

▲ 13.5 Brain Circuits in Major Depressive Disorder and Bipolar Disorder

JONATHAN B. SAVITZ, M.D., AND WAYNE C. DREVETS, M.D.

BACKGROUND

The lifetime prevalence rates of unipolar depression (UPD) in males and females of first-world countries are approximately 15 and 25 percent, respectively. The figures appear to be equally disheartening in developing countries: The 12-month prevalence of major depressive disorder in South Africa is roughly 5 percent. It is therefore not surprising that 25 percent of all visits to health care providers around the world are estimated by the World Health Organization (WHO) to be depression related. Bipolar disorder (BD) has equally serious implications for public health with the WHO listing the disorder as the sixth leading cause of disability in the world among people in the 15 to 44 year-old category in 1990. Recently, the National Comorbidity Survey Replication found that on average 27.2 and 65.5 workdays are lost in the United States each year among people with UPD and BD, respectively. Tragically, up to 30 percent of BD patients attempt suicide, approximately half of them successfully, with an odds ratio for attempts of about six compared to three for UPD.

These figures are perhaps partly explained by the modest efficacy of treatment. Only about half of all patients respond to a first-line trial of antidepressant therapy, and the mean drug–placebo difference in response rate is only 10 percent in the average randomized, controlled trial. The picture is even less sanguine for psychotherapy with most data showing psychotherapy to be equivalent to or less effective than pharmacotherapy despite the fact that clinical trials suffer from a selection bias for milder cases.

Clearly understanding the etiological and pathophysiological basis of affective illness is an imperative. Unfortunately, progress has been retarded by the sheer complexity of the neural systems involved in mood regulation, and thus current nosological systems are based on symptomatology rather than etiology. Despite these setbacks, advances in neuroimaging and genetics provide reasons for cautious optimism as psychiatry resolves to place itself on an equal footing with medical disciplines such as neurology. Here, the neuroimaging correlates of depression in the guise of both UPD and BD are reviewed and interpreted with reference to developmental and degenerative pathophysiological mechanisms.

NEUROANATOMY

Extensive interconnecting neural networks are responsible for the generation and regulation of mood and emotion. These networks can be at least partly subsumed under the iterative activity of three cortical–striatal–limbic circuits encompassing a dorsolateral/dorsomedial frontal circuit, an orbital frontal circuit, and a ventromedial frontal circuit, which includes the ventral aspects of the anterior cingulate cortex (ACC). These circuits operate in parallel with prefrontal–cortex–originating bidirectional projections to different nuclei of the striatum, globus pallidus (GP), thalamus, amygdala, hippocampus, hypothalamus, habenula, and periaqueductal gray (PAG). This concept is illustrated in Figure 13.5–1. Figures 13.5–2 and 13.5–3 show anatomical

Fig. 13.5–1
 Fig. 13.5–2
 Fig. 13.5–3

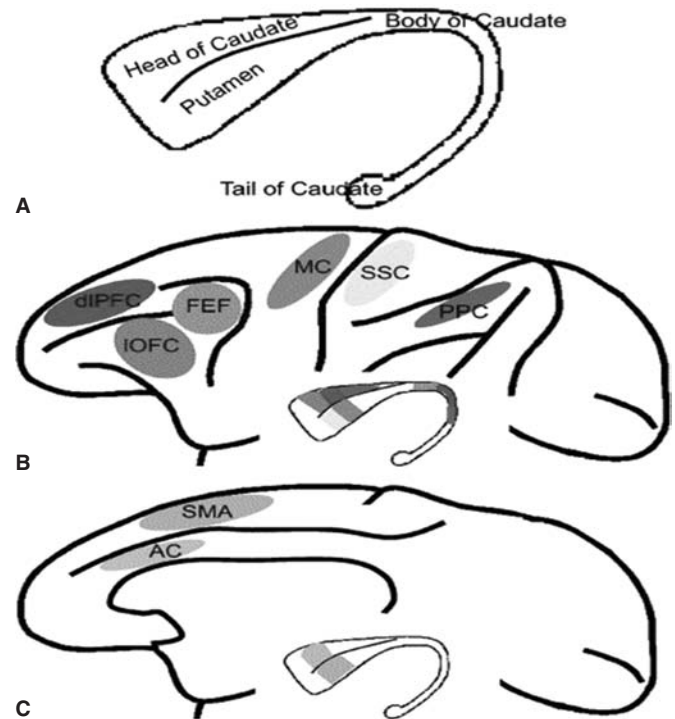


FIGURE 13.5–1. Topographically organized frontal basal ganglia pathways. (From Utter AA, Basso MA: The basal ganglia: An overview of circuits and function. *Neurosci Biobehav Rev.* 2008;32:333, with permission.)

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details of the orbital and ventromedial surfaces of the human brain, respectively.

Unfortunately, the limitations of current neuroimaging modalities preclude researchers from evaluating the activity or neuroanatomical changes associated with each of these circuits in isolation. Not only do these three networks interact with each other, but the diminutive size of many of these nuclei prohibits accurate analysis with current imaging technologies. The amygdala, for example, is a heterogeneous structure of at least 14 different nuclei, some of which may share homology with the adjacent structures such as the ventral striatum and olfactory cortex. Extant imaging data therefore focus on various structures of the prefrontal cortex, basal ganglia, and limbic system, and consequently this format will be followed here.

IMPORTANT METHODOLOGICAL POINTS

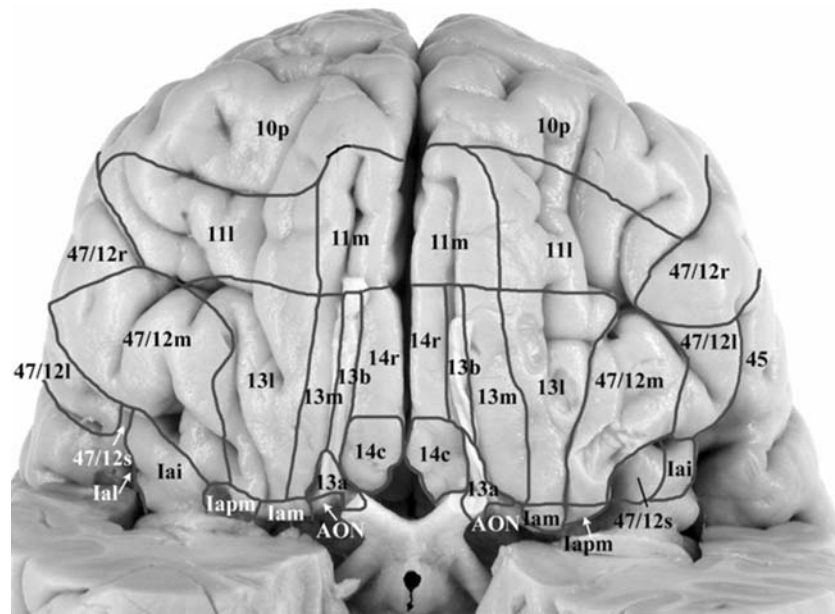
In order to read the neuroimaging literature, and indeed imaging genomics data, with a critical eye, the following methodological issues should be kept in mind:

(1) In many studies, participants are imaged on medication, possibly disguising the true nature of the underlying pathophysiological changes. Regional cerebral blood flow (rCBF) and metabolism of various neuroanatomical regions may be reduced by antidepressants, antipsychotics, and anxiolytics. In addition, psychotropic drugs have been shown to alter both the behavioral and the neurophysiological response to the emotionally valenced stimuli used as neurocognitive probes in functional magnetic resonance imaging (fMRI) studies.

Moreover, the neurotrophic effects of lithium, neuroleptics, and mood stabilizers on the hippocampus and other neural tissue have been persuasively demonstrated. Finally, synaptic plasticity or functional interactions between regions may also be altered by antidepressant

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FIGURE 13.5-2. Architectonic subregions of the orbital surface of the human brain. (From Ongur D, Ferry AT, Price JL: Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol.* 2003;460:425, with permission.)



drugs. For example, a recent fMRI study showed that depressed patients suffer from reduced functional coupling of the amygdala with diverse brain regions including the hippocampus, caudate, putamen, and ACC; an effect reversed by treatment with fluoxetine. A return of left amygdala activity to the normal range has been observed af-

ter antidepressant treatment in both depressed patients and healthy volunteers treated with citalopram.

(2) Positron emission tomography (PET) and fMRI measures of the metabolic activity or perfusion of small structures like the amygdala suffer from the problem of partial voluming effects. Inadequate spatial resolution of the region of interest causes adjacent white matter (WM) and neural tissue with lower metabolic rates to be included in the analysis, leading to an underestimation of metabolic activity. This was a particularly salient problem with older imaging technology, which was characterized by lower spatial resolution. Similarly, draining vein artifacts may bias the blood oxygenation level dependent (BOLD) changes measured by fMRI.

An example of this potential confound can be found in the authors' own work. Initially, evidence of reduced metabolic activity in conjunction with reduced volume of the subgenual ACC was found in the depressed phase of both UPD and BD. When metabolic measures were corrected for the partial volume averaging effects of the reduction in cortical volume, however, the data instead implied that subgenual ACC activity was elevated during depression. Another example is the consistent reports of both hypermetabolism and volume reductions of the amygdala. State-of-the-art PET imaging detects, on average, a 6 percent difference in amygdala activity between depressed patients and controls, but because of partial voluming effects, the true magnitude of the difference is likely to be closer to 70 percent.

A related point is that there is a danger that imaging resolution limitations may lead to the implicit reification of neuroanatomical function. In other words, gross anatomical structures may not be uniformly affected by mood disorders simply because they are imageable units.

(3) A great deal of genetic and phenotypic variation can be found within current nosological categories, and it is thus likely that the exact pattern of depression or BD-associated neuropathology will vary across subgroups of affectively ill patients. The relatively embryonic state of the field has unfortunately meant that these issues have thus far been largely neglected.

For example, there is some evidence that patients who are recurrently ill and those subjects who have experienced one lifetime episode of depression may differ from each other genetically. Other potentially salient variables that researchers do not usually address include differences in age of onset, family history of UPD or BD

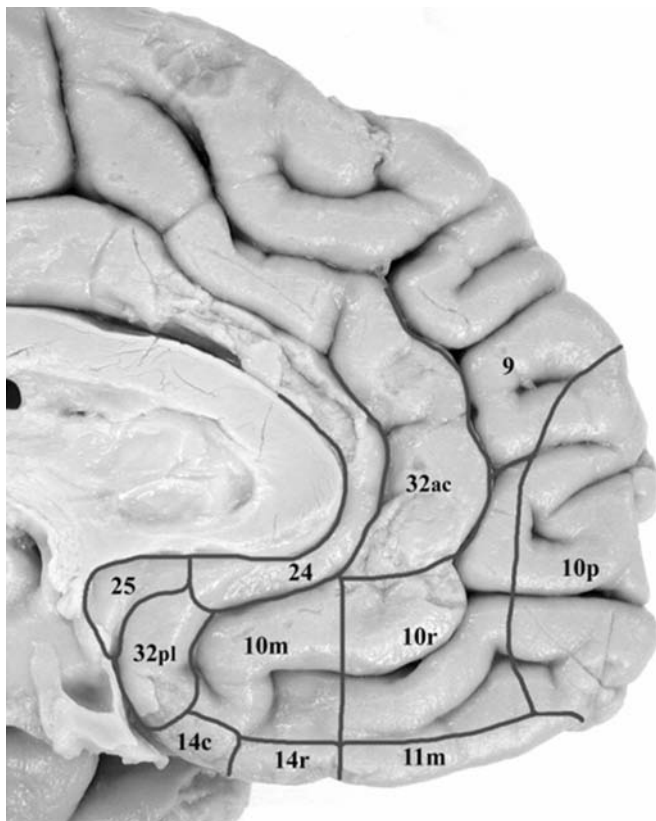


FIGURE 13.5-3. Architectonic subdivisions of the medial surface of the human brain. (From Ongur D, Ferry AT, Price JL: Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol.* 2003;460:425, with permission.)

illness, the effect of exposure to childhood trauma, and the presence of absence of a history of psychosis in BD participants. As will be pointed out below, findings from the pediatric BD literature often differ substantially from adult-derived data, possibly because of the inclusion of individuals with a broader phenotype of severe mood dysregulation (irritability and hyperarousal), which overlaps with attention-deficit/hyperactivity disorder (ADHD).

(4) The differences between the neuroimaging correlates of acutely symptomatic and remitted patients are likely to vary substantially depending on the brain structure or circuit under evaluation. Thus, it is not always clear whether results obtained from patients imaged in the depressed state can be extrapolated to remitted populations.

(5) Genetic association studies are plagued by false positive results, largely because with approximately 20,000 genes and multiple variants within each gene of interest, the a priori probability of a true association is low. Sample sizes in analyses that combine genetic and imaging data are by nature small, although this is offset to some extent by the relative precision of the phenotypic data that are collected. The problem can be partially ameliorated by targeted hypotheses.

EXCITOTOXICITY

Before a review of the imaging literature it may be instructive to discuss the dominant view regarding the pathogenesis of both GM and WM tissue volume loss recorded in the literature: Glutamate-induced excitotoxicity. Excessive glutamate release coupled with *N*-methyl-D-aspartate (NMDA) receptor stimulation can be toxic to astrocytes and oligodendrocytes as well as neurons. A significant rise in intracellular calcium levels depolarizes the mitochondria, producing free radicals such as nitric oxide and hydrogen peroxide, which directly damage the cell, as well as proapoptotic proteases and endonucleases. These toxic effects may also be potentiated by the release of proinflammatory cytokines such as tumour-necrosis factor α (TNF- α) that inhibit extracellular glutamate reuptake.

The link between psychological stress and excitotoxicity is believed to be at least partly mediated by glucocorticoid-induced inhibition of the glutamate transporters or an upregulation of the expression of NMDA receptor subunits together with activation of voltage-gated sodium channels and a modulation of calcium influx. Because most glutamate transporters are found on glial cells such as astrocytes,

dysfunction or loss of these cells may lead to a predisposition to excitotoxicity, which ultimately appears as MRI-measured volume decrements.

NEUROIMAGING FINDINGS

The Amygdala

The amygdala plays a pivotal role in imbuing perceptual stimuli with emotional significance, especially emotions such as fear, anger, and sadness, providing ostensible evidence for its involvement in depression.

Neuroimaging studies of the amygdala in patients with BD are characterized by an age-related dichotomy. In adults, the predominant pattern is one of increased amygdala volume, while in children and adolescents the reverse applies. Functional analyses of baseline metabolism or perfusion have been largely limited to the adult population and are indicative of increased activity, which in some cases correlates positively with severity of depression. Further, increased response of the amygdala to negatively valenced faces is a widely reported finding in the literature.

Because glutamate is largely responsible for the elevated activity observed in the functional imaging literature, reports of increased amygdalar volumes are counterintuitive. One suggestion is that elevated activity is an adaptive mechanism that enhances sensitivity to aversive stimuli, thereby facilitating fear conditioning and anxiety-related phenomenology. In order to achieve this goal, connections between the amygdala and its output structures such as the hippocampus, hypothalamus, nucleus basalis, PAG, and ventral tegmental area (VTA) need to be strengthened, hence the pattern of neuronal and dendritic hypertrophy. A simplified model of the effects of the physiological effects of amygdala dysfunction is shown in Figure 13.5-4.

Nevertheless, the structural imaging data are at odds with two recently published postmortem studies that have reported decreased neuronal somal size (suggestive of reduced axodendritic connections) in the lateral amygdaloid and accessory basal parvocellular nuclei and a decreased number and density of lateral amygdaloid nucleus neurons, respectively.

The postulated hypertrophy of the amygdala is also inconsistent with volume decrements seen in childhood BD. One possibility is that pediatric samples tend to be characterized by extensive comorbidity,

Fig. 13.5-4

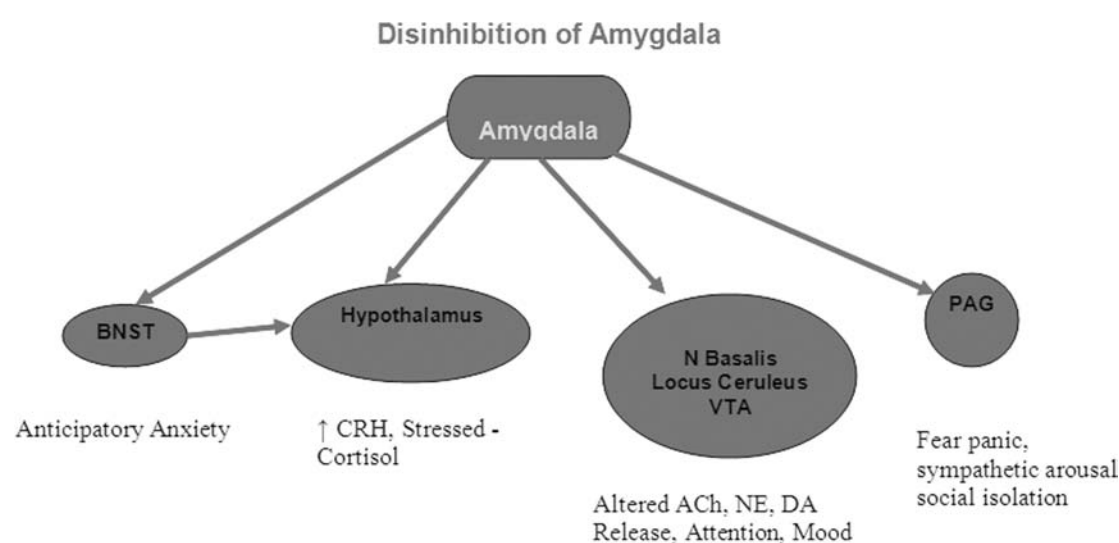


FIGURE 13.5-4. The physiological effects of amygdala disinhibition on associated limbic structures.

especially ADHD, which has been independently associated with gray matter (GM) volume loss. Developmental factors may also blur the picture. Certainly, in nonhuman primates the amygdala goes through an extensive period of functional maturation that mirrors changes in social behavior.

Reports of amygdalar volumetric decrements are more common in adult UPD samples. These data are congruent with histological data indicative of a lower density of glial cells in the amygdalae of patients with UPD, an effect that appears to be the result of changes in oligodendrocyte density of the left hemisphere.

Resting state functional data are largely suggestive of hypermetabolism, and this is echoed by BOLD responses to emotional challenges. For example, in one study Siegle and colleagues found that amygdalar responses to negative words were no longer visible after 10 seconds in healthy controls but persisted in depressed patients for at least 25 seconds, on average. This type of finding is consistently reported in the literature and may be ameliorated by antidepressant treatment, which is hypothesized to facilitate the reassertion of prefrontal cortex control over limbic structures like the amygdala.

Nevertheless, as alluded to above, the caveat associated with most analyses of the amygdala conducted to date is that the images for these studies were acquired using 1.5-T scanners, which do not have the resolution to allow for the adequate definition of the boundaries of this diminutive region because of its proximity to other GM structures such as the claustrum, hippocampus, and basal forebrain.

The Hippocampus

The hypothalamic-pituitary-adrenal (HPA) axis acts to modulate physiological arousal and the release of hippocampus-bound glucocorticoids, which facilitates hippocampal-mediated encoding and storage of important information together with its environmental context. Animal studies suggest that the hippocampus may in turn play an inhibitory role in the regulation of the amygdala as well as of HPA axis activity.

Preservation of hippocampal volume is an oft-recorded characteristic of UPD populations. Nevertheless, review of the literature elicited a significant number of studies detecting evidence of hippocampal atrophy in depressed patients as well as a postmortem study indicative of neuropil loss. The majority of these studies made use of elderly, middle-aged, or chronically ill populations, suggesting the presence of etiological heterogeneity.

Depression may be a prodromal symptom of dementia. Middle-aged individuals (often carriers of the apolipoprotein $\epsilon 4$ allele, a risk factor for Alzheimer's disease) may show subtle signs of cognitive dysfunction and parahippocampal metabolic changes more than a decade in advance of diagnosable dementia. Nonetheless, perhaps the more likely explanation in most samples is a depression-mediated pathological effect on neural, and in particular, hippocampal tissue.

The seminal studies of Sapolsky, McEwen, and colleagues highlighted the plastic response of the hippocampus to environmental vicissitudes. While generally adaptive, for example, plasticity is crucial for learning and memory as well as maintenance of goal-directed behavior, the potential for stress-induced plasticity may have "unintended" consequences, among them, neuronal damage.

Prolonged prenatal and adult stress in primates, rodents, and tree shrews leads to selective hippocampal damage including apoptosis, depressed long-term potentiation (LTP) and neurogenesis, as well as apical dendritic atrophy. Recent studies have suggested that astroglia and oligodendrocyte function is also impacted by chronic psychosocial stress, with significant reductions in cell number and volume. Analogous effects have been noted in posttraumatic stress disorder

(PTSD). As discussed above this process is likely mediated by glucocorticoid receptor binding, glutamate release, and excitotoxicity. Theoretically, hippocampal tissue loss may disinhibit the release of cortisol, resulting in an increased risk of excitotoxic events in different regions of the brain, including the hippocampus. See Figure 13.5–5.

Regarding BD, despite isolated reports of volumetric decrements, the predominant pattern is one of preservation of hippocampal tissue in adult populations. The discrepancy in UPD and BD hippocampal imaging findings may be an artifact of treatment with mood stabilizers such as lithium.

Animal studies originally demonstrated that lithium promotes hippocampal neurogenesis and LTP. Moore and colleagues found that a sample of BD patients treated for 4 weeks with lithium showed a 3 percent (24 cm³) increase in whole brain GM volumes from baseline. More recent studies comparing lithium-treated and non-lithium-treated groups have replicated these data with increased GM volumes recorded in large cortical areas, including the hippocampus.

Comparable effects have been noted with other classes of mood stabilizers, especially valproate. With the exception of the experimental drug tianeptine, the neurotrophic properties of antidepressants are less persuasive.

The Basal Ganglia

The basal ganglia (BG), made up of the caudate, putamen, GP, subthalamic nucleus (STN), and substantia nigra (SN), were traditionally conceptualized as a center of motoric integration. This view has, however, evolved over time as the neuropsychiatric symptoms of Parkinson's and Huntington's disease (PD and HD) patients became clear. Further, deep brain stimulation of these nuclei has been partially successful in the treatment of severe depression.

Motor, sensory, and emotional data appear to travel in parallel but segregated pathways between the prefrontal cortex, the BG, and subcortical structures in a topographically organized manner, as illustrated in Figure 13.5–1. More specifically, the striatum, which is composed of the caudate and putamen, receives excitatory input from the dorsal, orbital, and ventromedial regions of the frontal cortex. The dorsal aspects of the frontal lobe are connected to the dorsal caudate while the anterior cingulate cortex and orbitofrontal cortex project to the ventral and medial surfaces of the striatum and the anterior caudate, respectively (Fig. 13.5–1). In addition, the ventral or limbic striatum (ventral caudate, nucleus accumbens, and olfactory tubercle) receives dopaminergic input from the SN and VTA, glutamatergic input from the amygdala and thalamus, and serotonergic input from the dorsal raphe nucleus.

The complicated anatomical structure of the diverse array of nuclei making up the BG possibly explains the current lack of clarity in the imaging literature. Although a postmortem study of a combined UPD and BD sample detailed volumetric reductions of the left nucleus accumbens, the bilateral pallidum, and the right putamen, subjects with BD have generally failed to display morphometric changes to the caudate or putamen.

In contrast, some studies have suggested BD-associated striatal enlargement in both adult and pediatric samples. Metabolic activity or perfusion has also been reported to be elevated in manic or hypomanic as well as depressed samples. As in the case of the hippocampus, it is likely that these analyses are confounded by treatment effects. Enlargement of the BG nuclei is a well-known effect of antipsychotic medication, which is included in treatment regimens for BD patients.

To complicate matters further, reduced striatal volumes have been associated with length of bipolar illness and an older age of onset,

Fig. 13.5–5

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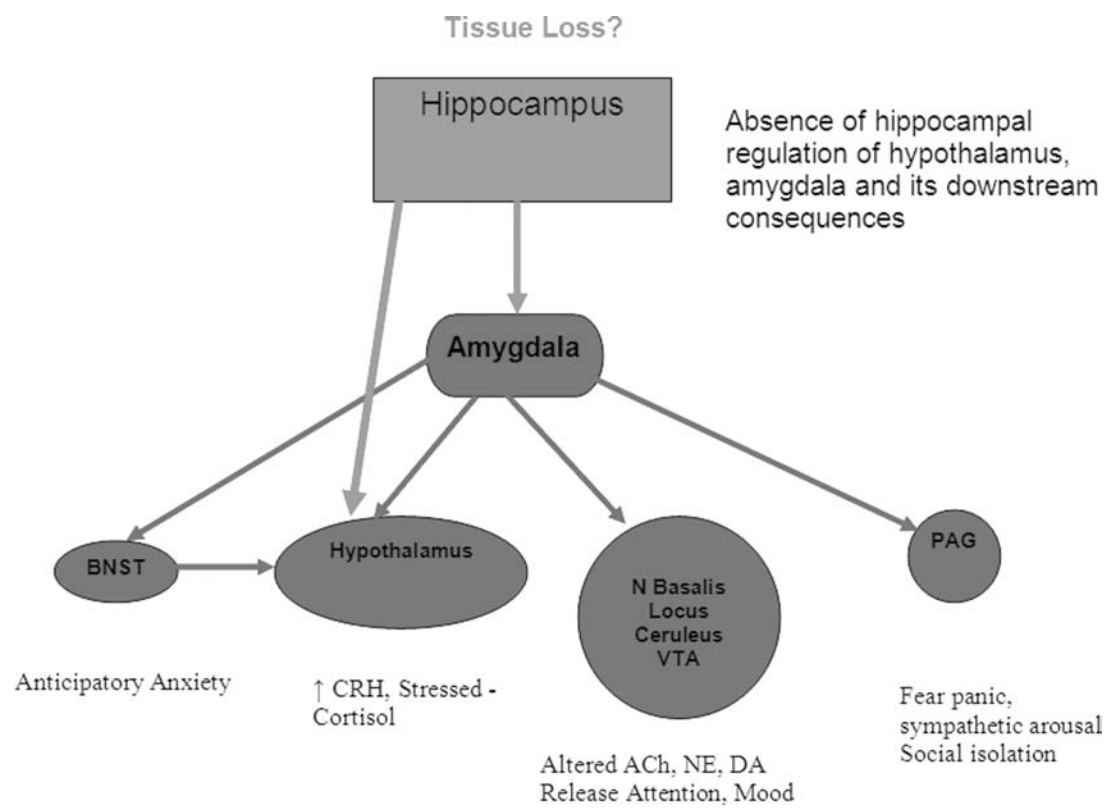


FIGURE 13.5-5. Dysregulation of hippocampal control over limbic structures and its potential effects.

suggesting a potential role for chronicity or cerebrovascular disease. This notion is consistent with reports of WM lesions of the BG in elderly patients with depression (see below). Nevertheless, striatal volume reductions have also been reported to be a marker of disease diathesis in the relatives of BD probands.

A number of early studies raised the possibility of BG volume reductions in UPD, although these data have generally not been borne out by subsequent analyses. As in the case of BD it is possible that volume loss is related to cerebrovascular disease, explaining why it is often associated with late-onset and chronicity or severity of illness. A number of studies have reported decreased activity of the striatum in UPD. Nevertheless, hypometabolism in combination with reports of tissue loss may be indicative of partial volume averaging rather than a genuine diminution in metabolic activity.

In summary, interpretation of imaging studies of the BG is rendered difficult by the mass of contradictory results yielded through diverse scanning methodologies and population samples. More definitive pronouncements will no doubt follow advances in imaging technology.

If striatal and, more generally, medial-temporal lobe tissue loss is indeed occurring in UPD or BD, then enlargement of the adjacent ventricular system, especially the lateral ventricles, may be reflective of this atrophic process.

Ventricular Abnormalities

The preponderance of evidence for ventricular enlargement (mostly of the third or lateral ventricles) in UPD has been obtained in old or chronically depressed samples with late-onset illness. Although, excitotoxic processes operating in medial-temporal or lateral-prefrontal cortical tissue could theoretically cause ventricular enlargement, the

degree of subcortical atrophy that needs to take place in order to manifest as ventricular enlargement is unclear. Certainly, the equivocal evidence for volume loss of the BG does not appear to gel with substantial tissue loss associated with ventriculomegaly. Further, many studies reporting ventriculomegaly included BD subjects with an early age of onset who are likely to have been prescribed lithium and other mood stabilizers that putatively preserve hippocampal tissue and reduce ventricle size.

Although factors such as chronic alcohol abuse and incipient neurological disorders with prodromal depression may be important, the most parsimonious explanation is that enlargement of the ventricles is a consequence of vascular pathology. The issue of vascular dementia will be discussed in more detail in the following subsection on WM abnormalities.

White Matter Changes

An elevated incidence of deep frontal white matter hyperintensities (WMHs), especially WMHs of the deep frontal cortex and BG, may be characteristic of UPD and BD. WMHs are bright, high-intensity signals seen on T2-weighted MRI scans that are caused by circumscribed increases in water content. They are most likely indicative of a decrease in the density of WM due to demyelination, atrophy of the neuropil, and ischemia-associated microangiopathy, among others. The phenomenon is prevalent in elderly populations, and most individuals will display WMHs by the age of 85.

While the onset of major depression peaks in adolescence and young adulthood, an increased incidence is also seen in elderly individuals, contributing to the idea that "vascular depression," associated with multiple subcortical infarcts of an ischemic origin, plays a role in this age group.

Many epidemiological studies of elderly community-based samples and cross-sectional analyses of matched control and UPD groups have lent credence to the relationship between late-onset depression and WM lesions. So too have postmortem analyses reporting WM disease of the dorsolateral prefrontal cortex (DLPFC) in samples of elderly, and even middle-aged, depressed patients. One possible explanation for the increased incidence of WMHs is a change in the behavior of oligodendrocyte cells that myelinate axons. Postmortem studies have reported a downregulation of oligodendrocyte-related gene expression and decreased oligodendrocyte density in depression and BD.

An unresolved issue is whether the WM pathology–depression relationship is one of cause or effect. Although it is likely that vascular pathology causes depression, some studies have made attempts to match patients and controls (or statistically control) for the presence of cardiovascular risk factors and still find elevated rates of WMHs in their depressed samples. It is thus theoretically possible that depression predisposes to the development of small WM lesions via some unknown mechanism.

Some researchers have speculated that excess depression-associated secretion of serotonin by blood platelet cells facilitates cellular aggregation and therefore predisposes to atherosclerosis, thrombosis, and vasoconstriction. Another possibility that has been raised is impaired regulation of cerebrovascular reactivity—the compensatory dilatory capacity of arterioles to dilatory stimuli.

In contrast to the senescence-associated pathology characteristic of UPD, a significant minority of young BD patients with a relatively typical age of onset show WM abnormalities on MRI scans. It is plausible that, as in the case of UPD, people with BD have an excess of atherosclerotic risk factors that lead to microvascular pathology at an even earlier age than UPD.

BD is associated with a significantly increased prevalence of cardiovascular disease risk factors such as smoking, obesity, diabetes mellitus (DM), hypertension, and dyslipidemia, which have in turn been directly associated with the development of WMHs. Further, drug abuse is prevalent in BD populations, and stimulant drug-induced vasoconstriction may lead to WMHs.

Nevertheless, this hypothesis fails to fully account for the WM pathology noted in some pediatric BD samples. Perhaps, WMHs may also co-occur with some type of developmental insult. The etiology of these precocious lesions is unclear. Obstetric complications are well known to be associated with schizophrenia but are less widely reported in BD. Nevertheless, it is possible that perinatal hypoxic events precipitate bipolar illness in a vulnerable minority. This may partly explain the high incidence of comorbid ADHD seen in pediatric samples: Adverse perinatal events are associated with at least one subtype of ADHD, and WM abnormalities have recently been linked to the presence of ADHD in low-birth-weight children.

The high incidence of WMHs seen by Ahearn and co-workers in the unaffected relatives of one particular BD family suggests that genetic factors may also be at play. For example, depression is a relatively common sequela of the genetic disorder cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). As mentioned above, a number of postmortem analyses have provided evidence for the altered expression of genes impacting myelin or oligodendrocyte function in both UPD and BD, and genes of this class such as oligodendrocyte lineage transcription factor 2 (*OLIG2*), neuregulin 1 (*NRG1*), and v-erb-a erythroblastic leukemia viral oncogene homolog 4 (*ERBB4*) have been directly associated with affective illness.

One consequence of the pattern of deep frontal WM pathology commonly seen in affective illness is a disruption of the pathways

linking subcortical regions such as the striatum to functionally homologous regions of the frontal cortex—a version of the so-called “disconnection syndrome” described in detail by Norman Geschwind in the 1960s. Figure 13.5–6 provides a visual outline of this hypothesis. In the following three subsections the key areas of the prefrontal cortex involved in the regulation of mood and cognition will be discussed.

The Orbital Frontal Circuit

The orbital frontal cortex (OFC) on the ventral surface of the frontal lobe (Fig. 13.5–2) receives inputs from the ventrolateral amygdala and other limbic tissue such as the entorhinal and perirhinal cortices. It also projects directly to the amygdala, hypothalamus, and brainstem, integrating limbic data with sensory input and providing an early analysis of the reward value or aversiveness of stimuli. These data are then iteratively processed by higher-level circuits such as the medial frontal cortex (vide infra), which act together with the OFC to guide behavior in terms of the emotional valence of these stimuli.

The OFC has been known to be important for the regulation of emotional and by implication, social behavior, at least as far back as the notorious mid-19th century case of Phineas Gage and his postlesion impropriety. In the interim, lesions to the broader OFC region have been reported to be associated with depression, mood instability, and anxiety in other clinical case studies, providing further evidence for the central role of this network in the self-regulation of emotion and behavior.

Elevated metabolic activity or perfusion of the OFC has been generally found in young to middle-aged UPD samples—particularly acutely depressed subjects. Congruent with these data, serotonin depletion paradigms have produced a similar effect in remitted patients, and treatment with antidepressant medication, psychotherapy, and deep-brain stimulation has been associated with decreased metabolism of the OFC.

A postmortem analysis carried out by Rajkowska and colleagues uncovered a 12 percent decrease in the thickness of the rostral (but not the caudal) and a 15 percent decrease in the middle OFC in depressed patients compared to those of healthy controls, a finding that the researchers attribute to neuronal shrinkage with an attendant reduction in the volume of the neuropil. Further, a 15 percent decrease in glial cell density was observed in the caudal OFC. In the same vein, elderly populations with later-onset depression have returned MRI-based evidence of bilateral volume reduction of the OFC, and this phenomenon has more recently been extended to middle-aged samples. The combination of potentially elevated OFC activity and tissue loss is consistent with the operation of an excitotoxic process, but once again, the fact that a significant number of the patients in the samples demonstrating volume reductions became ill after the age of 40 raises the issue of etiological heterogeneity.

GM volume reductions of the OFC have also been inconsistently reported in adult and pediatric BD samples, and evidence of reduced glial cell density and neuronal size in the caudal OFC has been noted in a postmortem analysis. Few functional studies of the OFC have been carried out in BD samples, and thus the relationship between structure and function in this population remains unknown.

The Ventromedial “Emotion” Circuit

Neuroimaging data suggest that the strategically located pericallosal tissue of the ventromedial prefrontal cortex known as the ACC (BA 24, 25, and 32) (Fig. 13.5–3) forms part of a visceromotor network that plays a pivotal role in translating OFC-derived valenced data into

Fig. 13.5–6

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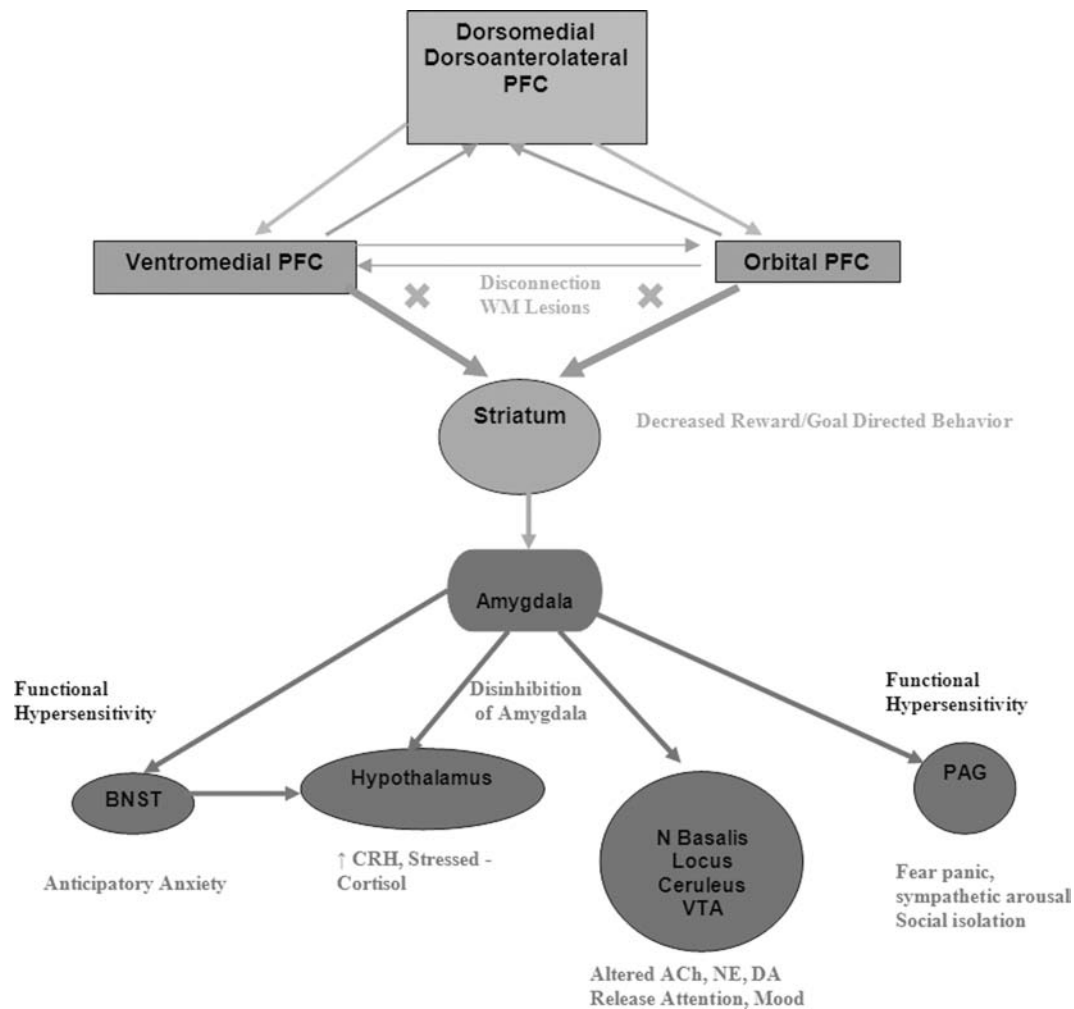


FIGURE 13.5-6. White matter lesions resulting in prefrontal cortex (PFC) basal ganglia disconnection and a hypothetical loss of PFC control over limbic nuclei.

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behavior. The importance of visceral responses to affective stimuli has been articulated by inter alia, Damasio and colleagues in the guise of the “somatic marker” (SM) hypothesis.

According to this model, a somatic marker—an unpleasant or positive viscerally generated stimulus such as anxiety or potential reward—is temporally paired with a predicted future outcome. This juxtaposition of cognitive and emotional inputs ensures competent decision-making in complex situations because it allows individuals to anticipate the future consequences of their actions.

Wayne Drevets and colleagues carried out the first well-controlled imaging study of the medial prefrontal cortex in affective illness. Both BD and UPD patients with a family history of affective illness showed left hemisphere GM loss in a region immediately ventral to the genu of the corpus callosum—the subgenual prefrontal cortex (SGPFC). Further, the medication-free patients displayed reduced metabolism of the left SGPFC as demonstrated by PET.

Decreased activity of, in particular, the left SGPFC has been recorded in many other studies of UPD, although more recent evidence of increased UPD- and BD-associated metabolic activity of the ventral emotion circuit suggests that the early reports may have been confounded by partial volume effects. Similarly, an anatomical region more ventral and caudal to the SGPFC (24/25), BA 32pl (Fig. 13.5-3), is also an integral part of the ventral “emotional” circuit and has shown tissue loss in an MRI study.

Changes in the metabolic activity of the ventromedial circuit have also been reported after successful treatment. Fluoxetine and sertraline have been associated with decreased bilateral and left-sided activity of the SGPFC, respectively. Moreover, two sleep deprivation studies showed a drop in elevated baseline levels of SGPFC activity in depressed patients who responded to the intervention. In another indication that these changes may be independent of treatment modality, deep-brain stimulation was associated with perfusion changes of the SGPFC in treatment responders.

Histological data constitute another strand of evidence implicating the SGPFC in UPD and BD. A reduction in the number of glial cells (but not neurons) in the SGPFC of patients with familial BD and UPD has been reported, possibly explaining the reduction in SGPFC volumes characteristic of the imaging literature. With the same set of brain tissue, these findings were partially replicated by another group who detected reduced glial density and neuronal size in the pregenual ACC of patients with UPD. Drevets and co-workers reported an analogous effect in the SGPFC of both familial and nonfamilial depression with glial cell density reductions of 24 and 41 percent, respectively. These data receive support from animal models of depression.

Rats subjected to 3 weeks of repeated restraint stress show a 16 to 20 percent reduction of apical dendritic spine density in the anterior cingulate region of the medial PFC, while a corresponding effect has also been noted in the pups of mothers exposed to prenatal stress.

These anatomical changes appear to correlate with behavior: Stress-associated retraction of apical dendrites in the medial PFC has been associated with retarded extinction learning in rodents and, more recently, humans. Healthy people with thinner ventromedial PFC tissue showed a greater galvanic skin response to conditioned stimuli during extinction learning. Chronic psychosocial stress may also impact glial cell function: Rats exposed to 5 weeks of daily social defeat have been reported to show a suppression of gliogenesis in the medial PFC; an effect reversed by fluoxetine.

Interestingly, ibotenic-acid-induced lesions of the rat infralimbic cortex have been shown to produce evidence for a lateralized effect: Right-sided but not left-sided lesions are anxiolytic. In contrast, left-sided lesions are anxiogenic and result in increased sympathetic activation and corticosterone-induced response to stress. Similarly, dopamine depletion of the left but not right medial PFC rendered animals vulnerable to stress-associated ulceration. The putatively differential effect of the two hemispheres appears to follow a phylogenetic continuum.

The potential for anosognosic and manic symptomatology after right-sided lesions and the emotional distress and depression often associated with left-hemisphere lesions were originally discussed by Babinski and Goldstein, respectively. More modern structural imaging studies have lent credence to the original clinical reports (although contradictory results have been published), and studies of idiopathic anxiety, depression, and BD have produced analogous findings.

The leitmotif running through most theoretical models of the physiological mechanisms underpinning these lateralized effects is that of a positive, emotion-producing, appetitive, reward-seeking circuit in the left frontal cortex that interacts in a dialectical manner with a mirror neural network in the right hemisphere. Conceivably, a disruption to the regulatory capacity of these circuits, such as disinhibition of the right hemisphere after left hemisphere damage, may lead to affective illness.

Consistent with the above hypothesis, differential hemispheric functional activity of the pericallosal tissue has been reported in UPD samples with predominantly left-sided hypometabolism of the ventromedial circuit. In line with these findings, decreased metabolism of the right SGPFC at baseline was found in one study to be predictive of an improved response to antidepressant therapy. Parallel findings of volume reductions of the ventral aspects of the left ACC are commonly observed in morphometric analyses.

The volumetric reductions seen in the left SGPFC should, however, inject a note of caution into discussions of SGPFC metabolism. Partial volume effects may have contributed to the original suggestions of hypometabolism.

A similar pattern obtained in BD samples with left-sided hypometabolism or right-sided hypermetabolism and left-sided tissue loss of the broader ventral ACC region has been noted in the literature. One might hypothesize the reverse pattern to apply to the manic state. Unfortunately, there is a dearth of imaging studies of hypomanic or manic patients although there are three reports of BD groups characterized by elevated blood flow in the left ventral ACC.

It is unclear whether the possible dichotomy in hemispheric activity is a stable trait that applies to euthymic populations or is a state-dependent phenomenon. The authors originally observed the effect in depressed but not remitted patients, and as alluded to above, Blumberg and colleagues reported that manic patients showed elevated blood flow in the left ACC compared with that of remitted individuals.

It should, however, be noted that most claims about hemispheric asymmetry of function are methodologically flawed because they are based on the observation that voxel-based activity in only one hemi-

sphere reaches statistical significance. It does not, however, necessarily follow from this that the two hemispheres are significantly different from each other.

The Dorsal “Cognitive” Circuit

The line between cognition and emotion is becoming increasingly blurred, and this is illustrated by Davidson and Irwin in their description of the DLPFC as mediator of “affective working memory”. The DLPFC allows for the “raw” limbic-derived emotional stimuli—the somatic marker of Damasio—which is refined through rounds of ever more comprehensive processing in the orbital and ventromedial circuits to be represented “online” so that it can drive goal-directed behavior. In this sense, the dorsal aspects of the frontal lobe discharge traditionally described executive processes such as response selection, inhibition, and error detection—the monitoring of actions to insure that they match intentions.

One explanation for depression is a deficit in the top-down inhibitory control of the DLPFC (and indeed other prefrontal regions) over the amygdala and other limbic tissue that may result in chronic limbic overactivity and negative emotions. Implicit in this deliberately oversimplified model (Fig. 13.5–7) is the notion that positive affect is primarily a consequence of the suppression of negative emotions.

Hypometabolism of the dorsal PFC is one of the most robust findings in both unipolar and bipolar depression and in some studies appears to normalize with successful treatment, lending support to the veridicality of the above-mentioned model of depression. Concerning the structural imaging data, global decreases in both GM and WM volume, including areas of the DLPFC, have been reported. Moreover, severity of depression has been reported to correlate negatively with GM volume of the DLPFC. Nevertheless, it should be noted that there are conflicting reports in the literature.

As is the case with the ventromedial PFC, one complication of this literature is the potentially lateralized function of the DLPFC. On the basis of the inchoate understanding of the lateralization of emotional processing, one would expect a preponderance of left dorsal cortex hypoactivation in depression. A number of studies that have recorded left-sided hypofunction or GM loss of the dorsal PFC in UPD. Furthermore, right hemisphere hypoactivation in UPD responders to sleep deprivation has been recorded, and a recent report demonstrated left-sided hypoactivity and right-sided hyperactivity in depressed patients, who as a group tended to judge pictures as more negatively valenced than healthy controls. This hypothetical lateralization of function could theoretically explain the minority of studies reporting increased activity and GM volume loss of the right DLPFC in depression.

The mechanism underlying the hypothesized hypometabolism of the (left) dorsal prefrontal cortex is unknown. One possibility is that the reduction in activity is an artifact of the partial voluming effect. Certainly, decreases in the volume of the dorsal cortex, although not always the lateral convexity, have been widely reported in UPD. Consistent with the notion of GM atrophy, a depression-associated decrease in neuronal size with a concomitant decline in large cell density and an increase in small neuron density in the DLPFC was reported in a postmortem histological study.

GM volume reductions of large areas of the DLPFC have been reported in medicated and remitted BD I patients and partially medicated, “stable” bipolar-spectrum individuals, respectively. More circumscribed volume reductions of BA 9 and the ACC immediately dorsal to the corpus callosum (CC) have been reported in a medicated, euthymic pediatric sample and a mixed BD I and BD II adult sample, respectively.

AU: Please provide first names for Babinski and Goldstein.

AU: Please provide a first name for Blumberg.

AU: Please provide first names for Davidson and Irwin. Fig. 13.5–7

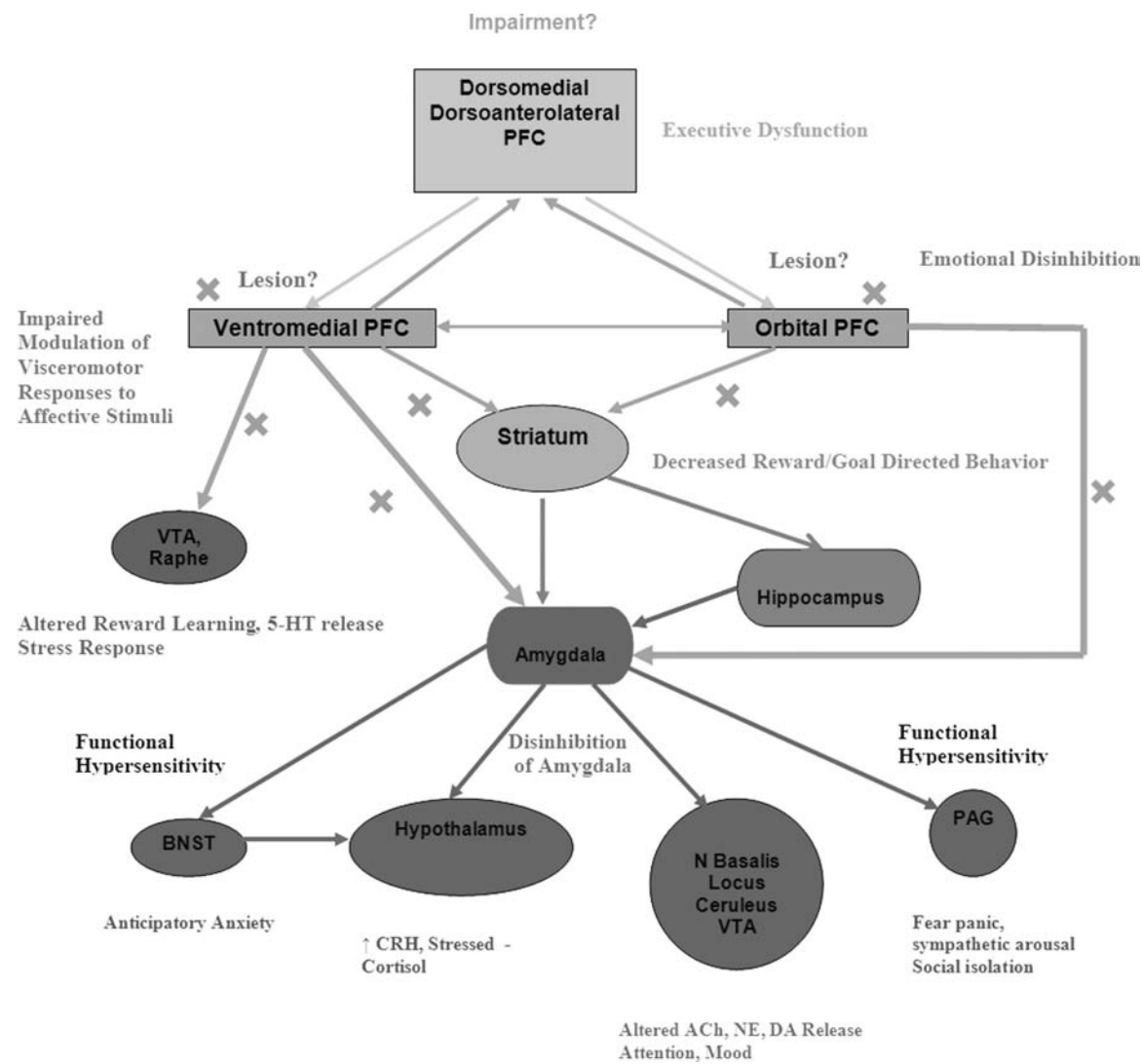


FIGURE 13.5-7. Abrogation of prefrontal control over limbic function as a model of depression.

One of the problems with a discussion of affective illness-related changes to the dorsal PFC is the large and functionally diverse area to which this term refers. More advanced imaging techniques have tended to suggest that volumetric loss and/or hypofunction is most salient in the superior gyrus (part of BA 9) rather than the middle gyrus and more lateralized regions of the dorsal PFC. This is an important point because the superior gyrus is strongly connected to regions of the ventromedial cortex and forms part of the visceromotor network.

Neurodevelopment versus Neurodegeneration

The heritability of BD converges on the 60 to 80 percent range while UPD is closer to the 40 percent mark. Thus although genetic factors play an important etiological role in affective disorders, the importance of environmental variables should not be discounted. In fact, the average concordance rate among monozygotic (MZ) and dizygotic (DZ) twins stands at approximately 40 and 10 percent, respectively, for BD and approximately 30 and 20 percent for UPD. One potentially important environmental variable is exposure to adversity. Childhood trauma has been associated with both depression and psychosis, and stressful life events are known to precipitate bouts of affective illness in both BD and UPD populations.

It is interesting to note that despite the pre-eminence of psychiatric genetic research current models of pathological change in affective illness are deeply rooted to these environmental contingencies. As alluded to above, functional and anatomical change in depression is often viewed as degenerative: Stress-induced, glutamate-mediated excitotoxicity leads to cellular pathology, which manifests itself as decreases in GM volume. In contrast, the role of genetically driven neuroplasticity is not usually explicitly addressed in contemporary models of illness-associated neuropathology even though genetic factors can quite easily be incorporated into both developmental and degenerative schemas.

The neurodegenerative hypothesis, which conceptualizes GM or WM volume loss as the downstream effect of pathological cellular changes induced by an environmental factor like psychological stress, will first be discussed. Given the clustering of UPD and BD in families, and some reports that GM volume loss only occurs in familial cases, one possibility is that psychological stress must also be familial in order for this conceptualization of illness to be valid.

Actually, there may be a familial or genetic component to the experience of life stress because of a phenomenon known as gene-environment correlation. Twin studies have demonstrated that people's retrospective reports of their childhoods, for example, parental

levels of accepting and rejecting behavior, encouragement of growth, and family warmth or cohesion, are under genetic influence.

There are at least three ways in which gene–environment correlation might apply in the case of the degenerative hypothesis. The parental genotype or affective disorder may exert an effect on parental behavior such that their children are reared in a high-stress environment. Here there is a correlation between passing on “stress-provoking” genes and providing a stressful family environment.

Secondly, it can be argued that people are selecting and shaping their environmental experiences on the basis of their genetic heritage, leading to preferential exposure to significantly stressful events and depression-associated neuroplastic changes in a subset of the population. This phenomenon may be related to the way in which individuals perceive or process information in their environment, an intrinsic bias often described as temperament. Certainly, so-called dysthymic or anxiety-related personality traits have been widely described in UPD individuals, while BD is characterized by various combinations of dysthymic, cyclothymic, and hypomanic traits. Because these traits are likely underpinned by genetic factors, temperament may mediate the impact of genes on environmental experiences.

Yet a third possibility is that genetic effects play no role in influencing exposure to stressors but moderate the physiological effect of these events on neural tissue.

One class of proteins potentially involved in this type of gene–environment interaction is the neurotrophins.

Neurotrophins are regulatory agents that mediate the differentiation, proliferation, migration, axonal growth, and survival of neurons. One of these enzymes, brain-derived neurotrophic factor (*BDNF*), increases forebrain serotonin fiber density and neurogenesis, prevents spontaneous and neurotoxin-induced cell death, and modulates the formation of synaptic connections, particularly in the prefrontal cortex and hippocampus.

Recent studies have suggested that the low expression (*met*) allele of a functional single nucleotide polymorphism (SNP) (Val66Met) of the *BDNF* gene may increase the probability of developing depression and cognitive impairment after exposure to childhood maltreatment. Perhaps through its reduced ability to protect against neurotoxicity, the *met* allele has also been reported to increase the risk of developing depression after stroke.

Another potential moderator of the stress response is central serotonergic activity. The binding of serotonin to postsynaptic 5-HT_{1A} receptors not only enhances the negative feedback inhibition of cortisol release in the PFC and hippocampus but also prevents dendritic cytoskeletal breakdown by catalyzing the release of the neurotrophic factor S100 β and indirectly inhibiting protein-kinase-induced apoptosis. The regulation of 5-HT_{1A} receptors in the raphe is at least partly controlled by a functional variant of the 5-HT_{1A} receptor gene (*HTR1A*) (rs6295) and the promoter length polymorphism of the serotonin transporter (*SLC6A4*) gene.

In contradistinction to the degenerative model, the developmental model advocates that neurophysiological changes precede the onset of affective illness. An interesting set of animal experiments has lent credence to this hypothesis: A line of rats, genetically bred to suffer from learned helplessness, display baseline hypometabolism of the amygdalae, BG, VTA, dorsal-frontal, medial OFC, and ACC, but increased metabolism of the SGPFC, hippocampi, and habenula. Moreover, the midbrain and brainstem regions were found to be disconnected from limbic forebrain regulation, congruent with models suggesting that the fundamental disturbance in depression is one of top-down regulatory control.

Clearly genetic manipulations cannot be carried out in humans, but one way of examining this issue is to compare the degree of variation

in regions of interest across the lifespan. Lupien and co-workers found that there was just as much variability in the hippocampal volumes of healthy young adults as older individuals, implying that volume decrements attributed to aging or stress could be reflective of neurodevelopmental differences. Specifically, a quarter of their subjects in the 18- to 24-year age group had hippocampal volumes as small as the average hippocampal size in their 60- to 75-year-old sample, and the mean difference in hippocampal volumes between the upper and lower quartiles of the young age group (12–16%) was greater than the volumetric reductions typically seen in depressed samples.

These data are congruent with a reported association between PTSD and smaller hippocampal volume in war veterans. Interestingly, the MZ twin brothers of the PTSD cohort who did not serve in the military also presented with smaller hippocampi than the control group, raising the possibility that hippocampal atrophy plays a causal role in the manifestation of PTSD.

Thus, the smaller volumes of various brain nuclei seen in affectively ill populations may not necessarily reflect an active pathological process.

Recent findings from the emerging field of imaging genomics also emphasize the importance of genetic influences. A variant of the neuregulin 1 (*NRG1*) gene, which is involved in the myelination process and has been implicated in both BD and schizophrenia, has in turn been associated with WM density and integrity of the internal capsule. Two nonsynonymous SNPs of another gene, proline dehydrogenase (oxidase) 1 (*PRODH*), have been associated with frontal WM volume reductions in schizophrenia. In another study, the short allele of the *SLC6A4* gene promoter polymorphism has been shown to be associated with increased resting cerebral blood flow in the amygdala and decreased perfusion of the ventromedial PFC in healthy individuals.

The neurodevelopmental hypothesis can also be evaluated by searching for neural changes in unaffected family members who presumably share a genetic diathesis for the disorder with their ill relatives. These studies are unfortunately uncommon, and no conclusions can be drawn at this point in time. One paper that compared MZ pairs discordant for BD with a control group of unaffected twins found that the right hippocampus was smaller in the affected twins but that both ill and well twins had larger caudate nuclei than the control twin pairs. In another study, genetic risk for BD was purportedly associated with reduced volume of the right anterior cingulate gyrus and ventral striatum. Similarly, a compensatory hypermetabolic response to a sadness induction paradigm has been observed in the medial frontal cortex of healthy BD relatives compared with background controls.

Concerning UPD, it was recently reported that the pediatric offspring of parents with major depression displayed greater amygdala and nucleus accumbens activity in response to fearful faces and lower nucleus accumbens activation in response to happy faces than a low-risk control group. A small number of serotonin depletion experiments have succeeded in inducing depressive symptoms in otherwise healthy relatives of UPD probands. In one case, 6 out of 20 healthy males with a family history of affective illness, but 0 out of 19 male controls displayed a lowering of mood in response to tryptophan depletion, which putatively decreases central serotonergic transmission. More recently, it was reported that under tryptophan depletion healthy individuals with a family history of depression show a greater lowering of mood and stronger amygdala response to fearful faces compared with those of background controls.

These potential neuroimaging endophenotypes are most likely genetically driven. Serotonergic activity not only modulates the impact of stressful events but is also a key regulator of neural development, impacting neurogenesis, apoptosis, and dendritic growth. For

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example, fluoxetine-induced suppression of the serotonin transporter during development has been shown to result in abnormalities of emotional behavior in mice. Recent data have also shown the direct effect of the *SLC6A4* promoter polymorphism on neural tissue, with increased hemodynamic response of the amygdala to fearful faces in short allele carriers.

Like the misguided question of nature versus nurture, the distinction between early, developmental, and later-onset stress-induced pathology is artificial. If depression and BD are polygenic disorders underpinned by many genes of small effect size, then affected individuals are likely to possess many different risk variants affecting multiple neuroanatomical pathways and a single point of origin is unlikely. Genetically determined subtleties of brain wiring may rather sensitize the individual to the effect of early trauma or even ubiquitous, relatively mild stressors.

For example, the short allele of the above-mentioned *SLC6A4* gene insertion/deletion promoter polymorphism (5-HTTLPR), first associated with anxiety-related personality traits more than a decade ago, is now one of the prototypical examples of a risk variant that interacts with adverse life experiences to predispose to psychopathology.

Pezawas and co-workers may have uncovered the neurobiology behind this process. They demonstrated that healthy carriers of the short allele display reduced functional connectivity between the amygdala and the SGPFC. Area 25 of the SGPFC exerts an inhibitory effect on the amygdala and thus a genetically determined attenuation of this negative-feedback loop may increase sensitivity to environmental adversity and, by implication, lead to maladaptive neuroplastic changes.

A nascent trend in the study of psychiatric disorders is a recognition of the potentially important role of epigenetic mechanisms in disease causation. Epigenetic inheritance refers to a regulated pattern of gene expression that is transmitted intact from one or other parent to their offspring. The process is mediated by the methylation and histone acetylation of cytosine residues and chromatin, respectively, leading to the activation or silencing of particular genes. The phenomenon is epigenetic because it results in phenotypic traits that are inherited independently of the informational content of deoxyribonucleic acid (DNA).

The dynamism of these epigenetic controls is intriguing. A number of rodent studies have demonstrated that stress sensitivity in rat pups is modulated by parental grooming behavior, which exerts its effect through a histone-modification-driven regulation of glucocorticoid receptor gene expression. If these biological mechanisms generalize to humans, then exposure to adversity may modify gene expression in pathways that impact neuroplasticity.

A Heuristic Model

For heuristic purposes, the neurophysiological changes associated with depression and BD can be viewed from both a top-down and bottom-up perspective. In the top-down model, impaired PFC function, or cortical-subcortical “disconnection,” disinhibits downstream limbic projections, altering emotional behavior. For example, disinhibition of the amygdala projections to the bed nucleus of the stria-terminalis (BNST), hypothalamus, and PAG would increase cortisol-releasing hormone (CRH) release and anxiety symptoms. Disinhibition of projections from the amygdala to the nucleus basalis, locus ceruleus, and VTA could account for the alterations in cholinergic (ACh), noradrenergic (NE), and dopaminergic (DA) transmission that may affect mood and attention. Finally, disinhibition of amygdala projections to the ventral striatum would attenuate reward-seeking and goal-directed behavior, potentially contributing to the anhedonia and amotivation characteristic of depression.

According to the bottom-up model the maladaptive genetic or environmentally driven plastic changes would originate in limbic nuclei such as the amygdala, raphe, and parahippocampus, resulting in functional hypersensitivity. Exposure to aversive environmental stimuli may further dysregulate the system, eventually resulting in cortical dysfunction akin to that proposed in top-down schemas.

The etiology of these changes is unclear but, as discussed above, is most likely to involve complex gene–environment interactions. Many examples of these interactions are likely to emerge over time and hold out great promise for disinterring the latent pathophysiological basis of affective illness.

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▲ 13.6 Mood Disorders: Intrapsychic and Interpersonal Aspects

JOHN C. MARKOWITZ, M.D., AND BARBARA L. MILROD, M.D.

The criteria listed in fourth revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) reliably define mood disorders but do not completely describe them or explain how patients experience them. Depressed patients suffer emotionally, cognitively, and physically. This section describes three key theoretical approaches that have been applied to mood disorders: Psychoanalytic/psychodynamic, cognitive, and interpersonal. They vary in their frequency of use in clinical practice and in the amount of research that they have received.

Theory has uses and limitations. Theory can help to organize thinking about depression and can pinpoint aspects of the syndrome. A theory can provide a narrative thread or focus to anchor a clinical formulation and to give coherence to a therapy. A theoretical approach is indeed necessary for clinicians to impose order on the overwhelming amount of clinical data with which patients present for treatment. Theories may also allow us to make predictions about treatment mechanisms and outcomes. We submit that an organizing theoretical framework is as essential to structure a psychotherapy as grammar is to speech. Hence understanding the theoretical backgrounds of psychotherapies is crucial for the psychotherapeutic clinician.

Theories should be considered approximations of the truth, needful of testing and subject to disconfirmation. Dogma and ideology have done psychiatrists and other mental health professionals more harm than good, for example, in separating psychotherapy and pharmacotherapy into opposing camps—a rift from the 1950s that is only now being healed. Inasmuch as the etiology of mood disorders is complex and no single theory can comprehensively explain it, rigid adherence to any theory is unwarranted and potentially problematic. Clinicians should understand and use multiple theories, flexibly choosing the optimal theoretical perspective to apply to a given patient's illness and then persevering in using that model for an appropriate course of treatment. (The authors of this chapter recommend formal training in any treatment modality the clinician plans to undertake. Theoretical understanding does not suffice.) On the other hand, to develop clinical expertise in any therapy, it is essential to be able to understand patients' problems through the lens of the theory underlying it.

Psychodynamic theory has the longest historical tradition. Both cognitive theory and psychodynamic theory largely focus on intrapsychic phenomena, whereas interpersonal theory, the newest and least formally developed, focuses more on interpersonal, extrapsychic reality. It is widely accepted that aspects of both cognitive and interpersonal theories derive from psychoanalysis. Each approach provides a

potentially useful explanation of the plight of the depressed patient. Although the utility of therapies derived from cognitive theory (cognitive behavioral therapy [CBT]) and interpersonal theory (interpersonal psychotherapy [IPT]) has been better tested for depression than psychodynamic therapy to date, no theories of depression have been formally tested in all of their assumptions. They are best considered working clinical models.

PSYCHODYNAMIC ASPECTS OF MOOD DISORDERS

A contemporary psychoanalytic understanding of mood disorders includes a comprehensive focus on biological underpinnings, cognitive function, and interpersonal situation and style. What is unique to psychoanalysis is its attention to intrapsychic, unconscious pressures in its consideration of psychological symptoms, including mood disorders. This section focuses largely on psychoanalytic theories of depression, although it should be noted that exciting, early outcome research in psychodynamic treatment of depression is currently underway. In order to describe intrapsychic aspects of mood disorders, several basic psychoanalytic ideas about mental life first must be defined:

(1) From a psychodynamic view, mental life exists on two levels: Both within the realm of consciousness and also within a less accessible realm, described as “*the unconscious*”. Psychic or emotional symptoms arise from aspects of mental life that are at least in part unconscious. This is true of mood disorders.

(2) Psychoanalysts have found it useful to conceptualize the mind as comprising three basic theoretical psychic structures, *the id*, *the ego*, and *the superego*. In brief, *the id* is considered the aspect of the mind that subsumes the drive derivatives and desires. *The ego* serves as intermediary between the id and the external world. It contains many intrapsychic functions, including motor action, perception, self-esteem, the relationship to reality, and the ability to modulate the drives and to modulate anxiety. Defense mechanisms, which are unconscious intrapsychic mechanisms employed to modulate both the drives and anxiety, are ego functions. *The superego* is conceptualized to comprise the person's value system. The superego can both punish and reward the person, depending upon whether or not his or her actions are consonant with his or her moral values.

(3) *Moods are pervasive ego states* that color the entire ego with the same affect state. Unlike simple affective responses to events, they are not focused but general, either because the affect is too strong or because the ego is too weak to contain a focused response. Because moods tend to be generalized states, they typically involve some degree of denial of the opposite feelings. From a psychoanalytic vantage, moods carry an unconscious significance, notwithstanding their presumed biological and neurotransmitter underpinnings.

(4) Since Freud's discovery of the importance of the unconscious in everyday mental life and of individuals' capacity to shut off unwanted, painful, emotionally laden experiences using defense mechanisms, our understanding of moods and symptoms has been enhanced by the recognition that these psychic phenomena represent a breakthrough of *unconscious fantasy* into consciousness. Persistent unconscious fantasies often underlie people's psychological symptoms, dreams, personalities, and important life choices.

(5) Freud initially described another central principle in the organization of mental life: That *people unconsciously avoid “unpleasure”* and that ideas that produce unpleasure are screened from consciousness by “repression,” or processes that we now call *defenses*. Clinically, the degree to which unpleasure is avoided varies from person to person, and Freud later modified his original theory about people