of this region, as indexed by hypometabolism, appears to be predictive of poor adaptive potential and eventual poor outcome. Presence of this metabolic signature in individual patients may be clinically useful in identifying those at risk for a difficult disease course.

FIGURE 3. **Predictive value of rostral cingulate metabolism in depression for 6-week treatment response. *Z*-score maps demonstrating differences in the direction of changes seen in pretreatment rostral cingulate glucose metabolism (Brodmann area 24a) in two groups of depressed patients compared with healthy control subjects. Rostral cingulate hypometabolism (right image, negative *z*-score shown in *green*) characterizes the eventual nonresponder group, in contrast to hypermetabolism (left image, positive *z*-score shown in *yellow*) seen in the eventual treatment responders.**



Treatment Effects

A final element in testing the model is to explicitly examine whether the regional abnormalities are static or dynamic. State-trait studies of acutely ill and remitted patient groups are one approach. An alternative with direct implications for the model is to examine how dorsal and ventral regions change with different treat-

ments and how these changes reflect overall and symptom-specific improvement.

Published studies demonstrate that recovery from depression is associated with normalization of certain regional abnormalities. Increases in dorsal frontal and dorsal anterior cingulate hypometabolism and hypoperfusion have been reported with drug therapy, suggesting that these defects are state markers of the illness.[27,29,123–125] On the other hand, studies of sleep deprivation and electroconvulsive therapy (ECT), as well as group comparisons of ill and remitted patients, suggest additional state and trait changes involving limbic and paralimbic regions including the anterior cingulate, ventral frontal cortex, subgenual cingulate, caudate, and amygdala.[29,90,101,126,127] However, the regions affected and the direction of the changes reported are variable across studies and across treatment modalities. This is particularly true of changes seen in the anterior cingulate, where differences in study design, the size and location of cingulate sampling, and data analysis strategies preclude making direct comparisons across experiments.[29,126,127]

In a recent study, we tested the validity of the model by using a pharmacological treatment trial in acutely ill depressed patients.[41–43] Fluoxetine treatment resulted in regional changes in both the dorsal compartment (prefrontal, premotor, dorsal anterior cingulate, and posterior cingulate) and the ventral compartment (subgenual cingulate area 25, anterior insula, hippocampus, and ventral frontal cortex). Clinical response was reflected in the direction of changes in dorsal neocortical and ventral paralimbic regions: dorsal frontal cortex increases were seen only in responders, and this increase was a normalization of the pretreatment hypometabolic pattern (Figure 2); ventral paralimbic areas showed decreases, and, unlike changes seen in dorsal neocortex, these were not due to the normalization of an abnormal metabolic pattern. Pretreatment metabolism in these regions was normal to slightly elevated, and symptom improvement was actually associated with new hypometabolism of these ventral paralimbic regions. In contrast, nonresponders with identical treatment showed an increase in metabolism in these same ventral regions. These divergent effects in responders and nonresponders suggest that there are differences in the adaptation of target regions to chronic serotonergic modulation in different patient groups. Studies using varying doses and different drugs are needed to validate this hypothesis.

Interpretation of Findings

These findings indicate that recovery requires both the inhibition of overactive paralimbic regions and the normalization of hypofunctioning dorsal neocortical sites (Figure 1, black arrows). A further inference is that, via the rostral and posterior cingulate, suppression of ventral paralimbic activity results in the disinhibition of the dorsal compartment. This theory is supported by the strong correlation of mood improvement with both dorsal compartment increases (dFr 46/9) and ventral compartment decreases (Cg 25, Hc). Remission of sleep and vegetative disturbances, on the other hand, correlated most significantly with ventral paralimbic suppression, and improved cognitive performance tracked primarily with normalization of dorsal prefrontal hypometabolism.[42,43]

Consistent with its role as a trait marker, rostral cingulate metabolism showed no change with treatment in either the responder or nonresponder group and did not correlate with improvement in any of the measured behaviors. As previously noted, the direct anatomical connections of this region to dorsal and ventral regions showing metabolic changes with treatment further supports its key regulatory role in modulating the interaction between the dorsal and ventral compartments.

Similarities Between Depression Recovery and Induced Sadness

The localization of the regional changes seen in patients with a good response to fluoxetine treatment is identical to that demonstrated in the induced sadness experiment (Figure 2). Recovery from depression is associated with decreases in ventral paralimbic areas and increases in the dorsal limbic and neocortical regions. Induction of transient sadness shows this identical pattern, but in reverse: increases in ventral paralimbic regions and decreases in dorsal neocortex. These shifts in the relative relationship between the ventral and dorsal compartments as a function of varying the overall mood state provide strong evidence for a reciprocal interaction among these regions in both health and disease (Figure 1).

Psychosurgical Parallels

The postulate that poor response reflects the inability to suppress ventral paralimbic regions (required for the release and normalization of dorsal neocortical areas) is further supported by the use of destructive limbic-paralimbic lesions (anterior leukotomy, subcallosal or superior cingulotomy) to alleviate severe refractory depression.[128–131] The model maintains that recovery requires the disinhibition or release of the abnormally functioning dorsal compartment by suppression or disconnection of ventral paralimbic inputs, an effect facilitated by these specific neurosurgical lesions.

CONCLUSIONS

Although many unanswered questions remain, this series of experiments provides strong support for the proposed componential model of depression. Sadness and depressive illness are both associated with decreases in dorsal limbic (anterior and posterior cingulate) and neocortical regions (prefrontal, premotor, parietal cortex) and relative increases in ventral paralimbic areas (subgenual cingulate, anterior insula, hypothalamus, caudate). While additional experimental studies are clearly needed, it is postulated that illness remission, whether facilitated by psychotherapy, medication, ECT, or surgery, requires the inhibition of overactive ventral areas with resulting disinhibition of underactive dorsal regions. Integrity of the rostral cingulate, with its direct anatomical connections to both compartments, appears to be additionally required for the occurrence of these adaptive responses. In the course of further testing of these hypotheses, this model will certainly evolve. For now, it provides a useful framework for facilitating the continued integration of functional imaging findings with ongoing basic neuroanatomical, neurochemical, electrophysiological, and developmental studies.[95–97,132–135] It is hoped that these strategies will contribute to the development of new system- and symptom-specific treatments and the elucidation of the pathogenesis of depression and related affective disorders.

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