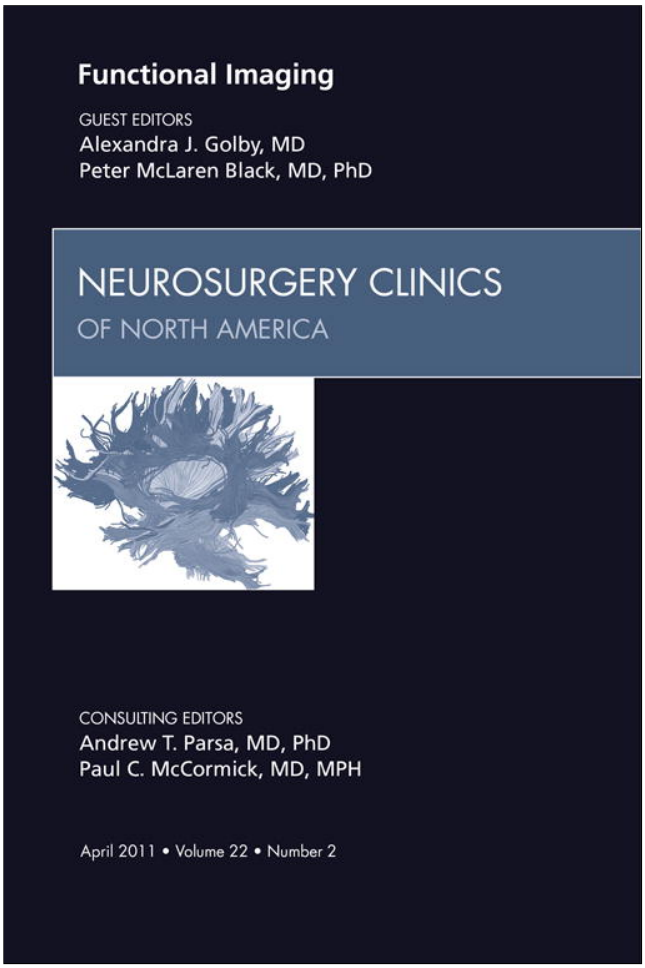

Identification of Neural Targets for the Treatment of Psychiatric Disorders: The Role of Functional Neuroimaging

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KEYWORDS

• Neuroimaging • Neurocircuitry • Psychiatric disorders
• Depression

Neurosurgical treatment of psychiatric disorders has a long history, influenced by evolving neurobiological models of symptom generation. In recent years, the advent of functional neuroimaging, along with advances in the cognitive and affective neurosciences, has revolutionized understanding of the functional neuroanatomy of psychiatric disease. The investigational use of techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), combined with advanced statistical methods, has led to the development of complex neurocircuitry-based models of an array of psychiatric disorders.

In addition to increasing our understanding of the pathophysiology of neuropsychiatric illness, functional neuroimaging studies are being used for detection, localization, and characterization of final common pathways of major psychiatric disease expression as a foundation for clinical advances. They are also playing a major role in the prediction of response to treatment; identification of biomarkers for risk/resilience; and guiding the development, monitoring, and assessment of targeted biologic therapies, including neurosurgical treatments, for several psychiatric disorders.

HISTORICAL BACKGROUND

Bodily Humors, Mental Faculties, and the Brain

Symptom localization in psychiatric illness has its historical roots in the fifth century BCE, a time at which bodily fluids called humors were believed to be the crucial elements of health and disease. Although it may have its origins in ancient Egypt, it was Hippocrates who systematized the humoral doctrine in a medical theory of mood and behavior based on the balance of the 4 humors: yellow and

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black bile, phlegm, and blood. The theory was later perpetuated by the Roman physician, Galen of Pergamon, who proposed in the first and second century CE that each bodily humor is related to particular mental faculties of perception, reason, or memory and their corresponding conditions of temperature and moisture. Mental illness was determined to be caused by a loss of 1 or more mental faculties and was treated by balancing the humors through the influence of the temperature/moisture along with the common practice of bloodletting.[1] In melancholia, it was presumed that the faculty of perception was impaired, whereas the faculty of reason was still intact. Black bile from the abdominal cavity was believed to darken the anterior section of the brain, clouding the faculty of perception and leading to long-lasting fear and sadness. It was believed that, with increasing severity, the illness spread to the other faculties.

Within that framework, a few influential pathologists began to associate particular mental faculties with certain parts of the brain. For example, the faculty of reason was believed to reside in the medial aspects of the brain, and memory was believed to be located in the cerebellum.[1–3] Similar classifications were made in cases of mania, in which the faculty of reason was most affected. Although the localization of mental disease remained largely unknown, Galen[4] emphasized both genetic/innate and external factors in his treatise *On the Affected Parts*:

> *Black bile arises in some people in large quantity either because of their original humoural constitution or by their customary diet … Like the thick phlegm, this heavy atrabilious blood obstructs the passage through the middle or posterior cavity of the brain and sometimes causes epilepsy. When its excess pervades the brain matter itself, it causes melancholy …*[4]

Avicenna, an Arabic physician and philosopher from the late tenth century, expanded on Galen's perspectives on mental illness and wrote extensively on the topic of melancholy, referring to the melancholy humor (black bile), melancholia the disease, and the melancholic disposition. He was also a pioneer in the association of physiology with emotion. His vast medical and scientific perspectives were published in *The Book of Healing* and fourteen-volume *Canon of Medicine* (1025), texts that influenced medicine into the eighteenth century throughout Europe.

Empirical investigation into the underlying factors influencing mental illness did not resurface until the sixteenth century, when detailed neuroanatomic illustrations were provided by Andreas Vesalius, now considered one of the founders of modern medicine. Vesalius used dissections of cadavers as the primary teaching tool, significantly advancing the understanding of brain and body anatomy through the method of direct observation. By the seventeenth century, the brain was established as the seat of most mental disease, and its association with black bile or melancholic humor was diminishing. Thomas Willis, a pioneer in research into the anatomy of the brain and nervous system, coined the term neurology in his influential medical texts, and proposed alternate chemical theories for the pathogenesis of melancholia. By the eighteenth century, knowledge of the central nervous system, along with detailed classifications of mental illness, had considerably increased in breadth and detail.

The Debate About Localization and the Emergence of Connectionist Models

The work of Willis and the advances made in understanding and describing neuroanatomy set the stage for the work of Franz Joseph Gall and the phrenologists, whose theories of cerebral surface localization in the late 1700s and early 1800s preceded the modern conceptions of cortical localization.[5] In the early 1800s, Gall and his collaborator J.C. Spurzheim developed a model of brain/mind relations in which specific functions were localized within areas of the cortex, with the size of the cortical region reflecting the development and activity of the corresponding function (**Fig. 1**).[6] They posited that the prominence of individual cortical areas could be assessed by measuring the prominence of the overlying skull.[6] After examining the skulls of a variety of subjects ranging from criminals and the mentally ill to prominent figures such as politicians, artists, and intellectuals, including Voltaire and Descartes, Gall described the localization of 27 different faculties in the cerebral cortex, including wisdom, passion, courage, love of offspring, cleverness, and murderous tendencies.[6–8] Gall's theory, ultimately known as phrenology, gained general popularity, but was ultimately vigorously attacked within the scientific community. Although well deserved on methodological grounds, the attack may also have been motivated by entrenched scientific perspectives and religious beliefs regarding the unity of soul and mind.[7,9] The most prominent detractor of phrenology was Pierre Flourens, a leading brain physiologist, who posited that all parts of the cortex are capable of performing all functions.[8]

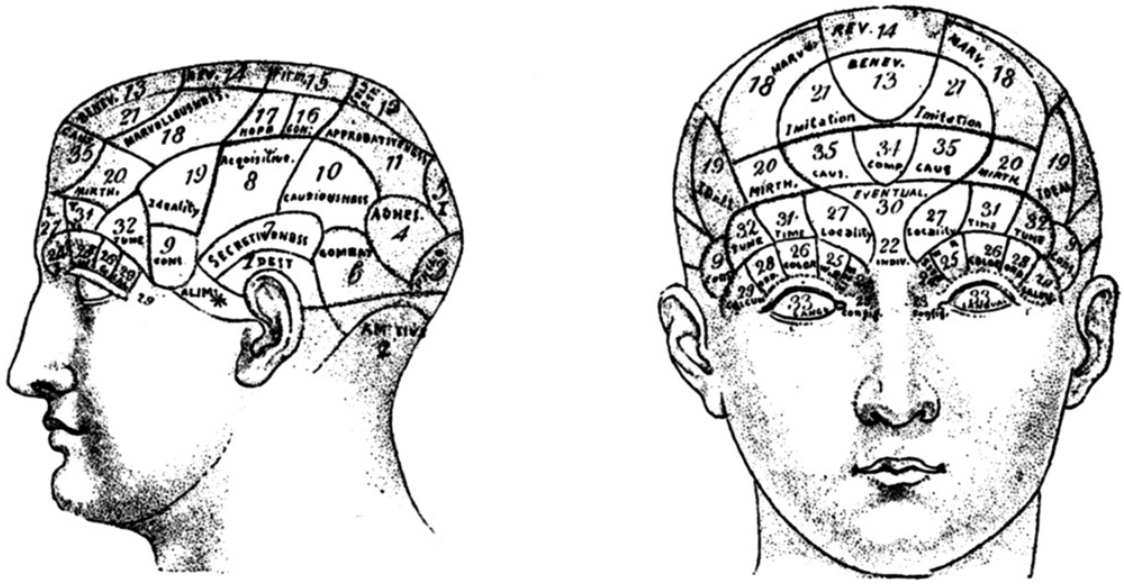

Fig. 1. Phrenological diagram from Spurzheim (1832). Gall and Spurzheim described the localization of 27 different faculties in the cerebral cortex including wisdom, passion, courage, love of offspring, cleverness, and murderous tendencies. (*Reproduced from* Buchanan's Journal of Man, November 1887.)

Although this antilocalizationist view, known as the theory of equipotentiality, gained ascendancy in the early nineteenth century, the question of cortical localization remained a topic of heated debate, kept active by numerous reports of speech dysfunction associated with frontal lesions (a localization suggested by Gall).[7] The French physician Jean-Baptiste Bouillaud, in particular, presented more than 100 cases in support of this association, famously wagering 500 francs, in 1848, that no one could find an example of a deep lesion in the anterior lobes in which speech was not affected.[9,10] Bouillaud's son-in-law, Simon Alexandre Ernest Aubertin, who was also a fierce proponent of localization, threw down a similar challenge, stating that he would renounce all his convictions about localization if 1 case could be shown in which speech was preserved despite massive lesions to both anterior lobes.[11]

A turning point in the debate occurred in 1861, 8 days after Aubertin's challenge, when Paul Broca, a well-respected neurologist who had not previously been active in the debate, delivered a report to the French Societe de'Anthropologie describing the case of a recently deceased patient who had suffered from right hemiplegia, loss of speech, and seizures. Following the patient's death, autopsy revealed a fluid-filled cavity the size of an egg in the left frontal lobe, providing dramatic support for the proposed localization of speech.[11] In the years that followed, Carl Wernicke published a monograph describing various types of aphasia related to lesions in differing brain regions and developed a model, known as associationism or connectionism, which explained disorders of language or cognition in terms of lesions to different combinations of specialized brain regions and/or the connections between them.[9,12] This model was quickly extended by neurologists such as Lichtheim, Liepmann, and Dejerine to explain syndromes such as pure word deafness, ideomotor apraxia, and alexia without agraphia.[12]

Application of Localization and Connectionist Models to Disorders of Emotion, Motivation, and Social Comportment

In the later years of the nineteenth century, several investigators used lesion or stimulation studies in animals, and autopsy findings in humans, to localize cortical functions. Although early efforts focused on motor areas, attention eventually turned toward localization of emotional, behavioral, and other mental functions. In the mid-1870s, David Ferrier described monkeys with frontal lobe damage who showed deficits in attention, appeared listless and dull, and proposed that thinking was inhibition of action. Eduard Hitzig, a German neuropsychiatrist, suggested that the capacity for abstract thought was affected by frontal lobe damage. Leonardo Bianchi, an Italian neurologist, described deficits involving social interaction, self-perception, and executive functions such as planning and decision making in monkeys with frontal lobe damage.[13] Supplementing these observations and theories was evidence drawn from the case of Phineas Gage, a railroad worker injured in 1848 when an explosion caused a tamping rod to enter his left cheek, shoot

through his frontal lobes, and exit through the midline of his skull near the junction of the coronal and sagittal sutures.[14,15] Alterations in Gage's behavioral disposition involving changes in emotional expression and regulation, as well as social decision making, provided further insight into frontal lobe functions, supporting the observations and investigations of Ferrier and others.[11]

Another development promoting investigation of the neural substrates of emotional processing and behavior was the adoption of evolutionary perspectives following the publication of Darwin's *Origin of Species* in 1859 and *Descent of Man* in 1871. In this context, Hughlings Jackson developed a hierarchal model of the brain in which functions are represented at multiple levels of organization acquired through the course of evolution. In this model, lower-level functions, which are simple, stereotyped, and automatic, are controlled by higher-level functions, which are more complex, flexible, and voluntary. Mental alterations produced by lesions in higher-level cortical structures result in impairment of associated cortical function but also reflect ongoing, but distorted, activity in the rest of the brain, including lower-level functions now released from inhibitory control.[16,17]

An evolutionary perspective can also be seen in the writings of James Papez, an American neuroanatomist, who in 1937 delineated a complex system of extensively interconnected brain structures mediating emotion.[18,19] The limbic circuit described by Papez[19] incorporates the phylogenetically primitive and morphologically simple structures surrounding the brainstem, including the cingulate and parahippocampal gyri, hippocampal formation, mamillary bodies, anterior thalamus, and hypothalamus. Papez viewed the cingulate as the "seat of dynamic vigilance by which environmental experiences are endowed with an emotional consciousness," and postulated that projections from the cingulate to other areas of cortex "add emotional coloring."[19] In accordance with theories originally postulated by Walter Cannon (1927, 1931), the functions of this limbic circuit could account for the striking autonomic and behavioral changes associated with bitemporal damage in the Kluver-Bucy syndrome, spontaneous laughter and crying produced by stimulation of the anterior thalamus, and sham rage seen in animals following removal of inhibitory cortex and accompanying increases in diencephalic activity.[20]

Paul MacLean further extended the limbic circuit delineated by Papez[19] to include the amygdala and septal nuclei. He developed an evolutionary model of the tripartite brain, in which the mammalian limbic network provides a variety of emotional and viscerosomatic reactions as it facilitates communication between the hypothalamus and frontal lobes.[18,19] In 1948, Ivan Yakovlev added the orbitofrontal cortex, precuneus, and insula to the limbic system. As discussed later, Papez, MacLean, and Yakovlev were correct in many of their assumptions regarding emotional expression and control.

With the advent of histochemical, immunocytochemical, and autoradiographic methods for tract tracing in the 1960s and 1970s, it became possible to identify the cortical-limbic circuit with more precision. Multiple research teams used these methods in postmortem human tissue and animal models to identify paths of atrophy caused by experimental lesions, guide future ablation techniques, and clarify cytoarchitectonic pathways.[21–23] Projections were identified from the amygdala to orbital and medial prefrontal, insular, and temporal regions (perirhinal cortex, lateral entorhinal cortex, piriform cortex, and hippocampus), mediodorsal thalamus, medial and lateral hypothalamus, periaqueductal gray, and other brainstem nuclei that are involved in visceral control and autonomic function.[21,23–27] More recent studies have been able to show that the bulk of incoming cortical projections terminate within the basolateral amygdaloid nuclei and reciprocally project back on cortical areas in a highly topographic manner.[22,28] The basolateral nuclei of the amygdala project to orbital and medial prefrontal regions, whereas central and medial nuclei have descending projections to the hypothalamus and brainstem that are largely inhibitory.[29]

The Emergence of Neuropsychiatry

In the late twentieth century, advances in several brain-related disciplines and methodologies laid the groundwork for the emergence of neuropsychiatry, a psychiatric subspecialty devoted to understanding emotional, behavioral, cognitive, and perceptual symptoms in terms of their functional neuroanatomy, whether in the context of neurologic or primary psychiatric conditions. One of these advances occurred in 1956, when a Symposium on Information Theory was held at the Massachusetts Institute of Technology. Participants were drawn from fields including artificial intelligence, cognitive psychology, and linguistics. Their interaction gave rise to the multidisciplinary field of cognitive science, which has at its core an attempt to understand mental functions in terms of information processing or computation.[30,31] Cognitive science has delineated ways in which the mind and brain seem to function in accord with computational constructs, developing promising models of

brain/mind function such as parallel processing and neural networks, and incorporating data and perspectives from philosophy and the neurosciences.

Another major advance occurred in 1965, when Norman Geschwind published *Disconnection Syndromes in Animals and Man*, establishing behavioral neurology.[32–34] Geschwind and his students revived and built on the nineteenth century connectionist tradition, elucidating the neural substrates of phenomena such as memory, attention, knowledge, and awareness. This neurologic subspecialty developed in conjunction with neuropsychology, a branch of psychology that arose in the wake of World War II in response to a need to characterize the effects of traumatic brain injury. In the following decades, the body of knowledge derived from these clinically based approaches was complemented by animal studies, most often in rats and nonhuman primates. These studies,[35–40] combined with contributions from ethology[41] and evolutionary psychology,[42] were particularly useful in the investigation of the social, motivational, and emotional functions that had been neglected by cognitive science, behavioral neurology, and neuropsychology.

In time, these disciplines (behavioral neurology, neuropsychology, cognitive science, animal studies of brain and behavior, evolutionary psychology, philosophy of mind, ethology, and developmental psychobiology, among others) grew increasingly intertwined and synergistic, to the extent that they are frequently referred to collectively as the cognitive and affective neurosciences. This interdisciplinary understanding of brain/mind functioning was adopted by the nascent field of neuropsychiatry, and applied to the investigation of the neural underpinnings of psychiatric disorders; an application made possible by the development of functional neuroimaging technologies (**Fig. 2**).

THE ROLE OF NEUROIMAGING IN THE DEVELOPMENT OF NEUROCIRCUITRY-BASED MODELS OF PSYCHIATRIC DISORDERS: THE EXAMPLE OF DEPRESSION

In 1980, Jacoby and Levi[43] published the first computed tomography (CT) study of patients with mood disorders; in 1983, Rangel-Guerra and colleagues[44] published the first MRI study of a similar population. These studies were followed, in subsequent years, by a plethora of structural and functional neuroimaging studies of patients with major depressive disorder (MDD) and bipolar disorder (BPD), as well as those experiencing depressive symptoms in the context of primary neurologic disorders or other medical illness. Current neuroimaging research uses analyses based on measurement of regional cerebral blood flow (CBF) or glucose metabolism (GLC); morphologic or volumetric abnormalities using voxel-based morphometry (VBM), cortical thickness, or diffusion weighted imaging (eg, diffusion tensor imaging); and multivariate statistical models to identify critical neurocircuitry, and quantify dysregulation in effective and functional connectivity.[45] Despite considerable variation in study design and methodology, as well as heterogeneity of study populations, significant progress has been made in the last 30 years in delineating the circuitry underlying major depression. This article reviews

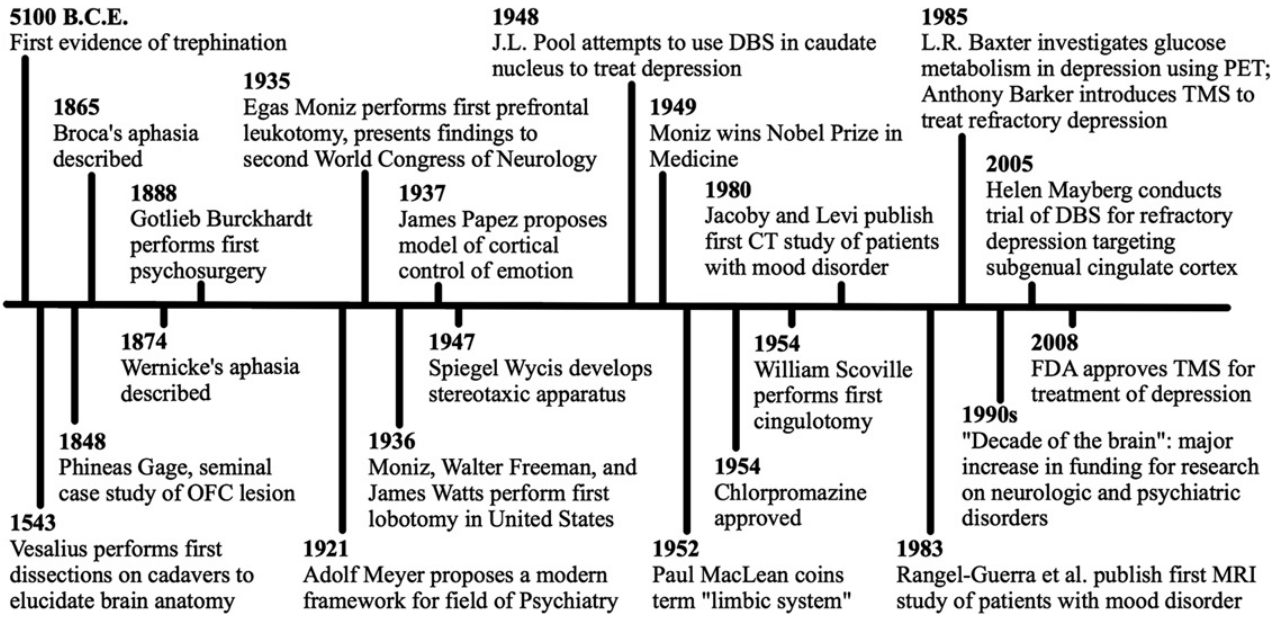

Fig. 2. Timeline for identification of neural targets for treatment of psychiatric disorders.

findings from the last 3 decades and provides evidence for emerging neurocircuitry models of mood disorders, focusing on critical circuits of cognition and emotion, particularly those brain networks regulating the evaluative, expressive, and experiential aspects of emotion.[46–48]

Morphologic and Volumetric Studies

Early studies

Early neuroradiological investigations, based on findings from pneumoencephalography (PEG; a method in which some cerebrospinal fluid is drained and replaced with air, oxygen, or helium to allow the structure of the brain to show up more clearly on a radiograph), indicated morphologic brain changes in patients with affective disorders undergoing subcaudate tractotomy.[49] The earliest CT studies of mood disorders from the early 1980s focused on sulcal and cerebral volume, along with gross structural differences in patients with mood disorders compared with healthy control subjects (see Refs.[50,51] for review). Although results were mixed, significantly increased ventricular size was the most consistent finding across most studies that used manual tracing to measure ventricular/brain ratio (VBR). This crude finding, also reported in conditions such as schizophrenia and alcohol abuse, is clearly nonspecific.[51]

A few studies reported that subcortical atrophy preceding neurologic insult or onset of neurodegenerative disease increases the likelihood of later onset of depression,[52,53] and evidence continues to accumulate that neurologic diseases involving subcortical abnormalities are associated with higher rates of depression.[50] There is also evidence for potential mediators of structural changes related to depression, including genetic predisposition, stress reactivity, and behavioral factors for risk and resiliency.[53,54] There are large volumes of research showing that exposure to increased levels of glucocorticoids can accelerate hippocampal neuron loss and lead to cognitive and affective impairments.[55] Some animal research suggests that maternal grooming early in life leads to increases in density of glucocorticoid receptors in both hippocampus and prefrontal cortex (PFC), which likely play an important role in developing resilience to stress later in life.[56,57] Although the evidence for effects of stress on structure and function is incomplete as it relates to depression, maladaptive stress responses have been shown to correlate positively with increased plasma cortisol levels, degree of hippocampal atrophy, decreased immune response, and decreases in neurogenesis and/or brain-derived neurotrophic factor.[58,59] Ineffective management of chronic stress (physical or psychogenic) is associated with blunted behavioral expression in the presence of stressors and impaired recovery of parasympathetic tone after a stressor is experienced.[53,60] Psychosocial stressors are also associated with the onset,[61,62] symptom severity,[63] and course of MDD.[60]

Investigations of regionally specific structural abnormalities in the 1990s were hampered by the paucity of standards for demarcating complex anatomic regions. Nonetheless, some studies found decreased width of PFC, and virtually all suggested that PFC is a key region in the neuroanatomic model of mood regulation.[50] Findings related to temporal and parietal regions were mixed. The advent of MRI volumetric studies brought improved resolution in distinguishing gray from white matter, allowing for gross morphologic characterizations of density of fiber tracts associated with myelination, anatomic connectivity, and neuronal degeneration. A few early controlled MRI studies found decreased total white matter volume and decreased frontal volumes in MDD and BPD, and a relative increase in gray matter specific to BPD,[64] whereas most studies found nonspecific global atrophy.[51] Several CT and MRI studies have also found increased rates of subcortical white matter or periventricular hyperintensities suggestive of cerebrovascular disease in patients with MDD and BPD, particularly in elderly patients.[50,64,65]

In general, the early structural imaging studies showed that white matter lesions throughout the frontal-striatal-thalamic circuitry are associated with depression. Volumetric abnormalities were most often found in the frontal lobes, but not consistently in any other region.[50,66]

Prefrontal cortices

More recent studies of patients with mood disorders have shown consistent abnormalities in morphometry of several specific medial prefrontal areas, anterior cingulate, and limbic regions.[50,67–70] Anatomic specificity has improved and allowed for more accurate functional localization to lateralized subdivisions of PFC. Based on cytoarchitectonic and functional considerations, the primate PFC has most often been delineated into subdivisions including the dorsolateral PFC (DLPFC), dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), and orbitofrontal cortex (OFC) sectors.[48,71,72] In addition, there seem to be important functional differences between the left and right sides within each of these subdivisions. In studies of naturally occurring lesions secondary to stroke or trauma, patients with damage to the

left hemisphere, specifically the left PFC, were found to be more likely to develop depressive symptoms compared with patients having homologous lesions in the right hemisphere.[72–74] This is consistent with studies of healthy subjects showing that positive mood and affect are associated with left DLPFC function,[72,73,75] whereas negative affect is associated with activation of right anterior PFC in the intact brain.[72] Although a few studies have reported that right hemisphere lesions have been associated with manic symptoms, mania has been less frequent than depression following stroke or brain injury.[72,74,76,77] The more recent literature has largely supported these lateralized observations across methodologies and in various contexts.[78–80]

Volumetric reductions have been observed with less consistency in OFC (BA 11/47) in both MDD and BPD, and in ventrolateral PFC (VLPFC) (BA 45) and DLPFC (BA 9/10) in BPD.[81–84] Some discrepancies may be related to the use of variable subregional specifications as targeted regions of interest (ROIs). In contrast with ROI-based structural studies, the use of VBM allows for voxel-by-voxel comparisons in regions that are difficult to define anatomically, by normalizing individual structural MRI scans to a standard template.[85] However, the VBM method poses risk for type II errors, such that small differences in volume located in other gray matter areas might be missed.

Using VBM methodology, a few studies have reported bilateral reductions in OFC volumes in patients with MDD compared with control subjects.[86,87] Reductions in cortical thickness have also been reported in patients with MDD.[88] Recently, VBM analyses in patients with BPD have revealed a strong correlation between decreased gray matter volume in left DLPFC and number of manic episodes,[89] consistent with the cognitive deficits observed in this population. Neither lifetime number of depressive episodes nor years of illness has been found to correlate with changes in gray matter volume, although voxel-based structural deficits in the left DLPFC were found to characterize a subgroup of people with recurrent MDD who respond poorly to antidepressants.[90]

Anterior cingulate cortex

The most prominent abnormality reported to date in MDD and BPD has been a marked (19%–48%) reduction in gray matter in left subgenual anterior cingulate cortex (sgACC, BA 25) (**Fig. 3**C).[48,85,91–100] This occurs early in the progression of the illness, as well as in young adults at high familial risk for MDD.[48,95] This finding has been shown to be stable over time. Botteron and colleagues[95] showed that patients with first onset depression had the same degree of volumetric reduction as did patients who had experienced recurrent episodes. Drevets and colleagues[100] showed no change in volume when patients were rescanned after a 3-month interval, regardless of whether their symptoms had resolved. A postmortem study by Ongur and colleagues[101,102] suggested a loss of glial cells as a potential cause. In comparison with unaffected control subjects, patients with MDD and BPD were found to have reduced density and number of glial cells in this region, a finding that was particularly robust in those subjects with a family history of depressive illness.[102,103] Some evidence suggests that left sgACC gray matter reduction may predate illness onset, and act as a biologic marker for familial risk of MDD or BPD.[48,66] Similarly, McDonald and colleagues (2004) showed an association between reduced volumes in right pregenual anterior cingulate cortex (pgACC) and sgACC and genetic risk for BPD.

Hippocampus

Studies examining volumetric changes of the hippocampus in depressed subjects have had mixed results, with findings influenced by a wide array of variables including duration of illness, severity of illness, age of onset, responsiveness to treatment, untreated days of illness, history of childhood abuse, and level of anxiety.[46,53,58,67,76,104–109] However, a recent meta-analysis of 36 studies (more than 2000 subjects) showed that depressed patients overall had significantly lower hippocampal volumes than healthy controls, most prominently in the left hippocampus,[104,106] consistent with studies showing an association between depression and abnormalities of context-dependent memory.[48] Hippocampal atrophy was seen only in those patients with a duration of illness greater than 2 years, or more than 1 depressive episode.[104] In addition, this effect was limited to children and middle-aged or older adults, and appeared to persist during symptom remission.[110] Young adults with MDD had hippocampal volumes equivalent to those seen in healthy controls, a result that has been postulated to reflect a reduced burden of illness in this population.[104]

A positive correlation has also been shown between hippocampal atrophy and extent of depressive symptoms, consistent with hippocampal sensitivity to stress-induced suppression of neurogenesis, and decreases in hippocampal volume associated with chronically increased glucocorticoids.[55,111] Shape analysis methodology

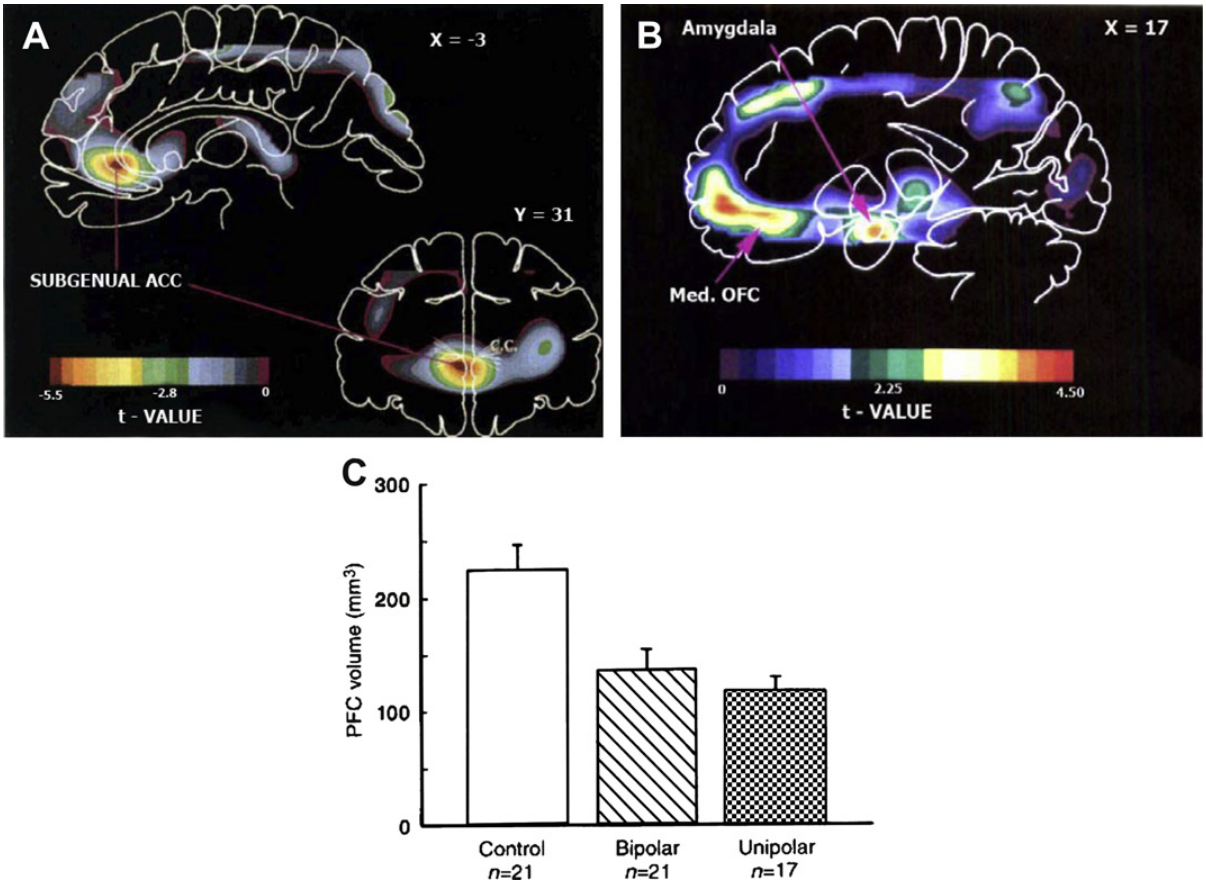

Fig. 3. Areas of abnormal glucose metabolism (*A*), CBF (*B*), and gray matter volume (*C*) in patients with MDD. (*A*) Decreased GLC in sgACC. (*B*) Increased amygdalar CBF. Abnormalities of CBF have also commonly been observed in rostral ACC, with normalization following pharmacologic and cognitive behavioral treatments.[92,131,144,239] (*C*) Reductions in sgACC gray matter volume in bipolar disorder and unipolar depression.[97] Significant reductions are observed irrespective of mood state and after covarying for age, gender, and whole brain volume.[100] (Fig. 3A: *Modified from* Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386(6627):826; with permission. Fig. 3B: *Modified from* Price JL, Carmichael ST, Drevets WC. Networks related to the orbital and medial prefrontal cortex; a substrate for emotional behavior? Prog Brain Res 1996;107:533; with permission. Fig. 3C: *Reproduced from* Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386(6627):826; with permission.)

used by Cole and colleagues[107] has localized subregional deformations to the CA1 subregion and the subiculum, the main output regions of the hippocampus. These specific deficits were limited to patients with 2 or fewer episodes of major depression. Although most studies reveal no differences in hippocampal volumes between male and female subjects with depression, a few report gender differences, with men showing a correlation between decreased left hippocampal volume (compared with controls) and length of depression, and women showing no such finding.[58,109,112] Within a group of female subjects, Vakili and colleagues[109] showed greater right hippocampal volume in those women who responded to medication than in those who did not.

Amygdala

Amygdalar volume in MDD or BPD (compared with healthy controls) has been reported to be increased in some studies and decreased in others[46,84,99,105,112–115]; higher volumes have been shown more often in patients with BPD,[84,106] whereas decreased volumes are more often found in cases of depression that are chronic or intermittent.[46] In keeping with these findings, Bowley and colleagues[116] reported substantially lower glial density in the amygdala in patients with MDD, and a recent metaregression analysis of patients with BPD found that those taking lithium were more likely to have increased gray matter volume in the amygdala.[84] Few studies have investigated gender differences; Hastings and colleagues[99] showed significantly smaller volumes in bilateral amygdalae of female depressed patients compared with depressed men.

Basal ganglia

Although morphometric studies of the basal ganglia have been mixed, most studies have

found caudate, putamen, and nucleus accumbens to be smaller in depressed subjects than in healthy controls.[64,117–122] Postmortem analysis has similarly shown volume decreases of up to 32%.[118] Lesions of the striatum and pallidum caused by/gliosis or calcifications are associated with depression, whereas mania has been observed after brain injury or stroke resulting in damage to the head of the right caudate nucleus.[77,123,124] In contrast, increases in striatal volume independent of illness duration have more often been shown in patients with BPD, as well as in their nonaffected twin siblings.[64] Aylward and colleagues (1996) reported increased caudate volumes in male, but not female, patients with BPD compared with controls.

Overall, structural imaging studies have been useful in identifying possible neuroanatomic substrates for depression; however, most results have been mixed, and this approach is clearly limited compared with methods that provide direct measures of energy metabolism, neurophysiologic abnormalities, or functional hemodynamic abnormalities. However, structural differences must be taken into account in the interpretation of functional findings.[102,125]

Functional Studies

Global findings

In an early functional neuroimaging study of MDD and BPD, Baxter and colleaguers[126] used fluorodeoxyglucose PET (FDG-PET) to scan patients in different mood states. Cerebral glucose metabolic rates were found to be globally reduced in bipolar patients in both depressed and mixed states in comparison with bipolar patients in manic states, patients with MDD, and normal controls. For subjects with BPD, whole brain metabolic rates were lowest in the depressed group, intermediate in the euthymic group, and greatest in the manic group, suggesting a state- specific, rather than trait-specific, finding.[126]

Frontal lobes

Functional abnormalities of PFC have been among the most robust findings in depression. Initial single-photon emission computed tomography (SPECT) and PET findings were variable, but most studies suggested maximal CBF reductions in left frontal cortex that normalize with treatment and form an inverse relationship with depression severity.[51,126–128] In 1993, Bench and colleagues[94,129] showed decreased CBF in the left DLPFC, left anterior cingulate cortex (ACC), and left angular gyrus using PET. Subsequent PET and SPECT studies confirmed these findings, supporting an inverse relationship between depression severity and frontal activity.[56] More recent studies have confirmed the presence of frontal abnormalities, but the direction of findings has been mixed (see Refs.[46,76,80,100,160] for comprehensive review), although some may be confounded by local reductions in gray matter volume, particularly on the left, as described earlier. The most consistent findings have been hypoactivity in dorsal portions of PFC and ACC, and hyperactivity in ventral and medial regions of PFC, including vmPFC, OFC, VLPFC, and anterior insula.[46,48,130] Normalization of this hyperactivity has been seen after treatment with pharmacotherapy,[92] cognitive behavioral therapy (CBT),[131] or deep brain stimulation of the ventral striatum.[132] Hypermetabolism in the frontal lobes has also been reported, but only in patients with pure familial MDD.[125] More often, hypermetabolism is found to be localized to the OFC region along with increased metabolism of the anterior insula during a major depressive episode.[69,125]

There seems to be a pattern of inverse activity in vmPFC and DLPFC, in which vmPFC is hyperactive in depressed patients at rest and healthy subjects during experimentally induced fear/anxiety, and decreases in activity during remission of symptoms, whereas DLPFC and dorsal cingulate are hypoactive at rest, and increase in activity during remission of symptoms.[59] In contrast, mania has been associated with decreased ventral and increased dorsal activity in PFC and ACC, perhaps resulting in inappropriate behavioral responses to changing inner drive and external environmental contexts.[133,134] Hypoactivation in dorsal PFC regions in depression may underlie alterations in psychomotor function, impairment of initiation and maintenance of goal-directed behavior, and difficulty suppressing automatic responses to emotion-related stimuli, resulting in perseveration of negative affect and decreased inhibitory control.

Anterior cingulate cortex

The ACC has been described as a “point of integration for visceral, attentional and affective information that is critical for self-regulation and adaptability.”[135] The ACC has extensive anatomic and functional connections with both dorsal and ventral aspects of frontal lobe networks. The ventral ACC connects with limbic and paralimbic regions such as the amygdala, nucleus accumbens, anterior insula, and autonomic brainstem motor nuclei (periaqueductal gray and parabrachial nucleus), and is assumed to be involved in regulating somatic, visceral, and autonomic responses to stressful events, emotional

expression, and social behavior.[80,136] The dorsal ACC connects with DLPFC (BA 46/9), posterior cingulate cortex (PCC), parietal cortex (BA 7), supplementary motor area, and spinal cord, and plays an important role in response selection and processing of cognitively demanding information.[80,136]

Imaging studies of depression in both MDD and BPD have shown abnormalities in ventral, rostral, and dorsal ACC metabolism and hemodynamic activity during a variety of emotion-induction tasks.[48,53,80,97,130,136–138] Abnormalities have been found most consistently in sgACC, supporting prominent structural abnormalities found in this region (see **Fig. 3**A, C).[46] Decreased sgACC metabolism and CBF has been shown in both medicated and unmedicated patients with depression using SPECT,[139] PET,[129,138,140,141] and fMRI.[100,137,142] These regional decreases have been reported to predate the onset of clinical symptoms[143] and predict recovery.[144] Decreases in dorsal regions of ACC (BA 24a/b/32) have also been reported.[80]

In contrast, there have also been reports of increased ACC, GLC, and CBF in the depressed versus remitted state, most often in dorsal and rostral aspects of ACC, including the subgenual and pregenual ACC,[130,145,146] a finding supported by activation in healthy subjects during experimentally induced sadness.[147–149] Metabolism in rostral ACC has been shown to correlate positively with severity of depression[150]; to decrease during remission induced by antidepressant drugs,[151] electroconvulsive therapy,[152] deep brain stimulation (DBS),[153] and placebo[154]; and to increase during relapse.

The inconsistent directionality of these findings may be caused by differential reductions in gray matter volume within heterogeneous study populations, and failure to account for partial volume effects in functional brain images with poor spatial resolution. When this volumetric deficit has been taken into account by correcting for partial volume effects and corresponding gray matter reduction, sgACC metabolism seems to be increased in unmedicated patients in the depressed state, and normal in medicated patients in remission.[48,76] Directional discrepancies may also reflect an inverse relationship between dorsal and ventral ACC similar to that seen in other dorsal and ventral frontal regions.

Along with studies showing strong modulatory connections to the lateral hypothalamus, these imaging studies suggest that sgACC activity may serve as an effective regulator of autonomic responsivity and, in conjunction with rostral and dorsal ACC, a predictor of treatment response. Mayberg[92] found that depressed patients who showed increased pretreatment resting state metabolism in rostral ACC (BA 24a/b) were more likely to respond to pharmacotherapy, whereas those in whom it was decreased remained significantly depressed after 6 weeks of treatment (**Fig. 4**A). In a pretreatment activation study involving negative emotional stimuli, Siegle and colleagues[144] showed that lower reactivity in sgACC, and higher pretreatment reactivity in the amygdale, were associated with improved response to CBT (see **Fig. 4**B). Studies suggest that rostral ACC may also have the capacity to facilitate restoration of dynamic equilibrium between the hypoactive dorsal and hyperactive ventral prefrontal circuitry through inhibitory modulation,[48] consistent with Thayer and Lane's[135] observation that rostral ACC is ideally positioned to modulate both dorsal and ventral prefrontal circuitry. Future studies will need to clarify the functional differences between dorsal and ventral ACC in relation to depressive subtypes.

Amygdala

Increases in resting amygdalar CBF and GLC metabolism have been consistently reported in individuals with mood disorders during both symptomatic and asymptomatic states, although this has not been reported in all depressive subtypes.[48,76,114,119] Increases correlate with severity of depression,[114] whereas decreases are seen with effective pharmacologic treatment, and correlate with clinical improvement.[114] Increased metabolism in the left amygdala has also been shown to correlate with plasma cortisol concentrations measured in stressful conditions in patients with MDD and BPD.[114]

Increases in left amygdalar CBF are also typically seen in healthy individuals during exposure to fear-related stimuli, a response that is present, but blunted, in both depressed adolescents and adults, perhaps because of increased regional resting metabolism.[114,155] Although healthy subjects display habituation of hemodynamic response to fear-related stimuli, prolonged blood oxygen level–dependent (BOLD) increases in bilateral amygdalae have been observed in patients with MDD and BPD,[156] suggesting dysfunctional fear conditioning mechanisms related to extinction. Current data suggest that the prolonged response to threat-related stimuli may be associated with right amygdalar dysfunction, whereas negative biases observed in mood and anxiety disorders may be associated with dysfunction of the left amygdala.[69]

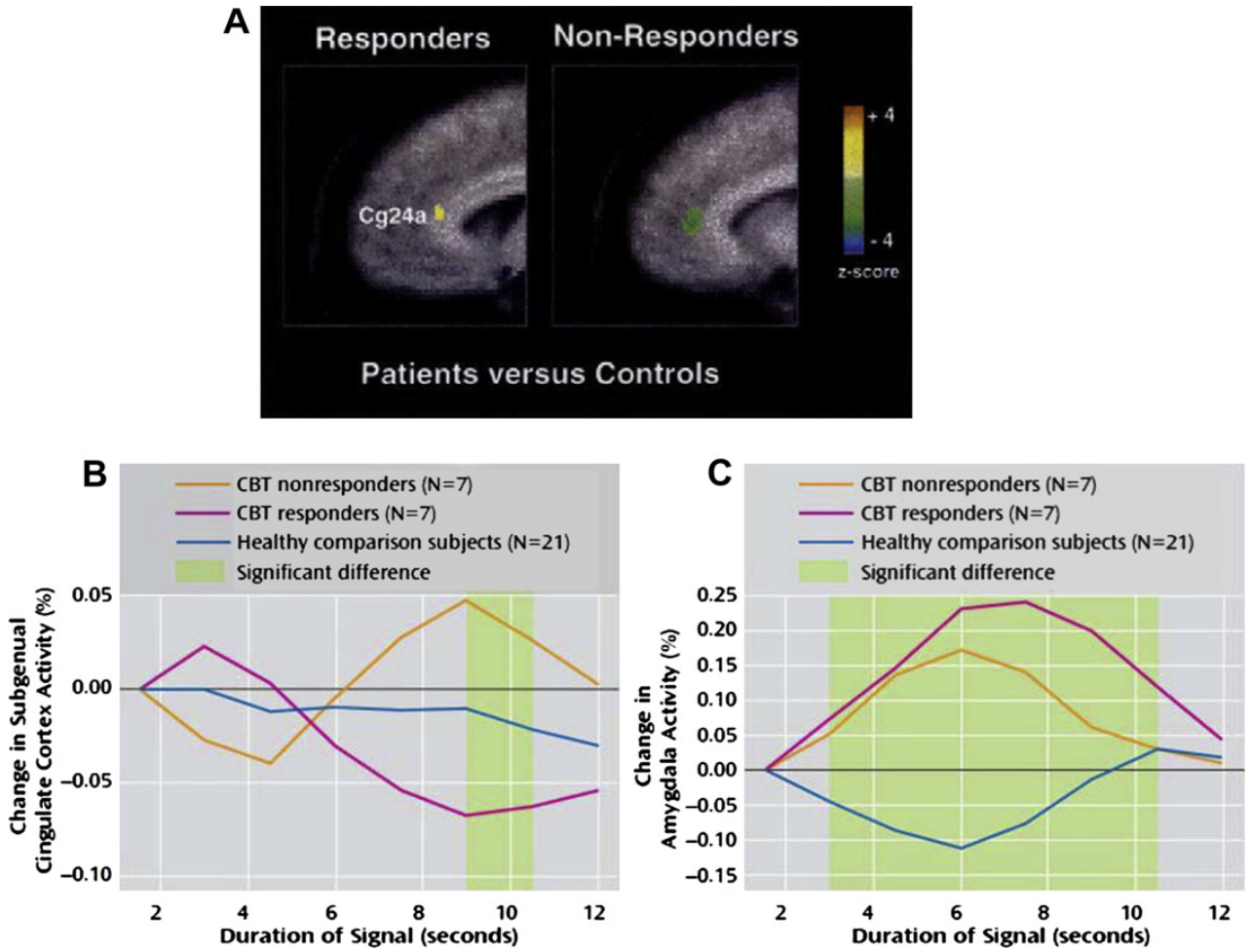

Fig. 4. Pretreatment CBF abnormalities in anterior cingulate cortex (ACC) and amygdala. (*A*) Depressed patients with high pretreatment resting metabolism in rostral ACC showed greater response to antidepressant medication; those with lower regional metabolism remained significantly depressed after 6 weeks of treatment. (*B*, *C*) Pretreatment changes in cingulate cortex (*B*) and amygdala (*C*) activity in response to negative emotional words in depressed versus healthy subjects. Positive response to CBT was associated with lower pretreatment reactivity in subgenual cingulate cortex (*B*) and higher pretreatment reactivity in amygdala (*C*). Shaded regions depict significant pretreatment differences in subgenual ACC responsivity between CBT responders and nonresponders (*B*), and in amygdalar responsitivity between depressed patients and healthy subjects (*C*). (Fig. 4A: *Reproduced from* Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;9(3):476; with permission. Fig. 4B, C: *Reproduced from* Siegle GJ, Carter CS, Thase ME. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatr 2006;163(4):736; with permission.)

Hippocampus

Although structural and histopathologic assessments of the hippocampus in depressed individuals have revealed significant abnormalities, functional abnormalities are rarely observed, with the exception that bilateral hippocampal hypoactivation has consistently been reported in studies of geriatric depression,[108] a condition commonly associated with memory impairment. Although there is a general lack of evidence for functional abnormalities in MDD or BPD, alterations in hippocampal neurogenesis have been associated with MDD, and some antidepressants have been shown to promote hippocampal neurogenesis.[106,157] Rather than an overall increase or decrease in hippocampal activation, dysregulation during context-dependent conditioning is more likely in MDD. Davidson and colleagues[80] suggest that there may be a link between inappropriate context-dependent affective responding and hippocampal atrophy, a suggestion that is consistent with the role of the hippocampus in context-specific memory formation and retrieval.

Mediodorsal thalamus

The mediodorsal thalamic nucleus has extensive connections with the amygdala and with ventral regions, as well as other PFC regions including OFC, VLPFC, and sgACC.[48,158] Depressed

patients with MDD and BPD have shown consistent increases in GLC and CBF in the left mediodorsal nucleus (MD),[67,119] implicating a limbic-thalamocortical circuit involving amygdala, MD, and medial PFC in depression.

Basal ganglia

Early PET studies showed state-dependent changes in CBF throughout the basal ganglia in both BPD and unipolar depression.[118,126,159] A significantly lower metabolic rate within the caudate nucleus has been observed in depressed patients in comparison with both normal controls and bipolar patients in the euthymic state,[125,126,146] although manic states have been associated with increased right compared with left striatal CBF,[133,160] and increased activity in the left head of the caudate associated with an ipsilateral increase in dorsal ACC.[133] Compared with healthy subjects, patients with both MDD and BPD show increased caudate CBF in response to aversive stimuli.[161,162]

Several recent studies have focused on anhedonia, the loss of interest or pleasure in activities, which constitutes a core symptom of depression, showing hypoactivity of regions associated with the processing of reward and positive stimuli in patients with depression. In depressed subjects and those with trait anhedonia, this symptom has been associated with decreased activity in ventral striatum (particularly nucleus accumbens) (**Fig. 5**) and dmPFC, a region associated with the processing of self-related stimuli,[161,163] as well as increases in vmPFC in response to positive stimuli and monetary reward. Anticipation of reward has been associated with abnormal activity in caudate and dorsal striatum.[67,161] Reduced volume of nucleus accumbens and anterior caudate, and decreased functional resting activity in rostral ACC, have also been associated with anhedonia.[164]

These data are consistent with the reduction in effortful and sustained positively motivated behavior seen across all subtypes of depressive disorder,[165] and suggest that inability to experience interest or pleasure in activities is associated with dysfunction of mesolimbic dopamine reward and prefrontal-striatal pathways. Psychotherapies designed to increase engagement with rewarding stimuli and reduce avoidance behaviors have been associated with increased metabolism in ventral striatum during monetary reward, and increased metabolism in dorsal striatum during reward anticipation.[166] In addition, it has been suggested that the presence of anhedonia could represent an endophenotype for particular subtypes of depressive disorder, with implications for advancing the understanding of depressive pathophysiology.[162]

Insula

Alterations in awareness of somatic characteristics related to self in MDD and BPD may be reflected in various somatovegetative symptoms associated with depression, along with an apparent hypervigilance to bodily changes, and exaggerated negative self-image.[167] The insula has been referred to as the interoceptive cortex, and shown to contain somatotopic representations of distinct feelings from the body (eg, pain, temperature, thirst, hunger, and other visceral sensations).[168] The posterior-to-anterior progression of neural processing through the insula provides a foundation for the sequential

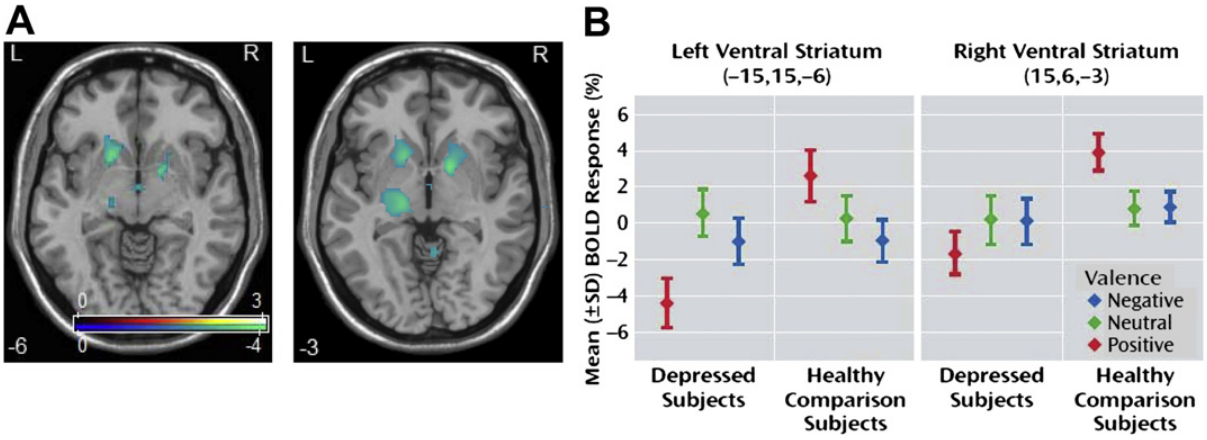

Fig. 5. Axial brain images (*A*) and graphs (*B*) showing significant bilateral ventral striatal decreases in activation to positive stimuli in depressed versus healthy subjects. The ventral striatum, particularly the nucleus accumbens, is associated with processing of reward and positive stimuli. Decreased activation was associated with anhedonia, or the inability to experience interest and pleasure. (*Data from* Epstein J, Pan H, Kocsis JH, et al. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. Am J Psychiatr 2006;163(10):1784–90.)

integration of the primary homeostatic condition of the body with salient features of the sensory environment, and then with motivational, hedonic, and social conditions represented in interconnected brain regions.[169] Studies in normal subjects have shown insular activation during anticipation of aversive stimuli, and in experimentally induced sadness,[141] suggesting a role for this structure in conveying aversive (or potentially aversive) visceral information to the amygdala. The insula has also been implicated in numerous studies involving the manipulation of emotion, and has been postulated to mediate self-awareness of behavioral patterns related to emotional expression, emotional control, and interpersonal relations.[170]

Evidence is accumulating for dysfunctional interoception in depression and anxiety, a finding integrated increasingly into neurocognitive models of depression.[47,141,171,172] Both early PET and more recent fMRI studies of patients with MDD have shown abnormal insular activity following interoceptive awareness tasks, or during experimentally induced sad autobiographical memories or negative self-relevant affective expression.[141,171,173,174] This altered insular activation, along with abnormal metabolism in medial PFC, may reflect an inability to shift the focus of perception/awareness from one's own body to the environment, consistent with the phenomenology of depression.[172] In keeping with this hypothesis, Wiebking and colleagues[172] showed a hypersensitive bodily awareness in patients with MDD compared with healthy controls that correlated positively with sustained activity in left anterior insula and severity of depression. Decreased activation of insular cortex in response to negative stimuli has also been reported in depressed patients, and observed to normalize following 2 weeks of treatment with venlafaxine, with correlation between symptom reduction and signal change in the left insular cortex.[175]

Connectivity studies

In recent years, functional neuroimaging research has focused increasingly on interregional neural interactions, most often via functional connectivity analyses that identify temporal correlations of low-frequency (0.01–0.1 Hz) BOLD fluctuations between spatially remote regions presumed to function as a network in the execution of a given task. Multivariate analyses have also identified spontaneous intrinsic activity in the resting brain that is anticorrelated with activity related to any particular attention-demanding task, and seems to be consistent across time and with anatomic connectivity.[176–180] This intrinsic activity is referred to as the default mode network (DMN).[176,177,181,182] The DMN increases in activity during passive states, in which individuals are left to themselves to think, and during spontaneous and experimentally induced stimulus-independent thought or the state of a wandering mind.[183,184]

The DMN involves 2 subsystems that interact with a common core, and overlap with circuitry associated with self-reflective thought.[181,182,185] Core areas of the DMN are the anterior medial prefrontal cortex (aMPFC) and PCC. The dorsal medial prefrontal cortex (dMPFC) subsystem includes the dMPFC, temporoparietal junction (TPJ), lateral temporal cortex (LTC), and temporal pole (TempP); the medial temporal lobe (MTL) subsystem includes the vmPFC, posterior inferior parietal lobe (pIPL), retrosplenial cortex (Rsp), parahippocampal cortex (PHC), and hippocampal formation (HF+).[181] The dMPFC subsystem preferentially engages when participants make self-referential judgments about their present situation or mental states, whereas the MTL subsystem preferentially engages during episodic judgments about the personal future.[181]

Several studies of depressed subjects have shown abnormalities in functional connectivity within the network of structures described earlier (see Broyd and colleagues[189] for review).[142,186–189] Depressed subjects at rest displayed increased DMN connectivity with sgACC, correlating positively with length of current depressive episode.[186,190] Increased connectivity between the DMN, the sgACC, and the thalamus has also been observed, suggesting increased incorporation of emotional processing at the expense of executive functions.[186] Grimm and colleagues[187] also found abnormalities in connectivity between vmPFC and PCC, in addition to sgACC.

In depressed individuals, attentional resources are disproportionately allocated from the external environment to internal experiences such as negative cognitions and sadness, manifested clinically as rumination.[165] Berman and colleagues[190] showed that resting state correlation between PCC and sgACC in depressed subjects correlates positively with self-reflective rumination. Anticorrelations or negative BOLD responses in the DMN, typical during emotional stimulation in healthy individuals, have been absent in patients with MDD, suggesting increased self-reflective processing.[187] Recently, Epstein and colleagues observed a failure to segregate emotional processing from cognitive and sensorimotor processing in depressed subjects viewing positive stimuli. In BPD patients, functional connectivity analyses have identified abnormal correlations between left ventral PFC, amygdala, and right ventral striatum, along with weak inverse correlations between

ventral PFC and dorsal PFC, providing support for behavioral observations of dysregulated affect and reward processing.[191] Although characterization using functional and effective connectivity methodology is in its infancy, existing data suggest that excessive activation of functional resting state networks in depressed subjects is associated with increases in ruminative thought, and with perseveration on negative, self-referential thoughts.[186,190]

Neurochemical Studies

Magnetic resonance spectroscopy (MRS) investigations into MDD and BPD have revealed a variety of abnormalities in brain chemistry. Decreased levels of γ-aminobutyric acid (GABA) have been observed in dmPFC and DLPFC,[192] consistent with postmortem studies showing reduced glial cell density in these regions. Glutamatergic abnormalities, as measured by the Glx peak, reflecting combined concentrations of glutamate plus glutamine, have also been observed in depressed subjects, and found to be linearly correlated with resting state functional connectivity between pgACC and anterior insula, a correlation not seen in healthy controls.[193] The most consistent finding has been abnormalities in the Cho signal, which is believed to reflect concentrations of choline-containing compounds, membrane turnover, and changes in synaptic plasticity.[194]

Choline abnormalities have also been reported in BPD. Several studies have shown increased choline concentrations in striatum and cingulate cortex that are independent of mood state or treatment with lithium.[160,195] One study of patients with BPD (compared with healthy controls) found lateralized differences in the cingulate: on the left, choline concentrations correlated positively with ratings of depression, whereas, on the right, choline was increased regardless of the presence of depressive symptoms.[160] Changes in *N*-acetyl aspartate (NAA), a marker for functional and structural neuronal integrity, have also been shown in BPD, with decreases reported in DLPFC and hippocampus of adolescents and adults with the disorder.[160] These data suggest a subcortical basis for the expression of bipolar symptoms, and impaired neural signaling during depressed states, especially in PFC and hippocampus.

Overall, the most common functional metabolic findings in patients with MDD and BPD, irrespective of mood state, are abnormalities in the amygdala and rostral ACC, including the subgenual and pregenual regions (see **Fig. 3**A, B). Some of these findings seem to normalize with pharmacologic or psychotherapeutic treatment and/or serve as predictors of treatment response (see **Fig. 4**).[56,130,131,144,145,152]

REFINING NEUROCIRCUITRY MODELS FOR MOOD DISORDERS: CURRENT PERSPECTIVES

The brain regions consistently implicated in the production of depressive signs and symptoms via neuroimaging, neuropsychological, and histopathologic methods are shown in **Fig. 6** within a schematic model of corticolimbic-insular-striatal-pallidal-thalamic circuitry (CLIPST).[46,48,50,53,69,119] Consistent with the wide variety of symptoms that comprise depression, the model includes structures involved in the processing of fear, reward, attention, motivation, memory, stress, social cognition, and somatic functions.[48,80,130] Depression may arise in the context of dysfunction of 1 or more of these regions, or because of a failure of coordinated interactions within or between the broader circuits. It is likely that different subtypes of depression are mediated by disorders localized to different brain areas, and respond accordingly to different treatments.

Prevailing models for mood disorders have focused on critical dissociations between the highly integrated dorsal and ventral circuits of the frontal lobe and their respective interactions with elements of the limbic system (amygdala, hippocampus, thalamus), basal ganglia, insula, and hypothalamic-pituitary-adrenal (HPA) axis.[68,76,97,129,130,139,142,196–198] Tract-tracing methods in animals have further subdivided ventral regions into orbital and medial prefrontal networks.[48,199] Recently, graph analytical and hierarchical clustering analysis of low-frequency, intrinsic functional BOLD connectivity in the resting brain has revealed distinct dorsomedial and ventromedial subsystems that interact with a common midline core (orbitomedial PFC [OMPFC] and PCC).[181] The dorsal circuit includes portions of the middle and superior frontal gyri on the lateral surface of the frontal lobe (BA 9/46/44); has dense interconnections with premotor areas; and projects to the dorsal cingulate (BA 24b/32), posterior cingulate (PCC, BA 29/30/31), inferior parietal cortex (BA 39/40), head of the caudate, and putamen.[46,69,130,200] The ventral circuit includes the medial and ventrolateral aspects of orbitofrontal cortex (BA 10/11/47/12) and has reciprocal projections with the adjacent anterior agranular insular cortex (AIC, BA 13), pgACC and sgACC (BA 24a/25/32), amygdala and hippocampus, ventromedial striatum, midline thalamic nuclei (PVT), and hypothalamus.[46,48,50,68] Behavioral observations of experimental lesions in animals[1,93,201,202] and naturally occurring

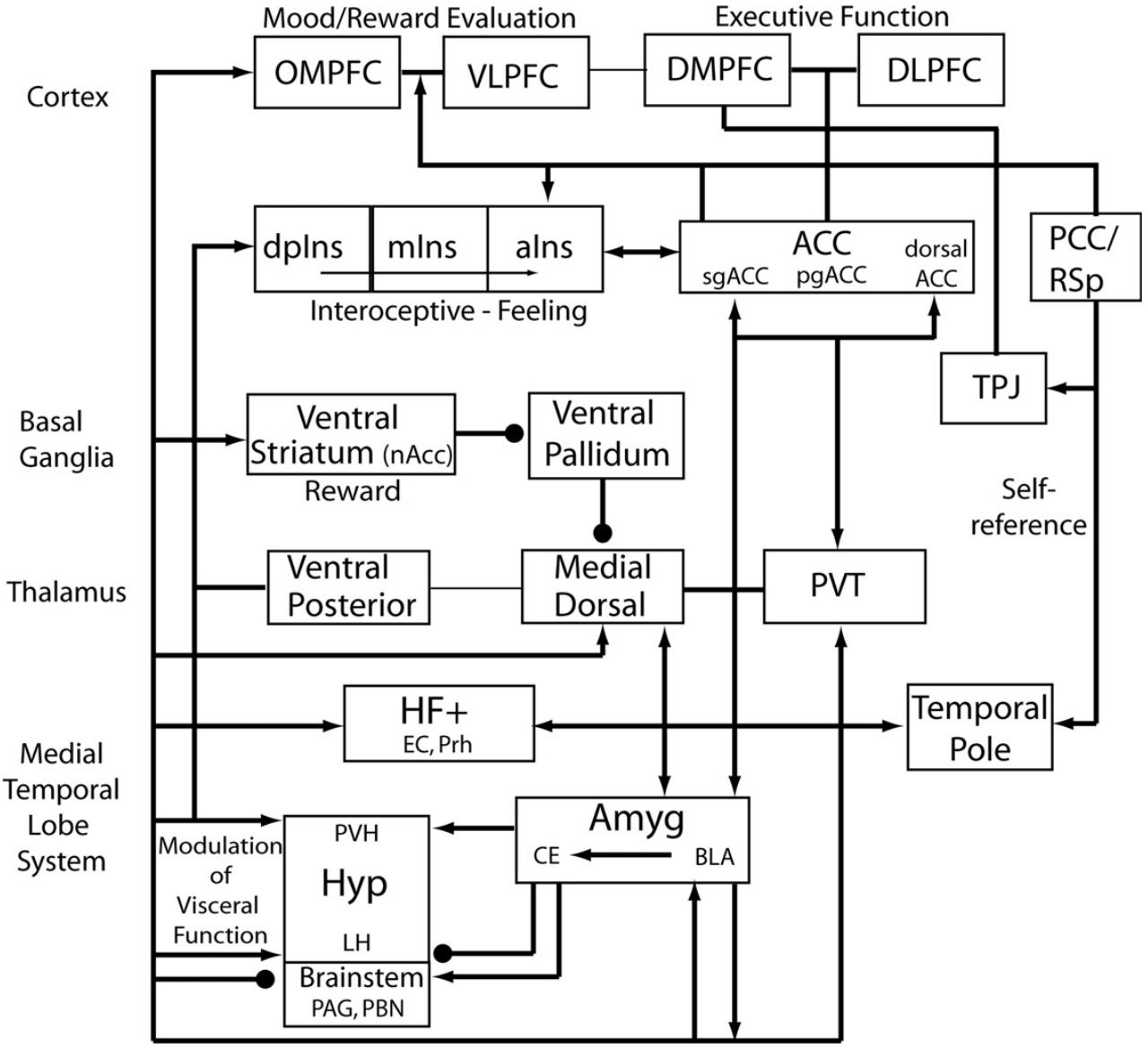

Fig. 6. Neuroanatomic model of circuitry implicated in depression by neuroimaging and neuropathological studies of mood disorders. Solid lines, anatomic connections; arrows, excitatory projections; terminal endings, strong inhibitory projections. ACC, anterior cingulate cortex; aIns, anterior insula; Amyg, amygdala; BLA, basolateral nucleus of the amygdale; CE, central nucleus of the amygdala; DLPFC, dorsolateral prefrontal cortex; dpIns, dorsal-posterior insula; EC, entorhinal cortex; HF+, hippocampal formation; LH, lateral hypothalamus; mIns, medial insula; nAcc, nucleus accumbens; OMPFC, orbitomedial prefrontal cortex; PAG, periacqueductal gray; PBN, peribrachial nucleus; Prh, perirhinal cortex; PVH, periventricular hypothalamus; PVT, periventricular thalamus; RSp, retrosplenial cortex; VLPFC, ventrolateral prefrontal cortex.

disorders in humans[14,149,203] provide ample evidence for the role of CLIPST circuitry in the pathophysiology of depression. Late-onset depression is associated with cerebrovascular disease and white matter changes within this network.[67,120,163,204,205] Traumatic brain injury to regions within the circuit is associated with hyperactivity, agitation, mood swings, irritability, excitation, impulsivity, hostility, and impaired affective evaluation.[174,203,206] The application of imaging techniques to the skull of Phineas Gage, the well-known exemplar of behavioral changes secondary to frontal lobe injury, suggests that the lesion affected left anterior OFC (BA 11/12), polar and anterior medial frontal cortices (BA 8/9/10/32), and possibly vmPFC and ACC (BA 24).[14,15] Specific abnormalities in CLIPST circuitry may also serve as biomarkers either for resilience to stress, or for risk of subsequent development of mood disorders.[55,207] There are data to suggest that structural and functional abnormalities caused by genetic endowment or early traumatic experience may initiate a pathologic process that remains presymptomatic through adolescence, but subsequently manifests at clinical levels after exposure to a significant stressor toward

which cognitive and emotional processing is maladaptive.[46,165,207]

In the model delineated earlier, lesions in any part of the circuitry could lead to a constellation of symptoms related to depression, but specific to the precise functional location. Dorsal circuitry is characterized as regulating executive functions (forming, maintaining, switching set), sensory discrimination, and cognitive forms of appraisal.[50,130,156,171,208] Lesions in dorsolateral circuitry lead to broadly defined deficits in executive function and working memory, whereas those in dorsomedial circuitry lead to deficits in reason and emotional expression.[149,208] Ventral circuitry is characterized as regulating affective, motivational, evaluative, and self-relevant processing.[93,125,174,203] Symptoms arising from ventral circuitry lesions may reflect dysregulated attempts to interrupt unreinforced aversive thoughts and emotions, raising the possibility that disturbed synaptic interactions between these regions and the amygdala, striatum, hypothalamus, or periaqueductal gray may impair the ability to inhibit unreinforced or maladaptive emotional, cognitive, and behavioral responses.

Generally, the functional neuroimaging studies described earlier show that sadness and depressive symptoms are associated with decreases in dorsal, and relative increases in ventral, circuit activity.[48,68,80,129,142,156,209,210] In response to a real or imagined threat, abnormalities in metabolism or function within the dorsal circuit may disinhibit the autonomic and emotional expression regulated by ventral circuitry. With successful pharmacologic or behavioral treatment, reversal of these findings is observed.[48,119,174] Current models of emotion regulation propose that depressive remission occurs when there is inhibition of the hyperactive ventral regions and activation of the previously hypofunctioning dorsal areas.[130,174,211] Based on the overwhelming evidence for abnormal functioning of the rostral ACC in depression, its strong reciprocal connections with both dorsal and ventral circuitry, and evidence that pretreatment metabolism in the BA 24a region uniquely predicts treatment response, the region is postulated to play a major regulatory role and to be necessary for adaptive behavioral change.[130] Disruption of the rostral cingulate is likely to have a significant effect on the CLIPST network, particularly those circuits regulating mood, cognition, and autonomic response.

Data from neuroimaging studies are consistent with cognitive models of psychopathology such that depressive episodes are caused, in part, by heightened limbic reactivity to emotionally significant events, followed by a form of cognitive reactivity that includes deployment of increased attentional resources to such events (ie, rumination) and results in negative attentional bias and recall.[165] The cognitive control of emotional appraisal in this context of real or imagined threat is significantly attenuated, and thus reappraisal of negative interpretations is limited. Cognitive models further propose that a negatively biased information processing system translates into stable dysfunctional attitudes with distorted negative interpretations (eg, selective abstraction, overgeneralization) of benign emotional experiences. Thus, depressive symptoms emerge from a continuous feedback loop of negative interpretations and attentional biases, with subjective and behavioral symptoms reinforcing one another.

CIRCUITRY-BASED NEUROTHERAPEUTICS

Neurosurgical treatment of psychiatric disease has a long and controversial history (**Box 1**). This approach is currently reserved for a select patient population characterized by severe and refractory symptoms, or strongly adverse side effects. Although neurosurgical treatments are most widely used for obsessive-compulsive disorder, various procedures have also been used for severe forms of refractory depression. The circuitry-based model described earlier provides insight into the physiologic mechanisms of the neurosurgical, DBS, and rapid transcranial magnetic stimulation (rTMS) treatments for refractory depression that have been reported in the literature.[92,212–215] In addition to their role in delineating this model, neuroimaging methods have also been instrumental in preoperative localization of targets and postoperative confirmation of lesion extent.

Stereotactic Ablation

The most effective surgical procedure for the treatment of refractory depression has been the subcaudate tractotomy, a procedure that involves interrupting white matter tracts that link various structures including vmPFC, basal forebrain, amygdale, and hypothalamus (**Fig. 8**).[200,215,219,220] In general, procedures that induce damage to vmPFC and/or its white matter connections have been reported to be efficacious in alleviating depression.[220] In a retrospective study of patients who had suffered severe mood or obsessive-compulsive disorders before surgery between 1979 and 1991, 84 of 249 (34%) had significantly reduced symptoms 1 year after subcaudate tractotomy.[221] Other procedures have included anterior cingulotomy, limbic leukotomy, anterior capsulotomy, bilateral amygdalotomy,

Box 1
History of psychosurgery

The earliest evidence of surgical methods targeting psychiatric illness comes from an archaeological site in France where skulls carbon dated to 5100 BCE were observed to contain carefully drilled holes rounded off by growth of new bony tissue, suggesting healing around the opening. Similar finds from subsequent eras suggest that the holes resulted from a surgical intervention called trephination, an opening of the cranium to relieve depressive symptoms along with headaches, seizures, or other spiritual or psychiatric disturbances.[215,216]

In the nineteenth century, neurobiologic models of mental dysfunction began to emerge, providing the groundwork for the development of somatic treatments. By the end of the century, increasing excitement surrounding connectionist models of mental function set the stage for the first psychosurgical intervention, a topectomy performed by Gottlieb Burckhardt, a Swiss psychiatrist. In 1888, Burckhardt removed cortical tissue from multiple foci in frontal, parietal, and temporal lobes in 6 patients characterized as aggressive and demented, with limited success.[215,216]

It was not until the 1930s that psychosurgery (now firmly focused on frontal incisions) gained prominence. Given the pressures of overcrowded psychiatric institutions and the limited success of other somatic therapies including convulsive, insulin shock, and hydrotherapy, the use of psychosurgery began to peak following World War II. More than 5000 outpatient lobotomies were performed in 1949 alone, and more than 15,000 more by the time the practice declined in the 1950s.[215–217]

The term psychosurgery was coined by Egas Moniz, a Portuguese neurologist credited as the first to target smaller areas of the frontal lobes, using either ethyl alcohol or a leucotome, for treatment of melancholy, anxiety, and delusions.[200,215–217] Along with a neurosurgical colleague, Almeida Lima, Moniz performed frontal leucotomies, targeting fibers that connect anterior frontal cortex with thalamic and cortical regions, with the intention of disrupting abnormally stabilized neural connections believed to be responsible for the fixed ideas that constitute mental illness.[202,216] Variations of the method were later used throughout the world to treat symptoms of psychosis.

In North America, James Watts, a neurosurgeon, and Walter Freeman, a neuropsychiatrist, refined the location and extent of the surgical lesion based on clinical responsiveness, and renamed the procedure frontal lobotomy, with minimal, standard, radical, and transorbital modifications (**Fig. 7**).[216,218] In 1942, Freeman and Watts reported that, of the first 200 patients to undergo frontal lobotomy, 63% manifested an improvement in symptoms, and noted that postmortem examination of some patients who had undergone the procedure confirmed retrograde degeneration in specific areas of the thalamus.[216] Transorbital lobotomies became the most common procedure for treating mental illness until the practice declined in the 1950s with the introduction of the antipsychotic drug, chlorpromazine, a safer, cheaper, more effective, and reversible treatment.

Despite the gains provided by the subsequent proliferation of pharmacologic treatments, it gradually became apparent that a surgical alternative might be useful for a select patient population characterized by severe and refractory symptoms, or strongly adverse side effects. In 1976, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research addressed this issue, creating guidelines for the ethical use and regulation of neurosurgical procedures for psychiatric disease.

bimedial leukotomy, orbital gyrus undercutting, thalomotomy, and hypothalamotomy.[200,219,222,223]

There is limited evidence directly comparing different procedures. Given the complexity of current models of depression, there are likely to be multiple sites of therapeutic action. It has been suggested that stereotactic ablation in discrete areas of CLIPST circuitry may alleviate treatment-refractory forms of depression through modification of downstream pathways in the network, in addition to reducing cortical mass and activity within the areas explicitly targeted. Reductions in volume and function of the reciprocal connections between ACC and several other structures, including OFC, amygdala, hippocampus and PCC, have been observed within 1 year of surgery.[222] Lesions of dorsal ACC might produce disinhibition of rostral ACC, which, in turn, might render patients more responsive to antidepressant pharmacotherapy after surgery. Alternatively, lesions of the cingulum might interrupt ascending influences of the amygdala on the dorsal circuitry.[69] Although neurosurgical treatments have shown some benefit for refractory

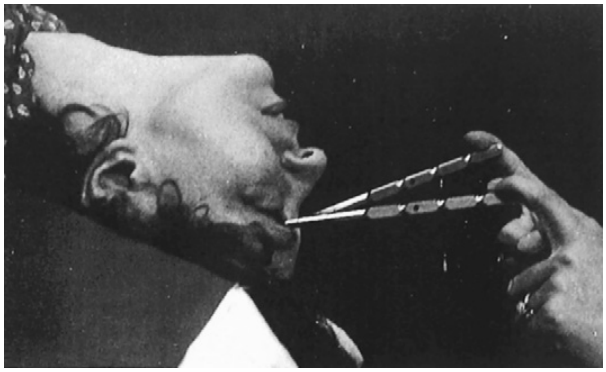

Fig. 7. The transorbital frontal lobotomy procedure, with 2 leucotome orbitoclasts positioned in the orbit. With little or no evidence for extent of lesion or standardized surgical procedures, patients were often given anesthesia in the form of electroconvulsive shock, followed by hammering of sturdy orbitoclasts through the orbital bone and up into neural tissue. (*Courtesy of* Walter Freeman III.)

forms of mood disorders, the current direction of the field is toward electrical, magnetic, and even modulation through focused ultrasound of neural structures for clinical purposes.

DBS

Subgenual anterior cingulate cortex

Following its introduction in the 1990s, high-frequency DBS, a less-invasive, reversible technique, gained popularity as a treatment of intractable forms of MDD.[130,212,214] Based on early circuit models of depression derived primarily from PET scan measures of GLC and CBF, the first region to be targeted was the sgACC (see **Fig. 8**).[130,214] Stimulation of the sgACC or the white matter tracts that lead to it (see **Fig. 8**) has been shown to induce remission of depression, with poststimulation decreases in cerebral flow to sgACC, and increases to PFC, correlating with clinical improvement.[153,222,224] Studies have further shown reversal and reresponse of effect with off-on-off-on design, lack of response with sham or subthreshold stimulation, and sustained 6- to 12-month improvement, supporting the effectiveness of sgACC DBS for treatment of depression.[212,224] Whether longer-term sustained response (ie, prevention of relapse) correlates with sgACC activity remains to be determined.[224]

Ventral anterior internal capsule/ventral striatum

A second brain region targeted for DBS in refractory depression has been the ventral anterior internal capsule/ventral striatum (VC/VS) (see **Fig. 8**).[132,225] Schlaepfer and colleagues[225] conducted preliminary studies to show that DBS in the nucleus accumbens was associated with clinical improvement when the stimulator was on, and worsening when it was turned off. A case of bilateral DBS of the accumbens for severe anxiety and secondary depression has also been reported.[212] A more recent study reported antidepressant, anti-anhedonic, and antianxiety effects of DBS to the nucleus accumbens, and associated metabolic decreases in sgACC, OFC, medial thalamus, PCC, and dmPFC.[132]

rTMS

rTMS is another noninvasive method for localized modulation of CLIPST circuitry.[226–232] Since its introduction in 1985, more than 40 randomized controlled trials of rTMS for depression have

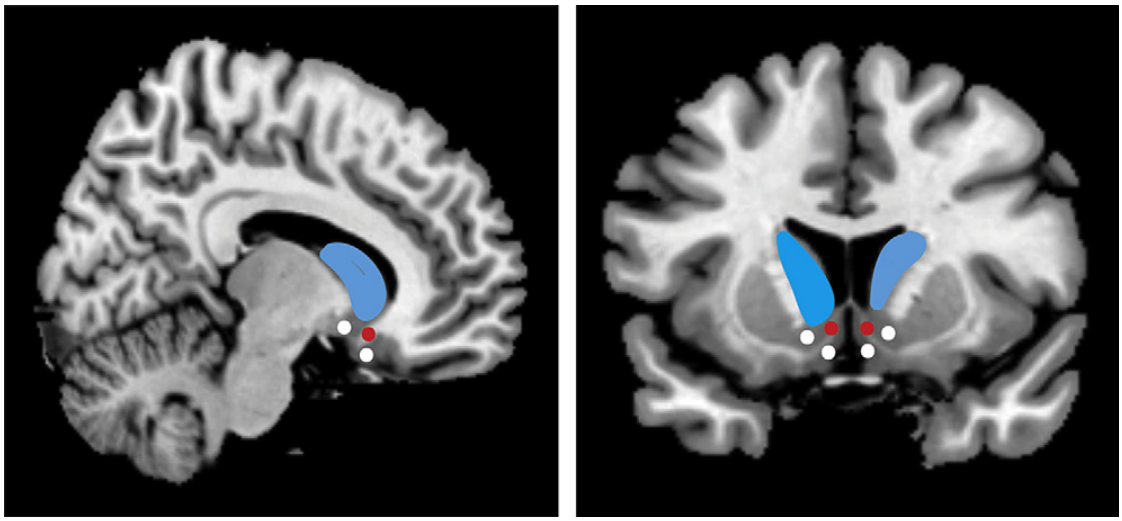

Fig. 8. Targets for stereotactic ablation and DBS treatments of refractory depression (shown in sagittal and coronal sections on a template brain). Red circles indicate targeted sites for subcaudate tractotomy: the substantia innominata (just inferior to the head of the caudate nucleus, in blue) is targeted with the goal of interrupting white matter tracts connecting OFC to subcortical structures. White circles indicate targeted sites (subgenual cingulate, nucleus accumbens) for deep brain stimulation.

been implemented, with mixed results.[232] A subset of these has examined pre- and posttreatment blood flow in rostral ACC. Nadeau and colleagues[229] found that pretreatment rostral ACC blood flow was correlated with reduction in depression severity following 10 days of 20 Hz rTMS over the left DLPFC. Similarly, increased pretreatment activity in rostral ACC was found to predict reduction of depressive symptoms following a 2-week trial of rTMS augmentation, or a 3-week trial of low-frequency stimulation over the right DLPFC.[230] In contrast, other studies have shown that lower pretreatment regional CBF in the rostral ACC was linked to greater rTMS response, whereas some have found no relationship between the 2 variables.[232] A recent meta-analysis concluded that the largest mean effect size for rTMS in treatment-resistant depression has occurred when right DLPFC has been targeted in the absence of pharmacotherapy.[228]

It is likely that ongoing advances in DBS and transcranial magnetic stimulation technologies will improve their clinical efficacy, and that these methods will be supplemented by additional reversible and possibly noninvasive localized treatments, such as focused ultrasound,[233,234] cranial electrotherapy stimulation,[235] or epidural cortical stimulation.[236] Unfolding topics of investigation, such as stem cell–based neuroprotective and neurorestorative strategies[237] and localized protein-based therapies using adeno-associated virus (AAV)–mediated gene transfer,[238] also hold great promise.

SUMMARY

The investigational use of functional neuroimaging has revolutionized understanding of the functional neuroanatomy of psychiatric disorders, giving rise to complex neurocircuitry-based models that provide a foundation for the development of neurosurgical and other targeted biologic treatments for psychiatric disorders. These techniques are also being used to identify biomarkers for risk/resilience factors, to elucidate clinical subtypes and final common pathways, to guide early intervention, and to predict treatment response. Although there is yet to be a standard, scientifically validated role for neuroimaging techniques in the clinical evaluation of individual patients suffering from mental illness, it is our hope that they will ultimately be used to diagnose pathophysiology based subclassifications of psychiatric disease, and to determine corresponding treatment approaches. Interventions requiring neurosurgical expertise are likely to play an important role in targeting specific neuropsychiatric symptom profiles, particularly in refractory cases.

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