The Continuing Evolution of Psychiatric Neurosurgery

By Brian Harris Kopell, MD, and Ali R. Rezai, MD

ABSTRACT

In this article, the authors examine the growth of the discipline of psychiatric surgery from the earliest lesioning procedures to the neuroaugmentative strategies used today. Special attention is paid to the neural circuitry that underlies psychiatric disorders and how surgical manipulation of these circuits might result in the amelioration of the disease state. Also examined is the effect that the technology curve has had on psychiatric surgery with regard to functional imaging and neurosurgical equipment. Finally, the authors use the current state of psychiatric surgery to speculate on some of the future directions that psychiatric neurosurgical procedures might take.

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INTRODUCTION

Few other medical treatments in history have been the focus of such controversy, debate, and misunderstanding as neurosurgery for psychiatric disorders. The term *psychosurgery*, which has traditionally been applied to these procedures, itself is a misnomer. *Psychosurgery* implies an intervention that directly targets the psyche or mind. Surgery for mental disorders intervenes on psychiatric patients' nervous systems in order to lessen their debilitating symptoms; therefore, the term *psychiatric neurosurgery* is a more accurate term and more reflective of the modern practice of these procedures.

Even as the practice of neurosurgery for psychiatric illness decreased in frequency following the introduction of Thorazine in 1954, the negative bias towards it continued to grow.[1] Charges of abuse and allegations of surgery for social control culminated in the establishment of a national commission in 1977 that examined psychiatric neurosurgical practices in the United States—from freehand frontal lobotomies to stereotactic lesioning procedures. Careful emphasis was taken to review the efficacy and safety of these procedures. As the chairman of the commission reported in his review, the findings were surprising: "We looked at the data and so they did not support our prejudices. I, for one, did not expect to come out in favor of psychosurgery. But we saw that some very sick people had been helped by it."[2] The commission was so impressed by the potential benefit of psychiatric neurosurgery that it recommended a review board be formed in order to study these procedures in a more scientific manner; nevertheless, this review board was never formed.

An extensive literature review by a pediatrician with a masters in public health was published by the Office of Technology Assessment in 1986 that cooled the ardor to perform psychiatric neurosurgical procedures. This review concluded that since psychiatric neurosurgery had never been studied in a randomized, double-blind prospective fashion, it should be considered experimental until a study proved otherwise. Coupled with the advent of newer, more effective psychotropic medications, psychiatric neurosurgery fell by the wayside. Today, only a few centers worldwide perform these procedures.

Nevertheless, there are several reasons to continue to evaluate the role of neurosurgery in treating psychiatric disease. Despite adherence to therapeutic guidelines and conscientious compliance, there still exists a population of psychiatric patients—particularly, among patients with obsessive-compulsive disorder (OCD)—who are refractory to conservative treatment with medications and psychotherapy. In the most recent review[3] of current treatment strategies, 15% to 30% of all OCD patients showed an unrelenting downward course despite all pharmacologic and psychotherapeutic treatments. Affective disorders, including major depression and bipolar disorder, similarly have a treatment-resistant subset of patients.[4,5] For some of these patients, surgery may still be a viable treatment alternative.

In addition to possibly being an effective treatment alternative for patients refractory to current pharmacologic and psychotherapeutic strategies, psychiatric neurosurgery may be cost-efficient. A study[6] has shown that psychiatric neurosurgery may be less expensive than long-term conservative treatments with medications and psychotherapy. In addition, other reports[7,8] show that the number and length of hospital visits were significantly decreased following psychiatric neurosurgery on severe OCD patients.

One of the challenges of treating psychiatric disease is the quantitative analysis of patients before and during the course of treatment. Modern psychiatric testing batteries, such as the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Clinical Global Impressions Scale, and the Hamilton Depression Scale (HAM-D), allow for more accurate, objective evaluations of patients undergoing psychiatric neurosurgery. Today, state-of-the-art brain imaging

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techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography, allow the clinical investigator a noninvasive method to directly and precisely localize brain function and anatomy. Together, these tools can help eliminate some shortcomings of past studies of psychiatric neurosurgery.

THE NEUROCIRCUITRY OF PSYCHIATRIC DISEASE

To perform psychiatric neurosurgery, appropriate surgical targets must be chosen; therefore, the pathophysiology of psychiatric disease must be elucidated. Our understanding of the neurocircuitry of psychiatric disorders is rapidly evolving. Cortico-basal ganglio-thalamic interaction is fundamental in the pathogenesis of various psychiatric diseases in humans (Figure 1). In the mid-1980s, DeLong et al[9] first suggested that there were two coordinated loops passing through the basal ganglia to the thalamus: (1) a "motor" loop that centers on the sensorimotor, caudate/putamen, globus pallidus (GP), thalamus, and premotor areas; and (2) an "associative" loop that involves cortical association areas, caudate/putamen, GP, subthalamic nucleus, and substantia nigra. The modern neurosurgical intervention in Parkinson's disease (PD) is based on this framework (Figure 2).

This article will focus on two of the most elucidated psychiatric diseases—OCD and affective disorders (both of which have been the targets of neurosurgical interventions).

Obsessive-Compulsive Disorder

While movement disorders, chronic pain, and psychiatric disease might seem dissimilar entities on the surface, they share common neural substrates. From the earliest observations of OCD, it was speculated that neuronal areas subserving motor function had a central role in its pathogenesis. Indeed, Freud[10] proposed that the neurologic substrate for the OCD patient's ego lies "at the motor end of the psychical system." Tourette disorder, a disease characterized by motor tics as well as OCD-like symptoms, demonstrates the phenomenon of a neural substrate capable of producing motor as well as psychiatric disease states. Studies[11,12] demonstrating the strong clinical and genetic association between Gilles de la Tourette syndrome and OCD suggest that the basal ganglia plays a central role in the pathogenesis of OCD symptoms. A basal ganglia circuit, similar to the one implicated in PD, has been proposed to explain the

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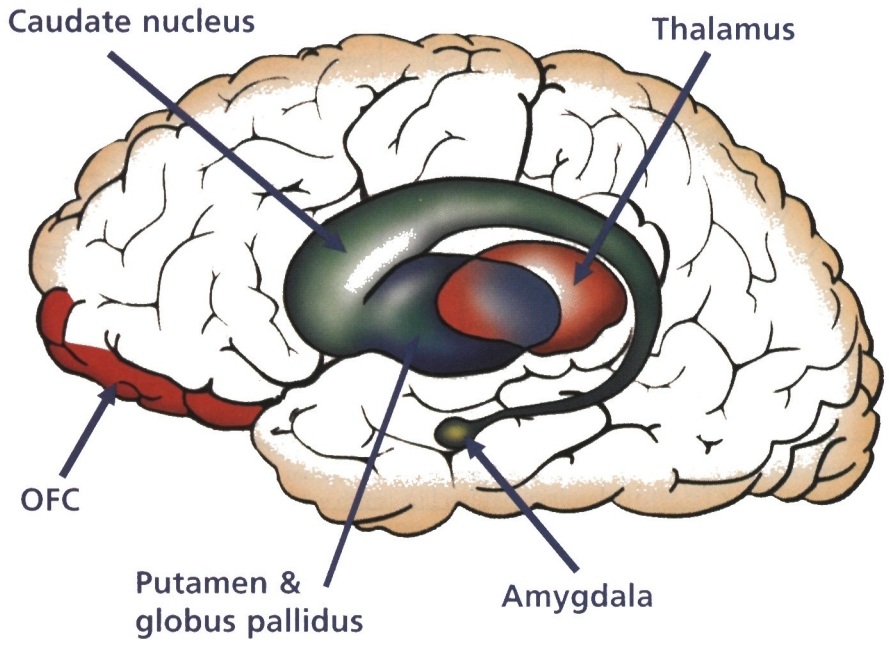

FIGURE 1. Basal ganglia and associated structures involved in psychiatric disorders. Note that medial structures, such as cingulate gyrus, fornix, mammillary bodies, hypothalamus, and midbrain nuclei, are not depicted.

OFC=orbitofrontal cerebral cortex.

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production of both motor and obsessional symptoms in Tourette disorder.[13] Further analysis of the clinical spectrum of PD has revealed many striking similarities between PD (a "motor" disease) and various psychiatric diseases, such as OCD and affective disorder.[14,15]

Based on these observations and the serotonergic hypothesis of OCD pathogenesis, Modell and colleagues[16] proposed a neuronal architecture for the basis of OCD. This model hypothesizes that the primary pathogenic mechanism lies in a dysregulation of the basal ganglia/limbic striatal circuits that modulate neuronal activity in and between posterior portions of the orbitofrontal cortex (OFC) and the medial, especially dorsomedial, thalamic nuclei (Figure 3).

There are three components to this neuronal model of OCD. The first involves a reciprocal positive-feedback loop involving the OFC and the dorsomedial thalamic (DM) nucleus by way of the anterior limb of the internal capsule. The corticothalamic projection is excitatory and mediated primarily by glutamate and aspartate. Although the reciprocal thalamocortical projection's neurotransmitter remains to be identified, multiple studies[14,16] suggest that it is also excitatory.

The second component of Modell's OCD model involves the OFC, the ventral striatum, the ventral pallidum, and the DM nucleus. While the transmissions of the ventral striatum to the ventral pallidum involve multiple neurotransmitters, including γ-aminobutyric acid (GABA) and substance P, the output of this pathway by way of the ventral pallidum to the thalamus is almost exclusively inhibitory, mediated by GABA. This component is thought to serve as a modulator for the excitatory positive-feedback orbitofrontal thalamic loop described earlier. Another vital aspect of this second component of the OCD model involves serotonergic projections from the dorsal raphe nuclei of the midbrain to the ventral striatum. These are speculated to be

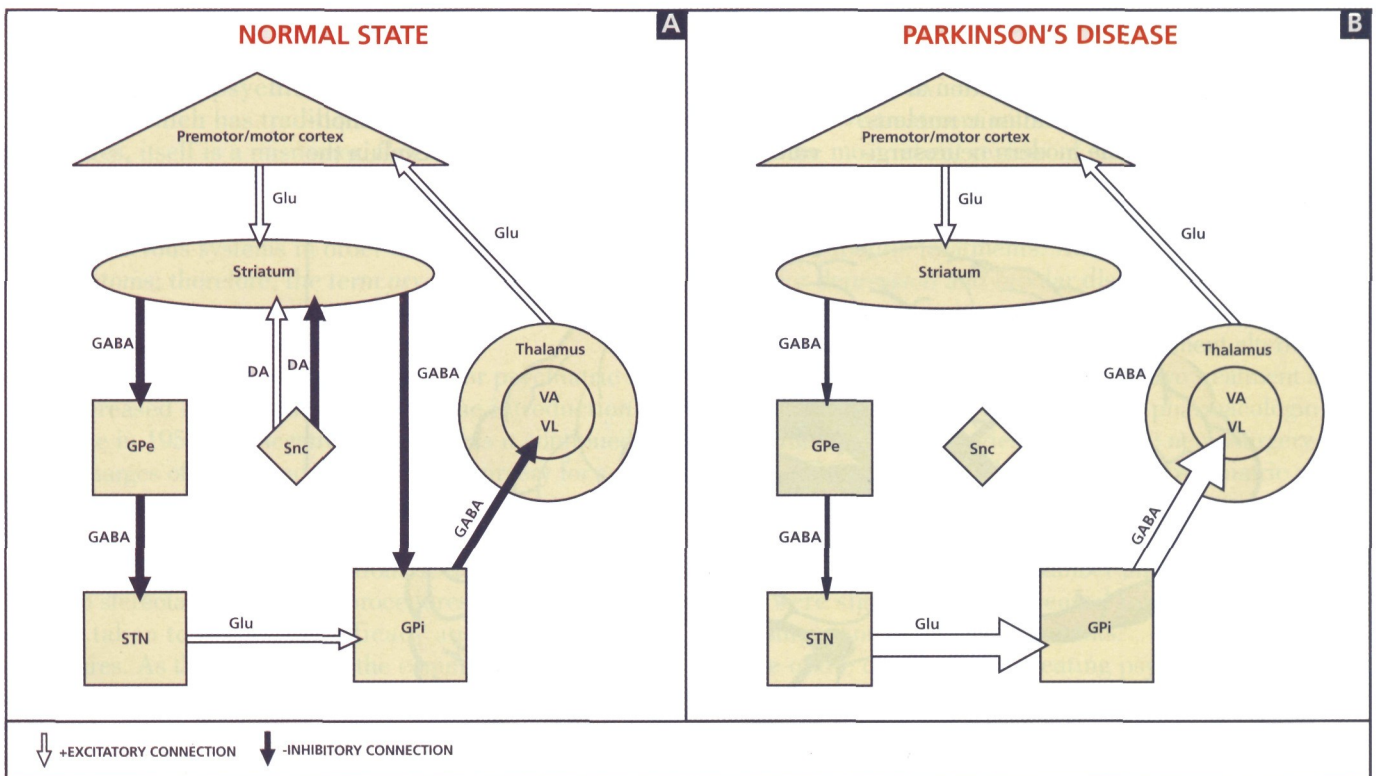

FIGURE 2. Schematic of basal ganglia function. Loss of dopaminergic input to the striatum due to substantia nigral degeneration results in dysregulation in basal ganglia function. The net effect is excessive inhibitory influence of the globus pallidus interna on the ventralis lateralis and ventralis anterior thalamic nuclei. Such abnormal inhibitory influence gives rise to the symptoms of Parkinson's disease. Black arrows represent inhibitory connections. White arrows represent excitatory connections.

Glu=glutamate; GABA=γ-aminobutyric acid; DA=dopamine; GPe=globus pallidus externa; Snc=substantia nigra pars compacta; VA=ventralis anterior thalamic nucleus; VL=ventralis lateralis thalamic nucleus; STN=subthalamic nucleus; GPi=globus pallidus interna.

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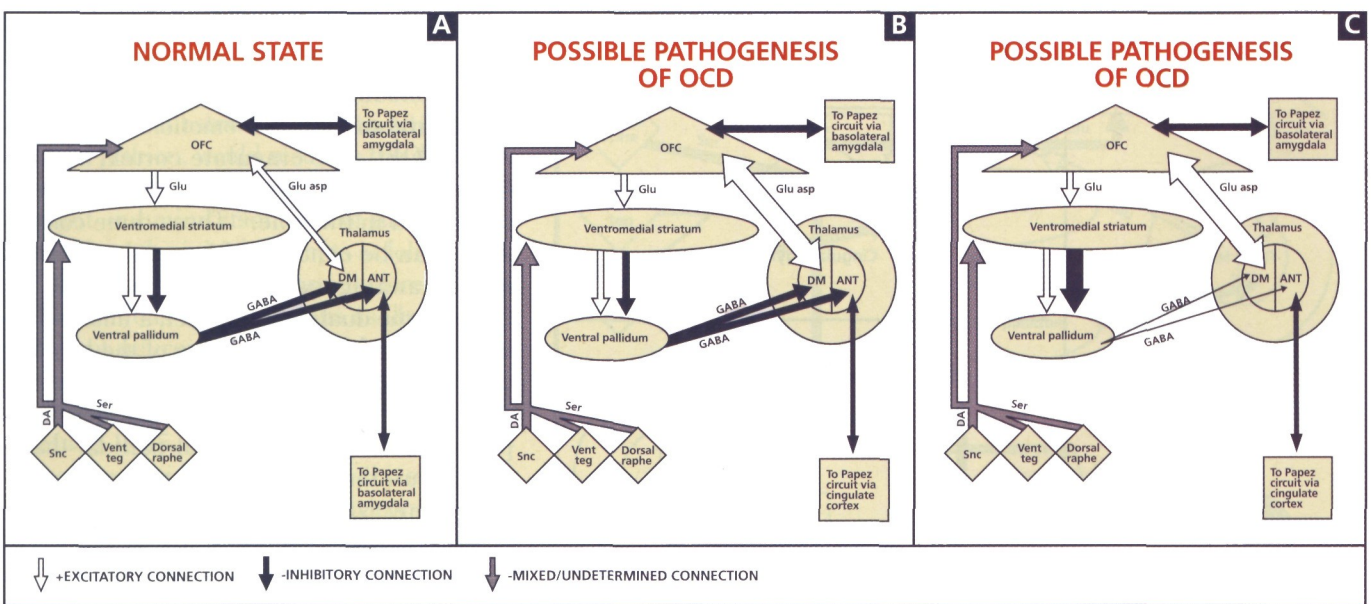
inhibitory in nature.

The third constituent of this model involves the limbic system and the Papez circuit (Figure 4). At its core, OCD is an anxiety disorder, and the impact of the patient's various obsessions and compulsions on his or her emotional state is the hallmark of the disease. In 1937, Papez[17] concluded that participation from the cerebral cortex is essential for the subjective emotional experience and that emotional expression is dependent on the integrative action of the hypothalamus. Papez devised a circuit based on his observations on neuroanatomic connections to integrate these two structures. The pathway begins from the hippocampal formation to the mamillary body via the fornix. The projection, via the mamillothalamic tract, continues to the anterior thalamic nuclei. From here, there are widespread connections to the cingulate gyrus. In the aforementioned OCD model, there are numerous connections to the Papez circuit via the DM nucleus and the OFC. These connections could subserve the anxiety/emotional component of OCD.

By synthesizing these three components, obsessive-compulsive (OC) symptoms could occur when an aberrant positive-feedback loop develops in the reciprocally excitatory frontothalamic neuronal pathway that is inadequately inhibited/modulated by striatopallidothalamic activity; thus, OC symptoms would be expected to appear when striatopallidothalamic activity is abnormally decreased or when orbitofrontothalamic activity is abnormally increased. Conversely, either increasing the modulating loop or decreasing the excitatory loop would be expected to result in a concomitant decrease in OCD symptom expression.[16] Additionally, modulation of the Papez circuit may in turn eliminate some of the disturbing affects that obsessions and compulsions have on a patient's emotional state. This mechanism is analogous to the model of PD in which dysregulation in the corpus striatum, secondary to loss of dopaminergic transmission from the substantia nigra pars compacta, results in the increase in tonic inhibition of the ventralis lateralis and ventralis anterior thalamic nuclei by the internal segment of the GP interna.



FIGURES 3. Schematic of OCD model. This diagram demonstrates the basal ganglia structures involved in the pathogenesis of OCD. The specific anatomic structures of the direct and indirect pathways (GPe, STN, GPi) shown in Figure 1 have been condensed into net excitatory/inhibitory influences for the purposes of clarity. The excitatory connections from the OFC to the ventromedial striatum and thalamus run through the anterior internal capsule and the substantia innominata. Abnormalities of dopaminergic and, especially, serotonergic influences on the orbitalfrontal cortex (OFC) and the ventromedial striatum could give rise to one of two different scenarios: An abnormal excess of reciprocally excitatory activity between the dorsomedial thalamus and the OFC (Figure 3B) or excessive activity through the direct basal ganglia pathway resulting in abnormally decreased inhibitory influence of the GPi on the DM thalamus (Figure 3C). Obsessive-compulsive symptoms would thus be expected to appear when striatopallidothalamic activity is abnormally decreased or when orbitofrontothalamic activity is abnormally increased.

OFC=orbitofrontal cerebral cortex; Glu=glutamate; Asp=aspartate; GABA=γ-aminobutyric acid; DM=dorsomedial thalamic nucleus; ANT=anterior thalamic nucleus; DA=dopamine; Ser=serotonin; Snc=substantia nigra pars compacta; Vent teg=ventral tegmentum of midbrain.

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"Basal ganglia dysregulation has also been implicated in the pathoneurophysiology of affective disorders, including major depression and bipolar disorder."

Recent functional imaging studies have consistently found evidence that corroborate this model of OCD pathogenesis. Increases in activation correlating with OC symptoms have been shown to occur in the OFC, the caudate, the thalamus, and the cingulate areas; however, PET and fMRI studies[18,19,20] show that treatment with appropriate medications—including selective serotonin reuptake inhibitors—and behavioral therapies, decreases the abnormally increased metabolism in these areas. Such areas of activation and responses to treatment might prove useful in assessing future neurosurgical treatments for OCD.

Affective Disorders

Basal ganglia dysregulation has also been implicated in the pathoneurophysiology of affective disorders, including major depression and bipolar disorder (Figure 5). Much of the work implicating the basal ganglia and other structures in the pathogenesis of affective disorders comes from imaging studies[21,22,23] using PET and fMRI. Abnormalities in metabolism have been demonstrated in the OFC, the cingulate, the basal ganglia, and the amygdala.

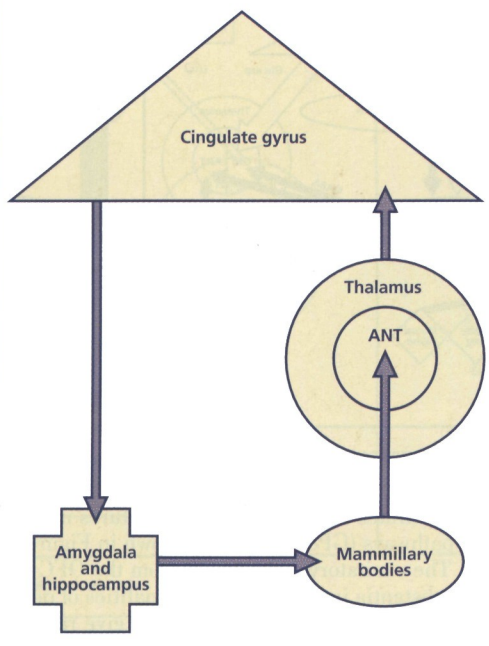

FIGURE 4. Schematic of Papez circuit. This diagram demonstrates the major anatomic structures and connections involved in the Papez circuit of emotion.

ANT=anterior thalamic nucleus.

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In order to examine affective disorders from a neurophysiological point of view, emotion can be divided into three components: (1) an expressive component (affect); (2) an internal/representitive component (mood); and (3) a modulatory component.[24] The expressive component of emotion, known as *affect*, represents the external manifestation of a person's internal emotional state. This can be further subdivided into two subcomponents: (1) endocrine/humoral; and (2) skeletomotor. Connections between the corticomedial amygdala and the hypothalamus via the stria terminalis regulate the release of cortisol and epinephrine in relation to emotional stimuli. Basolateral amygdala connections with the basal ganglia directly influence skeletomotor motivation and behaviors in response to emotional stimuli.

The structures subserving the internal representation of an emotional state, known as *mood*, remain obscure[25]; however, experimental experience implicates the amygdala, the frontal/cingulate cortices, the basal ganglia, and the hippocampus as possible underlying structures.[26] Certainly, the Papez circuit also contributes to this internal representation of emotional state. The third component represents a modulatory component between the expressive and internal emotional states; the medial OFC, the cingulate cortex, and the basolateral amygdala have been heavily implicated in this role.[27] These three components can be condensed into a dual circuit model, analogous to the one proposed for OCD. In the dual circuit model, a limbic-thalamic-cortical loop consisting of the basolateral amygdala, the DM nucleus, and the medial and ventrolateral frontal cortices runs parallel with a limbic-striatal-pallidal-thalamic circuit that consists of the ventral striatum, the ventral pallidum, and the thalamus.[28,29] It is possible that symptoms of affective disorders could be the result of an imbalance in the activity between these circuits. Given the numerous connections between these two proposed circuits and the limbic system, the Papez circuit must work in conjunction with these to fully express the symptoms of affective disorders.

It is important to remember that, unlike the model for PD, these models of psychiatric disease inherently have little basis in animal models; therefore, these proposed neural circuits are mostly based on anatomic connections and the aforementioned functional

imaging studies. While the proposed neural circuits may appear too simplified, they serve as a springboard for future functional imaging and physiological mapping studies from which neurosurgical and pharmacological therapies can be developed—similar to how such treatments were developed for PD.

THE STEREOTACTIC LESION: THE STANDARD APPROACH TO NEUROMODULATION

Surgical interventions to treat psychiatric disease date back to the earliest days of modern neurosurgery. As early as 1891, a Swiss psychiatrist named Burckhardt[30] reported the results of cortical excisions in psychiatric patients. In 1935, Nobel laureate Egas Moniz observed: "It is necessary to alter these synapse adjustments and change the paths chosen by the impulses in their constant passage so as to modify corresponding ideas and force thoughts into different channels...By upsetting the existing adjustments and setting in movement in other [connections], I [expect] to be able to transform the psychic reactions and to relieve the patient thereby."[31]

Moniz made the critical analytic jump to link the seemingly irrational behaviors and thoughts of psychiatric patients with a disordered neural substrate that, when altered in a surgical fashion, would result in the definitive change of the seemingly ethereal entities of thought and mind itself. All of these procedures, from the initial attempts at lobotomy to the stereotactic interventions explored below, utilize nervous system lesions as the primary means of neuromodulation—the process of altering neurological function for therapeutic benefit through neurosurgery.

Since 1935, neurosurgery has been performed for a wide variety of psychiatric disorders, from schizophrenia and anxiety disorders to sexual and eating disorders. The first procedures for psychiatric disease grew out of Fulton and Jacobsen's[32] observation that frontal lobe ablation could result in the lessening of anxiety states in chimpanzees. Indeed, the first neurosurgical procedure for psychiatric disease, the standard lobotomy, sought to interrupt white matter tracts associated with the frontal lobes. This procedure started as a rather extensive one and became more refined as the volume of brain in the surgical target became smaller. This trend towards increasingly discrete lesions culminated in applying stereotaxis to psychiatric neurosurgery. In 1947, Spiegel and Wycis[33] introduced the first subcortical stereotactic neurosurgical procedure performed on humans—the dorsomedial thalamotomy—which serves as the model on which all modern psychiatric neurosurgical procedures are based.

The four psychiatric neurosurgical procedures currently in use are cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leukotomy—all stereotactic interventions. These procedures are typically performed on severe, refractory psychiatric patients. First a patient must meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (*DSM-IV*) criteria for a particular psychiatric disease, such as OCD or affective disorder. Next, a patient must fail several rounds of treatment with multiple psychotropic medications combined with appropriate psychotherapy before he or she is considered for surgical treatment. Therapeutic failure is determined by quantitative analysis using the most appropriate

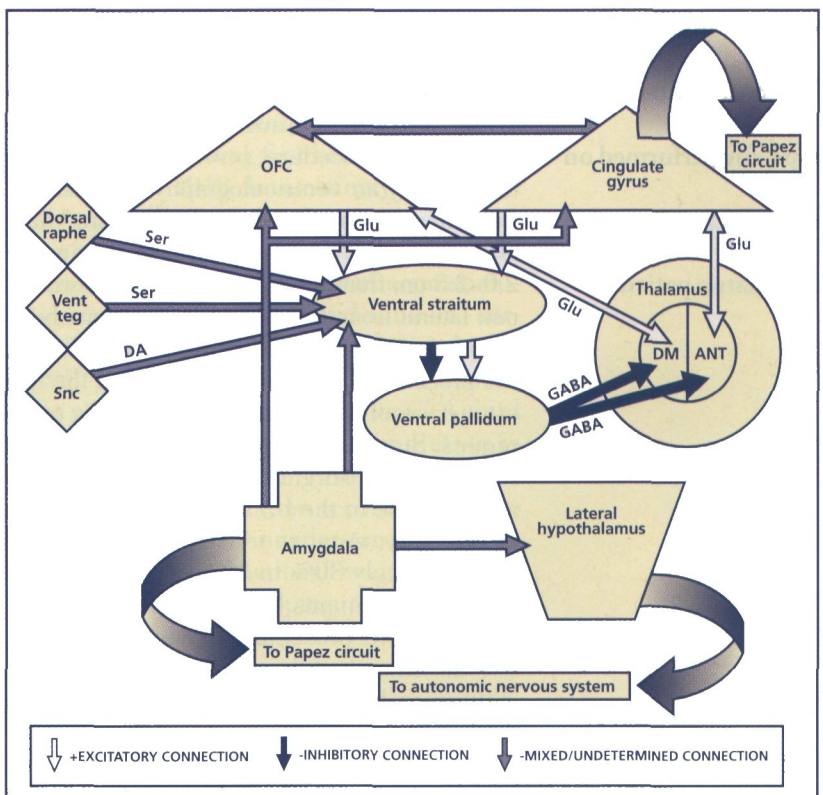

FIGURE 5. Schematic of affective disorder model. This diagram demonstrates the major anatomic structures and connections involved in the pathogenesis of major depression and bipolar disorder. As with obsessive-compulsive disorder, dysregulation through the basal ganglia could result in affective disorder symptoms.

OFC=orbitofrontal cerebral cortex; Ser=serotonin; Glu=glutamate; Vent teg=ventral tegmentum of midbrain; Snc=substantia nigra pars compacta; DA=dopamine; GABA=γ-aminobutyric acid; DM=dorsomedial thalamic nucleus; ANT=anterior thalamic nucleus.

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and accurate psychiatric batteries of tests available, such as Y-BOCS for OCD and HAM-D for depression. Finally, a multidisciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists, and neurosurgeons is assembled to form a consensus on whether the patient in question is both refractory to other treatments and an appropriate candidate for psychiatric neurosurgery. While many previous studies of psychiatric neurosurgery have significant flaws, most notably the inherent bias of a nonrandomized, nondouble-blind study as well as the lack of objective functional imaging techniques, they suggest a viable means of treatment for a subset of patients who may have no other treatment option.

Cingulotomy

The Basis for surgery on the cingulate gyrus dates back to observations[34] in the 1940s that severing fibers from the cingulate gyrus led to a decrease in anxiety-type states. In 1952, Whitty and colleagues[35] reported the first cingulectomy, in which a 4x1 cm section of cingulate gyrus was bilaterally resected. In 1967, Ballantine[36] introduced the modern stereotactic procedure, in which a lesion was targetted by air ventriculography and made in the anterior cingulate bilaterally using thermocoagulation. The lesion is typically made 2.0–2.5 cm from the tip of the frontal horns, 7 mm lateral from the midline, and 1 mm above the roof of the ventricles, bilaterally. Today, the procedure has been refined using the latest stereotactic equipment and imaging techniques. Stereotactic cingulotomy is the most reported neurosurgical procedure for psychiatric disease in the US and Canada. In terms of efficacy, most recent studies[37-39] show approximately 30% to 38% of all refractory psychiatric patients have significantly benefited from this procedure. Patients with affective disorders had the greatest efficacy rates, with major depressive patients showing a 60% response rate and bipolar disorder patients showing a 40% response rate. OCD patients had approximately a 30% response rate.[39] Some adverse side effects reported were seizures, weight or appetite changes, mania, and memory difficulties. It is difficult to quantify these adverse sequelae, since most of these studies involved a small cohort of patients. The largest risk (1% to 9%) was for seizures, which was easily controlled by Dilantin. In the largest published series of stereotactic cingulotomy, Ballantine and colleagues[6] reported no deaths among 696 patients and only 2 cases (0.3%) of hemiplegia from postoperative intracerebral hematomas.

Capsulotomy

Developed in Sweden by Lars Leksell and Talairach in France, anterior capsulotomy has been used as a treatment option for patients with refractory psychiatric illnesses since 1949. There are two forms of this procedure—both are stereotactic operations. One technique involves the use of radiofrequency, and the other uses γ-radiation to make the lesion. In both, the target area is between the anterior and middle thirds of the anterior limb of the internal capsule at the approximate level of the foramen of Monro. Specifically, the ideal target lays at 17 mm from the midline, 10 mm rostral to the anterior commissure, and 8 mm above the intercommissural line. The lesion is approximately 15–18 mm in length and 4–5 mm in width.[40,41] Recent studies[42,43] have reported significant efficacy rates from 35% to 60%. Although the experience with γ-capsulotomy is somewhat less than that with thermocoagulation, data[41,42] shows the two subtypes of anterior capsulotomy to be equally efficacious. Reported side effects involve aspects of frontal lobe dysfunction, which include personality changes, increases in impulsiveness, and memory difficulties. These transient side effects were found to correlate with T2 changes on MRI, consistent with postoperative edema. While the relative incidences of these sequelae vary from study to study, they are far lower than their respective efficacy rates and are considered avoidable aspects of this procedure.[43-45]

Subcaudate Tractotomy

Another stereotactic procedure geared towards interrupting fibers from the OFC to the thalamus is subcaudate tractotomy ("innominatomy"). Developed in London by Knight[46,47] in 1965, the operation was designed to relieve depressive, anxiety, and obsessional symptoms while minimizing postoperative epilepsy as well as cognitive and personality deficits. The lesion is created by multiple 1x7 mm rods of yttrium-90, a β-emitter that releases lethal radiation to tissue within 2 mm. These rods have a half-life of 68 hours, after which they become inert. The target site, a region of white matter localized beneath the

head of the caudate, known as the *substantia innominata*, has been traditionally localized by ventriculogram. A stereotactic apparatus places the rods after bilateral burr holes are made just above the frontal sinus and 15 mm from the midline. The lesion itself lays at the anteroposterior level of the planum sphenoidale, extending from 6–18 mm from the midline and being 20 mm long in an anteroposterior direction. Initially, placing 2 rows of 4 rods each made the lesion. Later studies, having refined the technique, added an extra rod to each row. Although the major indication for this procedure has been for refractory affective disorder, it has also shown great promise in the treatment of malignant OCD.[50] Recent studies[51,52] have reported significant relief or obliteration of debilitating symptoms in 33% to 45% of patients. There are very few reported cases of catastrophic postoperative complications. In a series of 1300 cases of subcaudate tractotomy, one set of authors[51] report only two deaths directly caused by the procedure. The most common side effect was postoperative confusion (10%) and minor decreases in verbal and visual memory tasks. The authors felt this transient phenomenon was mostly due to postoperative edema and, based on neuropsychological tests, found these deficits to resolve after 6 months.

Limbic Leukotomy

While the three aforementioned procedures target a single anatomic substrate, a fourth procedure is designed to interrupt fibers at two separate areas—a frontothalamic loop and an area of the Papez circuit. Termed *limbic leukotomy*, the procedure was developed in England by Desmond Kelly and Alan Richardson[53] in the early 1970s. The operation consists of three 6 mm thermocoagulative or cryogenic lesions in the lower medial quadrant of each frontal lobe (to interrupt frontothalamic connections) and two 6 mm lesions in each cingulum. The results for OCD (termed *obsessional neurosis* by the principal investigators) were excellent, with up to 89% of patients being significantly improved at 16 months postsurgical follow-up. Another study[54] showed 83% improvement rates at 20 months postsurgical follow up. No catastrophic complications have been reported. Although the investigators postoperatively found occurrences of confusion, headache, urinary incontinence, and lack of initiative in some patients, all side effects cleared within a few weeks.[53,54] Based on postoperative neuropsychological testing, the investigators found no permanent objective deficits or changes in concentration, memory, intelligence, or personality.[53,55,56]

THE NEUROAUGMENTATION ERA

We are on the verge of, quite arguably, one of the most important developments in the modern history of neurosurgery—the era of neuroaugmentation. To date, psychiatric neurosurgery has focused on minimizing damage to the nervous system and, when a lesion was necessary, making the smallest effective lesion. Neuroaugmentation, through electrical, chemical, as well as other emerging modalities, allows the neurosurgeon to ameliorate nervous system disorders through additive, not destructive, means.

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One of the most exciting advances with regard to neuroaugmentation in the last decade was the resurgence of neurostimulation techniques. Neurostimulation includes all neurosurgical interventions that utilize electrical stimulation as a therapeutic modality for neuromodulation. Electrical modulation of brain function as a therapeutic neurosurgical tool is not new, having first been performed by J. L. Pool[57] in 1948. Interestingly, much like stereotaxis, the first neurosurgical use of therapeutic brain stimulation was for psychiatric disease. Today's use of electrical neurostimulation consists of epidural and subdural surface electrodes and deep brain stimulation (DBS), in which an electrode is stereotactically placed in subcortical structures. A third technique of electric neurostimulation is vagus nerve stimulation (VNS). This renaissance of neurostimulation techniques is the direct result of a better understanding of neurophysiology from functional imaging studies, intraoperative brain mapping, and technological advances in implantable electrodes and programmable pulse generators. Combined with the latest developments in computer-guided, stereotactic brain navigation, which allows the exquisite targeting (up to 1 mm precision) of neural structures, neurostimulation has become the cornerstone of recent neuroaugmentative efforts.

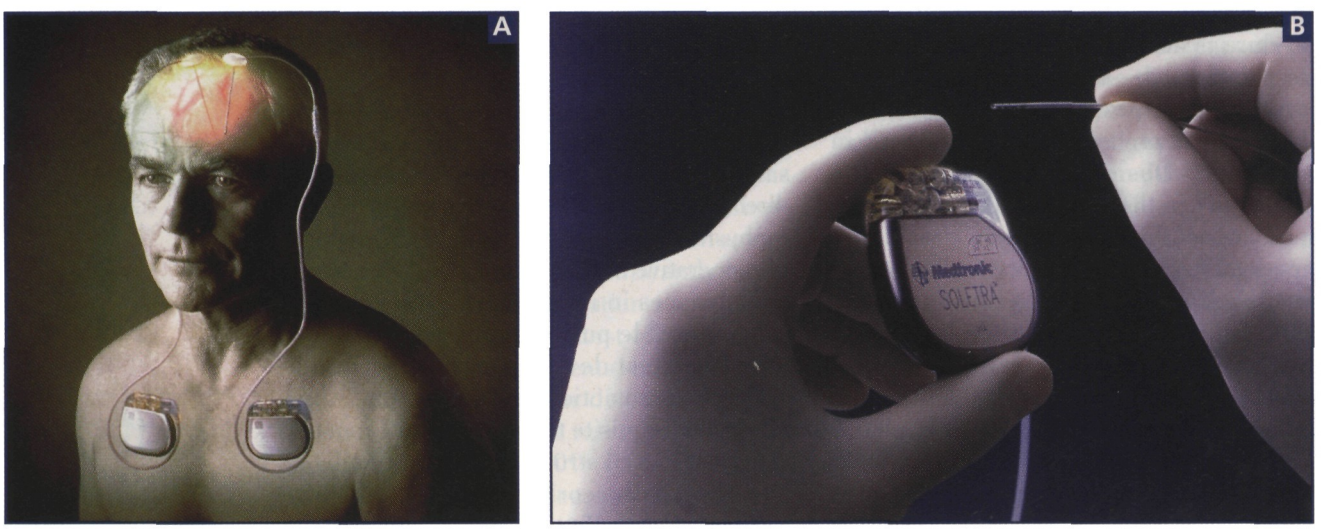
Neurostimulation has inherent advantages over previous lesioning procedures. Unlike a lesion, it is fully reversible and the stimulation can be dynamically adjusted according to a patient's changing symptoms and disease progression. Coupled with the fact that the stimu-

lation can be turned on and off without the patient's awareness, neurostimulation provides a unique opportunity for conducting double-blind studies; therefore, any given patient can serve as his or her own control group—something that could never be done with lesioning procedures due to ethical constraints on sham procedures.

Neurostimulation is now the standard of therapy for medically refractory PD, essential tremor, intention tremor, and various chronic pain syndromes. It is also being increasingly utilized for other disorders, such as intractable dystonia and epilepsy. The following question remains: Are neurostimulation techniques as safe and effective as their lesion-based counterparts? Based on recently published studies,[58,59] the answer is a resounding yes. In 1998, a *New England Journal of Medicine* study[58] reported that after one year of chronic DBS, advanced, medically refractory PD patients significantly improved with regard to symptoms and activities of daily living, with a concomitant 50% reduction in medication. In a recent randomized prospective study,[59] clinicians confirmed the inherent advantage of neurostimulation techniques over their lesioning counterparts. Schuurman et al[59] directly compared stereotactic thalamotomy with thalamic DBS for refractory tremor. They showed that DBS had fewer adverse side effects and was superior in overall improvement of daily functioning. The currently applied DBS system utilizes multicontact electrodes connected to a remotely programmable pulse generator (Figure 6).[60]

The exact mechanisms of neurostimulation are unknown. There are several prevailing theories explaining why electrical stimulation is effective in alleviating symptoms in various neural disorders. One theory suggests that stimulation acts like a reversible ablative lesion, inactivating nearby cells by a depolarization blockade. Such a phenomenon, occurring at high frequency (>100 Hz) stimulation, would remove afferented targets from any abnormal influences that the stimulated area might elicit. Electrical stimulation could also activate cells/axons by depolarization directly influencing activity in a neural circuit.[61] A third possibility involves the tonic influence of electrical stimulation on the resting potentials of target neurons. Such neurons, according to intrinsic voltage gate properties, would begin to fire at different frequencies than when they are free of stimulation influence. This, in turn, would alter the activity of the neural circuitry involving these targets. A recent fMRI study[62] had also shown selective activation of specific cortical and subcortical structures with DBS.

Certainly, the neurocircuitry of psychiatric diseases is far less elucidated than those subserving movement disorders. The striking similarity between the abnormal neural circuitry



FIGURES 6. Schematic of deep brain stimulation system. The photograph to the left (Figure 6A) is a typically implanted bilateral deep brain stimulation system. Note the location of stimulation electrodes and pulse generators. Also shown (Figure 6B) is a close-up of the implanted quadripolar electrode and the pulse generator.

Photos courtesy of Medtronic.

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of movement disorders and the proposed models of abnormal neural circuitry in psychiatric diseases, makes neuroaugmentation an attractive option for surgical intervention of refractory psychiatric conditions. Initial reports[63-65] on VNS for affective disorder and DBS for OCD are promising, and a number of further studies are in progress.

As a result of advances in our understanding of the pathophysiology of psychiatric disorders, we can explore other potential targets for pharmacological and/or surgical intervention.

With its central anatomical and physiological location, the thalamus has been a traditional target of ablative stereotactic procedures. Procedures, such as subcaudate tractotomy, limbic leukotomy, and capsulotomy, indirectly target the DM nucleus by interrupting the reciprocal connections between the frontal cortex and the thalamus. Another thalamic target for putative neuroaugmentative therapy is the anterior nucleus. With its rich connections to the cingulate gyrus, the anterior thalamic nucleus plays a vital role in the propagation of the Papez circuit. Surgical intervention in this area may serve to modulate the affect of psychiatric disease states, such as OCD and affective disorder.

The ventral striatum is implicated in the pathogenesis of many psychiatric diseases, including OCD and affective disorder. The ventral striatum serves as a vital link between the OFC and the basal ganglia. With its afferent projections from the substantia nigra, the raphe nucleus, and the centromedian thalamic nucleus, as well as its efferent projections through the GP, the caudate/putamen complex plays an important modulator role in connections from the frontal cortex to the thalamus.

Cortical targets, such as the OFC, may serve as a potential area for future intervention. The OFC is implicated in the pathogenesis of many psychiatric diseases, in which neural models are now being explored. Given the long history of well-known cognitive side effects of psychiatric neurosurgical procedures on the frontal lobe, it may seem that targeting the OFC might not be the ideal solution; however, modern imaging techniques, coupled with neuroaugmentation's inherent ability to modulate activity by dynamically controlled nondestructive input, suggests that targeting the OFC and other cortical areas may be of benefit.

Interestingly, during recent DBS interventions for PD, two separate groups[66,67] reported that subthalamic nucleus stimulation elicited depression and laughter from patients. This could prove interesting to explore for future neuroaugmentative therapies to treat affective disorder.

Since the currency of nervous system communication involves both electrical and chemical transactions, another modality for future neuroaugmentative therapy involves the use of chemicals. Already, drugs (ie, morphine and baclofen) are used in neuroaugmentative procedures for chronic pain and spastic disorders. As drug-delivery pumps and microcatheters are further improved, chemicals that mimic neurotransmitters or standard psychotropic medications could be delivered directly to brain targets in doses that would minimize systemic side effects.

CONCLUSIONS

We have reached an exciting crossroad for psychiatry and neurosurgery. The culmination of all aforementioned technologies have given new therapeutic options to explore. Stereotactic radiosurgical techniques, such as the γ-knife, have allowed neurosurgeons to refine lesioning procedures to the point of being bloodless. Neuroaugmentative techniques, combined with modern functional imaging and psychiatric batteries, offer investigators a tool to finally conduct a randomized, double-blind prospective study—something that has been lacking in researching psychiatric neurosurgery. Ultimately, electrical and chemical neuroaugmentative modalities could be merged with exquisite microprocessor controls that detect changes in neural function and can dynamically and automatically adjust neuromodulating input. These neuroaugmentative techniques could be combined with emerging molecular biological strategies, such as vector-based gene therapy, in order to replace entire neural networks that have become affected by psychiatric and other neurological diseases. Successful neurosurgical intervention in patients with various psychiatric diseases will lead to new insights into human brain function that will have long-reaching impacts on medicine and all aspects of neuroscience. CNS

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