Defining Neurocircuits in Depression

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Strategies toward treatment selection based on neuroimaging phenotypes

While many effective treatments are available to treat a major depressive episode, no clinical or biological markers identify which patients are likely to respond to a given treatment or explain why one treatment modality or class of medication is effective when another is not. With these clinical issues in mind, this article presents a synthesis of brain changes associated with clinical response to pharmacotherapy, cognitive-behavior therapy (CBT), and deep brain stimulation (DBS), identified using functional neuroimaging, with findings interpreted in the context of a data-driven depression model.

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In this network model, a major depressive episode is defined by the pattern of dysfunctional interactions among specific cingulate, paralimbic, subcortical, and frontal regions critical to maintaining emotional homeostasis under conditions of exogenous or endogenous stress. Identification of treatment-specific response patterns within this circuit framework not only enhances our understanding of brain mechanisms mediating diverse treatments but also provides a strategy for defining treatment resistance at a brain systems level. Studies designed to characterize variability in this putative depression “network” are highlighted as a critical step toward the eventual development of imaging-based clinical algorithms to optimize treatment selection in individual patients.

STRATEGIES FOR TREATMENT SELECTION: CURRENT SHORTCOMINGS

Options for the treatment of a major depressive episode include both pharmacologic and nonpharmacologic strategies. While randomized clinical trials demonstrate similar rates of response to CBT and antidepressant pharmacotherapy, there are no established algorithms to guide treatment selection. This is a critical pharmacologic actions, combined drug and CBT, or, in medication-resistant patients, electroconvulsive therapy. Few studies, however, have evaluated the role of medication following nonresponse to psychotherapy, nor are there many studies evaluating the efficacy of psychotherapy following medication nonresponse. Illustrating the importance of such trials, a recently published retrospective study found a differential advantage for psychotherapy over medication treatment resistance, is growing increasingly critical with the availability of new somatic strategies, including repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and, most recently, DBS. Identifying which patients are likely to respond (or not) to such treatments would be an important advance, particularly given the invasive nature of some of these new interventions.

Functional neuroimaging provides testable strategies toward these clinical goals. To illustrate this potential, data demonstrating unique change patterns mediating successful and unsuccessful outcomes to specific antidepressant treatments are presented in this article. These treatment-specific change patterns are discussed in the context of a theoretical depression circuit model, providing an integrative framework for future testing of novel therapeutic approaches.

CME EDUCATIONAL OBJECTIVES

1. Describe functional neuroimaging abnormalities in patients with major depression and sources of scan pattern variability in published studies.
2. Discuss which brain regions are affected by different treatments.
3. Identify differences between response and nonresponse to different treatments at the brain systems level.

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Depression is conceptualized as a systems-level disorder affecting select cortical, subcortical, and limbic regions and their related neurotransmitter and molecular mediators.
extension of a long neurological tradition of symptom localization and necessary step towards the effective synthesis of convergent and divergent findings described in the published literature. A first assumption is that depression is unlikely a disease of a single gene, brain region, or neurotransmitter system. Rather, it is conceptualized as a systems-level disorder affecting select cortical, subcortical, and limbic regions and their related neurotransmitter and molecular mediators. In support of this hypothesis, structure-function correlations of patients with depression who have both acquired brain lesions and neurodegenerative disorders provide a critical anatomical perspective, consistently identifying involvement of frontal cortex and the striatum. In primary affective disorders, structural abnormalities have been identified in the amygdala, the hippocampus, and both the orbital frontal and prefrontal cortex. In animal models, comparative cytoarchitectural and connectivity studies confirm the involvement of pathways linking the cingulate and other limbic structures with the frontal cortex, striatum, thalamus, hypothalamus, and brainstem in various emotional behaviors. Disruption of these pathways might therefore be seen as the likely pathological substrate for psychiatric syndromes such as depression, where sustained negative mood is coupled with disturbances in motivation, motor performance, cognition and circadian functions.

A major depressive episode is further viewed as the net result of failed regulation of this integrated system under circumstances of cognitive, emotional, or somatic stress (Figure 1). While mechanisms driving this “system dysfunction” are not yet characterized, several factors appear to be strong contributors, including genetic vulnerability, affective temperament, and developmental insults. A viable systems model must accommodate not only these etiologic variables but also the variability in symptom presentation seen among patients with depression. Treatments for depression similarly are viewed within this neurocircuit framework, with different modes of treatment modulating distinct neural targets, resulting in a variety of complementary chemical and molecular adaptations and homeostatic effects that re-establish a normal mood state.

**Current Model**

To define an organizational structure meeting these characteristics, we have integrated findings from a series of functional neuroimaging studies of depression with published nonhuman primate anatomical, electrophysiological, and tract-tracing experiments into a theoretical depression model (Figure 2). Included are data from experiments on specific brain lesions and neurological disorders, blood flow changes in resting state patterns of regional metabolism in patients with primary depression, changes in metabolism with various types of antidepressant treatments, and studies of acute mood change and emotional processing in healthy volunteers and various patient and at-risk populations. Regions within the model are clustered into working compartments based on consistent patterns of behavior across different experiments. These functional groupings further attempt to accommodate the major defining symptom clusters of major depression (e.g., mood, motor, cognitive, circadian), as well as brain regions associated with specific cognitive, motivational, and autonomic functions of obvious relevance.

Furthermore, selective modulation of specific sites seen as primary targets facilitates the observed widespread, reciprocal changes in cortical and limbic regions across studies of various antidepressant treatments. The synchronized modulation of dysfunctional cingulo-frontal pathways is considered critical for illness remission, regardless of treatment modality, accommodating pharmacotherapy as well as cognitive and surgical interventions. Strategies to test and distinguish disease-specific and response-specific functional interactions among regions in this depression network are highlighted in the following sections. While a variety of imaging methods — positron emission tomography (PET), single photon emission com-
computed tomography, functional magnetic resonance imaging, magnetic resonance spectroscopy, evoked potentials, magnetoencephalography, optical imaging — are capable of quantifying a wide range of physiological parameters relevant to the study of major depression, we will focus here on resting state blood flow and glucose metabolism measures using PET.

NEUROIMAGING EVIDENCE OF PHENOTYPE VARIABILITY

Across the many imaging studies of primary depression, frontal and cingulate abnormalities are most commonly reported; a pattern also was seen in neurological depressions. Other limbic–paralimbic (ie, amygdala, anterior temporal, insula), and subcortical (ie, basal ganglia, thalamus) abnormalities also have been identified, but the findings are more variable. Across studies, the most robust and best-replicated finding is that of decreased frontal lobe function, although normal frontal as well as frontal hyperactivity also has been reported (Figure 3). Localization of abnormalities within the frontal lobe includes dorsolateral and ventral lateral prefrontal cortex (Brodmann Areas 9,46,10,47), as well as orbital frontal and ventral medial frontal cortices (Brodmann Areas 11,32,10). Findings generally are bilateral, although asymmetries are described. Cingulate changes also are seen commonly and consistently involve anterior dorsal sectors (Brodmann Areas 24a-c). An anatomical key to these referenced Brodmann regions is shown in Figure 4 (see page 263).

Differences among patient subgroups (eg, unipolar, bipolar, neurological, familial, melancholic, reactive), as well as heterogeneous expression of clinical symptoms such as illness severity, cognitive impairment, anxiety, and psychomotor slowing, are thought to contribute to the described variance, but there is not yet a consensus. The best-replicated behavioral correlate of a resting state abnormality in depression is that of an inverse relationship between prefrontal activity and depression severity.22 Prefrontal activity also has been linked to psychomotor speed and executive functions; parietal and parahippocampus with anxiety; medial frontal and cingu-
presence of such clinical symptom variability within a given patient cohort does not appear to explain the "consistent" inconsistencies in the published imaging literature. Therefore, alternative explanations for frontal hypermetabolic and hypometabolic profiles seen in seemingly comparable experimental groups are needed, particularly if these techniques are ever to have relevance to the clinical evaluation of individual patients.

Alternatively, one can consider variable patterns from a systems perspective, where dysregulated "network" activity identified in the baseline depressed state is seen to reflect both foci of primary dysfunction and sites of adaptive (and maladaptive) compensatory processes (Figure 5, see page 264). Such a construct would theoretically accommodate the reported variability among published depression cohorts, as well as the recognized heterogeneity of depressive symptoms and purported etiologic risk factors. Thus, the observed depressive behavior is understood as the sum of these various synergistic and competing brain responses to a depressogenic trigger, likely influenced by factors including heredity, temperament, early-life experiences, and previous depressive episodes.

Hypothetically, in the setting of sustained overactivity of the regulatory "network" (whatever its cause), an exaggerated or hypersensitive compensatory response may result in an agitated, mood-reactive, ruminative depressive state in one patient, whereas failure to initiate or maintain any such compensatory response may lead to anergy, psychomotor retardation, mood nonreactivity, and apathy in an equally severe second patient. In this context, one might hypothesize that patients in a sustained but partial compensatory state will respond to either pharmacologic or cognitive treatments, consistent with empirical clinical experience as well as randomized controlled studies. On the other hand, extreme states of this compensatory network (either overactive or underactive) will require specific treatments.

A more severe impairment or failure of this compensatory network will identify treatment-resistant patients and a need for more aggressive interventions. It therefore is postulated that a specific neural signature ultimately may provide a therapeutic road map for optimal treatment selection for major depression if baseline variability and associated change patterns with different treatment interventions can be characterized fully.

**BRAIN TARGETS OF ANTIDEPRESSANT TREATMENTS**

As seen in studies of the baseline depressed state, PET measures of regional glucose metabolism and regional cerebral blood flow have also proven to be sensitive indices of changing brain function following various treatments. Changes in cortical (ie, prefrontal, parietal), limbic–paralimbic (ie, cingulate, amygdala, insula), and subcortical (ie, caudate/pallidum, thalamus, brainstem) regions have been described following such diverse treatments as medication, psychotherapy, sleep deprivation, electroconvulsive therapy (ECT), rTMS, ablative surgery, and DBS. While normalization of frontal abnormalities is the best-replicated finding, other regional effects are reported with variable patterns with different treatments. These modality–specific effects are consistent with the hypothesis that different interventions modulate specific regional targets, resulting in a variety of complementary, adaptive chemical and molecular changes sufficient to re-establish a euthymic, remitted state. The functional neural architecture of these observed change patterns for pharmacotherapy and psychotherapy are contrasted below.

**Pharmacotherapy**

Pre-clinical studies of antidepressant
medications emphasize a “bottom-up” chain of events, including aminergic reuptake inhibition and associated presynaptic autoregulatory desensitization, upregulation and downregulation of multiple post-synaptic receptor sites, and receptor-mediated second messenger and neurotrophic intracellular signaling effects.12,13,30 Requisite brain regions mediating these events are unknown, although putative primary sites of action are described in the dorsal raphe, locus ceruleus, hippocampus, and hypothalamus, with secondary changes in frontal and other cortical regions.

Neuroimaging studies of antidepressant effects demonstrate differential acute and chronic subcortical and cortical changes,15,16,28,29,35 consistent with the time course and location of changes identified in animal studies.30 Across studies of antidepressant response to short-term treatment (6 to 12 weeks), prefrontal cortical changes are the most consistently reported, with normalization of frontal overactivity and underactivity both described. Additionally, changes are seen in limbic and subcortical regions, with decreases in activity observed most commonly.

Our own studies of selective serotonin reuptake inhibitor (SSRI) pharmacotherapy, using both paroxetine and fluoxetine, consistently have identified a pattern that includes frontal, parietal, brainstem, and posterior cingulate increases and striatal, thalamic, hippocampal, and subgenual cingulate decreases (Figure 6, see page 265).15–18 The time courses of these medication effects and differences between responders and nonresponders have provided additional localizing clues about critical brain changes mediating depression remission with this class of medication.

To evaluate these time-dependent brain changes, male inpatients treated with fluoxetine using a placebo-controlled double blind design15,17 were scanned before and after 1 week and 6 weeks of chronic treatment. Anatomically concordant metabolic changes were seen with both active fluoxetine and placebo response after 6 weeks (relative to baseline), with increases in prefrontal, parietal, and posterior cingulate regions as well as decreases in the subgenual cingulate. However, additional changes were seen only with active medication in the insula, striatum, and hippocampus. There were no regional changes unique to the placebo responders. While not tested by an extended continuation study, it was speculated from these findings that the hippocampal, brainstem, striatal, and insula changes seen uniquely in active drug-treated responders might be critical to maintaining clinical response long-term. In support of this argument, failed response to active fluoxetine was associated with persistent hippocampal increases and posterior cingulate decreases—the pattern seen in all active drug-treated subjects after 1 week of treatment, irrespective of eventual outcome.15

The reversal of the first week’s pattern at 6 weeks in only those patients who showed clinical improvement suggests a process of neural adaptation in specific brain regions with chronic treatment. These responder—nonresponder differences are consistent with the time course and location of changes identified in animal studies of SSRI antidepressants, which emphasize early brainstem and hippocampal changes and late cortical effects.12,30

Without a comparable study contrasting sham treatment to a nonpharmacologic treatment modality, one could easily conclude from these findings that the subgenual cingulate and prefrontal changes shared by both active and sham medication reflect a final common pathway for depression remission. At the time these data were first analyzed, there were not yet published studies demonstrating patterns specific to psychotherapy or cognitive therapy (with or without a sham condition) to negate such a conclusion. If the common subgenual...
and prefrontal changes seen in the fluoxetine-placebo study were in fact due to nonspecific psychological effects, one would expect similar and likely more robust changes with a more formal course of a specific psychological intervention. As is illustrated in the next section, such a hypothesis proved incorrect.

**Psychotherapy**

In contrast to pharmacologic treatments, theoretical models of CBT action in the treatment of depression generally implicate "top-down" mechanisms, as the intervention focuses on modifying attention and memory functions involved in the mediation of depression-relevant explicit cognitions, affective bias, and maladaptive information processing, putatively localized to orbital, medial frontal, prefrontal, and anterior cingulate regions.\(^{31,32}\) The time course of symptom changes with CBT further supports an initial cortical site of action, as improvement in cognition (eg, hopelessness) precede other changes (eg, vegetative symptoms) — a timeline not typical in patients treated with pharmacotherapy.\(^{33}\)

Recent functional imaging studies examining brain changes following interpersonal psychotherapy (IPT) and CBT report a variety of regional effects, most prominently decreases in prefrontal cortex,\(^{18,28,29}\) but with differential nonfrontal changes depending on the specific therapy employed (ie, CBT versus IPT). Brody and colleagues,\(^{28}\) for example, identified comparable prefrontal and cingulate decreases with both IPT and paroxetine, with no unique changes for either treatment.

Our own study comparing remission to cognitive behavioral therapy versus paroxetine\(^{18}\) also identified changes in the frontal cortex and cingulate, but with unique regional change patterns for the two treatments (Figure 6). Anatomically concordant but functionally opposite change patterns were seen in the prefrontal, parietal, and posterior cingulate cortices (as CBT decreases, paroxetine increases) and the hippocampus (as CBT increases, paroxetine decreases). Unique, treatment-specific regional changes included medial and orbital frontal decreases and mid-cingulate increases with CBT, and subgenual cingulate and thalamic decreases with paroxetine.

![Figure 6](image)

**Figure 6.** Metabolic change patterns with paroxetine and cognitive-behavior therapy treatment. Fluoro-deoxyglucose PET scans, pre- versus post-treatment changes: axial (A), coronal (B), and sagittal (C) views. A pattern of prefrontal, parietal, and posterior cingulate increases (Column A) and hippocampal decreases (Column B) is seen with remission mediated by paroxetine. The reverse pattern is seen with CBT. Additional unique changes are seen with each treatment (Column C): decreases in subgenual cingulate (Cg25) and thalamus with paroxetine; increases in mid cingulate (24c) and decreases in medial (9/10) and orbital frontal (11) with cognitive-behavior therapy. Adapted from Goldapple et al.\(^{18}\)

![Figure 7](image)

**Figure 7.** Baseline network patterns distinguishing response outcomes to different treatments. A prescribed analytic model linking prefrontal (PF9), medial frontal (mF10), orbital frontal (OF11), subgenual cingulate (Cg25), rostral cingulate (Cg24a), anterior thalamus (aTh), and hippocampus (hc), was used to test for overall differences between separate cohorts of depressed subjects subdivided as a function of treatment type and response outcome. Pathways differences among three treatment groups are illustrated. Solid arrows represent positive path coefficients (positive effect of a region on its target); dotted arrows represent negative path coefficients. Values of path coefficients are not shown but are represented by thickness of arrows. Light Grey: common paths across comparison groups. Green: significant paths distinguishing cognitive-behavior therapy responders; Blue: significant paths distinguishing selective serotonin reuptake inhibitor responders; Red: significant paths distinguishing treatment-resistant patients. Adapted from Seminowicz et al.\(^{26}\)

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While neither responder–nonresponder differences nor the time course was evaluated, inferences from the IPT and CBT studies suggest that prefrontal changes occur early with psychotherapy, as it is seen with both treatments despite differences in the degree of response (partial response at 8 weeks in the IPT study; remission at 16 weeks in the CBT study). The additional increases in hippocampus and mid-cingulate and decreases in orbital frontal and medial frontal cortices seen in the CBT study may additionally reflect three things: late-occurring effects with the more chronic treatment course, remission as opposed to response correlates, or CBT-specific effects. Systematic studies of the time course of brain changes in responders and nonresponders to both IPT and CBT will be required to determine the most likely explanation.

In support of CBT-specific effects in medial frontal and cingulate regions are studies of emotional self-reference and cognitive control performed in nondepressed subjects demonstrating similar regional effects to those seen with CBT. An important last observation is that there was no overlap between the pattern of brain changes seen with either psychotherapy or placebo. Such differences not only support the obvious conclusion that psychotherapy is an active treatment with modality specific effects on regional brain function but also provide evidence that placebo response is not simply a non-specific type of psychotherapy.

**RESPONSE PREDICTORS**

In light of the observed change differences between responders and nonresponders to a given treatment and variable brain changes with response to disparate treatments, an obvious related question is whether baseline scan patterns might effectively predict treatment outcome or guide treatment selection. Toward these goals, retrospective analyses have reported consistently that increased pretreatment activity in the rostral anterior cingulate (Brodmann Area 24a) distinguishes eventual responders from nonresponders to several different antidepressant interventions, most notably, medication and sleep deprivation.

These findings initially were interpreted as physiological differences among patient subgroups critical to brain plasticity or adaptation to illness, including propensity to respond to treatment. Evidence of persistent hypermetabolism in patients who remain in full remission on continued SSR1 treatment for more than 1 year further suggested a critical compensatory or adaptive role for the rostral cingulate in maintaining clinical response long-term. Cingulate activity, however, does not appear to distinguish among responders to different treatment modalities.

To look for other markers that might identify preferential response to CBT or medication, the known variability in prefrontal cortex previously seen was revisited. Surprisingly, in contrast to the anterior cingulate findings, baseline frontal patterns, as illustrated in Figure 3, were uninformative as a predictor of treatment response. In fact, published treatment studies of various interventions describe both hypermetabolic and hypometabolic baseline frontal patterns in patients who eventually improve. Taken together, these observations suggest a more complex interaction between the cingulate and frontal cortex than previously appreciated.

**Model Based Response–Group Differences**

To further explore these apparent response subtype differences, an alternative analytic strategy was employed that more directly tested our circuit model of depression. In a meta-analysis of the baseline fluoro-deoxyglucose PET scans from the previously described treatment studies of SSRI pharmacotherapy and CBT, the strength and direction of ef-
fective connections between regions in a predefined seven-region model structure were estimated using structural equation modeling. The prescribed model showed significantly different baseline patterns of best fit for different subgroups of patients defined by response outcome (Figure 7, see page 265): a predominantly cortical pattern was found in the CBT responder group; a limbic–cortical pattern in the paroxetine responder group; and a limbic–subcortical pattern in more treatment-resistant patients. Examination of clinical and demographic variables did not similarly distinguish the groups.

While preliminary, these structural equation modeling contrasts provide early proof of principle that this type of functional connectivity approach may be useful in identifying treatment-response subtypes among seemingly comparable groups of patients with depression. Ongoing studies are examining this possibility using various multivariate analytic strategies. Interestingly, it was the use of this multivariate approach that confirmed a more central role for the subgenual cingulate (Brodman Area 25) rather than the rostral anterior cingulate (Brodman Area 24) in defining potential depression subtypes. As these methods are refined, prospectively studies testing the predictive power of putative treatment-specific response subtypes are anticipated.

**DIRECT MODULATION OF THE DEPRESSION NETWORK USING DBS**

Among the series of studies described, the involvement of the subgenual cingulate (Cg25) is prominent. Not only are changes in this region critical for antidepressant response to active and placebo pharmacotherapy but functional connectivity of this region also best characterizes treatment response and resistance. Anatomical changes on structural MRI scans and postmortem identification of glial abnormalities are reported in samples of patients with depression. In addition, structural and functional variability in this region has been recently linked to a normal polymorphism in the serotonin transporter.

These converging anatomical findings complement a large functional imaging consistent with predictions from both the animal studies and our functional connectivity network meta-analyses. Continued refinement of this neural circuit depression model, informed by genetic advances and basic preclinical studies, may ultimately provide a clinically relevant perspective of the depression phenotype at the neural systems level with effects on the diagnosis and management of individual patients.

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