Chapter 42
Not Your Father's Lobotomy: Psychiatric Surgery Revisited

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DO NOTHING VERSUS DO SOMETHING: THE LEGACY OF LOBOTOMY

Over the past few years, interest in neurosurgery for psychiatric disorders has surged, largely owing to the success of neuromodulation devices such as Deep Brain Stimulation (DBS) for movement disorder surgery. With DBS now considered the gold standard of surgical treatment for advanced cases of Parkinson's disease (PD), psychiatric surgery has become the new "cutting edge" of functional and restorative neurosurgical investigations. Yet, psychiatric surgery has an additional hurdle beyond the technical and epistemological challenges of any new medicine. It has to shed its own history. The connotations of the words "psychosurgery," "lobotomy," and "human experimentation" are obstacles beyond those usually encountered in the laboratory and operating room. In short, psychiatric neurosurgery enters the arena already possessing a bad name; an ignoble legacy that is more than a century old.

The Swiss psychiatrist Gottlieb Burckhardt, in reporting the results of cortical excisions for psychiatric symptoms in 1891 , felt compelled to justify himself to his doubting colleagues: Doctors are different by nature. One stands fast in the old principle: "primum non nocere"; the other states: "melius anceps remedium quam nullum." I belong naturally to the second category…Every new surgical approach must first seek its special indications and contraindications and methods, and every path that leads to new victories is lined with the crosses of the dead. I do not believe that we should allow this to hold us back…

"First, do no harm," the dictum of the Physician to leave the patient in no worse shape than initially encountered, versus "Better an unknown cure than nothing at all," the desire to alleviate a patient's suffering with a seemingly new "cure," despite a lack of insight into the physiology of the disease in question. It is this fundamental struggle between the obligation of the physician to remain cautious and the desire to help those in need that define the efforts to intervene surgically on the mentally ill. Other therapies, including the surgical treatment for Parkinson's disease, have successfully developed after a period of empiric surgical experimentation. However, the same will no longer be possible with psychosurgery, given the given its emotional connotation to the general public.

In 1935, a fateful meeting occurred. At the Second World Congress of Neurology in London, John Fulton and Carlyle Jacobsen presented their work showing behavioral changes in chimpanzees after ablation of frontal lobe areas. (Fig. 42.1)Fulton and Jacobsen made the observation that frontal lobe ablation could result in the lessening of "anxiety states" in chimpanzees. In attendance at that meeting was a Portuguese neurologist by the name of Egas Moniz and an American neuropsychiatrist by the name of Walter Freeman. (Figs. 42.2 and 42.3)

Drawing from Fulton and Jacobsen's data, as well as synthesizing case reports of neurosurgeons operating on various frontal lobe lesions at the time, Egas Moniz formulated a bold plan: to sever the white matter bundles connecting frontal lobe regions with the rest of the brain, the frontal leucotomy. He convinced a young neurosurgeon in Libson, Almeida Lima, to undertake the procedure and a series of twenty patients commenced. (Fig. 42.4) In 1936, Walter Freeman happened upon Moniz's initial communications regarding frontal leucotomy in the journal Lisboa Medicina and brought the "Miracle of Moniz" to the United States, having convinced a neurosurgeon by the name of

James Watts to help him in his endeavor. They modified the Moniz technique, abandoning the Moniz leucotome for a dull, flat knife known as a bistoury (Fig. 42.5) and, approached from the side rather than the top (Figs. 42.6 and 42.7) in an effort to streamline the procedure. The Moniz procedure, frontal leucotomy, became the Freeman-Watts technique, the prefrontal or standard lobotomy.

Yet this was not enough for Freeman. Drawing from an obscure report of an Italian psychiatrist, Amarro Fiamberti, Freeman developed the transorbital lobotomy, a procedure in which the frontal white matter is cut by a metal spike inserted through the thin bony orbit above the eye. Freeman's initial choice to accomplish this procedure was the common ice pick. Although Freeman, refined the common house tool into what he called a "transorbital leucotome," he envisioned the procedure being able to be performed by any surgically untrained physician after the most minimal of instruction. "Every physician his own lobotomist." In 1948, Freeman, with ice pick in hand, traveled across the country to fulfill what he considered to be an unanswered need (Fig. 42.8) . It did not take long for Watts to sever his ties with Freeman. Like other neurosurgeons, he was horrified at the ghastly treatment patients received under Freeman's new procedure. Yet "free" from his restrictive association with Watts, Freeman operated in earnest. Freeman and Watts recorded 625 operations between 1936 and 1948. By 1957, Freeman had lobotomized another 2400 patients. In one 12-day period, he operated on 225. Time magazine heralded the age of "mass lobotomies."

"What are these terrible things I hear about you doing lobotomies in your office with an ice pick?" scolded John Fulton, whose animal work was the basis for lobotomy. "Why not use a shot gun?" Freeman calmly responded that his transorbital procedure was "much less traumatizing than a shotgun and almost as quick." In the end, Freeman's kind of psychiatric surgery was not stopped by the outrage of colleagues, but by the advent of chlorpromazine, which was approved by the Food and Drug Administration in 1954. The death knell for psychiatric neurosurgery had sounded, yet Freeman carried on his one-man war. On occasion, Freeman would dump shoeboxes crammed with letters from "grateful" lobotomized patients onto the desks of skeptical colleagues. They, however, remained unconvinced. Freeman died in 1972, at the age of seventy-six.

THE STEREOTACTIC ERA

Yet even as lobotomy was dying, psychiatric surgery was to be reborn as the herald of a new frontier in neurosurgical practice: the application of stereotaxis. In 1947, Wycis and Spiegel introduced the dorsomedial thalamotomy, the first subcortical stereotactic neurosurgical procedure performed on humans and the model on which modern psychiatric neurosurgical procedures are based. , The process of stereotaxis involves the definition of the brain as volume in a Cartesian three-dimensional space. This space can be referenced to a specific coordinate system. The process allowed, for the very first time in history, precise accuracy and the ability to reach subcortical structures with minimal disruption of brain tissue. These stereotactic techniques have been coupled with the latest developments in computer database, functional imaging, and physiological recording technology.

The four psychiatric neurosurgical procedures that benefited from these techniques are cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. Today, only cingulotomy, capsulotomy, and limbic leucotomy are practiced with any frequency. Many of the following studies of psychiatric neurosurgery do have significant flaws, most notably the inherent bias of a nonrandomized, nondouble-blind study. They do, however, suggest a viable means of treatment for a subset of patients who may have no other options. It is important to place these procedures in the context of the physiological systems previously described to make sense of their functional strategy. Ultimately,

all of the following procedures seek to modulate the activity of the dorsolateral frontal, orbitofrontal, and cingulate cortices and their interactions with the basal ganglia and thalamus.

Cingulotomy

In 1967, Ballantine introduced the modern stereotactic procedure in which a thermocoagulative lesion, localized by air ventriculography, was made bilaterally in the anterior cingulate. The lesion is typically 2 to 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. Such a lesion would be expected to affect the cortico-striato-thalamo-cortical (CSTC) loops by interrupting reciprocal activity from the dorsal anterior cingulate cortex (ACC) to the orbitofrontal gyrus (OFC), amygdala, and hippocampus via the cingulum bundle. , The procedure performed today has been refined using the latest stereotactic equipment and imaging techniques. Stereotactic cingulotomy is the most reported neurosurgical procedure for psychiatric disease in the United States and Canada. Historically, response rates for patients with obsessive-compulsive disorder (OCD)-like symptoms following cingulotomy were reported as high as 56%. However, the studies were hampered by investigational bias and lack of modern psychiatric assessment tools. In 2002, the most recent study of cingulotomy for OCD, 44 patients were studied prospectively using current methodologies and rigorous screening. At a mean of 32 months after one or more cingulotomies, 32% of the patients met conservative criteria for response and 14% were partial-responders. For major depression, the largest study reported a 68% response rate, with 42% of patients being reported as "recovered." A more recent study, performed in the era of MRI guidance, corroborated these results with 60% of 34 patients with unipolar depression responding to treatment.

No deaths have been reported with an experience of 1000 cingulotomies performed at Massachusetts General Hospital, with clinical significant hemorrhage rate at 0.03 %. , Other adverse effects include seizures and hydrocephalus with rates similar to other stereotactic procedures. There have been no significant permanent behavioral or cognitive changes reported.16

Capsulotomy

Developed in Sweden by Lars Leksell and in France by Jean Talairach, anterior capsulotomy has been in use for refractory psychiatric illness since 1949. There are two forms of this procedure, both of which are stereotactic operations. One technique involves the use of radiofrequency and the other uses gamma radiation to make the lesion. In either case, the target area is between the anterior and middle third of the anterior limb of the internal capsule at the approximate level of the foramen of Monro. Specifically, the most commonly used 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 to 18 mm in length and 4 to 5 mm in width. , A recent study of gamma capsulotomy has a modified target that has evolved based on recent results. This modified target centers specifically around the ventral aspect of the anterior internal capsule. Anterior capsulotomy probably exerts its effects on psychiatric symptoms by interrupting ventral fibers in the anterior internal capsule from the OFC and subgenual ACC to medial, dorsomedial and anterior thalamic nuclei.

Historically, response rates have been reported in the range of 48 to 78 %.16 Again, these studies were often retrospective and lacking in modern psychiatric assessment tools. Preliminary findings from an ongoing study of gamma capsulotomy utilizing modern response measures indicate a 27% response in patients receiving a single-shot

bilateral lesion and 62% response rate in patients receiving two pairs of bilateral lesions.16

No deaths have been reported owing to capsulotomy itself. A single patient has been reported to have committed suicide in the perioperative period. Headaches, confusion, urinary incontinence, weight gain, and lethargy have all been reported with stereotactic thermocoagulative capsulotomy, although these adverse effects have been generally transient. In a sample of 200 thermocoagulative capsulotomy patients, no significant changes to behavior or cognition were measured. The Providence group's experience with gamma capsulotomy has also found evidence of transient headaches and cerebral edema. Three of 31 patients had small, asymptomatic caudate infarctions. Although there were no group decrements in cognitive and personality testing, 1 of 31 patients developed a persistent mild frontal lobe syndrome manifested by apathy and amotivation.

Subcaudate Tractotomy

Another stereotactic procedure geared towards interrupting fibers from the orbitofrontal cortex to the thalamus is subcaudate tractotomy (innominatomy). Developed by Geoffrey Knight in 1965 in London, the operation was designed to relieve depressive, anxiety, and obsession symptoms while minimizing postoperative epilepsy, as well as cognitive and personality deficits. , The lesion is created by placement of multiple 1 x 7 mm rods of yttrium-90, a beta-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 and 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 to 18 mm from the midline and being 20 mm long in an anteroposterior direction. Initially, placing two rows of four rods each made the lesion. Later studies, having refined the technique, have created the lesion by RF thermocoagulation. Such a lesion would be expected to interrupt reciprocal connections involving OFC and subgenual ACC to the striatum and thalamus. Also, amygdalofugal fibers to OFC and subgenual ACC would be affected.

Depression has been the most common diagnosis for patients undergoing this technique. A review of the literature has revealed a response rate of 55 to 68 %. OCD patients undergoing this procedure have been shown to have similar response rates in the range of 50 %.16 The most comprehensive review of subcaudate tractotomy included 1300 patients. In this study, 40 to 60% of patients lead normal to near-normal lives. Only 1 % of subcaudate tractotomy patients committed suicide compared with a 15 % rate of suicide among patients with similar major affective disorders (AD).16

As with other stereotactic interventions, the most common side effects were transient headache, confusion, and lethargy. One death was reported as a direct result of the surgery. In a 1975 study, 6.7 % of 208 patients had mild long-term personality changes, whereas a study in 1994 reported no such changes in 1300 patients.16 As experience with cingulotomy and capsulotomy became more prevalent and political difficulties with psychiatric surgery persisted, subcaudate tractotomy fell by the wayside.

Limbic Leucotomy

Whereas the three aforementioned procedures each target a single anatomic substrate, limbic leucotomy is designed

to interrupt fibers at two separate areas, one involving a frontothalamic loop and the other involving an area of the Papez circuit. Termed limbic leucotomy, the procedure was developed in England by Desmond Kelly and Alan Richardson in the early 1970s. The operation itself 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. Essentially it is a combined subcaudate tractotomy and cingulotomy. This intervention would impact on multiple CSTC loop systems as defined above.

In 2002, the most recent experience with limbic leucotomy using modern diagnostic and system assessment procedures found a 50% response rate in OCD and depression patients. Historically, Kelly and his collaborators reported no deaths or seizures in a prospective group of 66 patients. Again, transient headaches, lethargy, apathy, and incontinence were the most common side effects. One patient had severe memory impairment owing to improper lesion placement, whereas 12 % had persistent lethargy in an average follow up of 16 months. More recent experience with limbic leucotomy corroborates the incidence of these adverse effects.21

INTO THE FUTURE: THE NEUROCIRCUITRY OF PSYCHIATRIC DISEASE

Our understanding of the neurocircuitry of psychiatric disorders is rapidly evolving. What is most strongly supported is the role of CSTC loops in the pathophysiology of psychiatric symptoms. In the mid-1980s, Alexander et al. , suggested there were at least five functionally segregated basal ganglia thalamotocortical circuits. These circuits were hypothesized to be anatomically segregated and to subserve different physiological functions. One, a "motor" circuit, centers on the sensorimotor portions of the caudate/putamen, globus pallidus, substantia nigra, thalamus, and premotor areas. Other loops include the oculomotor, dorsolateral prefrontal, anterior cingulate, and lateral orbitofrontal cortex.31 Each of these circuits is segregated through the aforementioned basal ganglionic structures and has specific cortical projections. (Fig. 42.9)

Within each circuit are "direct" and "indirect" pathways. (Fig. 42.10) The "direct" pathway has two excitatory and two inhibitory pathways, making it a net positive feedback loop. The "indirect" pathway with its three inhibitory and one excitatory connection can be conceived of as a net negative feedback loop.14 In the case of the latter three circuits, the cortical areas involved are the dorsolateral prefrontal, the cingulate, and the orbitofrontal cortices as opposed to the pre-motor and motor cortices involved with the "motor" loop. It is based on this framework that modern neurosurgical intervention in Parkinson's disease (PD) has been developed. A similar scheme can be used to develop a strategy for the surgical intervention of psychiatric disorders. Again, one major limitation facing the development of psychiatric surgery is that a convincing animal model to test hypotheses for OCD and other psychiatric disease does not exist. Although the situation is somewhat better for depression, there remain few system studies of the circuitry that is hypothesized to underlie the development of depression.

For the purposes of this chapter, two of the most elucidated psychiatric diseases that have been the targets of neurosurgical interventions will be discussed. They in turn can be used as a framework to begin to study the use of DBS as a surgical strategy for the treatment of psychiatric disease in general.

Obsessive-Compulsive Disorder

Cortico-striato-thalamocortical interactions are strongly implicated in the pathogenesis of psychiatric disease in

humans and specifically in the mediation of OCD symptoms and its response to treatment. Evidence for this is derived from several sources, which are discussed below.

Whereas movement disorders and psychiatric disease might seem dissimilar on the surface, common neural substrates are implicated in their symptomatology. From the earliest observations of OCD, the central role of neuronal areas subserving motor function in its pathogenesis has been speculated Tourette's disorder, a disease characterized by motor tics as well as OCD-like symptoms, demonstrates the possibility of a neural substrate capable of producing motor as well as psychiatric disease states. Studies demonstrating the strong clinical and genetic association between Tourette syndrome and OCD have suggested the central role of the basal ganglia in the genesis of OCD symptoms. , A similar basal ganglia circuit to the one implicated in PD has been proposed to explain the production of both motor and obsessional symptoms in Tourette's syndrome. Further analysis of the clinical spectrum of PD has revealed many striking similarities between the "motor" disease of PD and the psychiatric diseases of OCD and AD.

Neuropharmacological hypotheses of OCD pathophysiology have also implicated CSTC loops in the pathogenesis of OCD. There is strong evidence that serotonergic systems modulate OCD symptoms. Potent inhibitors of serotonin transporter function (serotonin reuptake inhibitors [SRI]) are unique among antidepressants in producing at least some clinical benefit in most patients with OCD. Interestingly, both the serotonin transporter and some serotonin receptor subtypes, such as 5-HT2A and 5-HT2C, implicated in OCD are highly expressed in the ventral striatum where they could influence the functioning of the CSTC and functionally-related circuits, which are of most interest in OCD. In theory, other neurotransmitter systems within CSTC loops may play a role in susceptibility, course, or response to OCD treatment. For example, dopaminergic mechanisms have been implicated by controlled studies demonstrating that neuroleptics, ineffective as monotherapy in OCD, are beneficial when added to ongoing SRI treatment. Other CSTC neurotransmitter systems that are candidates for involvement in OCD on the basis of the anatomical localization or functional roles in cortico-striato-pallidothalamic circuits include glutamate, $\gamma-$aminobutyric acid (GABA), Substance P, cholinergic, and endogenous opiod mechanisms.

Based on these observations and those of several other authors, one can begin to construct a neuronal architecture for the basis of OCD and develop a rationale for surgical intervention. (Fig. 42.11) When constructing such a model, it is important to recognize how rapidly our knowledge of psychiatric pathoneurophysiology is changing. What is most evident is that it is unlikely that a single center or anatomic or physiological defect is responsible for the pathogenesis of psychiatric symptoms (e.g., loss of dopamine in PD). It is more likely that a dysregulation between several neural circuits is involved in the genesis of the disorder. From this follows a slightly different strategy for psychiatric neurosurgery than what has transpired in the past with movement disorder surgery. Historically, in movement disorder surgery, surgical intervention focused on specific anatomic areas thought to either be hyper- or hypoactive. Surgical procedures were designed to "rectify" this over- or underactivity. Just as this picture has grown more complex in movement disorders through animal models and functional imaging, in psychiatric conditions, it is becoming evident that there are several surgical targets that could potentially modulate entire neural systems and thus bring about an amelioration of symptoms. This systems approach is vital in assessing the somewhat conflicting data in the literature and making the choice of a surgical target. The multicircuit 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 portions of the orbitofrontal and anterior cingulate cortices as well as the medial, dorsomedial and anterior thalamic nuclei. ,14,

There are three components to this neuronal model of OCD. The first involves a reciprocal positive-feedback loop involving the orbital and prefrontal cortex and the dorsomedial (DM) thalamic 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 suggest it to be excitatory and, most probably, glutamatergic.45,

The second component of the OCD model involves the orbitofrontal/prefrontal cortex, the ventral caudate, the dorsomedial pallidum, and the intralaminar, anterior and DM thalamic nuclei. Alexander et al. outlined this relationship in their OFC - CSTC loop. While projections from the ventral striatum to the dorsomedial pallidum involve multiple neurotransmitters including GABA and substance P, the output of this pathway by way of the dorsomedial 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 inhibitory in nature.

The third constituent of this model involves the limbic system and the circuit of Papez. Many manifestations of OCD have features in common with anxiety disorder. 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 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 (Fig. 42.12) based on his observations on neuroanatomic connections to integrate these two structures. The pathway begins from the hippocampal formation to the mammillary body via the fornix. The projection, via the mammillothalamic tract, continues on 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 nuclei and the OFC. There are also heavy projections from the anterior cingulate cortex (ACC) to the nucleus accumbens region of the striatum. These connections could subserve the anxiety/emotional component of OCD.

Recent functional imaging studies have consistently found evidence that corroborate this model of OCD pathogenesis. It is important to assess functional imaging data of psychiatric disease carefully as there are overlaps of activation phenomenon between normal and psychiatric patients. Furthermore, it is often difficult to distinguish changes that are markers for symptom amelioration versus activity subserving "normal" function. Nevertheless, functional imaging data does further implicate the role of CSTC loops in OCD. This appears in both the neutral and provoked state. The neutral state is considered the baseline obsessional and compulsive behavior of the OCD patient. The provoked state occurs when the OCD patient is presented with a stimulus known to exacerbate his or her OCD profile. After treatment with appropriate medications, including selective serotonin reuptake inhibitors (SSRI), and behavioral therapies, these areas of abnormally increased metabolism were shown to decrease by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies.55,14, Such areas of activation and responses to treatment might prove useful in assessing future neurosurgical treatments for OCD.

Affective Disorder

CSTC interaction has been implicated in the pathoneurophysiology of ADs, including major depression (MD) and

bipolar disorder. (Fig. 42.13)Other limbic elements are important as well, including the amygdala, hippocampus, and the hypothalamic-pituitary axis (HPA). Symptoms of AD have cognitive, motor, affective, and neuroendrocrinological components, each with its own particular neural circuit. , 14

The neural circuitry of AD seems to consist of a dorsal, a ventral, and a modulatory component. The dorsal component, involved with the motor and cognitive aspects of AD, consists of the prefrontal, dorsal anterior cingulate, and premotor cortices. This compartment accesses the dorsal striatum and projects to the thalamus via its projections from the dorsomedial portion of the pallidum, closing the loop. Next, a ventral component, involved with affective aspects of depression, consists of the subgenual anterior cingulate (Brodmann's area 25), orbitofrontal, and insular cortices. Interaction with the ventral striatum through the medial/rostral pallidum and subsequently the thalamus, closes this component.

Finally, there is a modulatory component consisting of the pregenual ACC, the amygdala and the HPA (hypothalamic-pituitary axis), which is thought to regulate relative ventral-dorsal component activity and subserve the neuroendocrine aspects of AD symptoms. The Amygdala-HPA axis and the pregenual ACC modulate the aforementioned ventral-dorsal compartment relationship via the amygdala's tendency to drive activity to the ventral compartment and the pregenual ACC's inhibitory projections to both compartments. The hippocampus, in turn, modulates activity in HPA.

With regard to the endocrine and humoral aspects of depression, 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, indirectly via connections such as the ventral amygdalofugal pathway and direct cortical connections, influence skeletomotor motivation and behaviors in response to emotional stimuli.

These three components can be condensed into a model analogous to the one proposed for OCD. In this model, faulty transmission, such as altered levels of excitability and temporal patterning of activity in parallel, but interconnected, CSTC systems can be associated with depression symptoms: a ventral affective and limbic-thalamocortical loop consisting of the cingulate, OFC, and the anterior or dorsomedial thalamic nuclei; a dorsal cognitive thalamocortical loop consisting of the prefrontal, premotor and cingulate cortices and the anterior or dorsomedial thalamic nuclei, and a modulating circuit consisting of the amygdala and the HPA.

Much of the work implicating the basal ganglia and other structures in the pathogenesis of AD is derived from imaging studies using PET and fMRI. The neuroimaging of AD is hampered by the heterogeneity of the disease; however, some consistent features are evident. Abnormalities in metabolism have been demonstrated in the OFC, cingulate cortex, basal ganglia, and amygdala. , , Increased metabolism has been found in orbitofrontal, anterior insular, and subgenual cingulate cortices in transient states of sadness and major depression episodes. Conversely, decreased metabolism has been demonstrated in the dorsolateral prefrontal cortex in MD and transient sadness. Both of these findings have been reversed with successful treatment. Finally, increased metabolism in the amygdala, also reversed by treatment, has been associated with depressed patients. Metabolism in the subgenual cingulate and hippocampus has been variable.14 Based on functional imaging data, there seems to be a relative increase in activity in the ventral compartment and hypoactivity in the dorsal compartment. Reciprocal inhibitory connections between the dorsal and ventral compartments, combined with amygdala hyperactivity and abnormal hippocampal activity could generate this

overall relationship leading to AD symptoms. With regard to the implication of these interactions for DBS for AD, "Thus, successful treatment of MD (via any of a number of modalities) may rely on some combination of deactivation of the ventral compartment, inhibition of the amygdala, stimulation (or protection) of the hippocampus..." 14 It is important to remember that, unlike the model for PD, these models of psychiatric disease, because of their inherent nature, have little support from animal models. Whereas some models for depression exist, and a number of models of OCD have been proposed, all have significant limitations. There is recently more interest in developing models of different component symptoms of syndromes and of associated and predisposing factors. Future work in this area may yet yield some appropriate animal models.

Neural circuit models of psychiatric disease are based on anatomic connections and the aforementioned functional imaging studies. One major concern, especially for depression, but also true for OCD, is that there are significant disagreements among researchers over models of affective disorders. Another aspect of the above models involves not only the physiological and anatomic connections themselves, but also the "weights" of the connections. There are bodies of evidence implicating involvement of the above brain circuits in symptoms of OCD and depression, and in emotional processing more generally, including "dispositional mood" (personality traits such as neuroticism and extraversion) that seem to have major influence on risk on psychopathology. , Thus, although these models may seem too simple, they serve as a springboard for future functional imaging and physiological mapping studies and form the basis from which neurosurgical and pharmacological therapies can be developed in a similar fashion as they were for PD.

BRAIN STIMULATION FOR PSYCHIATRIC DISORDERS

Neurostimulation has inherent advantages over previous lesioning procedures. Unlike a lesion, it is fully reversible and the stimulation can be adjusted according to a patient¡¦s changing symptoms and disease progression. Coupled with the fact that the stimulation can potentially be turned on or off without the patient¡¦s awareness, neurostimulation provides a unique opportunity for double blinding studies. A given patient can then serve as his or her own control, something that could never be done with lesioning procedures owing to ethical constraints on sham procedures.

Historically, there also have been efforts to treat psychiatric symptoms surgically with an electrical modality. In general, these studies suffered from nonstringent patient selection, imaging modalities, and rigorous psychiatric assessments. Looking at these studies should not imply any degree of efficacy, but should merely to serve as possibilities for future efforts.

In 1979, a group headed by Gert Dieckmann at the Universitat des Saarlandes reported their experience with bilateral mediothalamic DBS for the control of phobias. The electrode was placed in the region of the parafasicular complex in the intralaminar thalamic nuclei. Low frequency stimulation (5 Hz), confirmed by EEG response over the frontal lobes, resulted in amelioration of phobias and obsessional symptoms at 1-year follow up. Such stimulation was not needed to be continuous as the patient was able to relieve her symptoms with stimulation on demand. No specific side effects were reported except for self-reported ¡§unpleasant¡¨ feelings at higher frequency (50 Hz) stimulation.

In the 1970s R.G. Heath performed a series of procedures utilizing cerebellar vermian stimulation for psychiatric

disease. Although much of this particular work can be criticized for its inconsistent patient selection, it was unique in that it was the first stimulation procedure that did not address a particular ¡§target.¡¨ Instead, Heath demonstrated that the efficacy of vermian stimulation was a simultaneous up regulation of septal region activity concomitant with a down regulation of amygdala region activity-truly one of the first functional neurosurgical efforts that addressed a disease state based on a network rather than a localized anatomical target. With a 2.5 year follow up period, Heath reported a ¡§moderate to significant¡¨ response in five of six depression patients and five of five obsessional patients. Based on the psychiatric and cognitive effects seen in recent movement disorder surgery, it is apparent that modulation of neural systems subserving psychiatric phenomenon can be accomplished by the electrical neurostimulation technology known today as deep brain stimulation (DBS).

The largest published experience to date is with DBS of the STN for PD; however, the STN is not merely a motor nucleus. The STN, although a critical component of the motor loop through the basal ganglia, is also involved in other aspects of function. At least three other loops, the limbic, the dorsolateral prefrontal, and orbitofrontal, and probably many more, also pass through the STN.30 (Figs. 42.14 and 42.15) The STN is only 8 mm long, 10 mm wide, and 6 mm deep with a cell population of approximately 540,000 neurons. It stands to reason that DBS in STN, which has been shown to modulate motor activity, could also alter the activity through these other non-motor systems through the expected current spread that occurs at typical PD DBS parameters. This would be expected to enact changes in neuropsychological behaviors.

Indeed, changes in mood have been widely reported in patients undergoing STN DBS for Parkinson¡¦s disease. In the largest series of STN DBS patients to date focusing on the cognitive changes after surgery, Ardouin et al. reported a general improvement in mood in STN DBS patients. A careful review of the literature reveals a general improvement in symptoms of anxiety and depression among studies of STN DBS patients. Whether these affective improvements are owing to changes in dopaminergic medications, or an improvement in disease symptoms remains to be demonstrated. In 1999, Kumar reported the induction of laughter in two Parkinson¡¦s disease patients. One was undergoing bilateral stimulation, the other unilateral. As the stimulation amplitude was increased, ¡§the men described a feeling of well-being,¡¨ and a ¡§burst of highly contagious, natural-sounding laughter¡¨ was reported. This group explored this phenomenon further in 2001. MRI scans revealed that the electrodes seemed to be in the appropriate position in the STN and the contacts stimulated were the same ones that had the anti-Parkinsonian effects. Both of these patients enjoyed marked improvement in their PD symptoms. Dopaminergic medications were reduced by greater than 90%. Induction of laughter occurred at a pulse width of 90 fÝs that was 50% greater than the 60 fÝs used for anti-Parksinsonian effects. The larger than normal levels of stimulation, coupled with the typical location of the contacts used to induce ¡§mirthful¡¨ laughter suggests that the ventromedial and medial portion of the STN, considered associative and limbic areas respectively, might have been involved in mediating this phenomenon. Additionally, it cannot be ruled out that the higher levels of stimulation induced laughter by its effect on surrounding structures. There are direct connections from the most medial parts of the STN to the ventral tegemental area. The lateral hypothalamus is just medial to the STN. Stimulation of either of these structures may activate dopaminergic and/or serotonergic structures related to the medial forebrain bundle. Subjective feelings of pleasure have been reported in humans undergoing stimulation of these areas.

In addition to improvements in mood, OC symptoms have been ameliorated by STN DBS. In 2002, Mallet et al. reported their experience with two PD patients with OCD (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] scores 23 and 26). Placement of the DBS electrodes occurred in a part of STN more medial and anterior than anticipated. At

typical settings for anti-PD effects, both patients had greater than an 80% reduction in Y-BOCS scores. Also of note, one patient only had a modest (less than anticipated improvement in UPDRS scores, 27%) improvement in PD symptoms, suggesting that the improvement of OC symptoms occurred independent from motor symptom changes.

Exacerbations of psychiatric symptoms have also been reported with STN DBS. In the New England Journal of Medicine, a case report detailing the emergence of acute depression in one bilateral STN DBS patient was published in 1999. During a postoperative evaluation, stimulation of the most distal contact of the left DBS electrode resulted in ¡§the patient¡¦s face expressed profound sadness,¡¨ with typical stimulation parameters for the control of Parkinsonian symptoms. The patient expressed feelings of worthlessness and despair. The depression immediately ceased upon withdrawal of the stimulation. The depression was reproducible upon future stimulations of the same contact on the left side. Subsequent imaging indicated that the responsible contact was in the central portion of the substantia nigra pars reticulata (SNr), including part of the pars compacta. Mania and anxiety provocation, and visual hallucinations have also been reported with STN DBS. , , Again, whether these responses are owing to direct effects of stimulation on STN, SNr, and/or surrounding structures, remains to be explored.

Globus pallidus interna (GPi) DBS has also been shown to have effects on psychiatric manifestations. In 2001, Higginson et al. reported a significant decrease in anxiety symptoms after GPi DBS for Parkinson¡¦s disease. Although the exact target was not given, it is assumed that the standard posteroventral pallidal target was used. Most intriguing by their results is that this improvement in anxiety is statistically independent of PD symptom amelioration, suggesting a direct effect on the neurocircuitry modulating anxiety symptoms.

There are currently only a few published reports using DBS specifically for the treatment of psychiatric disorders. In 1999, a joint investigative group from Belgium and Sweden released an initial communication in The Lancet. In this report, the group implanted a Model 3887 Pisces Quad Compact electrode (Medtronic, Inc), generally used for spinal cord stimulation, into the internal capsules of four OCD patients. The target coordinates, though not specified, were ¡§identical to those aimed for capsulotomy.¡¨ Also, the specific patient selection criteria were not explicitly revealed. In three of the four patients, ¡§some beneficial effects,¡¨ were observed. As an illustration of this benefit, the authors describe the results of one patient, a 39 year-old female with a 20-year history of OCD. Unipolar stimulation commenced with all four contacts serving as cathode. The stimulation parameters were defined as 5V, 100 Hz, 210 ƒÝs PW. After 2 weeks, the patient reported a 90% reduction in her obsessive compulsive behaviors. Although she was assessed in a double-blind fashion, no scores were given with regard to standard measures of mood or OCD symptoms.

In June 2003, this same group published the long-term follow up of their initial data presented in 1999. The data from six patients who were implanted with bilateral DBS electrodes in the internal capsule with follow up ranging from 3 to 31 months were presented. Patient selection criteria were narrowly and specifically defined utilizing Y-BOCS and Global Assessment of Function (GAF) scores. Targeting data was more explicitly given with the tip of the electrode from one of the patients (with the best clinical result) placed at 13 mm lateral to midline on the right, 14 mm lateral to midline on the left, 3.5 mm anterior to the anterior commissure, at the level of the intercommissural plane. Of interest is that while stimulating Contacts 1 and 2 in the internal capsule, the most distal electrode (0) was in the region of the nucleus accumbens.

Under double-blinded conditions (both patient and evaluating psychiatrist did not know the stimulation state), four of

the six implanted patients were assessed in a crossover design using Y-BOCS, Clinical Global Severity (CGS), Clinical Global Improvement (CGI), and the Beck Depression Inventory (BDI). One patient, in whom a different DBS electrode (3487A) was used, did not receive any benefit. No specific targeting data was given for this patient. Another patient required such high voltages for stimulation that battery replacement had to occur every 5 months with only limited beneficial effects. The electrodes were electively removed. Both patients underwent standard RF capsulotomy. Pulse width and frequency (210 ƒŶs, and 100 Hz respectively) were kept constant. Voltages varied from patient to patient ranging from 4 to 10.5 V. Preoperative medication regimens were kept constant.

With chronic stimulation, three of the six patients were considered responders with improvements on Y-BOCS of at least 35%. Another patient receiving chronic DBS had some improvement, but less than 35%, and was considered a nonresponder. Two other patients, as previously mentioned, never made it to the assessment phase, and must also be considered nonresponders. In the ¡§off¡¨ state, the three responding patients had worsening mood and OC symptoms that returned to baseline. Also of note, the group included some functional imaging data. Although the specifics of the timing of the imaging with regard to implantation date or of the scanning protocol used, the group demonstrated activations in the right and left striatum, pons, right frontal cortex, and superior/middle temporal/lateral occipital cortices bilaterally on fMRI in one patient. PET scanning showed some trends towards decreased frontal metabolism after 3 months of chronic DBS in three patients.

There were no infections, no deaths, and no hemorrhages related to the implantation itself. Although no specific neuropsychological safety data was given, the group reports no significant changes in vegetative function, and no manic behaviors. They did, however, observe ¡§some signs of cognitive and behavioral disinhibition¡¨ with high-amplitude stimulation in two patients. Such behaviors immediately disappeared when the amplitude was decreased.

Another published report is from a group at the Loyola University Medical Center. In 2003, they published a case report of DBS on the anterior internal capsule for OCD. Although full details of diagnosis were not given in this report, the patient, a 35-year-old female, had severe illness and functional impairment, reflected by a Y-BOCS score of 34 and a GAF score of 40.

Bilateral DBS electrodes (a standard model for DBS-3387) were placed in a target considerably more lateral and anterior to the Belgium/Sweden group: 18 mm lateral to midline, 13 mm anterior to anterior commissure, at the level of the foramen of Monro. Stimulation parameters were kept constant at 2 V, 210 ƒŶs PW, 100 Hz. Unipolar stimulation was used, but no mention was made of which contact served as the cathode. At a 10-month follow-up examination, the patient returned to work with all compulsions ¡§abated¡¨. After 3 months, her Y-BOCS score fell to 7. No adverse effects were reported.

In 2003, a group from Cologne, Germany published their results using DBS for OCD. Their target, the shell of the nucleus accumbens (NAc), is in a similar anatomic area as the groups employing DBS in the ventral anterior internal capsule. Noting the relatively higher voltages used in capsular DBS for OCD, the group chose the NAc owing to its proximity to the ventral internal capsule and its relationship to the amygdala, the prefrontal and orbitofrontal cortex, and the dorsomedial thalamus, all areas implicated in the pathogenesis of OCD. NAc DBS was performed in the right nucleus accumbens in four patients. Three of the four patients had a ¡§nearly total recovery¡¨ of their OCD, although explicit Y-BOCS scores were not given. The fourth patient was noted to have had the DBS electrode not in the target area.

In 2003, Visser-Vandewalle et al. described their experience with DBS in Gilles de la Tourette syndrome (GTS) in three patients. Two DBS electrodes were inserted into the thalamus at the following coordinates: 3(right)/5(left) mm lateral to midline, 4 mm posterior to the midcommissural point, at the level of the intercommissural plane. This roughly corresponds to the ventralis oralis internus (Voi) complex dorsally and the CM nucleus ventrally. Stimulation of the left target resulted in reduction of tic behavior, while stimulation of the right electrode resulted in a feeling of well-being. Stimulation occurred continuously at 2 to 3 V, 60 to 100 Hz, and 210 ƒÝs pulse width. With up to 5 years follow-up, there was a 70 to 90% reduction in tics. The group also reported improvements in the behavioral aspects, including mood, of the patients, although exact measurements were not given.

In 2005, Mayberg et al. published their results utilizing a method of DBS for major depression. Based on PET data, the group observed that there was a consistent link between changes in metabolism in the subgenual cingulate cortex (Brodmann area 25) and response to antidepressant medications. Bilateral implantation of DBS electrodes were implanted into area 25 in six patients. At a 6-month follow-up examination, four of the six implanted patients were determined to have had their depression go into remission, defined by a 50 % reduction in their Hamilton Depression Rating Scale (HAM-D) scores. The group also demonstrated a functional imaging correlate of the efficacy of subgenual cingulated DBS as the clinical responders demonstrated a decrease in metabolism in area 25 compared with preoperative baseline PET scans. This change in area 25 metabolism is consistent with other responders to other therapeutic modalities for depression. It is interesting to note a potential disparity between the current views on the physiopathology of psychiatric disorders and the efficacy demonstrated in the deep brain stimulation series.

There is an increasing belief that psychiatric changes cannot be attributed to a center of mood or behavior but, rather, are secondary to an imbalance in communication of multiple neuronal loops. However, the efficacy of DBS is typically attributed to a small generated electrical field encompassing a very limited amount of cerebral tissue. Perhaps, the stimulation generated at a certain target propagates downstream into the rest of the circuitry, gaining an amplified effect. Alternatively, it is possible that the limitations so far encountered with the proposed therapies are owing not only to difficulties in patient selection, but also to the restricted effect generated by the focal electrical field upon the overall circuitry. Future analysis may reveal that the best results might not come from one stereotactic target versus another but, instead, by a combination of neuromodulatory strategies affecting discrete circuits.

CONCLUSION: THIS IS NOT YOUR FATHER¡¦S LOBOTOMY

Critics often ask if neurosurgery for mental disorders should be allowed to die out. Indeed, the fact that the term ¡§psychosurgery¡¨ is avoided today indicates the historical burden associated with psychiatric surgery. However, there are dramatic changes that have taken place since the days of Freeman¡¦s transorbital lobotomy¡Xin technological acumen, knowledge and understanding of brain circuitry, regulatory strictures, and appreciation of the importance of informed consent and other ethical considerations¡X which make the current environment vastly different and more conducive to safer studies. What also must be emphasized, however, is the severity and intractable nature of the disease that these surgical interventions would be used to treat. While we have an obligation to protect these patients from unsafe therapies, we also are compelled to investigate procedures that may help them.

The initial experience with DBS for psychiatric disease gives the following impressions: that under strictly controlled situations, the surgery can be performed with an acceptable side effect burden and that the neural systems

underlying psychiatric disease can be modulated by neurostimulation. The benefits previously outlined in some patients gives hope that a more definitive therapy might be developed. One aspect of these future therapies will no doubt involve advances in the technology of neurostimulation and DBS. Another route will involve the development of a better understanding of the neural networks targeted for surgical intervention. DBS, with its dynamic ability to modulate the nervous system coupled with its inherent reversibility, might prove especially important in the surgical treatment of psychiatric disorders. However, several caveats must be taken into consideration. These efforts must be done only in tertiary care centers, where multidisciplinary expertise can be brought to bear on a surgical strategy that has been historically fraught with dangers. Also, we must bear in mind that our initial efforts must not be thought of, or presented as therapeutic in the traditional sense. Therapy is a tested and proven maneuver for the amelioration of symptoms.

DBS for psychiatric conditions, in its present incarnation, is an experimental endeavor. However, we are at a unique nexus of technologies: stereotaxis, DBS, functional imaging, and microelectrode physiological monitoring. The opportunity for breakthroughs in the surgical treatment for intractable psychiatric illness has never been better. Indeed, the ultimate breakthrough regarding a neurostimulation-based surgical therapy for intractable psychiatric disease may very well indeed cement the concept of psychiatric disease as neurological disorder in the minds of the public, much in the same way that movement disorders such as Parkinson¡¦s disease is. The removal of this stigma may serve the millions who suffer greatly from psychiatric maladies more than any pharmacological, psychotherapeutic, or surgical intervention. Primum non nocere¡Vmelius anceps remedium quam nullum. So long as we always guard this crucial balance, the psychiatric surgery currently in development will not be our father¡¦s lobotomy.

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Fig. 42.1 Cortical areas ablated in Fulton's experiments (from Egas Moniz Centenary. Scientific Reports. Libson 1977 pg.146).

Fig. 42.2 Egas Moniz (www.epub.org.br/cm/n02/historia/lobotomy.htm).

Fig. 42.3 Walter Freeman (www.epub.org.br/cm/n02/historia/lobotomy.htm).

Fig. 42.4 Almeida Lima (RP Feldman & JT Goodrich: Psychosurgery: A historical overview. Neurosurgery 2001, 48: 647-659).

Fig. 42.5 A bistoury, a dull, flat knife used in the modifed Moniz technique (www.gggodwin.com/17-18m.jpg).

Fig. 42.6 Demonstration of the approach of Moniz procedure (frontal leucotomy) (E Hitchcock, L Laitinen, K Vaernet. Psychosurgery. Proceedings of the second International Conference on Psychosurgery. Charles C. Thomas. Springfield , 1972).

Fig. 42.7 Demonstration of the approach in the Freeman-Watts procedure (prefrontal or standard lobotomy) (Freeman W, Watts J: Psychosurgery: In the Treatment of Mental Disorders and Intractable Pain. Springfield, Charles C Thomas, 1950, ed 2).

Fig. 42.8 Walter Freeman in a Winnebago. (Pressman, Last Resort—see endnotes of paper. Pg. 406).

Fig. 42.9 Diagram of the Cortico-striato-thalamocortical (CSTC) loops modeled by Delong et al.

Fig. 42.10 Diagram depicting the direct and indirect pathways through the striatothalamic circuit.

Fig. 42.11 Anatomic schematic of OCD neural circuitry.

Fig. 42.12 The Papez circuit (Laitinen L, Livingston K. Surgical Approaches in Psychiatry. Proceedings of the 3rd International Congress of Psychosurgery. MTP Lancaster, 1973)

Fig. 42.13 Anatomic schematic of AD neural circuitry.

Fig. 42.14 The Cingulate/Limbic cortico-striato-thalamocortical circuit of Alexander and Delong.

Fig. 42.15 The Orbitofrontal/Prefrontal cortico-striato-thalamocortical circuit of Alexander/Delong.

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