Surgery for psychiatric disorders has intrigued the psychiatric, neurological, and neurosurgical communities as well as the lay public for the past 70 years. Few other therapies have generated such controversy, enthusiasm, misconception, and, at times, indiscriminate use. Recent advances in image guidance, devices, and stereotactic procedures, as well as rapid expansion of our knowledge of the functional neuroanatomy of the major psychiatric disorders has led to renewed interest in neurosurgical approaches to these conditions. This issue of the Neurosurgery Clinics of North America was envisioned with the purpose of compiling the perspectives of experts on the cutting edge of research in the neurosurgical treatment of psychiatric disorders.

Currently, the two most common psychiatric disorders amenable to surgical intervention are obsessive-compulsive disorder (OCD) and major depression. OCD affects 4 to 7 million people in the United States at an annual cost of $8 billion per year and was among the 10 leading medical or psychiatric causes of disability in developed countries (1998 World Health Organization study). Conservative estimates of the lifetime prevalence of major depression are from 2.6% to 5.5% in men and 6.0% to 11.8% in women. Approximately 50% to 85% of patients with major depression experience recurrent episodes of illness. In addition to subjective distress, the disorder can be a cause of profound disability, with pervasively negative effects on marital, parental, social, vocational, and other life functions.

Advances in the efficacy, safety, and tolerability of treatments for OCD and depression have been made in the past 20 years. However, a significant number of patients with OCD and major depression refractory to nonsurgical treatments remain severely ill. These individuals, who are living lives of hopeless desperation, may ultimately face the tragic end of suicide. The hope that surgery can offer relief to these patients from agony and suffering is the fundamental imperative that demands ongoing research in this area.

It is clear that psychiatric neurosurgery will undergo a rapid evolution over the next decade. Today, dedicated multidisciplinary teams specializing in treating psychiatric patients have at their disposal the entire spectrum of modern functional neurosurgical techniques, including lesioning, radiosurgery, and neurostimulation. Advances in our understanding of the functional neuroanatomy and electrophysiology of the relevant circuitry underlying these conditions will increasingly guide placement of lesions or deep brain stimulation (DBS) electrodes. To promote further growth in this field, centers with psychiatric and surgical expertise must design studies that are prospective and randomized, using reliable and validated diagnostic and evaluation tools that measure changes in symptoms and quality of life.
To critically examine neurosurgery for psychiatric disorders, we must start by carefully examining the past. Kopell et al provide a historical perspective that reminds us of the complexities of psychosurgery and an enduring caution for the future. These historical endeavors were limited by a lack of scientific rationale and other limitations such as surgical techniques and devices, vague patient selection, indiscriminate use, and nonstandardized evaluations. In spite of the decline of surgery for psychiatric disorders since the 1950s, early studies of stereotactic lesioning demonstrated significant improvements in symptoms of patients with major depression and OCD with few cognitive or neurological side effects. Current stereotactic methods, using considerably smaller and more precisely located targets, have much lower morbidity. Neuroimaging research has focused attention on the relationship between activity in specific neuroanatomical networks and psychiatric symptoms and on changes after effective treatment. The articles by Rauch and Greenberg et al provide an overview of the scientific foundation and the emerging therapeutic strategies being explored today.

The articles by Greenberg, Cosgrove, and Chang et al consider the evidence for the safety and efficacy of lesioning procedures. The evidence has definite limitations but nevertheless sheds light on critical issues in assessing the long-term effectiveness and morbidity associated with anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy. Jeanmonod et al describe a novel lesioning approach to neuropsychiatric disorders based on recent evidence related to thalamocortical dysrhythmias that their group have shown are present in these conditions. Nuttin et al present recent data on the use of DBS technology for the treatment of OCD.

Two additional novel somatic treatments for refractory depression have also been the subject of systematic study over the past decade. George et al review the neurobiologic rationale and summarize treatment outcome data for transcranial magnetic stimulation, while Carpenter et al review similar evidence for vagal nerve stimulation.

Given the past history of the field, it is particularly important that research in this area move forward on a solid scientific and ethical foundation. Collaborative efforts between centers with dedicated multidisciplinary teams of psychiatrists, neurosurgeons, and basic scientists are needed to develop treatments with proven efficacy and safety before the premature introduction of these procedures into routine clinical use. In this context, we have included an editorial reprinted from a recent publication of the OCD-DBS collaborative group in neurosurgery that focuses on recommendations for future research efforts in this area. Finally, any publication focusing on surgery for psychiatric disorders must include a thoughtful discussion of the ethical implications of these procedures. Fins et al offer a careful and considered review of the ethical issues in this field, including issues of informed consent.

Together, these articles provide a comprehensive overview of the current state of surgery for psychiatric disorders and the complex issues surrounding the re-emergence of this field. They represent a window into what promises to be an exciting future for the development of novel neurosurgical approaches to psychiatric disorders that are based on the neurobiologic basis of these conditions.

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Letter to the editor

Deep brain stimulation for psychiatric disorders

There is increasing interest in the use of deep brain stimulation (DBS) as a treatment for patients with psychiatric conditions. For example, the preliminary results from the first trials, reported by Nuttin et al [1], have shown that DBS may have beneficial effects in patients with severe obsessive-compulsive disorder (OCD) that is refractory to treatment. These preliminary results suggest that DBS may have a role in the treatment of patients with intractable OCD. Treatment of psychiatric patients with DBS remains investigational, however, and is not considered standard therapy.

Concern regarding the use of neurosurgery for the treatment of patients with psychiatric illnesses is attributable largely to the indiscriminate and widespread application of extensive, destructive procedures before the stereotactic era. The tragic example of frontal lobotomy, which was performed many times before adequate long-term safety data were available, remains an enduring caution.

Given this history, it is incumbent on the scientific community to respect the dignity of patients who may be included in studies by ensuring adequate protection while providing access to potential therapeutic innovations. We recommend that all investigators adhere to comprehensive standards that protect this potentially vulnerable population while they pursue valuable clinical research. Toward that end, we urge that investigators who are engaged in this research establish multidisciplinary, multicenter teams to systematically investigate DBS in OCD. On the basis of our experience, we recommend that studies aimed at investigating the use of DBS to treat patients with psychiatric illnesses meet the following minimum requirements.

1. An ethics committee (eg, the Institutional Review Board in the United States) that will have ongoing oversight of the project should approve the investigational protocol.
2. A patient assessment committee should evaluate each patient as a possible candidate for inclusion in the protocol. The role of this committee is to ensure that potential candidates meet certain medical and psychiatric criteria and are appropriate for inclusion in the study and to monitor the adequacy of the consent process. Patient assessment committees should be constituted broadly to achieve an ethically valid consensus, and they should have the opportunity to obtain independent capacity assessments when indicated.
3. Candidates for DBS surgery should meet defined criteria for severity, chronicity, disability, and treatment refractoriness.
4. The use of DBS should be limited solely to those patients with decision-making capacity who are able to provide their own informed consent. Patient consent should be maintained and monitored throughout the process, and patients should be free to halt their participation voluntarily.
5. Patient selection, surgical treatment, device programming, and comprehensive, regular psychiatric follow-up should be conducted at or supervised by a clinical research center.
6. The investigative team should include specialists from the following disciplines, and they should work in close collaboration:
   a. A functional neurosurgical team with established experience in DBS.
   b. A team of psychiatrists with extensive experience in the psychiatric condition under investigation.
   c. Preferably, both of the preceding groups should have some experience in neurosurgical treatment for psychiatric disorders. If not, close consultation with experienced centers is indicated.
7. Investigators must disclose potential conflicts of interest to regulatory bodies such as ethics committees or institutional review boards and to potential enrollees during the informed consent process.
8. The surgery should be performed only to restore normal function and relieve patients’ distress and suffering.
9. The procedure should be performed to improve patients’ lives and never for political, law enforcement, or social purposes.

In our experience, embarking on this type of research requires a major commitment of time, energy, and resources across disciplines before and after device implantation. DBS has the potential to offer hope for severely ill patients, but investigations in this area should proceed cautiously to maintain the public trust necessary for scientific progress.

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Psychiatric neurosurgery: a historical perspective

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Why intervene surgically to treat psychiatric disorders? Certainly, past efforts have been marked with ambiguous results at best and have been associated with ignoble circumstances at worst. Yet, the impetus to explore the surgical options in psychiatric treatment has once again arisen.

The legacy of Moniz, Fulton, and Freeman

The birth, flourishing, and demise of psychosurgery in the early twentieth century may serve to caution our current endeavor to intervene surgically in psychiatric patients. In the hands of the most prominent physicians and Nobel laureates of the age, despite the best of intentions, such intervention led to virtual worldwide banning of a seemingly promising surgical venue. This is the tale of a treatment whose promise remains largely unknown and unfulfilled even today. Why the descent from mainstream “miracle” to medical anathema?

When Paul Broca presented his case of patient M. Leborgne (“Tan”) in front of the Parisian Anthropological Society meeting in 1861, he ushered in the age of localization (Fig. 1). Localization married the concepts of behavior and function with a precisely defined anatomic neural substrate. Before this, Franz Joseph Gall’s phrenology (Fig. 2) tried to localize function based on cranial landmarks, but it was Broca’s work that looked specifically to the brain. It was the concept of localization that allowed the surgical intervention on neural function. It was the first step at unlocking the “black box.”

Medical scientists and clinicians soon seized on the idea of localization in the treatment of mental disorders. In the late 1800s, Friedrich Goltz performed experiments on dogs in which removal of the temporal lobes resulted in animals that were more tame and calmer than the ones not operated on [1]. In 1891, drawing from these animal studies, a Swiss psychiatrist named Gottlieb Burckhardt (Fig. 3) reported the results a series of surgical procedures in which he drilled holes in the heads of six severely agitated psychiatric patients and extracted sections of their frontal lobes [2]. Although in Burckhardt’s series of six patients, three were considered “successes” and two “partial successes,” pressure from his colleagues led him to abandon his efforts.

It might seem surprising, almost inconceivable, that such a rapid leap from animal experiments in the laboratory to clinical practice on human beings could take place; however, it is this phenomenon that is fundamental to understanding the rise and ultimate fall of psychosurgery in the twentieth century. Indeed Burckhardt’s report itself ends with a bold challenge to the fundamental practice of medicine:

Doctors are different by nature. One stands fast in the old principle: “\textit{primum non nocere};” the other states: “\textit{melius aniceps 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

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believe that we should allow this to hold us back... [3]

"First, do no harm (primum non nocere)" versus "Better an unknown cure than nothing at all (melius anceps remedium quam nullum)." The battle line for psychosurgery in the early twentieth century was drawn. It is this fundamental struggle between the obligation of the physician to remain cautious and the desire to help those in need that would define the efforts to intervene surgically in the mentally ill.

In 1929, at the age of 30 years, John F. Fulton became the chairman of Yale University’s Department of Physiology (Fig. 4). His research interest was an extension of Sherrington’s thought: to reveal the relations among neural systems, it was necessary to cut the connecting pathways in progressively higher neuroanatomic levels of the system. The lower level thus becomes disconnected or "disinhibited" and reveals itself through changes in neurologic behavior. Fulton applied this approach to frontal lobe function in chimpanzees, yet he found that "turning to questions involving perception, learning, memory, and other higher intellectual faculties, objective data are far more difficult to obtain." [4] This discovery would echo the troubles clinicians would have a decade later as the proliferation of lobotomy raged out of control. In the short run, however, it led Fulton to collaboration with a recently hired psychologist, Carlyle Jacobsen.

Then, in 1935, another fateful meeting occurred. At the Second World Congress of Neurology in London, Fulton and Jacobsen presented their work showing behavioral changes in chimpanzees after ablation of frontal lobe areas (Fig. 5) [5]. Fulton and Jacobsen made the observation that frontal lobe ablation could result in the lessening of "anxiety states" in chimpanzees [6]. 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. 6 and 7).

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 made this observation in 1935:

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 [7].

Moniz made the critical analytic jump linking the seemingly irrational behaviors and thoughts of psychiatric patients with an anatomically "normal" but disordered neural substrate—a concrete neural substrate which, when altered in a surgical fashion, would result in definitive change of the seemingly ethereal entities of thought and mind itself. His plan was to sever the white matter bundles connecting frontal lobe regions with the rest of the brain, the frontal leukotomy. He convinced a young neurosurgeon in Lisbon, Almeida Lima (Fig. 8), to undertake the procedure, and a series of 20 patients commenced. Despite this bold leap into human clinical practice, Moniz realized that his inspiration from animal data was a tenuous one: "...it is not possible to obtain experimental subjects among animals... [There simply existed too] great a difference between the psychic life of man and that of animals... [8]"
In 1936, Walter Freeman chanced on Moniz’s initial communications regarding frontal leukotomy in the obscure journal *Lisboa Medicina*. His contemporaries who treated psychiatric maladies with psychotherapy, useless prattle by his account, had frustrated Freeman, a neuropsychiatrist of the “organicist” school, who held that psychiatric illness had a tangible basis in neuropathophysiology. Freeman, too, recognized that the scientific basis for the procedure was “naive”; nevertheless, here was “something tangible, something that an organicist like myself could understand and appreciate” [9]. For Freeman, a therapy that was untried and possibly dangerous was better than the status quo. Freeman wrote to Moniz in May of 1936, telling him of his inspiration and his intention to apply Moniz’s procedure in the United States.

Why would scientists of such renown as Moniz and of such promise as Freeman be so hasty in applying such a radical and virtually unfounded remedy? Why did *melius aniceps remedium quam nullum* become so much more important and more seductive than *primum non nocere*? Why did “do something” become more imperative than “first, do no harm”?

Medicine is an art that is not practiced in the idealized bubble of science. Science is the realm of theory, hypothesis, and the experimental model. It deals with the currency of truth and hard fact. Medicine is where science meets all the human foibles, hopes, prejudices, and desires to
“do something.” “[Medicine] is more wrapped up in human, time-dependent concerns than is generally admitted” [10].

Nowhere was this desire to “do something” stronger than in the field of psychiatry at the dawn of the twentieth century. Indeed, there were no drugs or medical procedures available that were used to treat the specific symptoms of mental illness. Even with the advent of powerful drugs, such as barbiturates, there was little ground gained in the ability to change the emotional and mental dynamics of psychiatric disease. “Therapeutic nihilism” was the philosophy of treatment among psychiatrists at this time, because patients were allowed by default to languish according to the natural history of their disease. Then, beginning in the 1930s, a wave of “somatic” therapies began to “revolutionize” psychiatric practice (Fig. 9). The most important of these “shock” treatments were injections of metrazol (camphor), insulin-induced hypoglycemic comas, and electroconvulsive therapy, all designed to trigger convulsions and states of unconsciousness in the patient. Although extremely welcomed because of their clinical “effectiveness,” in these early versions, shock therapies were dangerous and difficult to manage. Insulin-therapy was cost- and labor-intensive, because these patients required constant vigilance from nurses and medical staff. Furthermore, patients were terrified of entering into the near-death states of insulin coma. The seizures of metrazol and electroconvulsive therapies, unmodified by anesthesia or muscle relaxants, often had the byproduct of spinal and long bone fractures. Yet, these unfortunate side effects were tolerated because of the ability of these “somatic” treatments to alter the clinical course of a patient’s mental disease and, more importantly, increase the number of discharges from inpatient facilities.

The economic environment of inpatient psychiatric care in the nascent twentieth century is also central to understanding the widespread adoption of such a risky and uncertain treatment as psychosurgery by the medical community. The inpatient psychiatric institutions of the early twentieth century had become a vast network of juggernaut institutions, some containing as many as 10,000 patients. Inpatient admissions were climbing at an alarming rate. By 1940, there were 480,000 psychiatric inpatients, equal to the total...
number of beds in all nonpsychiatric hospitals combined [11]. As the number of admissions increased, the discharge rate decreased. With the lack of effective therapies, the rate of recoveries dropped. Evidence mounted that any patient hospitalized for longer than 2 years would stay until death. The mathematics of this situation led to vast overcrowding and inhuman conditions (Fig. 10). It was not uncommon for institutions to house twice the number of patients for which they were designed. Scenes of 100 cots placed side by side in a ward built for 25 leading to elderly patients climbing over one another to use the toilet pervaded the inpatient psychiatric landscape [12]. Albert Maisel’s pictorial essay in the May 1946 edition of Life magazine described the inpatient mental health system as “little more than concentration camps on the Belsen pattern.” Even the psychiatrists themselves began to lose hope. In a communication that appeared in Psychiatric Quarterly in 1945, one psychiatrist equated inpatient psychiatric admission as being “identical with doom” [13]. Therapeutic nihilism coupled with an overcrowded and economically overwhelmed inpatient psychiatric system was fertile ground for an untested, untried, and largely scientifically unsupported “miracle.” Freeman brought the miracle of Moniz to the United States in 1936.

Freeman, having convinced a young neurosurgeon by the name of James Watts to work with him (himself a former student of Fulton’s), began a series of patients in September of 1936. They considered their initial patient, A.H., a resounding success. In their initial communication they noted: “She was well dressed, talked in a low, natural tone...showed excellent appreciation of her changed condition. Her husband asserts that she is more normal than she has ever been” [14].

This was a middle-aged woman who suffered from “agitated depression,” having had a habit of wild outbursts in which “she exposed herself before the window and urinated upon the floor” [15]. Emboldened by their success, they rapidly proceeded with an increasing number of patients. They also modified the Moniz procedure, abandoning the Moniz leukotome for a dull flat knife known as a bistoury (Fig. 11) and approaching from the side as opposed to the top (Figs. 12 and 13). The Moniz procedure, frontal leukotomy, became the Freeman-Watts technique, the prefrontal or standard lobotomy.

Within a year, Freeman and Watts were eager to share the results of their successes with the
professional community. Freeman would note that the choosing of patients based on disease type was critical to the procedure’s success, with depressive and obsessional types faring best and schizophrenics faring worst (in fact, five of six schizophrenics in his series showed no improvement) [16]. The initial response from the professional community, especially among psychiatrists, was hostile. They believed that the procedure was too radical and too unfounded in its scientific basis. One psychiatrist wrote: “[It is like] burning down the house to roast a pig ... What has Moniz accomplished? ... No one knows ... least of all Moniz” [17].

Initially, Fulton rose to defend the work of Freeman and Watts. Although he acknowledged the tenuous scientific link between animal studies and clinical practice, he thought that there was rich opportunity for research and significant promise for the procedure. Using his professional reputation among neurologists and psychiatrists as well as his ties to neurosurgeons (indeed, he was the Harvey Cushing Society’s second president), he echoed the need for a procedure to relieve the overburdening of the national psychiatric hospitals. He was in solid support of the medical community proceeding with the operations but predicated this support on the concept of carefully designed clinical trials in elite academic institutions [18]. Fulton won support for the Freeman, Watts, and Moniz procedure, but his warnings fell on deaf ears. The procedure was soon to spread throughout the medical community.

By the end of 1937, James Lyerly, a well-respected community neurosurgeon and a founding member of the Harvey Cushing Society, began applying the Freeman-Watts technique in Florida. He modified the Freeman-Watts procedure that he believed was a “blind” one by using a brain speculum so that the white matter to be cut was exposed to visual inspection. In 1 year, Lyerly had operated on 19 patients and presented his results at the meeting of the Florida Medical Association. Four previously chronically institutionalized patients had already been discharged. None died. None had any “serious complications.” Lyerly called the procedure, “nothing less than miraculous” [19]. Other neurosurgeons took notice. Francis Grant, Chief of the Neurosurgical Service at the Hospital of the University of Pennsylvania,
and W. Jason Mixter at the Massachusetts General Hospital began performing lobotomies in 1938. By 1939, J.G. Love of the Mayo Clinic traveled to Florida to learn the procedure from Lyerly so that he could start a series of lobotomies.

With the publication of Freeman and Watts’ *Psychosurgery* in 1942, the fervor over the success of the lobotomy spread from the professional community to the lay community. Using his flair for the dramatic, Freeman dispensed with the customary scientific format and instead presented what was equivalent to pulp nonfiction:

**Surgeon:** Well, the operation is over now anyway, isn’t it?

**Patient:** Yes, I’m glad it is. You know I wasn’t dreading this particularly. I’m glad you did it under local because I wanted to see what it was all about.

**Surgeon:** Did you feel anything particularly during the operation?

**Patient:** No, there wasn’t any real pain except when the first needle went in. Drilling through the skull was rather peculiar, but it didn’t hurt at all. Now, it’s just as if that vague unformed apprehension that has been with me all these years suddenly cleared up [20].

The lay public was especially taken with Freeman and Watts’ book. One state hospital superintendent wrote to Freeman that his 17-year-old daughter read it and told him: “Daddy, this is the most interesting medical book that I have ever seen. Even I can read it and understand what I am reading about” [21]. Soon, lay publications, such as *The New York Times, Time, Life, Newsweek,* and *Reader’s Digest,* were sensationalizing the successes of the prefrontal lobotomy.

Once both the profession and the public recognized lobotomy as a treatment of vast potential, its fate ceased to be in the hands of Fulton, Freeman, or any one person. Psychosurgery’s fragile connection to the laboratory and the scientific community would begin to grow weaker and weaker. Fulton once envisioned the psychosurgery effort as an experimental one, the task of rigorously controlled academic institutions and off limits to the community practitioner. Now, every aspect of the medical community was participating in the psychosurgery “miracle.” A “clinical drift” effect was evident as the procedure became free from any constraints. Initially, Freeman and other fervent supporters of lobotomy warned that the procedure should be used...
sparingly in cases of schizophrenia because of its poor clinical effect compared with other psychiatric diseases; however, they were ignored in the desire to “do something” for a group of patients who had no alternative form of therapy available.

Fig. 10. The Incontinent Ward, Byberry State Hospital. (From Pressman J. Last resort. Psychosurgery and the limits of medicine. Cambridge: Cambridge University Press; 1998. p. 149; with permission.)

Fig. 11. Examples of bistoury knives. (Available at: www.ggodwin.com/17-18m.jpg.)

Psychosurgery’s most ardent proponent ironically exemplified this clinical drift. At the end of World War II, prefrontal lobotomy was entering its heyday. Freeman, however, was looking to expand the use of his procedure. Gone were the days of “surgery of last resort”; Freeman wished to operate on a “better grade” of patient, including those recently institutionalized as well as those not hospitalized. Freeman was frustrated with Watts’ veto power over patients who he believed were not disabled enough by their illness. Freeman thought that the rate-limiting step to psychosurgery’s dissemination was, in fact, the neurosurgeon, being too few in number and too expensive in cost. Thus, with an ice pick, Freeman severed psychosurgery’s final ties with its roots, those of neurosurgery itself.

Drawing from an obscure report of an Italian psychiatrist, Amaro Fiamberti, Freeman developed the transorbital lobotomy, a ghastly procedure in which the frontal white matter is cut by a metal spike inserted through the thin bony orbit above the eye [22]. Freeman’s initial choice to accomplish this procedure was the common ice pick (Fig. 14). 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 instruction, with “every physician his own lobotomist” [23]. By 1948, Freeman, with ice pick in hand, traveled across the country to fulfill what he considered was an unanswered need (Fig. 15). It did not take long for Watts to sever his ties with Freeman. Like other neurosurgeons, he was horrified at the ghastly treatment that the patient received under Freeman’s new procedure. Patients were not draped in sterile linen, and there was no surgical backup if a hemorrhage did occur. 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 [24]. In one 12-day period, he operated on 225 patients. *Time* magazine heralded the age of “mass lobotomies” [25].

Fulton was appalled at Freeman’s new course of action. “What are these terrible things I hear about you doing lobotomies in your office with an ice pick?...Why not use a shot gun” [26], Fulton’s incredulous missive to Freeman seethed. Freeman did not relent, claiming that the transorbital procedure was “much less traumatizing than a shotgun and almost as quick” [26]. Their conflict exemplified their personal philosophies regarding the leap from laboratory to clinic and the growing chasm between psychiatric neurosurgery and its physiologic roots. Fulton believed that the most reliable and safe medical knowledge came from a combination of basic animal research coupled to a few rigorously designed and executed clinical trials. Fulton realized that the complete lack of reliable objective testing methods available to psychiatry at the time made it impossible to track lobotomy’s efficacy from any scientific point of view. Conversely, the most important question to Freeman was, “Did it work?” [27]. What counted to Freeman were not intelligence tests but the
successful return of patients to everyday life. *Primum non nocere* versus *Melius aniceps remedium quam nullum*. Yet, even as psychosurgery’s most ardent scientific proponents began to question the widespread use of lobotomy, the procedure had become as mainstream a treatment as appendectomy. The awarding of the Nobel Prize to Egas Moniz in 1949 typified the simultaneous legitimization of lobotomy amid growing concerns regarding its efficacy and side effects. From 1936 to the mid-1950s, approximately 20,000 psychosurgical procedures, virtually all frontal lobotomies of some form, were performed in the United States [28].

Then, it was over. Ironically, it was a surgeon who helped end the “golden age” of psychosurgery and usher in the pharmacologic age of psychiatry. In 1952, Henri Laborit, a surgeon in Paris, was looking for a way to reduce surgical shock in his patients. Having tried antihistamines, generally used to fight allergies, he noticed that when he gave a strong dose to his patients, their mental state changed. No longer did they seem anxious about their upcoming surgery; in fact, they were rather indifferent. A fellow surgeon passed the word to his brother-in-law, a psychiatrist named Pierre Deniker. Deniker’s interest was piqued, and he ordered some chlorpromazine to try on his most agitated and uncontrollable patients.

The results were stunning. Patients who had stood in one spot without moving for weeks and patients who had to be restrained because of violent behavior could now make contact with others and be left without supervision.

In 1954, the U.S. Food and Drug Administration approved chlorpromazine, and it took the field of psychiatry by storm. The death knell for psychiatric neurosurgery was sounded; yet, in Freeman’s case, it fell on deaf ears. Freeman carried on his one-man war. He was relentless in his attempt to convince his colleagues to perform more of his procedures. On occasion, Freeman would dump shoe boxes crammed with letters from “grateful” lobotomized patients onto the desks of skeptical colleagues. They remained unconvinced. Freeman died in 1972 at the age of 76 years [29].

Yet, as this interest waned, technologic developments, especially in the realm of stereotaxis, ushered in a second wave of psychiatric neurosurgery.

The stereotactic era

Indeed, the first modern neurosurgical procedure for psychiatric disease, the frontal leukotomy, 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. As the experience with frontal lobotomy increased, there was some suggestion that minimizing cortical damage and focusing on the white matter tracts could retain efficacy while minimizing side effects. This trend
toward increasingly discrete subcortical lesions culminated in the application of stereotaxis on psychiatric neurosurgical procedures. The second wave of psychosurgery was born. In 1947, Wycis and Spiegel introduced the dorsomedial thalamotomy [30,31], the first subcortical stereotactic neurosurgical procedure performed on human beings and 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, which are all stereotactic interventions. These procedures are typically performed on the severe and refractory psychiatric patient. First, a patient must meet Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria for a particular psychiatric disease such as obsessive-compulsive disorder (OCD) or affective disorder. Next, a patient must fail several rounds of treatment with multiple psychotropic medications combined with appropriate psychotherapy before he/she is considered for surgical treatment. Therapeutic failure is determined by quantitative analysis using the most appropriate and accurate psychiatric batteries of tests available, such as the Yale-Brown obsessive-compulsive scale (Y-BOCS), the Clinical Global Impression (CGI), and the Hamilton Depression scale for depression (HAM-D). When surgical treatment is ultimately considered, a multidisciplinary team consisting of psychiatrists, neuropsychologists, neurologists, lawyers, clergy, bioethicists and neurosurgeons is assembled to make sure the patient in question is both refractory and appropriate. Although many of the following studies of psychiatric neurosurgery have had significant flaws, most notably, the inherent bias of a nonrandomized non-double-blind study and the lack of objective functional imaging techniques, they do suggest a viable means of treatment for a subset of patients who may have no other options. The procedures themselves are described below. Their safety and efficacy for their main current indications, intractable OCD and depression, are considered at length in the article by Greenberg and his colleagues in this issue.

Cingulotomy

Surgery on the cingulate gyrus dates back to observations in the 1940s that severing fibers from the cingulate gyrus led to a decrease in anxiety type states [32]. In 1952, Whitty et al [33] reported their cingulectomy, in which a 4-cm × 1-cm section of cingulate gyrus was resected bilaterally. In 1967, Ballantine et al [34] introduced the modern stereotactic procedure in which a lesion, localized by air ventriculography and made using thermocoagulation, was made bilaterally in the anterior cingulate. The lesion is typically made bilaterally 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 (Fig. 16). The procedure performed today has been refined using the latest in stereotactic equipment and imaging techniques. Stereotactic cingulotomy is the most frequently reported neurosurgical procedure for psychiatric disease in the United States and Canada.

Capsulotomy

Developed in Sweden by Lars Leksell and by Talairach in France, 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 third and middle third of the anterior limb of the internal capsule at the approximate level of the foramen of Monro. Specifically, the ideal target lays 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 (Fig. 17) [35,36].
Fig. 16. Typical cingulotomy lesions. (From Laitinen L, Livingston K. Surgical approaches in psychiatry. Proceedings of the Third International Congress of Psychosurgery. Lancaster: MTP; 1973; with permission.)

Fig. 17. Capsulotomy lesion sites. (From Hitchcock E, Ballantine H, Meyerson B. Modern concepts in psychiatric surgery. Proceedings of the Fifth World Congress of Psychiatric Surgery. Elsevier/North-Holland Biomedical Press; 1979; with permission.)
Subcaudate tractotomy

Another stereotactic procedure geared toward interrupting fibers from the orbitofrontal cortex to the thalamus is subcaudate tractotomy (innominateotomy). Developed by Knight in 1965 in London, the operation was designed to relieve depressive, anxiety, and obsession symptoms while minimizing postoperative epilepsy and cognitive/personality deficits [37,38]. The lesion is created by multiple 1-mm × 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 known as the substantia innominata, has traditionally been 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 (Fig. 18). Initially, placing two rows of four rods each made the lesion. Later studies, having refined the technique, have created the lesion by radiofrequency thermocoagulation [39].

Limbic leukotomy

Although the other three aforementioned procedures each target a single anatomic substrate, a fourth procedure is designed to interrupt fibers at two separate areas, one involving a frontothalamic loop and the other involving an area of the Papez circuit (Fig. 19). Called limbic leukotomy, 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 (Fig. 20).

What now?

Despite the fact that neurosurgery for psychiatric illness decreased in frequency in the latter half of the twentieth century and that neurosurgical technologic developments like stereotaxis vastly improved the quality of the surgical intervention itself, the negative bias toward its practice continued to grow. Like the human behavioral example of Newton’s third law of motion, the fervor with which psychosurgery was welcomed in the first half of the twentieth century became an ardent backlash against what was regarded as a reckless and sinister procedure. In the United States, charges of abuse and allegations of surgery for social control culminated in the establishment of a National Commission in 1977. This board examined all the neurosurgical procedures performed in the United States from the freehand frontal lobotomies to the stereotactic lesioning procedures. Careful emphasis was taken to review the efficacy and safety of these procedures. The National Commission’s findings were surprising, as the Chairman reported in his review: “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” [40].
The National Commission was so impressed by the potential benefit of psychiatric neurosurgery that it recommended a review board be formed to study these procedures in a more scientific manner. This review board was never formed, however.

There are several reasons to continue to evaluate the role of neurosurgery in the treatment of psychiatric disease. Despite adherence to therapeutic guidelines and conscientious compliance, there still exists a population of psychiatric patients who are refractory to aggressive conventional treatment with medication and empirically proven psychotherapies. A particularly intractable population exists among OCD patients. By most reviews of current treatment strategies, approximately 10% of all OCD patients show an unrelenting downward course despite all psychotherapeutic and pharmacologic treatments [41,42]. Because it is estimated that 3% of the world’s population suffers from OCD, this alone is a substantial patient population. Affective disorder, which includes major depression and bipolar disorder, similarly has a treatment-resistant subset of patients [43,44]. For some of these patients, surgery may still be a viable treatment alternative in the psychiatrists’ armamentarium.

It should be made clear that the end point for untreated psychiatric disease is dismal. Setting aside the loss of productivity on both a personal and professional level, self-mutilation and suicide can be the final tragic outcome for a significant number of these refractory psychiatric patients. Treatment-resistant mental disorders, in any of their forms, must be looked on as degenerative and potentially fatal neurologic illnesses.

The promise of a modern undertaking of psychiatric neurosurgery is that it is no longer equivalent to lobotomy. We benefit from the technological leaps that have occurred over the past 50 years. One of the challenges in treating psychiatric disease during the zenith of lobotomy was the quantitative analysis of patients throughout the course of treatment. Modern psychiatric testing batteries, such as the Y-BOCS, CGI, and HAM-D, allow for a more accurate and objective evaluation of patients undergoing psychiatric neurosurgical procedures in ways that were not previously available.

Neurosurgical practice has also grown tremendously since the heyday of frontal lobotomy. Today’s neurosurgeon, bolstered by technological advancements in stereotactic equipment coupled with the advent of intraoperative microelectrode recording, can hit physiologic targets with a degree of accuracy never before possible. Furthermore, techniques have been developed that allow the neurosurgeon to modulate neurologic function while minimizing the risk to the patient. Stereotactic radiosurgery, exemplified by such devices as the gamma knife, enables lesions to be made without any upfront risk to the patient. Perhaps the neurosurgical technical development that holds the most significance for psychiatric neuro-

Fig. 19. Papez circuit. (From Laitinen L, Livingston K. Surgical approaches in psychiatry. Proceedings of the Third International Congress of Psychosurgery. Lancaster: MTP; 1973; with permission.)
surgery is deep brain stimulation (DBS). With its ability to modulate neuronal function without the necessity of a permanent lesion, DBS has already become the mainstay of the neurosurgical treatment of movement disorders. Because previous efforts to prove the efficacy of surgical intervention in psychiatric disease have been hampered by the lack of double-blind studies, DBS, with its inherent ability to be turned “on” and “off,” might prove particularly useful.

Our knowledge of the pathophysiology underlying psychiatric disease has also grown. Today, state-of-the art imaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG), allow the clinical investigator a noninvasive method of directly and precisely localizing brain function and anatomy. Although experimental, these imaging techniques allow us to evaluate human brain function directly without having the potential misdirection that animal models may entail. This highlights the difference between the surgical efforts for movement disorders and psychiatric disease: although the experimental animal model has bolstered movement disorder surgery, the inherent lack of valid animal models in the latter has hindered efforts. This intermediate link between animal physiologic models and clinical practice is a fundamental paradigm shift with respect to the initial efforts with lobotomy. As our knowledge of the circuitry underlying psychiatric disease increases, better surgical targets will become apparent. Such a link between functional imaging and surgical practice has already been demonstrated in the endeavors in chronic pain and movement disorders. Together, these tools can help to eliminate some of the shortcomings of past studies of psychiatric neurosurgical procedures.

As we re-explore surgery's role in psychiatric treatment, we have learned from the example of lobotomy that we must tread carefully. Our initial efforts, of course, must remain firmly in the realm of a limited number of academic institutions. Ultimately, because of the vast resources implicit in the multidisciplinary approach, psychiatric neurosurgery may never enter community practice. Despite all these improvements and the heeding of past
mistakes, patients and clinicians alike must always be cognizant of the potential dangers in this task. Nevertheless, past efforts suggest that a real potential to benefit some extremely sick people may exist. It is up to future multidisciplinary endeavors conducted in carefully controlled centers of academic expertise to determine whether this potential is either real or folly.

References


Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues

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The effectiveness and tolerability of treatments for obsessive-compulsive disorder (OCD) and depression have seen impressive improvements over past decades. Nonetheless, some patients with either disorder continue to manifest severe chronic illness that is refractory to treatment. For them, modern neurosurgical procedures remain a therapeutic option. Psychiatric neurosurgery remains controversial, largely because indiscriminate use of prefrontal lobotomy in the middle of the twentieth century frequently produced significant deficits in emotional responsiveness and motivation, sometimes with little or no therapeutic benefit. Although the historical experience remains an enduring caution, current stereotactic methods using considerably smaller and more precisely located targets have much lower morbidity. Moreover, an increasingly specific neurobiologic rationale for psychiatric neurosurgery is being developed. Neuroimaging research has focused attention on the relations between activity in specific neuroanatomic networks and psychiatric symptoms and on changes in such relations after effective treatment. A small number of prospective studies support the view that neurosurgery may be of benefit to patients who fail to improve with the best available conventional treatment. This article considers the efficacy and safety of lesion procedures. The evidence has important limitations but sheds light on critical issues in assessing the long-term effectiveness and morbidity associated with existing procedures, including anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leukotomy. The same methodologic issues arise when considering the newer nondestructive techniques that are currently in development for the treatment of intractable psychiatric illness, including deep brain stimulation. Determining the effectiveness and side effect burden of neurosurgery for intractable psychiatric illness is a task primarily for psychiatrists, collaborating closely with neurosurgeons, neurologists, and neuropsychologists in specialized multidisciplinary teams.

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OCD is common, affecting from 2% to 3% of the population, or 4 to 7 million people in the United States [1,2]. Prevalence seems to be similar in other countries and cultures. The illness is characterized by recurrent thoughts, images, feelings, or behaviors that persist against the patient’s attempts to eliminate them and which are accompanied by marked and often overwhelming anxiety. OCD typically begins in childhood or adolescence. Symptoms, and the distress resulting from them, are usually chronic [3,4]. OCD is associated with significant, and often dramatic, impairment in social and occupational functioning [1]. Total costs of the disorder in the United States were estimated at $8 billion per year in 1990, including $2.1 billion in direct costs and $5.9 billion in indirect costs related to lost productivity [5]. OCD was among the 10 leading medical or psychiatric causes of disability in developed countries in a 1998 World Health Organization study [6]. The disorder tends to be familial, with the risk 1.5 to 3 times higher in individuals with an affected first-degree relative [4].

Specific treatments for OCD have been developed over the past decades, significantly improving patients' lives. Current behavioral and pharmacologic therapies are far from universally effective, however. It is estimated that they provide substantial benefit to only 50 to 70% of patients seeking treatment [1]. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, fluvoxamine, citalopram and paroxetine, are the mainstay of pharmacologic treatment. Clomipramine, a tricyclic antidepressant and a potent but non-serotonin reuptake inhibitor, is a second-line agent. Even when effective, side effects may substantially limit the treatment adherence usually necessary for ongoing symptom relief. For example, one study found that more than half of patients who responded to an adequate trial of a serotonin reuptake inhibitor stop taking the medicine within 2 years because of sexual dysfunction, weight gain, or sedation [7]. Medication augmentation strategies can benefit patients who fail to respond to SSRI monotherapy [8,9]. Typical and atypical neuroleptics are effective in controlled studies but impose an additional side effect burden. These include sedation, weight gain, extrapyramidal reactions, and, especially for typical neuroleptics, a risk of tardive dyskinesia or tardive dystonia over time. Clonazepam also seems to be partially effective as an augmenting agent but, as with other benzodiazepines, is sedating and may induce dependence.

Behavior therapy is particularly useful for OCD and holds a central place in effective treatment regimens. After the symptoms and their environmental triggers are characterized in an individual patient, the therapy involves deliberate provocation of increases in anxiety by exposure to those triggers while encouraging resistance to compulsive rituals. The anxiety and compulsive urges typically become progressively more transient and less intense as therapy continues. Behavior therapy is effective in 70% to 80% of patients completing a course of treatment. A substantial number of OCD sufferers find that the distress induced as a necessary part of the therapy is intolerable, however, and either refuse to start or
fail to complete it. Particularly for seriously ill patients, it seems that the most effective treatment is a combination of expert medication management and intensive behavior therapy offered by experts at specialized treatment centers. Unfortunately, such optimal therapy is not widely available and is also expensive, limiting its application to only a few individuals presenting for treatment. Even when the best available medication and behavior therapies are applied, an estimated 10% of patients remain severely affected. This group suffers from intractable OCD, with tremendous suffering and overall functional impairment.

**Depression**

Major depression is characterized by depressed mood, apathy, anhedonia, appetite and weight disturbance, sleep disruption, psychomotor abnormalities, fatigue, guilt, impaired concentration, and suicidal ideation and behavior [10]. Delusions, hallucinations, and catatonia are sometimes present. Depression is quite common; in the United States, conservative estimates place its prevalence at 2.6% to 5.5% in men and 6.0% to 11.8% in women [11]. The disorder tends to be familial, with the risk 1.5 to 3 times higher in individuals with an affected first-degree relative [10]. The average age of onset is the late 20s, but it may develop at any age. Approximately 50% to 85% of patients with major depression experience recurrent episodes of illness [12]. In addition to subjective distress, the disorder can be a cause of profound disability, with pervasively negative effects on marital, parental, social, vocational, and academic role function [13]. The recent Global Burden of Disease Study identified depression as the fourth leading cause of disability in the world and the leading cause of disability in adults [6]. Death from suicide is a major direct complication of the illness, but depression can also exacerbate the course of other psychiatric and medical conditions, with increases in both morbidity and mortality often reported.

More than 20 drugs are approved or commonly used to treat depression in the United States [14]. Efficacy for these agents is well established [15]. Available antidepressant drugs can be grouped into four major categories: tricyclics and tetracyclics, SSRIs, monoamine oxidase inhibitors (MAOIs), and other drugs acting on biogenic amine systems. Less severe forms of the illness can be treated effectively with certain forms of psychotherapy and light therapy [14]. Combinations of these various approaches are frequently employed in clinical practice, particularly in the management of complicated or refractory cases [16]. More severe forms of depression are often treated with electroconvulsive therapy (ECT), which has been in use for this indication for nearly 70 years and is still considered a gold standard of antidepressant treatment. ECT can be associated with significant adverse effects, however, most prominently memory loss. Moreover, ECT is often viewed by the lay public (and many nonpsychiatric physicians) as primitive, punitive, and potentially neurotoxic.

Despite the availability of effective treatments, a substantial proportion of patients fail to recover from episodes of depression. Fava and Davidson [17] estimated that 29% to 46% of depressed patients fail to respond fully to an antidepressant trial in which adequate dosing and duration have occurred. Using rigorous operational criteria, Little et al [18] observed an 18.9% rate of refractoriness in depressed geriatric patients treated in a university tertiary care setting.

**Current awareness of psychiatric neurosurgery**

Neurosurgical treatment for intractable psychiatric illness has gradually become more visible to the general public, in part because of recent attention paid by the media to the therapeutic potential of deep brain stimulation in psychiatry. Most psychiatrists, in contrast, have been aware that modern lesion procedures offered a last avenue of hope for patients with intractable OCD and depression for the last several decades. This awareness is based on past retrospective studies and, more recently, on a small number of prospective investigations. For example, a survey published in 1984 found that 78% of adult psychiatrists in the United Kingdom had referred patients for subcaudate tractotomy, mainly for refractory depression and OCD [19]. Later data indicate that referrals for psychiatric neurosurgery in Britain continued at roughly the same rate from 1979 to 1993, although the proportion of patients accepted for surgery was reduced from 50% to 60% to about 20% during that period. This decline resulted from the institution of high-dose medication trials as a screening criterion, and more patients responded to such trials before surgery [20].

A later survey of psychiatrists in the United States, published in 1999 [21], likewise showed widespread awareness of psychiatric neurosurgery and a willingness to consider it for selected patients. Eighty-three percent of a random sample
of American Psychiatric Association members replied that they knew about neurosurgical treatment for intractable OCD: 74% of psychiatrists in the same survey indicated that they would consider referring appropriate patients. So, despite the advances in conventional behavior therapy and medication treatments that had occurred by the end of the twentieth century, there remained a recognition that neurosurgery might be appropriate for a small group of patients with otherwise intractable illness. Anecdotal experience of one of us found a similar high degree of awareness of neurosurgery for intractable OCD recently. At a 2002 psychopharmacology review course, 85% of an audience of 124 psychiatrists responded that they knew of psychiatric neurosurgery for OCD. In this unsystematic sample, the majority (68%) indicated that they would consider referring patients with intractable illness (B. Greenberg, unpublished observations).

Importantly, acceptance for surgical treatment by the few centers with specialized teams of psychiatric and neurosurgical experts requires that patients meet rigorous entry criteria. Patients must be capable of fully informed consent. Careful multidisciplinary review is undertaken to establish accuracy of diagnoses and that the illness is treatment refractory. For OCD, this includes, in part, establishing that definitive medication trials and behavior therapy conducted by clinicians expert in treating refractory illness have failed to provide adequate benefit [22,23]. Similarly, a detailed review of the response to prior treatment trials, and the adequacy of those trials, is made for patients with intractable depression. There are important absolute and relative contraindications and procedural safeguards. Prospective data on potential adverse effects on cognition and personality are systematically collected before and for years after the procedures. These issues are discussed in more detail at the end of this article.

Awareness of current neurosurgical procedures among psychiatrists occurs against a background of advances in our understanding of the neuroanatomic bases of OCD and, increasingly, depression (see the article by Rauch in this issue) [24,25]. Recent US Food and Drug Administration (FDA) approvals of deep brain stimulation for treatment-refractory tremor and Parkinson disease and increasing therapeutic use of these techniques in other countries have also enhanced consideration of the potential of neurosurgery for intractable psychiatric illness. Still, neurosurgical treatment of patients with OCD, major affective illness, and other psychiatric conditions has a long and controversial past. In the midst of gradually emerging newer information and cautious optimism about the potential for newer procedures, the adverse consequences of psychiatric neurosurgery in the middle of the twentieth century remain in the minds of physicians, psychotherapists, patients, and society at large. The powerful social and scientific legacies of the past indiscriminate use of prefrontal lobotomy are considered at length in the article by Koppell and Rezai in this issue. Later in this issue, Fins considers ethical implications emerging from this history in light of present developments. That article, and an editorial statement by the OCD-DBS Collaborative Group [26] reprinted in this issue, focus especially on recommendations for future research in this area. To introduce some key issues here, a few features of the early experience and literature are briefly mentioned.

Some lessons of history

Reports of the deleterious sequelae of radical destructive operations have had a lasting impact. A negative perspective persists, overshadowing any benefits that accrued. Irreversible and sometimes devastating adverse effects were common after lobotomy. Nevertheless, a careful reading of that early literature also leads to the conclusion that some patients were helped by these procedures:

A woman, who for some thirty years had suffered from obsessive fear of contamination and who had scrubbed not only the toilet seat but the whole bathroom for an hour or so before using the toilet and then for an hour or more afterward in an effort to spare others from the danger of contamination... Following her operation, for a long period this woman manifested the same tendency toward compulsive cleaning of the bathroom before and after evaluation even though she admitted that she did not feel the same anxiety and fear of contaminating others that had previously been present. The compulsive activity gradually disappeared during the ensuing years. Freeman and Watts, 1950 [27].

This case vignette illustrates several important issues. One is that OCD, particularly when severe, is generally a chronic illness. Another point is that the first effect of the operation was a reduction in anxiety, even though compulsive behavior
continued. The response to treatment was usually slow, especially in severely affected individuals. In this example, the compulsive cleaning gradually abated over a period of years, despite the radical nature of that operation. For the much more focal lesion procedures used currently, the best evidence is also that maximal improvement takes months to years (see the article by Cosgrove et al in this issue) [28]. The reasons for this are poorly understood and likely multifactorial. Research on neurosurgical treatments for intractable OCD should take into account that the course of response is likely to be prolonged and may depend on the availability of, and adherence to, postsurgical behavior therapy.

Freeman and Watts depicted responses to lobotomy like that cited previously in terms of the dominant psychodynamic model of the day:

We have compared the emotion to the fixing agent that prevents a photographic image from fading back into obscurity. Remove the emotion and the image gradually fades. Prefrontal lobotomy bleaches the affect attached to the ego. Freeman and Watts, 1950 [27].

Although not intended by the authors, this understanding also hinted at the possibility that emotional blunting after neurosurgery could go well beyond a reduction in distress caused by OCD symptoms. In 1947, Rylander [29] gave a compelling glimpse of this and other adverse effects after the Freeman and Watts prefrontal lobotomy procedure. He studied changes in personality and cognition in great detail over time in a series of eight patients, in some cases, by having a patient join his own household. In one patient, a 28-year-old woman suffering from “anxiety periods, with compulsive and hysterical fits,” the resulting catastrophically diminished emotional capacity after lobotomy is vividly described by her mother:

She is my daughter but yet a different person. She is with me in body but her soul is in some way lost. Those deep feelings, those tendernesses, are gone. G. Rylander, 1947 [29].

It is because of such adverse effects that lobotomy was permanently abandoned. One of the crucial lessons of this history is that research on psychiatric neurosurgery must systematically assess patients for potential changes in personality, including emotional responsiveness and motivation.

Development of modern lesion procedures

Speigel and Wycis, who began stereotactic neurosurgery in patients, were the first to report that dorsomedial thalamotomies improved obsessive-compulsive symptoms. Their stereotactic procedure was much less radical than lobotomy but still dangerous. Because the lesioning electrodes were placed in a highly vascular structure without modern imaging guidance, hemorrhages were frequent and 10% of the patients died, mainly for this reason [30]. Later, during the 1950s and 1960s, several groups of neurosurgeons and psychiatrists, mainly in Europe, explored the therapeutic effects of selective lesions made under stereotactic guidance. The development of these techniques was informed at first not by specific empiric evidence but by the general ideas that frontosubcortical (and particularly frontothalamic) connections were important in higher brain function and that limbic networks modulate emotion [22,31–34].

The aim was to sever connections between subcortical structures and the frontal lobes. The procedures developed most successfully (Fig. 1) were subcaudate tractotomy, anterior capsulotomy, cingulotomy, and limbic leucotomy (a combination of subcaudate tractotomy and cingulotomy). Subcaudate tractotomy and anterior capsulotomy in particular interrupt connections of orbital and medial prefrontal cortex to the thalamus. The target of anterior cingulotomy, the most widely performed and recognized procedure in the United States, is within cingulate cortex itself.

All these operations remain in use for a small number of patients with intractable neuropsychiatric disorders. Their primary indications are intractable OCD and major depression. Effects of these procedures on a small number of patients with severe non-OCD anxiety disorders have also been reported. Although developed before the era of functional and modern structural neuroimaging, each of these techniques would be expected to affect activity within networks suggested by neuroimaging studies to be important in OCD and depression (see the article by Rauch in this issue).

What follows is a relatively brief description of these four procedures. The evidence of their safety and efficacy is presented in subsequent sections. The reader is referred to the article by Cosgrove and colleagues in this issue for recent perspectives based on their experience in Boston with anterior cingulotomy.
Subcaudate tractotomy

In this procedure, lesions intended to interrupt orbitofrontal-subcortical connections are made under the head of the caudate nucleus in the substantia innominata [35]. This approach was developed by Geoffrey Knight in the United Kingdom in 1964 as an attempt to limit adverse effects by restricting lesion size. Radioactive yttrium-90 seeds were placed at targets under the head of the caudate nucleus. A total lesion volume of approximately 4 mL resulted. In addition to intractable OCD and depression, subcaudate tractotomy has also been used for other severe anxiety disorders. More than 1300 of these operations were performed in the United Kingdom from the period of its first development until the early 1990s. There is a more recent report of a modified technique of subcaudate tractotomy [36].

Anterior capsulotomy

This procedure targets the fiber bundles in the anterior limb of the internal capsule connecting the frontal lobes and thalamus [37,38]. Talairach and co-workers were the first to make selective lesions there. Although therapeutic effects in schizophrenia were considered unsatisfactory, results in patients with severe anxiety were better. Capsulotomy was further developed and used in a large series of patients by Lars Leksell and colleagues at the Karolinska Institute in Sweden, starting in the 1950s. After craniotomy, thermocoagulation lesions were made bilaterally using bipolar electrodes placed in the anterior third of the capsule. This procedure is now called open capsulotomy or thermocapsulotomy, in contrast to the newer technique of gamma knife capsulotomy. The gamma knife procedure has been the focus of ongoing research in Providence, Rhode Island, over the past decade. The particular intent of gamma knife capsulotomy in the United States has been to target connections between dorsomedial thalamus and orbital and medial prefrontal cortex. In the United States, gamma knife anterior capsulotomy has been used almost exclusively for intractable OCD. As discussed later in this article, trials of deep brain stimulation at the capsulotomy target site for intractable OCD are underway.

Anterior cingulotomy

Originally conceived by Fulton as a treatment for psychiatric disorders, cingulotomy’s first use was actually for intractable pain. The procedure was later applied to psychiatric disorders when mood and anxiety symptoms were found to improve in pain patients. Whitty et al [39] first reported the effects of cingulotomy in OCD, followed by Kullberg [40] and his colleagues. It is the work of Ballantine and his colleagues at the Massachusetts General Hospital in Boston, however, that is responsible for cingulotomy being the best known and most widely used procedure for intractable psychiatric illness in North America. Beginning in 1962, this group demonstrated that anterior cingulotomy had a favorable safety profile. This investigative team has performed approximately 1000 cingulotomies, studying its efficacy for a range of psychiatric indications. Current
indications for anterior cingulotomy include intractable pain, depression, and OCD. The targets for this procedure are located in the anterior cingulate cortex (Brodmann areas 24 and 32) adjacent to the underlying fibers of the cingulum bundle. Under local anesthesia, thermocoagulation electrodes are used to make lesions on each side through bilateral burr holes. Initially, ventriculography was used to guide lesion placement. In 1991, this was replaced by MRI guidance. Two or three sets of bilateral lesions are made using radiofrequency electrodes (see the article by Cosgrove and Rauch in this issue). Because the intent is to produce the smallest effective lesion, the procedure is often done in stages. About 40% of patients return months later for a lesion-extending second operation to enhance efficacy. As currently practiced, the resulting total lesion volume is in the range of 4 to 6 mL [41].

Limbic leucotomy

Kelley and colleagues [42] developed this multtarget procedure in the 1970s, which, in essence, combines the bilateral lesions of cingulotomy with those of subcaudate tractotomy. The latter set of lesions may have a more anterior placement than is typical for subcaudate tractotomy, however. Interestingly, the effects of intraoperative electric stimulation have been used to identify the surgical target for this procedure. Lesions at sites where stimulation induced marked autonomic changes were believed to be the most effective [43]. Thermocoagulation or cryoprobes are used. Indications for limbic leucotomy have historically been intractable depression, OCD, and some other severe anxiety disorders. Recent evidence suggests that limbic leucotomy may also be of benefit to patients with severe repetitive self-injurious behaviors occurring in the setting of severe tic disorders [44].

Safety

The adverse effect profiles of the more focal surgical interventions of the past 40 years have been notably more benign than that of lobotomy. The major operative complications of the open neurosurgical approaches have included infection, hemorrhage, seizures, and weight gain. Such side effects have been relatively rare. The risk of postoperative epilepsy has been estimated at less than 1%. The risk of changes in cognitive function and personality after these procedures has been carefully studied. Using comprehensive batteries of measures taken after surgery, several independent groups of investigators have evaluated the effects of capsulotomy, cingulotomy, subcaudate tractotomy, and limbic leucotomy. Persistent deterioration of intellectual function has been relatively rare in patients with severe OCD and depression who underwent these procedures [23,45,46]. Moreover, in several instances, improved performance on cognitive measures has been documented, presumably as a result of symptomatic improvement.

Subcaudate tractotomy

Adverse effects

Postoperative side effects were reported to include headache, confusion, or somnolence, typically lasting 1 week at most, in a 1975 study of 208 patients who underwent subcaudate tractotomy, mainly for depression but including some OCD patients. Individuals were followed for a mean of 2.5 years. Transient disinhibition after surgery was described as common. Longer term adverse effects included mild untoward personality change in 6.7% of patients. Seizures were reported in 2.2%. One death occurred as a direct complication of surgery, resulting from migration of one of the yttrium seeds. Three of the 208 patients died by suicide during the follow-up period. A later review reported on 1300 patients who had subcaudate tractotomy up until 1993 [20]. Again, intractable depression was the most common diagnosis; a smaller number of patients had the surgery for intractable OCD. The rate of seizures was similar to that reported previously. In contrast, persistent adverse personality changes were not found. There were no deaths as a complication of surgery. Compared with a comparison group of patients with major affective disorders, the subcaudate tractotomy group showed a markedly lower suicide rate: 1% after surgery compared with 15% in patients with affective illness who were not treated surgically.

Anterior capsulotomy

Adverse effects

Adverse effects of open anterior capsulotomy in the initial series of 116 patients described by Leksell and colleagues [47] included postoperative headache, incontinence, or confusion. The duration of confusion, which frequently lasted as long as 1 week, influenced the length of the hospital stay.

In a later group of 24 patients with OCD followed prospectively, side effects of thermocapsulotomy included one intraoperative hemorrhage
without neurologic sequelae and 1 patient who developed seizures. There were transient episodes of confusion during the first week in 19 of 22 patients available for follow-up as well as occasional nocturnal incontinence. Fatigue was present in 7 patients (29%), 4 (17%) described poor memory, and 2 patients (8%) had “slovenliness.” One patient committed suicide in the postoperative phase, and 8 patients suffered from depression severe enough to require treatment. Excessive fatigue was a complaint in 7 patients, and 4 had poor memory. Weight gain was common after open capsulotomy, with an average increase of about 10% in patients in this sample [38].

In another report, no significant cognitive dysfunction or adverse personality changes were found on a psychometric test battery administered to a sample of 200 capsulotomy patients [46]. In contrast, a small study found perseverative responses to be more common after thermocapsulotomy in 5 patients with a severe, treatment-refractory, non-OCD anxiety disorder [48].

Differences in rates of adverse effects across studies seem due, at least partly, to differences in the volume of tissue lesioned, although this is not fully clear in published reports. The same seems to be true for procedure efficacy; that is, the effectiveness and the side effect burden of the open procedure both appeared to increase with greater lesion volume [41].

Most recently, the Providence group has found that gamma capsulotomy was generally well tolerated and effective for patients with otherwise intractable OCD. The lesions resulting from the gamma capsulotomy procedure are generally smaller than those produced by open thermocapsulotomy. Adverse events included transient cerebral edema and headache (in 6 of 31 patients [20%]), small asymptomatic caudate infarctions (3 of 31 patients [10%]), and possible exacerbation of preexisting bipolar mania (2 of 31 patients [6%]). No group decrements were observed on cognitive or personality testing. Nevertheless, 1 of 31 patients (3%) developed a persistent mild frontal lobe syndrome, including apathy and amotivation (S. Ramussen et al, manuscript in preparation).

**Anterior cingulotomy**

**Adverse effects**

In the Massachusetts General Hospital experience of approximately 1000 anterior cingulotomies, there have been no deaths from the surgical procedure itself [41]. The incidence of hemiplegia secondary to intraoperative hemorrhage in the era before image-guided surgery was estimated to be 0.03%. There has been only one stroke in the era of MRI-guided cingulotomy. Side effects in the immediate postoperative period include headache, nausea, and difficulty with urination, usually resolving within days. Seizure incidence has ranged from 1% to 5%. This effect was seen particularly in patients with a prior seizure history.

In the most recent series [28], 9 of 44 patients (20%) had at least one adverse effect after cingulotomy. In two cases, sequelae were enduring: seizures responsive to ongoing anticonvulsant treatment and worsening of preexisting urinary incontinence as a result of prostate cancer. Another patient developed edema and hydrocephalus requiring ventriculostomy. In addition, 2 patients reported worsened memory, and 1 patient described apathy and decreased energy. Those behavioral symptoms resolved within 1 year after surgery.

Although transient memory problems were reported by up to 5% of patients overall, an independent analysis concluded that no significant cognitive or behavioral impairments occurred in a series of 34 patients undergoing cingulotomy for intractable psychiatric illness. A later study of 57 additional patients reached the same conclusion. [41,49–51]. In fact, in these reports, patients are noted to exhibit improved cognitive function, perhaps because symptom reduction after cingulotomy facilitated test performance. One study [52] described subtle impairment of attention, however, and another [53] described mild alterations of intention and self-initiated action after cingulotomy for chronic pain. It has been speculated [28] that cingulotomy may be less likely to produce cognitive deficits in OCD or major depression because anterior cingulate dysfunction may already be intrinsic to those disorders.

In that series [28], one patient (2%) committed suicide approximately 6 years after cingulotomy. This patient’s OCD symptoms had improved after surgery. Before cingulotomy, the patient had a long history of severe depression, with more than 8 years of nearly continuous suicidal thinking and a prior suicide attempt.

**Limbic leucotomy**

**Adverse effects**

Kelly and his collaborators have described the effects of limbic leucotomy in several reports. In an initial prospective study of 66 patients, no
seizures and no deaths resulted from the procedure. Early postoperative side effects included headache, lethargy, apathy, and incontinence lasting from days to weeks. Postoperative confusion lasted for days at least; patients frequently remained hospitalized for more than 1 week for this reason. Patients were subsequently followed for an average of 16 months. One patient had severe memory impairment attributable to improper lesion placement. Twelve percent of patients had persistent lethargy in that series. IQ testing showed a slight improvement for this group after limbic leucotomy [54].

A recent report of 21 patients undergoing limbic leucotomy for OCD or depression at Massachusetts General Hospital [55] found the adverse effects noted in previous reports, including apathy, urinary incontinence, and memory impairment. These side effects were infrequent and transient.

**Effectiveness**

Reports on efficacy of current neurosurgical procedures for intractable psychiatric illness span a period of more than 40 years. Psychiatric and neurosurgical methods used have therefore varied over time. Several limitations result. Illness definitions were not necessarily consistent across sites or over time. Outcome measures have also differed. Furthermore, effective medication and cognitive-behavioral treatments only appeared after the earliest reports. Because it was later required that these be systematically tried before patients would be eligible for surgery, only the more recent studies have enrolled patients most similar to those who would be potential candidates for such procedures today. Furthermore, earlier reports of the effectiveness of these procedures were retrospective and typically described relatively small patient samples. More recent investigations of these treatments are prospective, with generally larger sample sizes.

Direct comparisons of any two procedures at the same center, for example, the study by Kullberg [40], are rare, and randomized controlled trials are nonexistent. One reason for this is that sham procedures involving craniotomy have generally been considered unethical. It is important in this regard that the newer procedures of gamma knife capsulotomy and deep brain stimulation lend themselves more easily to controlled trials.

**Subcaudate tractotomy**

*Effectiveness*

Depression has been the most common diagnosis for patients undergoing this procedure. In an early report, Strom-Olsen and Carlisle [56] described beneficial effects in depressed patients who underwent stereotactic subcaudate tractotomy.

A subsequent report from this group, in which structured interviews were used, described a 55% response rate in a total of 96 depressed patients operated on through 1973 and followed for 2.5 years on average [35]. More recently, in their review of the same group’s experience from 1979 to 1991, Hodgkiss et al [57] classified 34% of depressed patients as “recovered” or “well” and 32% as “improved” of a total 183 such patients who had undergone the surgery. Malizia [58] found similar rates of response.

OCD patients also reportedly benefit from subcaudate tractotomy. Strom-Olsen and Carlisle [56] reported that of 20 OCD patients, 10 were either fully recovered or with only slight residual symptoms 3 months after subcaudate tractotomy. Four of these patients subsequently relapsed over a 2-year follow-up period. Goktepe et al [35] subsequently described a response rate of 50% in a second sample of OCD patients after subcaudate tractotomy. A response rate of 62.5% in patients with severe non-OCD anxiety disorders was also noted in that sample. In contrast, efficacy was poor for patients diagnosed with schizophrenia, substance abuse, or personality disorders.

The most comprehensive review of responses to subcaudate tractotomy included 1300 cases. Published in 1994, it concluded that subcaudate tractotomy enabled 40% to 60% of patients to lead normal or near-normal lives [20]. As noted previously, compared with a suicide rate of 15% in patients with similar major affective disorders, 1% of patients committed suicide after subcaudate tractotomy. Those investigators suggested that several clinical features were predictors of positive response. These included (1) major depression, (2) an onset that is sudden or occurs in midlife or the peripartum period, (3) a positive family history, and (4) a prior response to ECT treatment.

**Anterior capsulotomy**

*Effectiveness*

Leksell’s group initially reported that half of those patients with obsessional neurosis and just less than half (48%) of depressed patients (of
a total sample of 116, which also included patients with schizophrenia and nonobsessional anxiety) had satisfactory outcomes. Although modern rating scales were not used, criteria for judging improvement were strict. Only patients who were free of symptoms or much improved were judged to be responders. Herner [47] reported that the obsessional patients in this series benefited most after capsulotomy. After follow-up ranging from 2 to 6 years, outcome was “good” or “fair” in 14 of 18 patients (78%) who underwent open capsulotomy in the 1950s. A study by Bingley et al [37] found that 25 of 35 patients (71%) were either symptom-free or much improved an average of 35 months after thermocapsulotomy. Twenty-four of these patients had been unable to work before surgery because of OCD symptoms; 20 resumed work after surgery.

Mindus and Jenike [59] retrospectively reviewed all cases of capsulotomy reported by the early 1990s. They judged that 64% of 213 patients for whom adequate information was available could be considered responders. Response could not be determined in 149 of the total of 362 patients, however, and it is not fully clear if the patients for whom response could be determined were representative of the entire sample.

A later prospective study of capsulotomy for intractable OCD found that 16 of 35 patients (46%) were judged symptom-free by independent psychiatrists and that 9 more were much improved, giving a response rate of 70% overall [60].

The effectiveness of lesion enlargement in OCD patients unresponsive to an initial thermocapsulotomy was addressed by Burzaco [61]. He reported that in 17 OCD patients of a total of 85 who did not respond to the first procedure, half were judged to have a satisfactory outcome after reoperation.

Preliminary findings from an ongoing study of anterior capsulotomy performed using the gamma knife also find evidence of efficacy (S.A. Rasmussen et al, manuscript in preparation). In the first series of 15 patients, single bilateral lesions in the anterior capsule lacked therapeutic effects. After placement of a second set of bilateral lesions, improvement began to occur in some patients. Using a conservative definition of therapeutic response, 4 of 15 patients had at least a 35% drop on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) plus a minimum 15-point improvement on the Global Assessment Scale on 5-year follow-up.

A subsequent group of 16 patients received two pairs of bilateral lesions during one session. At the 3-year follow-up, 10 of 16 (62%) met this response criterion. Anecdotally, after surgery, adherence to and success of behavioral therapy seemed much enhanced in responders. Overall, improvement, judged by conservative criteria, was faster and occurred in more patients after the one-stage, double, bilateral gamma capsulotomy procedure. The therapeutic response, once achieved, was generally stable.

**Anterior cingulotomy**

**Effectiveness**

Whitty and colleagues [39] were the first to report the effects of cingulotomy in OCD. Four of the initial sample of five patients showed significant improvement in symptoms and function. Later, Kullberg [40] reported that 4 of 13 (31%) OCD patients improved significantly after cingulotomy. In a larger sample, Ballantine and colleagues [62] reported marked improvement in 17 of 32 (35%) obsessional patients after cingulotomy. Of those, 8 were almost symptom-free and 9 others had marked symptom reduction. Including these individuals and other patients judged to have significant but less marked benefit, a total of 56% of OCD patients noted significant improvement an average of 8.6 years after the procedure [62]. A later study using more current methods of diagnosis and severity assessment was reported by Jenike and colleagues [63]. They retrospectively evaluated 33 patients meeting criteria for OCD who had undergone cingulotomy at the Massachusetts General Hospital over a 25-year period. Using the Y-BOCS and the Clinical Global Improvement Scale, the authors estimated that 25% to 30% of the patients benefited substantially from the operation. In a subsequent prospective study of 18 severely ill treatment-refractory OCD patients, they found that 5 of 18 (28%) met conservative criteria for being much or very much improved. Three of the 18 patients had lesser but still notable benefit, giving an overall rate of significant improvement of 44% [63].

In the most recent prospective study, 44 OCD patients were studied using current methodologies, including rigorous screening and review. Empirically validated symptom and quality of life assessments were used. Thus, the diagnosis was certain to be intractable OCD (ie, severe OCD refractory to adequate trials of available treatments). At a mean of 32 months after one or more cingulotomies, 14 patients (32%) met conservative criteria for treatment response and 6 others (14%)
were partial responders. Thus, 20 patients (45%) were at least partial responders at long-term follow-up after one or more cingulotomies [28].

For depression, Ballantine et al [62] reported that of 118 depressed patients treated with stereotactic cingulotomy, 42% were “recovered” or “well” and 24% were “improved.” A later review of 34 patients who underwent cingulotomy in the era of MRI guidance found that 60% of patients with unipolar depression had favorable responses.

**Limbic Leucotomy Effectiveness**

An initial report from Mitchell-Heggs and colleagues [54] described 89% of 27 OCD patients as improved at a postoperative follow-up of 16 months. Bartlett and Bridges [64] later disputed these results, noting that patients with significant residual symptoms were included in the 89% improvement rate. Kelly [65] then extended his group’s original findings and reported on 49 patients, including the group of 27 described in the original report by Mitchell-Heggs et al [54]. He found that 84% of the patients were improved at a mean follow-up of 20 months [65].

In their initial report, Mitchell-Heggs et al [54] also described a 78% response in patients with major depression. The sample sizes were relatively small, however, and the patients were less well characterized than in some studies.

Using modern diagnostic and symptom assessment procedures, Montoya and colleagues [55] found positive responses (conservatively defined) in 36 or 50% of 21 patients who underwent limbic leucotomy for OCD or depression at the Massachusetts General Hospital after a mean follow-up of 26 months.

Price and colleagues [44] recently reported beneficial responses to limbic leucotomy in five patients with otherwise intractable severe repetitive self-mutilation occurring in the setting of tic-like behaviors.

**Summary**

Intractable OCD and depression cause tremendous suffering in those affected and in their families. The impaired ability to function of those affected imposes a heavy burden on society as a whole.

Existing data suggest that lesion procedures offer benefit to a large proportion (ranging from about 35%–70%) of patients with intractable OCD and depression. The literature also suggests that although serious long-term adverse events have occurred, these are relatively infrequent overall. Methodologic limitations of the earlier reports on any of these procedures were described previously in this article. The major academic centers conducting this work have since been obtaining systematic prospective data using modern assessment tools. Nevertheless, even with improved methodologies, more recent studies confront some remaining issues that have been difficult to overcome fully.

First, the number of patients who have received any one procedure has been relatively small, constraining statistical power. This limits the ability of researchers to enhance patient selection based on clinical characteristics. This is important, because patients with intractable OCD and depression referred for neurosurgery have high rates of comorbid Axis I diagnoses, personality disorders, and functional impairments, which may have value in predicting response. Other features, such as age of onset, chronicity, and symptom subtypes, may be likewise useful. Another key factor in response may be postoperative management, which has varied most over time but also across patients enrolled in trials. As noted previously, randomized controlled trials of neurosurgical treatment for intractable psychiatric illness have not been reported, although one has been proposed for gamma knife capsulotomy in intractable OCD [23]. The development of deep brain stimulation has also made sham-controlled studies possible and also allows within-patient designs to be considered.

Bearing these problems in mind, the literature does provide important guidance on a number of key points, including approaches to referral, patient selection, and the need for long-term prospective follow-up and postoperative management. Nevertheless, important gaps in knowledge remain in all these areas. Research is expected to narrow these gaps in a number of ways, including patient selection, optimizing the procedures themselves, and understanding the mechanisms of therapeutic action. Neuroimaging studies will play a key role in achieving these aims (see the article by Rauch in this issue). So will cross-species translational research on the anatomy and physiology of the pathways implicated in the pathophysiology and response to treatment in these disorders.

Future research in psychiatric neurosurgery must proceed cautiously. A recent editorial
statement of the OCD-DBS Collaborative Group [26] recommends a minimum set of standards for any multidisciplinary teams contemplating work in this domain. The rationale for those standards is found throughout this issue and is especially developed in the article by Fins. The need for safe and effective therapeutic options for people suffering with these severe illnesses is just as clear. The experience over the last several decades provides grounds for careful optimism that refined lesion procedures or reversible deep brain stimulation may relieve suffering and improve the lives of people with these devastating disorders.

References


Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders

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Contemporary neuroimaging methods have been influential in advancing neurobiologic models of psychiatric disorders. Providing means for measuring indices of human brain structure and function in vivo, these tools enable investigators to test hypotheses about pathophysiology, the changes associated with treatment, and predictors of treatment response [1]. In general, it is anticipated that neuroimaging research will substantially contribute to the ultimate achievement of a pathophysiology-based diagnostic scheme in psychiatry and also help to elucidate the mechanisms of action by which treatments have their effects. Moreover, as the neuroscience of psychiatry evolves, it should be possible to rationally develop new and superior treatments as well as to predict treatment outcomes in a manner that could optimally guide selection among alternative treatments for individual patients in the clinical setting.

As reviewed in this issue, a variety of neurosurgical treatments have been developed in an effort to help people suffering from severe and otherwise treatment-refractory psychiatric disorders—principally obsessive-compulsive disorder (OCD) or major depression (MD). To date, clinical reports suggest that the effectiveness of contemporary neurosurgical treatment for these indications is only modest, whereas the potential for adverse effects is still considerable. Thus, it would be of great value to find ways to improve outcome. One goal is to refine neurosurgical treatments for OCD and MD so that they are safer and more effective; another goal is to identify selection criteria, based on predictors of response, that would enable patients who are unlikely to have good outcomes forego the risks and costs of neurosurgical treatment.

In fact, despite a resurgence of interest and accelerated research in this field, little is known regarding the mechanisms by which neurosurgical treatments for OCD and MD have their beneficial effects. Given recent advances in neuroimaging and neurocircuitry models of these disorders, however, the time seems ripe for a fruitful synthesis of psychiatric neuroimaging and neurosurgical data. I would propose that there is great opportunity for synergy at this interface: neuroimaging and neurocircuitry models of disease can help to guide practical progress in the domain of neurosurgical treatment, and, reciprocally, data from neurosurgical treatment research can provide feedback to inform evolving models of psychiatric disease.

Toward that end, in the current article, I describe neurocircuitry models of OCD and MD, focusing on relevant neuroimaging data. I then review the neuroanatomy of psychiatric neurosurgical procedures and related neuroimaging findings. Finally, I present anticipated future directions of research in this field. This article necessarily extends previous reviews that I have written, together with my colleagues, on related topics [2–6].

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Neuroimaging and neurocircuitry models of obsessive compulsive disorder

Neurocircuitry model of obsessive-compulsive disorder and related disorders

Contemporary neurobiologic models of OCD and related disorders have focused on cortico-striato-thalamo-cortical (CSTC) circuitry. In fact, the influential reviews by Alexander and colleagues [7,8] describing segregated parallel CSTC circuits provided an important framework for subsequent theories of pathophysiology in OCD. Specifically, it has been proposed that the CSTC circuits involving orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and the caudate nucleus are central to the pathophysiology of OCD [6,9]. Further, there is a convergence of evidence to suggest that some primary pathologic process within the striatum might underlie the CSTC dysfunction in OCD. The prevailing theory suggests that a relative imbalance favoring the direct versus indirect pathways within this circuitry lead to overactivity (ie, amplification) within OFC and ACC, the caudate nucleus, and the thalamus resonant with failed striato-thalamic inhibition (ie, filtration) within this same circuitry.

This basic scheme has been extended to provide a comprehensive model for a group of purportedly related disorders called “obsessive compulsive spectrum disorders,” encompassing Tourette syndrome (TS), trichotillomania, and body dysmorphic disorder as well as OCD. The “striatal topography model” of OC spectrum disorders suggests that these diseases share the attribute of CSTC dysfunction due to primary striatal pathology and that the clinical picture in each case reflects the topography of pathology within the striatum and hence the constellation of dysfunction across CSTC circuits [6,10]. To elaborate, the notion is that OCD and body dysmorphic disorder, the OC spectrum disorders characterized by intrusive cognitive and visuospatial symptoms, involve caudate pathology, whereas TS and trichotillomania, principally characterized by intrusive sensorimotor symptoms, involve pathology within the putamen and dysfunction of sensorimotor CSTC circuitry.

Most recently, pioneering neuroanatomic research by Haber and colleagues [11] has provided a scheme for considering CSTC function that emphasizes a cascading spiral interaction, rather than segregation, across CSTC circuits. This model of normal CSTC function suggests a flow of information from motivation to cognition to motor behavior. This raises the possibility that OCD (as well as other OC spectrum disorders) might not reflect dysfunction within a single segregated CSTC circuit but rather represent a failure in the smooth cascade of information across the various CSTC circuits. For instance, in the case of OCD, cognitions and motivations to act seem to persist (as obsessions with attendant anxiety, respectively) such that motor output fails to reset these thoughts and motivations, hence driving stereotyped motor repetition (compulsions).

It is evident that neurobiologic models of OCD and related disorders have evolved in parallel with our understanding of the relevant basic neuroscience as well as with accrual of data from patient studies. In this regard, it is useful to review the findings of pertinent psychiatric neuroimaging research.

Neuroimaging studies of obsessive-compulsive disorder

There is now an impressive array of different neuroimaging techniques that can be used in a complementary fashion to advance psychiatric neuroscience. Here, I systematically review how these various methods have been employed to develop a cohesive neurobiologic model of OCD.

Morphometric MRI studies have been performed to test hypotheses regarding regional brain volumes in OCD. In adults with OCD versus healthy comparison subjects, findings of subtle volumetric abnormalities involving the striatum have predominated [12–14]. Moreover, whereas the caudate has been principally implicated in OCD, consistent with the striatal topography model of OC spectrum disorders, studies of TS [15,16] and trichotillomania [17] have principally implicated the putamen or lenticulate, although an initial study of body dysmorphic disorder has also found a subtle abnormality involving the caudate [18].

Such morphometric methods have only modest sensitivity, and some studies have failed to find striatal abnormalities in OCD [19]. Magnetic resonance spectroscopy (MRS) provides a means for measuring the relative concentration of certain endogenous chemical compounds in vivo. In particular, N-acetyl aspartate (NAA) is an MRS-visible compound thought to serve as a marker for healthy neuronal density. Thus, reduced levels of NAA can be detected as...
a possibly more sensitive indication of regional neuronal degeneration or maldevelopment characterized by lower neuronal density or sparse arborization. Interestingly, a series of MRS studies of OCD have found reduced striatal NAA [20,21] but normal NAA levels within the lenticulate [22]. These findings converge well with morphometric MRI results and are also consistent with neuroimmunologic research, which indicates that some cases of OCD and related disorders can occur as a consequence of autoimmune-mediated striatal degeneration [23].

There have been several isolated reports of regional volumetric abnormalities beyond the striatum in OCD. In adults, these have included gross increases in white matter volume [12,24] and reduced volumes of OFC and amygdala [25]; in children, these have included abnormal thalamic and putamen volumes [26,27]. Similarly, a single report of reduced NAA within the ACC in OCD has been published [21].

Functional neuroimaging studies of OCD have likewise produced convergent results implicating OFC, ACC, and the caudate. Neutral state (including nominal resting state) studies have been performed to test hypotheses regarding baseline differences in regional brain activity between patients with OCD and healthy comparison subjects. Across numerous such studies, the most consistent findings in OCD have been relative hyperactivity of OFC, ACC, and, to a lesser extent, the caudate nucleus [28–30].

Symptom provocation methods have been used in conjunction with functional imaging to test hypotheses regarding the brain regions that exhibit changes in activity level in association with OCD patients experiencing obsessions and the urge to perform compulsions. Again, several studies have yielded convergent findings that most consistently indicate increases in activity within OFC, ACC, and the caudate nucleus during the OCD symptomatic state versus a control state [31–34]. Given that such studies are confounded by nonspecific anxiety, it has been instructive to contrast the brain activity pattern associated with OCD symptoms with the patterns reported for other anxiety disorders. In this context, symptom provocation studies of other anxiety disorders, such as posttraumatic stress disorder and specific phobias [35,36], have frequently found activation of ACC and other anterior paralimbic regions, whereas the recruitment of the caudate nucleus and anterolateral OFC seems to be somewhat more specific to the symptomatic state in OCD. Moreover, pharmacologic induction of anxiety attacks in healthy subjects has likewise been associated with increased activity within anterior paralimbic regions but not in anterolateral OFC or the caudate nucleus [37].

Pre- and posttreatment neuroimaging studies are conducted to test hypotheses regarding changes in brain activity profiles associated with successful reduction in symptoms. Several such studies have been performed to investigate the neural correlates of OCD symptom reduction after treatment with serotonergic reuptake inhibitors as well as behavior therapies. A series of studies have demonstrated a reduction of activity within OFC, ACC, and the caudate nucleus after successful treatment of OCD [38–41]. Further, in one of these studies, an interregional correlation analysis indicated that at the pretreatment time point, there was an abnormal positive correlation between right OFC and the right caudate, which was neutralized after successful treatment [40].

Pretreatment neuroimaging data can also be used to test hypotheses regarding predictors of treatment response. A series of studies of this type in OCD have indicated that pretreatment activity within OFC predicts subsequent treatment response [41–44]. To elaborate, in patients with OCD, higher levels of OFC hyperactivity were associated with poorer subsequent responses to treatment with serotonergic reuptake inhibitors [41–44]. Interestingly, in contrast, higher levels of OFC hyperactivity were associated with better subsequent responses to treatment with behavior therapy [42]. These findings are consistent with the idea that serotonergic reuptake inhibitors might have their antiobsessional effects via their action within OFC [45] and that behavioral therapy may have its beneficial antiobsessional effects via extinction mediated by frontoamygdala interactions [6].

Cognitive activation studies have been performed in conjunction with functional neuroimaging methods to test hypotheses regarding the functional integrity of striato-thalamic circuitry in the context of an implicit sequence learning task. Implicit (ie, nonconscious, automatic) sequence learning is known to be normally mediated by CSTC circuitry, and this function may be right-lateralized to some extent [46–48]. Interestingly, however, when patients with OCD were studied while performing such a task, although they exhibited a capacity to learn the sequence information that was comparable to normal subjects, they failed to recruit the right striatum in a normal
fashion [49,50]. Moreover, OCD subjects showed aberrant bilateral medial temporal activation (not seen in normal subjects during implicit sequence learning) in a manner similar to that evidenced when normal subjects are learning information consciously [49–51]. These findings in OCD have been replicated and seem to indicate that patients with OCD are deficient at recruiting the striatum in the service of thalamic gating [49,50,52]. This may explain why patients with OCD have intrusions of information into consciousness that might otherwise be processed nonconsciously by individuals without OCD.

Taken together, neuroimaging studies of OCD support a cohesive model. There is hyperactivity at rest within the OFC-caudate CSTC circuit, which is exaggerated during symptom provocation and attenuated after successful treatment. A similar profile is present within ACC, although this seems to be a more nonspecific finding across anxiety states. Of clinical relevance, activity within OFC predicts subsequent response to treatment with medication or behavior therapy. Further, MRI and MRS studies suggest striatal pathology, which is consistent with cognitive activation studies that indicate deficits in striatal recruitment and thalamic gating as well as possible compensation via hippocampal activation.

Of note, patients with OCD plus comorbid MD exhibit a profile that differs from that of patients with OCD alone [53]. This is particularly germane to the focus of this review, because most patients with severe treatment-refractory OCD who receive neurosurgical treatment also suffer from comorbid MD. Resting state neuroimaging data suggest that patients with OCD plus MD have lower metabolism within the caudate, thalamus, and hippocampus than patients with OCD alone [53]. Further, functional imaging data from before and after treatment with paroxetine suggest that patients with OCD plus MD exhibit increased activity within the striatum after successful treatment, whereas patients with OCD alone exhibit decreased activity within the striatum after treatment [54].

Neuroimaging and neurocircuitry models of major depression

Neurocircuitry model of major depression

Similar to OCD, neuroimaging-motivated neurobiologic models of MD have also involved CSTC circuitry. In addition to the limbic CSTC circuit, prevailing models of MD have focused on other critical elements of the limbic system, namely, the amygdala and hippocampus as well as the hypothalamic-pituitary-adrenal (HPA) axis [2,55–61]. In general, it is useful to consider the clinical characteristics of MD as they relate to different functional domains, which, in turn, map onto a corresponding functional anatomy [57]. MD episodes (both in unipolar MD and bipolar disorder) are characterized by cognitive, motor, and neuroendocrinologic as well as affective disturbances. At the cortical level, the cognitive and motor deficits of MD may be explained by dysfunction within a “dorsal compartment,” including anterior, dorsal and lateral prefrontal cortex; dorsal ACC; and parietal cortex as well as premotor cortex. The affective symptoms of MD may be related to dysfunction within a paralimbic “ventral compartment,” including subgenual ACC, OFC, and anterior insular cortex. These dorsal and ventral compartments communicate with their striatal counterparts; the dorsal compartment is linked to the dorsal (cognitive/motor) striatum, and the ventral compartment is linked to the ventral (limbic) striatum. Interestingly, the dorsal and ventral compartments seem to be reciprocally inhibitory [36,62–64]. Thus, in MD, grossly, there appears to be hypoactivity within the dorsal compartment and hyperactivity within the ventral compartment.

Importantly, a triad of areas seem to play a critical role in mediating the balance of activity between the ventral and dorsal compartments both in health and disease. The amygdala is positioned to assess the reward and threat value of external stimuli and has the capacity to drive the balance of activity toward the ventral compartment. The pregenual ACC has the capacity to facilitate the restoration of dynamic equilibrium between the compartments via its inhibitory influence over both dorsal and ventral elements [36,62–64]. Finally, the hippocampus, in addition to its role in cognition, has reciprocal connections with the amygdala and projects to the hypothalamus to influence the HPA axis as well as other functions that are disturbed in depression, such as sleep and appetite. Therefore, it is proposed that amygdala hyperactivity and hippocampal inefficacy may be central to the pathophysiology of MD. Of note, it has been proposed that exposure to stress during early development or chronically could represent a risk factor for the evolution of such a profile [65]. Thus, successful treatment of MD (via any of a number of modalities) may
Neuroimaging studies of major depression

In comparison to OCD, the neuroimaging literature on MD is more abundant and more difficult to interpret parsimoniously. The complexity of this area has been exacerbated by clinical heterogeneity; MD studies have included mixed cohorts as well as more homogeneous cohorts of patients with unipolar MD and bipolar MD as well as MD in the elderly and in the context of primary neurologic disorders. In addition, early disparities in how various neuroanatomic terms were applied contributed to confusion over how apparently discrepant findings could be reconciled. Most recently, careful neuroanatomic studies along with functional neuroimaging studies, including those investigating mood states in normal subjects and studies of changes associated with various antidepressant treatments, have begun to yield a more cohesive picture of MD pathophysiology and its resolution.

Structural neuroimaging studies of MD using morphometric MRI segmentation methods have shown reduced volumes of the hippocampus [60,66–71] and the striatum [72,73]. Of note, findings within the striatum have been less consistent [74,75], and studies that segmented the hippocampus and amygdala conjointly have often been negative [76]. MRI studies have also found reduced volumes in prefrontal cortex [73,77], and cortical parcellation methods have been applied to discover reduced volume in subgenual cortex [56,78] and OFC [79]. These structural imaging findings resonate with postmortem studies of MD, which have revealed glial cell loss in subgenual cortex [80] as well as reduced glia and smaller neurons within OFC [81] and cell atrophy within dorsolateral prefrontal cortex [82].

Neutral state functional imaging studies have demonstrated hyperactivity within OFC and anterior insular cortex during MD episodes [83–87]. Although initial studies of MD indicated reduced activity within subgenual cortex [56,88], subsequent correction for reduced volume in that area has revealed relative hyperactivity [56]. Further, these same areas seem to exhibit elevated activity during induced states of transient sadness [59,89] and reduction of hyperactivity in the context of successful antidepressant treatment [59,86,88,90]. Of note, however, activity within OFC seems to be inversely correlated with MD symptom severity (as well as with anxiety in some cases), suggesting that this region may be recruited in a compensatory fashion [34,55,86].

Elements of the dorsal compartment, including anterior and dorsolateral prefrontal cortex as well as dorsal ACC, have been found to exhibit reduced activity during MD episodes [91]. Likewise, reduction in activity within the dorsal compartment has been observed during transient induction of sad mood [59]. Conversely, hypoactivity in these regions returns toward normal after successful antidepressant treatment of patients with MD [59,92]. Moreover, cognitive activation studies have indicated an attenuated capacity for patients with MD to recruit dorsal ACC successfully [93].

The amygdala has been found to be hyperactive in neutral state studies of patients with MD [86,94], and there is some suggestion that this finding might be left-lateralized [86]. The severity of MD symptoms is correlated with amygdala activity [86]. Although hyperactivity within this region is attenuated with successful treatment, some residual hyperactivity may persist even during extended remission of MD [86]. Functional imaging studies using pictures of human faces displaying various emotional expressions have provided a means for assessing amygdala responsivity to social cues of varying arousal value and valence [95,96]. Further, by presenting such face stimuli beneath the level of conscious awareness, it has been possible to probe automatic aspects of such amygdala responses relatively dissociated from the top-down influences of frontal cortex [97]. Using this approach in conjunction with functional MRI, it has been found that patients with posttraumatic stress disorder exhibit exaggerated responsivity within the right amygdala to threat-related stimuli [98]. Interestingly, a subsequent analogous study of patients with MD revealed exaggerated amygdala responses within the left amygdala; moreover, the exaggerated response in the left amygdala was attenuated toward normal after successful treatment with antidepressant medication [99]. Importantly, recent functional imaging studies of healthy subjects seem to suggest that the right amygdala may be more temporally dynamic in its response, exhibiting prompt habituation effects, whereas the left amygdala seems to exhibit a more temporally stable response that is highly valence dependent.
This provides a framework for understanding lateralized differences in amygdala function across mood and anxiety disorders. To elaborate, the prevailing negative bias that is characteristic of MD could be associated with left amygdala dysfunction, and the exaggerated response and failure to habituate to threat-related stimuli that is characteristic of selected anxiety disorders could be associated with right amygdala dysfunction [101]. This could also help to explain the high comorbidity that is observed across mood and anxiety disorders, given that various etiologies of amygdala dysfunction might be agnostic to the laterality of pathology.

Although studies of MD have repeatedly noted volumetric reductions in the hippocampus, resting state functional neuroimaging studies have rarely found hypoactivity in this region [53,102]. Rather, during the course of a successful trial of antidepressant medication, MD patients seemed to exhibit increased activity within the hippocampus at week 1 and subsequent decreases in hippocampal activity by week 6 [58]. Likewise, although resting state functional imaging studies of MD have not typically indicated baseline abnormalities in pregenual ACC, pretreatment levels of activity within this area have been found to predict subsequent response to antidepressant medication [103]. Specifically, individuals with higher levels of pregenual ACC activity before treatment exhibited a superior antidepressant treatment response.

Anatomy and imaging of neurosurgical treatments for major depression and obsessive-compulsive disorder

As outlined in detail throughout this issue, ablative neurosurgical treatments for OCD and MD include anterior cingulotomy, subcaudate tractotomy, limbic leukotomy, and anterior capsulotomy. In fact, the neuroanatomic ramifications of these ablative procedures remain incompletely understood.

In the case of anterior cingulotomy, the lesions are placed within dorsal ACC and typically impinge on the cingulum bundle [104]. Thus, in addition to reducing cortical mass and activity within dorsal ACC, it is likely that these lesions modify cingulo-striatal projections and disinhibit pregenual ACC. Given the composition of the cingulum bundle, it is also possible that its disruption in cingulotomy could influence reciprocal connections between the ACC and several other structures, including OFC, the amygdala, the hippocampus, or posterior cingulate cortex [105]. In fact, comparisons of presurgical with postsurgical MRI data indicate that volume may be reduced within the caudate nucleus and posterior cingulate cortex by 6 to 12 months after anterior cingulotomy [104,106]. Given the prevailing neurocircuitry model of OCD, these are all potential sites of therapeutic action. Of note, posterior cingulate cortex is well positioned to modulate activity within the OFC-caudate CSTC circuit [107–110]. Interestingly, a recent functional neuroimaging study of OCD demonstrated that presurgical activity within posterior cingulate cortex correlated with subsequent response after anterior cingulotomy [111]. Given the prevailing neurocircuitry model of MD, it might be more appealing to consider that lesions of dorsal ACC might produce disinhibition of pregenual ACC, which, in turn, might render patients more responsive to antidepressant pharmacotherapy after surgery. Alternatively, lesions of the cingulum might interrupt ascending influences of the amygdala on the dorsal compartment.

In the case of subcaudate tractotomy as well as bilateral orbitomedial leukotomy, the lesions are purportedly placed so as to interrupt fibers of passage connecting OFC and subgenual ACC to the thalamus. For orbitomedial leukotomy, the lesions might also disrupt amygdalofugal fibers to OFC and subgenual ACC [112]. In OCD, interruption of reciprocal projections between OFC and the thalamus would theoretically decrease reverberating (amplified) activity in the OFC-caudate CSTC, leading to reduced OCD symptoms. Likewise, in MD, reducing activity within the ventral compartment, such as directly lesioning subgenual ACC or OFC, would be hypothesized to reduce symptoms. A single case study of bilateral orbitomedial leukotomy has demonstrated reduced activity within OFC, ACC, the caudate, and the thalamus in a woman with OCD when comparing postsurgical with presurgical regional cerebral metabolism [113]. Such findings are confounded by symptomatic improvement of OCD, however, which characteristically yields this profile of attenuated hyperactivity throughout the circuit.

In the case of limbic leukotomy, lesions similar to those of anterior cingulotomy and subcaudate tractotomy are combined. Hence, this multisite operation would presumably combine the benefits (as well as the potential adverse effects) of the two
aforementioned procedures. A single case study of limbic leukotomy has demonstrated reduced activity within the caudate nuclei in a patient with OCD and TS when comparing postsurgical with presurgical regional cerebral oxygen metabolism [114]. Clinically, the patient exhibited improvement in both OCD and TS symptoms after limbic leukotomy.

In the case of anterior capsulotomy, lesions of the ventral portion of the anterior limb of the anterior capsule are likewise purported to interrupt OFC/subgenual ACC–thalamic connections. Moreover, the placement of these lesions may also compromise adjacent territories of the striatum. This can occur if the lesions interrupt fronto-striatal projections, if the lesions themselves impinge on the striatum, or if infiltration of edema surrounding the lesions encroaches on the striatum itself or on fronto-striatal projections. Again, for OCD, disruption of pathologic CSTC circuitry at the level of OFC-caudate or reciprocal OFC-thalamic communications could underlie the therapeutic effects of anterior capsulotomy. For MD, deactivation of subgenual ACC or disruption of interconnections among the elements of the ventral compartment is a plausible mode of therapeutic action for anterior capsulotomy. Interestingly, an MRI study of anterior capsulotomy for OCD and other anxiety disorders indicated that appropriate placement of lesions within the right anterior capsule was critical to subsequent therapeutic response [115]. Furthermore, functional imaging data from a small cohort of patients with severe anxiety disorders undergoing anterior capsulotomy demonstrated reductions in activity within orbitomedial frontal cortex from presurgical to postsurgical scans [116].

Summary and future directions

Neuroimaging research has helped to provide a progressively sound basis for constructing neurocircuitry models of OCD and MD. Still, our understanding of the pathophysiologic underpinnings of these disorders remains only tentative. Similarly, current knowledge regarding the neurobiologic consequences of contemporary psychiatric neurosurgical procedures is quite limited. Although extrapolation from nonhuman primate data can be informative, obtaining additional data from human subjects is essential to understanding the mechanisms by which psychiatric neurosurgery has its effects. Furthermore, advancing science in this domain is essential to optimizing neurosurgical treatment for psychiatric disorders in the future. It is foreseeable that progress in this area could lead to the identification of superior targets for ablative procedures, more effective selection of appropriate surgical candidates, and/or individualized interventions (eg, whereby targets are individually determined for each patient).

With the advent of deep brain stimulation, there are now opportunities to more flexibly (and reversibly) modulate activity within neural circuits of interest [117]. This promises the potential to advance our understanding of OCD and MD pathophysiology while systematically progressing toward improved neurosurgical treatments for the most severe and treatment-refractory forms of these diseases. Controlled treatment trials in this area should include a parallel neuroimaging component to maximize the clinical and scientific benefits derived from these efforts.

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Stereotactic cingulotomy

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Since its introduction in 1936, surgery for psychiatric illness has had a long and controversial history for various scientific, moral, and ethical reasons. Many different neurosurgical procedures have been performed on a variety of cortical and subcortical targets. Initially, Moniz [1] performed prefrontal leukotomies by injection of absolute alcohol into the frontal lobes and reported “worthwhile” improvement in 14 of 20 patients. Moniz [2] later described his experience with larger numbers of patients after more specific and restricted frontal lobe lesions were created using a leukotome. Freeman and Watts [3] subsequently described their prefrontal lobotomy, which was performed with a specially designed calibrated instrument that was inserted blindly to the midline and swept back and forth to interrupt surgically the white matter tracts in the frontal lobes. The authors noted that to achieve the best results, the lesion had to involve the medial frontal lobes and, by definition, the cingulate gyri.

These early operations were associated with significant mortality and morbidity. Tooth and Newton [4] reviewed 10,365 standard prefrontal lobotomy operations performed between 1943 and 1954 and confirmed that the rate of “improvement” was approximately 70% but also reported a 6% mortality, 1% epilepsy rate, and 1.5% marked disinhibition. These complications underscored the need for a less radical and more specific approach to the surgery.

Fulton [5] was the first to suggest that the anterior cingulum would be an appropriate target for psychosurgical intervention, and cingulotomy was initially carried out as an open procedure [6,7]. Foltz and White [8] reported their experience with stereotactic cingulotomy for intractable pain and noted that the best results were in those patients with concurrent anxiety-depressive states. Ballantine and Giriunas [9] subsequently demonstrated the safety and efficacy of cingulotomy in a large number of patients with psychiatric illness, and it has been the surgical procedure of choice in North America over the last 30 years.

Currently, the accepted therapeutic approach to most psychiatric disease involves a combination of well-supervised pharmacologic, behavioral, and, in some instances, electroconvulsive therapies. Not all patients respond to these modern treatment methods, however, and many remain severely disabled. Some of these patients might be considered appropriate candidates for surgical intervention if the therapeutic result and overall level of functioning could be improved.

In this article, we explore the anatomic and physiologic basis for cingulotomy and the indications for surgery. Guidelines for the appropriate selection of surgical candidates are presented along with details of the operative technique. Finally, the results and complications of cingulotomy are reviewed and compared with those of other common psychosurgical procedures.

Anatomic and physiologic rationale for cingulotomy

In 1937, the same year that Moniz [1] reported his initial experience with prefrontal lobotomy, Papez [10] postulated that a reverberating circuit in the human brain might be responsible for emotion, anxiety, and memory. The components of this rudimentary limbic system included the...
hypothalamus, septal nuclei, hippocampi, mamil- 
ary bodies, anterior thalamic nuclei, cingulate 
gyri, and their interconnections. It was sub-
to incorporate paralimbic structures, including 
orbital frontal, insular, and anterior temporal 
cortices; the amygdala; and dorsomedial thalamic 
nuclei.

Although the exact mechanisms are unknown, 
there is mounting evidence that the limbic system, 
including the cingulate gyrus and its interconnec-
tions, plays a central role in the pathophysiology 
of major depressive disorder (MDD), obsessive-
compulsive disorder (OCD), and other anxiety 
disorders. Electric stimulation of the anterior 
cingulum and subcaudate region has been shown 
to alter both autonomic responses and anxiety 
levels in human beings [12]. Stimulation of the 
hypothalamus in animals produces autonomic, 
endocrine, and complex motor effects, which 
suggests that the hypothalamus integrates and co-
ordinates the behavioral expression of emotional 
states [13]. The limbic system, which includes the 
cingulate gyrus, has direct input to the hypo-
thalamus and seems to be strategically located 
to mediate and interconnect somatic and visceral 
stimuli with higher cortical functions. Therefore, 
it is likely that certain psychiatric disorders 
-ie, MDD, OCD, other anxiety disorders) may 
reflect a final common pathway of limbic system 
dysregulation.

Data from clinical and neuroimaging studies 
have also converged to implicate the cortico-
striatothalamic circuits in the pathophysiology of 
OCD [14–16]. The frontal-striatal-pallidothal-
amic-frontal loop, which has been so well char-
acterized for its control of motor function in 
Parkinson’s disease, may also explain some fea-
tures of OCD. From a clinical perspective, rare 
neurologic movement disorders like Von Economo’s 
encephalitis and Sydenham’s chorea are known 
to affect the basal ganglia and have been asso-
ciated with obsessive and compulsive symptoms 
[17]. Many patients with Tourette’s syndrome 
(TS), another disorder of the basal ganglia car-
characterized by coprolalia and motor tics, 
have significant OCD symptoms throughout their 
lives [18]. Orbitofrontal and cingulate cortex has 
also been implicated in OCD, because the cog-
nitive and behavioral features associated with 
lesions in this area, such as decreased response 
hibition, inflexibility, and overattention to 
irrelevant details, are reminiscent of OCD symp-
toms. MRI has also demonstrated specific brain 
lesions in the frontal, temporal, and cingulate 
areas in some cases of new-onset OCD [19]. 
Detailed morphometric analysis of MRI scans in 
OCD patients has also suggested focal abnor-
malities in striatal areas with subtle volumetric 
abnormalities involving caudate nuclei [20]. 

Positron emission tomography (PET) studies 
have provided perhaps the most compelling 
evidence for implicating orbitofrontal cortex, 
cingulate cortex, and basal ganglia dysfunction 
in OCD. PET 18F-fluorodeoxyglucose studies in 
children and adults have consistently reported 
significant elevation of absolute glucose metabolic 
rates for the cerebral hemispheres and orbital gyri 
and somewhat less consistent elevation for the 
caudate nucleus in OCD patients as compared to 
normal controls [21–23]. In one study of clomi-
pramine treatment in childhood-onset OCD, 6 
patients who failed to respond had significantly 
higher right anterior cingulate and right orbital 
metabolism than did 11 drug-responsive patients 
[24]. Two reports have found regional decreases 
in metabolic activity correlating with a decrease 
in severity of OCD symptoms as measured by 
the Yale-Brown Obsessive-Compulsive Scale 
(YBOCS) after successful pharmacologic or be-
havioral treatment; one reported decreased cau-
date activity, and the other reported decreased 
right orbitofrontal metabolism [21,25]. In a small 
series of patients with chronic anxiety disorder 
and severe phobias, activation PET studies 
performed as the patients were presented with 
stimuli to recreate their fears demonstrated 
consistently increased regional cerebral blood flow 
(rCBF) in the anterior cingulate cortices, orbito-
frontal cortex, left thalamus, and right caudate 
nucleus [26].

Currently, one can only speculate how disrup-
tion of different pathways in the limbic system 
or cingulate gyri might normalize activity, leading to 
symptom improvement. Recently, Rauch et al [27] 
reported atrophy in the caudate body in subjects 
who had undergone one or more cingulotomies 
approximately 6 months before morphometric 
MRI studies. Such investigations are beginning to 
demonstrate the functional connectivity of the 
cingulate gyri with subcortical nuclei. This may 
explain how lesions in one anatomic area might 
affect the integrity and function of other brain 
regions. Clinical observations suggest that OCD 
and MDD patients do not improve immediately 
after psychosurgery but that several weeks to 
months are required for positive clinical effects to 
be fully manifest. Thus, it is likely that secondary
neural degeneration or metabolic alterations in brain areas other than the region where the lesions are actually made may be involved in the therapeutic effect.

Neurochemical models suggest that the affective and anxiety disorders may be mediated via monoaminergic systems. In particular, the serotonergic system has received emphasis with respect to OCD. Because of the diffuse nature of the monoaminergic projections and their role as neuromodulators, however, these models are not particularly instructive in terms of the functional neuroanatomy relevant to different neurosurgical treatments as they are currently employed. Nevertheless, lesions in the cingulate cortex or other targets in the limbic system may ultimately modify these diffuse monoaminergic systems to exert a beneficial effect.

Although the exact neuroanatomic and neurochemical mechanisms underlying depression, OCD, and other anxiety states remain unclear, it is clear that the basal ganglia, limbic system, and cingulate cortex in particular play a principal role in the pathophysiology of these diseases. Similarly, lesions that affect these target areas might be expected to modulate neuropsychiatric dysfunction (the reader is referred to the article by Rauch et al in this issue for a more comprehensive presentation of these issues).

**Patient selection**

Only patients with severe, chronic, disabling, and treatment-refractory psychiatric illness should be considered for cingulotomy. Chronicity in this context refers to the enduring nature of the illness without extended periods of symptomatic relief and may be less important than the severity of the illness. The severity of the patient’s illness must be manifest both in terms of subjective distress and a decrement in psychosocial functioning. The illness must prove to be refractory to systematic trials of pharmacologic, psychologic, and, when appropriate, electroconvulsive therapy before considering neurosurgical intervention. As in all medical decisions, the potential benefit from such an intervention must be balanced against the risks imposed by surgery.

Thoughtful assessment of psychosurgical candidacy requires that criteria for severity, chronicity, disability, and treatment refractoriness be operationalized to form guidelines. In this regard, chronicity would require at least 1 year of enduring symptoms without significant remission, although practically speaking, confirmation of treatment refractoriness usually requires more than 5 years of illness before surgery. Severity is usually measured using validated clinical research instruments corresponding to specific indicators, such as a YBOCS score of greater than 20 for OCD or a Beck Depression Inventory (BDI) score greater than 30. Disability may be reflected, for instance, by a Global Assessment of Function (GAF) score of less than 50.

The major psychiatric diagnostic groups as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised (DSM-III-R) that might benefit from surgical intervention include OCD and major affective disorder (ie, unipolar major depression or bipolar disorder) [28]. In many instances, patients present with mixed disorders combining symptoms of anxiety, depression, and OCD, and these patients remain candidates for surgery. Schizophrenia is not currently considered an indication for surgery. A history of personality disorder, substance abuse, or other significant axis II symptomatology is often a relative contraindication to surgery.

To determine that their psychiatric illness is refractory to treatment despite appropriate care, all patients must be referred for surgical intervention by their treating psychiatrist. The referring psychiatrist must demonstrate an ongoing commitment to the patient and the evaluation process and must also agree to be responsible for postoperative management. Detailed questionnaires that document the extent and severity of the illness as well as a thorough account of the diagnostic and therapeutic history must be provided by the psychiatrist. The specifics of pharmacologic trials should include the agents used, dose, duration, response, and reason for discontinuation for any suboptimal trial. Adequate trials of electroconvulsive therapy or behavioral therapy when clinically appropriate must also be demonstrated.

The patient and family must also agree to participate completely in the evaluation process as well as in the postoperative psychiatric treatment program. In general, only adult patients (older than 18 years) who are able to render informed consent and who express a genuine desire and commitment to proceed with surgery are accepted.

If the patient meets these criteria, at our institution, he or she would undergo a more detailed presurgical screening evaluation by an experienced multidisciplinary group of psychiatrists,
neurosurgeons, and neurologists (Cingulotomy Assessment Committee). A thorough review of the medical record is carried out to ensure that the illness is indeed refractory to an exhaustive array of conventional therapies. The Massachusetts General Hospital (MGH) evaluation also includes an electroencephalogram (EEG), brain MRI, neuropsychologic testing, and independently conducted clinical examinations by a psychiatrist, neurologist, and neurosurgeon in the outpatient setting. An electrocardiogram and appropriate blood tests are obtained to assess medical risks and to exclude organic etiologies for mental status abnormalities. Validated clinical research instruments (eg, YBOCS, BDI, GAF, Minnesota Mutiphasic Personality Inventory [MMPI]) are employed to quantify psychiatric symptom severity and outcomes. There must be unanimous agreement that the patient satisfies selection criteria, that the surgery is indicated, and that the requirements for informed consent are fulfilled. A family member or close relative must also understand the evaluation process and the indications for, risks of, and alternatives to surgery and must agree to be available to provide emotional support for the patient during the hospitalization.

**Surgical technique**

Cingulotomy was initially performed using ventriculography for surgical guidance, but over the past decade, this has been replaced by MRI–guided stereotactic techniques. This allows for more accurate placement of the lesions and direct visualization of individual differences in cingulate and ventricular anatomy.

The procedure is carried out under mild sedation and local anesthesia. A T1-weighted stereotactic MRI scan is obtained (echo time [TE] = 10 milliseconds, repetition time [TR] = 600 milliseconds), and using the mid sagittal scan as a reference, oblique coronal sections (4-mm thick, 1-mm interval) are selected in a plane parallel to the proposed trajectory of the thermocoagulation probe and spanning the entire anterior cingulum and frontal horns of the lateral ventricles. Target coordinates are calculated for a point 2 to 5 mm above the roof of the lateral ventricle, 7 mm from the midline, and 20 to 25 mm posterior to the tip of the frontal horns [29]. After calculation of the stereotactic target coordinates, a limited bicoronal scalp incision is made, and burr holes are placed bilaterally just anterior to the coronal suture and 1.5 to 2.0 cm from the midline. After dural opening and cauterization of the pia, a standard thermistor-equipped thermocoagulation electrode (Radionics, Burlington, MA) with a 10-mm non-insulated tip is introduced to the target and heated to 85°C for 90 seconds. If necessary, the electrode can be withdrawn 5 to 10 mm, and an additional lesion is made superiorly using the same parameters to ensure complete destruction of the cingulum. The resulting lesion is approximately 15 to 20 mm in height and 10 mm in diameter and should encompass the cingulum from the roof of the ventricle to the cingulate sulcus. The procedure is then carried out in an identical fashion on the opposite side. Intraoperative stimulation is not performed routinely, but neurologic testing is carried out during lesioning to ensure that no impairment of motor or sensory function, especially in the lower extremities, is incurred. On the day after surgery, a postoperative MRI scan is obtained to document the placement and extent of the lesions (Fig. 1).

Although the patient may experience an immediate reduction in anxiety, there is generally a delay to the onset of beneficial effect on depression and OCD. This latency may be as long as 6 to 12 weeks and must be clearly explained to the patient and referring psychiatrist. If there has been no response to the initial cingulotomy after 3 to 6 months, reoperation and enlargement of the cingulotomy lesion are considered (Fig. 2).

Using the surgical techniques described previously, additional lesions can be placed anterior to the initial cingulotomy. The MGH experience suggests that 40% to 50% of patients require repeat surgery and that better long-term outcomes are achieved with repeat surgery and multiple lesions in the cingulate gyrus. Therefore, over the past several years, three separate lesions have been placed at the initial operation, incorporating approximately 2.0 to 2.5 cm of anterior cingulate cortex (Fig. 3). If this operation does not provide satisfactory improvement in the patient’s symptoms, the cingulotomy can be converted to a limbic leukotomy at a later date by placing a lesion in the subcaudate region bilaterally.

**Results**

The results of bilateral cingulotomy in 198 patients suffering from a variety of psychiatric disorders were reported retrospectively by Ballantine et al [30] in 1987. With a mean follow-up of
8.6 years, 62% of patients with severe affective disorder were found to have had worthwhile improvement. Similarly, in patients with OCD, approximately 56% were found to have undergone worthwhile improvement. In 14 patients suffering from nonobsessive anxiety disorders, 50% were found to be functionally well and 29% were found to have shown marked improvement. Valid criticism of these results included the concern that many of these patients might not have met modern DSM-IV-R criteria for their psychiatric disorder and that the assessment of outcome was performed by biased observers, namely, the referring psychiatrists, using subjective rating scales.

A retrospective study was therefore devised to evaluate cingulotomy in the treatment of OCD using independent observers and strict outcome criteria. Of the 35 patients who were operated on for refractory OCD, 33 met modern DSM-IV-R criteria for OCD. In addition, at least 25% to 30% of patients demonstrated substantial benefit from the procedure as defined by a 50% improvement in their YBOCS and a Clinical Global Improvement [CGI] outcome of very much improved or much improved) and 2 others were considered to be possible responders (>35% improvement in their YBOCS or a CGI outcome of very much improved or much improved), for an overall response rate of 28% to 40% [32]. Average duration of follow-up was longer than 2 years. Overall, the entire group improved significantly in terms of functional status, and no serious adverse effects were found. This was the first study to demonstrate in a prospective fashion that cingulotomy is an effective intervention in OCD patients as measured by standardized psychiatric rating scales and independent observers. Recently, another prospective study with long-term follow-up by the same group of investigators reported inhibitors (SSRIs). It was thought that many of these patients might have responded positively to the SSRIs and thus were not truly refractory to treatment.

A prospective study was therefore undertaken using independent observers and clinically validated outcome rating scales. Of 18 OCD patients in this study who underwent cingulotomy at the MGH after failing all modern pharmacotherapies, including the SSRIs, 5 met conservative criteria as treatment responders (>35% improvement in their YBOCS and a CGI outcome of very much improved or much improved) and 2 others were considered to be possible responders (>35% improvement in their YBOCS or a CGI outcome of very much improved or much improved), for an overall response rate of 28% to 40% [32]. Average duration of follow-up was longer than 2 years. Overall, the entire group improved significantly in terms of functional status, and no serious adverse effects were found. This was the first study to demonstrate in a prospective fashion that cingulotomy is an effective intervention in OCD patients as measured by standardized psychiatric rating scales and independent observers. Recently, another prospective study with long-term follow-up by the same group of investigators reported

Fig. 1. Midsagittal (A) and axial (B) T1-weighted MRI scans obtained 48 hours after a single anterior cingulotomy lesion. The acute hemorrhagic lesion undergoes a dramatic reduction in size as the edema resolves.
similar findings in 44 treatment-refractory OCD patients [33]. Between 32% and 45% of patients were judged to be responders, with a mean follow-up of almost 3 years.

In more than 800 cingulotomies performed at the MGH since 1962, there have been no deaths and only two infections. Two acute subdural hematomas occurred early on in the series secondary to laceration of a cortical artery at the time of introduction of ventricular needles, but only 1 patient suffered permanent neurologic impairment. One patient suffered a delayed intracerebral hematoma after a fall 4 weeks after surgery but suffered no long-term neurologic deficits. An independent analysis of 34 patients who underwent cingulotomy demonstrated no significant behavioral or intellectual deficits as a result of the cingulate lesions themselves [34]. A subsequent evaluation of 57 patients before and after cingulotomy found no evidence of lasting neurologic or behavioral deficits after surgery. A comparison of preoperative and postoperative Weschler IQ scores demonstrated significant gains after surgery. This improvement was greatest in

Fig. 2. Axial T1-weighted MRI scans obtained 48 hours after repeat anterior cingulotomy. Note the original lesion placed 12 months earlier and the acute lesion anteriorly.

Fig. 3. Midsagittal (A) and axial (B) T1-weighted MRI scans obtained 48 hours after three anterior cingulotomy lesions ablating approximately 2.5 cm of cingulate cortex.
patients with chronic pain and depression but negligible in those with the diagnosis of schizophrenia [35].

Overall, it appears that cingulotomy is a useful intervention in many patients with severe treatment-refractory major depression or OCD. Using subjective rating scales, approximately 60% to 70% of patients show significant improvement. When more objective clinically validated rating scales are used to assess outcome, approximately 30% to 45% of patients who undergo cingulotomy are considered to be responders. Although this response rate may appear low at first glance, one must remember that all patients were completely refractory to every available treatment and that any measurable improvement might thus be considered salutary.

Discussion

Although any patient with a severe psychiatric illness was once considered a candidate for surgical intervention, it is now clear that the prudent indications for psychosurgery are more restrictive. There is general agreement among centers that patients with major affective disorder, chronic anxiety states, and OCD are the best candidates for surgery. It can be safely concluded that schizophrenia is not an indication for psychosurgery, although patients with concomitant psychotic disorders and depression might still be helped with surgery and should not be excluded. Personality disorders and psychoactive substance use disorder are also significant relative contraindications to surgery.

Appropriate selection of patients for surgery remains the major responsibility of the psychiatrist, guided by the informed and expert opinions of the other members of the psychosurgical team. Advanced neuroimaging data may ultimately aid in optimal patient selection, and preliminary PET studies of patients with OCD indicate that presurgical cerebral metabolic rates within a territory of posterior cingulate cortex predict subsequent outcome after cingulotomy [36]. If preoperative evaluation could select those patients with a better chance of responding favorably to cingulotomy, overall success rates could be greatly improved.

Much of the controversy surrounding the use of psychosurgery may be attributed to the indiscriminate application and high morbidity seen with the early surgical procedures. Stereotactic techniques have certainly minimized side effects, but the issue of case selection remains a major consideration. Cingulotomy has been the preferred surgical intervention in our experience because it provides substantial relief to a significant number of patients and is associated with a low incidence of complications or adverse events [29]. Many other centers believe that alternative surgical interventions, such as subcaudate tractotomy, limbic leukotomy, or anterior capsulotomy, can provide better results in a similar patient population.

Subcaudate tractotomy was introduced by Knight [37] in Great Britain in 1964 as one of the first attempts to restrict the size of the surgical lesion and therefore minimize the side effects seen with standard prefrontal lobotomy. The aim was to interrupt white matter tracts between orbital cortex and subcortical structures by placing a lesion in the region of the substantia innominata just below the head of the caudate nucleus. Surgical indications included major depressive illness, OCD, and anxiety states as well as a variety of other psychiatric diagnoses. The original surgical procedure was performed using stereotactically implanted radioactive yttrium 90 seeds, which yielded large lesional volumes of approximately 2000 mm³. Currently, smaller lesions in are created by thermocoagulation with MRI stereotactic guidance.

In patients with depression and OCD, total improvement or improvement with minimal symptoms was clinically observed in two thirds of the patients. The best review of the surgical results for subcaudate tractotomy was presented by Goktepe et al [38] in 1975. Using a five-point global scale and rating scales for depression and anxiety, they reviewed 208 patients with a mean follow-up of 2.5 years. Of the 134 patients available for structured interview, good results were seen in 68% of patients suffering from depression, 62.5% of patients with anxiety states, and 50% of patients with obsessive neurosis. Patients with schizophrenia, personality disorder, drug abuse, or alcohol abuse did poorly. Some patients who had only temporary benefit from the initial lesion had second lesions created lateral to the first, with good results seen in about half of these individuals.

The incidence of complications was small but included postoperative seizures in 2.2% of patients and undesirable personality traits in 6.7%. Transient disinhibition was common. Of the 25 patients who had died at the time of review, 3 had committed suicide. One patient died from
inadvertent destruction of the hypothalamus when a yttrium seed migrated off target.

Limbic leukotomy was introduced by Kelly et al [39] in 1973 and combines subcaudate tractotomy with anterior cingulotomy. This procedure was designed to disconnect orbital-frontal-thalamic pathways with the former lesion and to interrupt an important portion of Papez’s circuit with the latter. Kelly et al [39] reasoned that these two lesions might lead to a better result for the symptoms of OCD than either lesion alone. Indications for surgical intervention included obsessional neurosis, anxiety states, depression, and a variety of other psychiatric diagnoses. This stereotactic procedure placed three small (6-mm diameter) lesions in the lower medial quadrant of each frontal lobe and two lesions in each cingulate gyrus.

Using the same five-point scale described in the study of Goktepe [38], 66 patients were assessed before and after surgery (mean follow-up of 16 months). In patients with obsessional neurosis, 89% were clinically improved; in chronic anxiety, 66% were improved; in depression, 78% were improved; and in a small number of schizophrenics, more than 80% were improved [40]. Kelly et al [41] later reported in 49 patients with OCD that 84% were improved 20 months after surgery. They too noted that postoperative symptom improvement was not immediate, with a fluctuating but progressive reduction of symptoms over the first postoperative year. Although many patients complained of lethargy, confusion, and lack of sphincter control in the early postoperative period, persistent complications were rare. No patients developed seizures after surgery, 1 patient suffered severe memory loss because of improper lesion placement, and 12% of patients complained of persistent lethargy. Measurements of IQ showed slight improvement after surgery.

Recently, the results of a more modern series of MRI-guided stereotactic limbic leukotomy were reported in 21 patients [42]. Mean follow-up was longer than 2 years, and 35% to 50% of patients were considered to be treatment responders using clinically validated rating scales. Transient side effects were more common than after either cingulotomy or subcaudate tractotomy alone, with permanent minor memory loss or urinary difficulties observed in approximately 10% of patients.

Although Talairach et al [43] were the first to describe anterior capsulotomy, Leksell popularized the procedure for patients with a variety of psychiatric disorders [44]. The aim was to interrupt presumed frontothalamic connections in the anterior limb of the internal capsule, where they pass between the head of the caudate nucleus and the putamen. Clinical indications initially included schizophrenia, depression, chronic anxiety states, and obsessional neurosis but are currently almost entirely limited to OCD.

The target coordinates as described by Leksell are in the anterior one third of the anterior limb of the internal capsule 5 mm behind the tip of the frontal horns and 20 mm lateral to the midline at the level of the intercomissural plane. Lesions were created by thermocoagulation using a bipolar electrode system and were typically approximately 15 mm in height and 4 to 5 mm in diameter.

In the first 116 patients operated on by Leksell, 50% of patients with obsessional neurosis and 48% of depressed patients had a satisfactory response [44]. Only 20% of patients with anxiety neurosis and 14% of patients with schizophrenia were improved. In this classification system, only patients who were free of symptoms or markedly improved were judged as having a satisfactory response. Of the patients who were rated as worse after capsulotomy, 9 were schizophrenics, 4 were depressives, and 3 were obsessives. In another series of 35 patients with OCD who underwent capsulotomy and were followed prospectively by independent psychiatrists, 16 were rated as free of symptoms and 9 were much improved, for an overall satisfactory result of 70% [45]. In a review of all cases of capsulotomy previously reported in the literature, Mindus et al [46] found sufficient data to categorize outcome in 213 of 362 patients. Of these, 137 [64%] were deemed to have a satisfactory result.

More recently, Mindus et al [47] followed 24 patients prospectively with standardized rating scales. Complications of the surgery included transient episodes of confusion during the first week in 19 of 22 patients available for follow-up, with occasional nocturnal incontinence. One patient was noted to have an intracranial hemorrhage without neurologic sequelae, and 1 patient suffered seizures. One patient committed suicide in the postoperative phase, and 8 patients suffered from depression requiring treatment. Excessive fatigue was a complaint in 7 patients, and 4 had poor memory. Two patients showed slovenliness. Weight gain is common after capsulotomy, with an overall mean weight gain of about 10% in all patients. No evidence of cognitive dysfunction has been reported in 200 capsulotomy patients studied using a variety of psychometric tests. Reoperation
was required in 2 patients who did not achieve a satisfactory result, with only 1 improving after the second operation. Burzaco [48] subjected 17 of his 85 patients to a second procedure during which the lesions were enlarged, and half of these reoperations yielded satisfactory results.

In 1977, Kullberg [49] attempted to compare cingulotomy and capsulotomy in the treatment of 26 patients in a randomized fashion. Six of 13 capsulotomy patients and 3 of 13 cingulotomy patients were better, but transient deterioration in mental status was much more marked after capsulotomy than after cingulotomy.

With currently available data, it is impossible to determine whether there is one optimal surgical technique or strategy. The obstacles that prevent a direct comparison of results across centers include diagnostic inaccuracies, nonstandardized presurgical evaluation tools, center bias, and varied outcome assessment scales. In virtually all published reports, however, some modification of the Pippard Postoperative Rating Scale, CGI scale, or equivalent has been used to determine clinical outcome [50]. The Pippard scale rates outcome in five categories as follows: A = very much improved, B = much improved, C = slightly improved, D = unchanged, and E = worse. The CGI expands the scale and rates outcome as follows: 1 = very much improved, 2 = much improved, 3 = slightly improved, 4 = unchanged, 5 = slightly worse, 6 = much worse, and 7 = very much worse.

Although comparisons are imperfect and the rating of outcome is subjective, these scales do seem to have some clinical validity. If a Pippard outcome of A and B or a CGI outcome of 1 or 2 is considered satisfactory, cingulotomy was effective in 56% of patients with OCD, subcaudate tractotomy in 50%, limbic leukotomy in 61%, and capsulotomy in 67%. In patients with major affective disorder, cingulotomy was effective in 65%, subcaudate tractotomy in 68%, limbic leukotomy in 78%, and capsulotomy in 55% [51].

The difficulty with these results is that they were obtained many years ago before the availability of modern psychopharmacologic treatments. Patients who undergo surgery today have a much wider range of drug therapies and tend to be much more resistant to treatment. Comparing current outcomes with historical results can therefore be misleading. Direct comparisons of the relative efficacy of the various modern surgical options will only be possible when centers report their experience using validated objective rating scales (eg, YBOCS, BDI). Based on current methods of comparison, the clinical superiority of any one procedure is not convincing. Although many centers claim advantages for their specific surgical intervention, we are unable to determine whether one of the four major psychosurgical procedures is superior to the others at this point. Cingulotomy is more commonly performed in the United States, whereas in Europe, capsulotomy and limbic leukotomy are more prevalent. They all seem to be roughly equivalent from a therapeutic point of view, but in terms of unwanted side effects, cingulotomy seems to be the safest of all procedures currently performed.

Regardless of the choice of procedure, surgical failures should be investigated, and if the lesion size or location is suboptimal, consideration should be given to another procedure. At least 45% of patients undergoing cingulotomy require repeat operation, with good results being salvaged in half [29]. Because of this high rate of reoperation in cingulotomy, we now recommend placement of three lesions in each cingulate gyrus at the first operation to ablate approximately 2.5 cm of the gyrus. The exact size or volume of tissue required for an effective outcome at each of the target sites has yet to be determined.

Although controversy exists regarding the exact choice of surgical procedure to be employed, there is unanimous agreement that the presurgical evaluation be performed by committed multidisciplinary teams with expertise and experience in the surgical treatment of psychiatric illness. Diagnosis based on the DSM-III-R or DSM-N-R classification scheme is encouraged, and although it is impossible to mandate uniformly across all centers, prospective trials employing standardized clinical instruments with long-term follow-up are needed.

Comparisons of preoperative and postoperative functional status remain an important parameter in addition to targeting psychiatric symptoms in characterizing outcome. All centers with experience emphasize the importance of rehabilitation after surgery and the need for ongoing psychiatric follow-up. The operation is not a panacea and should be considered as only one aspect in the overall management of these patients.

Summary

Cingulotomy can be helpful in certain patients with severe, disabling, and treatment-refractory major affective disorders, OCD, and chronic
anxiety states. This form of psychosurgical treatment should only be carried out by an expert multidisciplinary team with experience in these disorders. Cingulotomy should be considered as one part of an entire treatment plan and must be followed by an appropriate psychiatric rehabilitation program. Many patients are greatly improved after cingulotomy, and the complications or side effects are few. Cingulotomy remains an important therapeutic option for disabling psychiatric disease and is probably underutilized.

References


Single photon emission computed tomography imaging in obsessive-compulsive disorder and for stereotactic bilateral anterior cingulotomy

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Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder involving intrinsic and repetitive thoughts as well as ritualistic and irrational behavior that causes marked distress [1,2]. Kodala et al [3] have reported the lifetime and 6-month prevalence rates to be 2.9% and 1.6%, respectively. Recently, the neurobiologic basis of OCD has received much attention, with many modalities of evidence suggesting a neurologic basis for OCD. Some of the most important information has resulted from functional neuroimaging studies using functional MRI (fMRI), single photon emission tomography (SPECT), and positron emission tomography (PET) [4–10].

Neuroimaging studies provide evidence for a role in OCD of the specific frontal-subcortical brain circuit connecting the orbitofrontal cortex, the anterior cingulate gyrus, and elements of the basal ganglia and thalamus [10,11]. These defined regions in the pathogenesis of OCD were predominantly determined based on PET studies. Compared with the consistent metabolic alteration recorded on PET, the published data on blood flow studies with SPECT have been inconsistent and variable in determining cortical and subcortical structures with abnormal perfusion patterns. There may be a number of reasons for this, including inconsistency of SPECT data analysis, low spatial scanner resolution, different scanning techniques, subject variation, and intraindividual variation because of the presence or absence of OCD symptoms at the time of injection. In particular, semiquantitative measurements of the radioactivity within regions of interest (ROIs) after normalization to the cerebellar uptake are currently used as an analytic method; however, the ROI method is subjective to operator bias in that large ROIs may dilute small activation sites but small ROIs may not differentiate activation sites from noise.

Recently, voxel-based analysis using statistical parametric mapping (SPM) has become available, and in this system, an activated region is compared with a control area by statistical processes after assigning some threshold values and a probability value [12]. The resultant SPM data are more accurate than conventional semiquantitative measurements [13]. Using this sophisticated analysis method, many functional neuroimaging studies have been performed with PET; however, few SPECT data have been reported.

In this report, we evaluate the role of SPECT in OCD diagnosis by comparing the brain SPECT images of drug-free OCD patients with those of normal controls and drug-naive schizophrenia patients. We then explore the role of SPECT in surgical outcome after bilateral anterior cingulotomy.

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by comparing pre- and postoperative brain SPECT imaging.

**Single photon emission computed tomography for obsessive-compulsive disorder diagnosis**

Seven patients with severe primary OCD (six men and one woman) were studied. The mean age (±SD) was 25.4 ± 4.7 years. All patients met the Diagnostic and Statistical Manual for Mental Disorder, 4th Edition (DSM-IV), (American Psychiatric Association, 1994) criteria for OCD as evaluated by two independent psychiatrists and a neurosurgeon who is experienced in psychosurgery. Their mean onset age of symptoms was 19.3 ± 4.7 years, and the duration of symptoms was 6.3 ± 5.5 years (range: 2–27 years). No patients had any psychotropic medications in the 4 weeks before SPECT study. The main compulsive symptoms were washing, checking, and hoarding. Exclusion criteria included histories of central neurologic disorders, tics, or substance abuse. The severity of OCD behavior was quantified by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [14], revealing an overall total score of 28.9 ± 3.23. The depression and anxiety scales were also evaluated using the Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A) [15,16], revealing results of 13.6 ± 4.1 and 12.8 ± 2.6, respectively (Table 1).

The control group consisted of seven normal volunteers (four men and three women) with a mean age of 30.6 ± 6.8 years. These healthy subjects had no psychiatric or neurologic illnesses. Nine drug-naive cases of schizophrenia (three undifferentiated and six paranoid types) were also included for comparison purposes. The mean age of the schizophrenia group was 28.4 ± 8.2 years.

**Single photon emission computed tomography and surgical outcome**

Fifteen refractory OCD patients underwent bilateral stereotactic anterior cingulotomy using MRI guidance. Thirteen patients in this group were followed up for more than a year (mean follow-up of 22.4 months) (Table 2). Criteria for surgical candidacy included the following:

1. The patient fulfills current diagnostic criteria for OCD.
2. The duration of illness exceeds 3 years.
3. The disorder is causing substantial suffering as evidenced by ratings.
4. The disorder is causing substantial reduction in the patient’s psychosocial functioning as evidenced by ratings.
5. Current and up-to-date treatment options have been tried systemically for at least 3 years without appreciable effect on the symptoms or have had to be discontinued because of intolerable side effects.
6. If a comorbid psychiatric condition is present, this disorder must also have been thoroughly addressed with appropriate trials of first-line treatments.
7. The prognosis, without neurosurgical intervention, is considered poor.
8. The patient gives informed consent.
9. The patient agrees to participate in the preoperative evaluation program and postoperative rehabilitation program.

Also excluded from consideration for surgery were patients younger than 18 years of age or older than 60 years of age, a complicating axis I diagnosis (eg, organic brain syndrome; delusional disorder; manifest abuse of alcohol, sedatives, or illicit drugs); a complicating current axis II

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age (years)</th>
<th>Onset age (years)</th>
<th>Symptom duration (years)</th>
<th>Y-BOCS</th>
<th>HAM-D</th>
<th>HAM-A</th>
<th>Main symptoms</th>
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<td>18</td>
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<td>O, C</td>
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**Table 1**

Clinical findings of obsessive-compulsive disorder patients for study I

*Abbreviations: M, male; F, female; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; W, washing; C, checking; O, obsession; H, hoarding; R, ordering.*
diagnosis from clusters A (e.g., paranoid personality disorder) or B (e.g., antisocial or histrionic personality disorder); and a complicating current axis III diagnosis with brain pathologic findings (e.g., atrophy, tumors).

The mean age of the patients (nine men and four women) was 35.8 <sup>±</sup> 9.9 years. The average symptom onset age was 24.7 <sup>±</sup> 10.2 years, and symptom duration was 10.5 <sup>±</sup> 5.3 years. No patients had taken any psychotropic medications in the 4 weeks before SPECT study (before and after surgery).

**Surgical procedure**

Patients were placed under local anesthesia, and bilateral burr holes were made in front of the coronal suture 20 mm laterally from the midline. Stereotactic localization of the targets was achieved using the MRI-compatible Leksell stereotactic frame (Elekta Instruments, Atlanta, GA) on a General Electric Signa 1.5-T unit (Milwaukee, WI). A 1.8-mm electrode with a 10-mm bare tip (Radionics, Burlington, MA) was inserted into the target to create radiofrequency thermocoagulation lesions at 85°C for 90 seconds using a lesion generator (RFG-3C; Radionics). Four lesions along two tracks were created on either side of the anterior cingulate gyrus. The first lesion was made 15 mm posterior to the frontal horn of the lateral ventricle, 2 mm above the roof of the ventricle, and 7 mm lateral to the midline. The electrode was then withdrawn 8 mm to produce the second lesion. The third lesion was made 22 mm posterior to the frontal horn of the lateral ventricle, 2 mm above the roof of the ventricle, and 7 mm lateral to the midline. The electrode was then withdrawn 8 mm to produce the fourth lesion. The result was an elliptocylindrically shaped lesion approximately 18 mm high, 13 mm in anteroposterior (AP) dimension, and 6 mm in lateral dimension (Figs. 1 and 2). Fig. 1 demonstrates the diffuse perilesional edema along the radiofrequency lesions immediately after cingulotomy. This edema resolved gradually, however. Fig. 2 demonstrates the resolved perilesional edema along the radiofrequency lesions 3 months after cingulotomy. Lesions were confined to the anterior cingulate gyrus.

**Imaging procedures**

The SPECT procedure was performed for patients and controls after an intravenous injection of 740 MBq of Tc 99m ethyl cysteinate (ECD). Brain images were obtained using a brain-dedicated annular crystal gamma camera (RASPECT; Digital Scintigraphic Incorporation, Waltham, MA) equipped with low-energy, high-resolution, parallel-hole collimators. The SPECT study was acquired in a 128 × 128 matrix with 3° of angular increment for 20 minutes. Transaxial images were obtained by the filtered-back projection method using a Butterworth filter (cutoff frequency of 1.1 cycle per centimeter, order no. 10). Attenuation correction was performed by Chang’s method, and coronal and sagittal images were calculated.

### Table 2
Clinical findings of obsessive-compulsive disorder patients for study II

<table>
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<tr>
<th>Case</th>
<th>Sex/Age (years)</th>
<th>Onset age (years)</th>
<th>Symptom duration (years)</th>
<th>Y-BOCS</th>
<th>CGI-S</th>
<th>HAM-D</th>
<th>HAM-A</th>
<th>Main symptoms</th>
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<td>S</td>
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</table>

*Abbreviations:* M, male; F, female; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; CGI-S, Clinical Global Improvement of Severity Scale; W, washing; C, checking; O, obsession; H, hoarding; R, ordering; S, sin.
Statistical parametric mapping

Analysis of data was performed on a SUN UltraSpare 10 workstation (Sun Microsystems, Silicon Valley, CA) using automatic image registration (AIR) [17] and SPM (SPM96; Institute of Neurology, University College of London, London, UK) software [18]. After attenuation and scatter correction, the reconstructed SPECT data were reformatted into Analyze (Mayo Foundation, Baltimore, MD) header format consisting of 4096 bytes of header, 1.67 mm of x and y pixel size, 3.34 mm of slice thickness, and 2 bytes of signed integer of pixel values. The SPECT images of the

Fig. 1. T2-weighted MRI 3 days after cingulotomy demonstrated the diffuse perilesional edema along the radiofrequency lesions. (A) The axial image. (B) The coronal image.

Fig. 2. T1- and T2-weighted MRI 3 months after cingulotomy demonstrated the resolved perilesional edema along the radiofrequency lesions. Lesions were confined in the anterior cingulate gyrus. (A) T2-weighted axial image. (B) T1-weighted axial image. (C) The coronal image.
normal and patient groups were separately coregistered to remove variations resulting from differences in the size and shape of individual brains. The parameters for co-registration were: intra-modality, 5000 pixel value for thresholds to be used for organ of interest in both the standard and the reslice images, linear algorithm, 12 affine parameter model for controlling the number of degrees of freedom used in registration, and trilinear interpolation. The data were then normalized to a PET template (MNI template; Montreal Neurological Institute, Montreal, Quebec, Canada) [2,18,19] and smoothed with 8-mm Full Width Half Maximum (FWHM) before SPM statistical analysis. The statistical analysis was performed to compare the mean SPECT images of the OCD group with those of the schizophrenia and normal control groups and the postoperative images with preoperative images in the surgical group. The resulting $t$ statistic, $\text{SPM}_t$, was transformed to $\text{SPM}_Z$ with a threshold of 3.09 or 1.64. The statistical results were displayed by rendering on the reference three-dimensional MRI images with a probability value of 0.001 or 0.05 and a corrected extent threshold probability value of 0.05 for $\text{SPM}_Z$. Individual OCD images were also compared with the normal group by shifting the SPM parameters to a probability value of 0.005 and a $Z$ value of 2.58. For graphic presentation of the results, sections were displayed as transverse, sagittal, and coronal slices with hot color maps.

**Neuropsychologic evaluation**

Patients were evaluated using a battery of neuropsychologic/neuropsychologic evaluation methods designed to measure the functional domains of language, visual integration, learning and memory, executive control, attention, motor control, and general intellectual function. The neurocognitive battery of tests to assess each domain consisted of the following standardized tests with well-established reliability and validity: intellectual functioning by the Korean Wechsler Adult Intelligence Scale (K-WAIS); verbal memory, including immediate and delayed memory, by Hopkins Verbal Learning Test (HVLT); visuospatial construction and memory, including immediate and delayed memory, by the Rey-Osterrieth Complex Figure Test (RCFT); attention and executive functions by the Wisconsin Card Sorting Test (WCST) and Stroop test; and verbal fluency by Controlled Oral Word Association Test (COWA).

In addition to this battery of standard neuropsychologic tests, we evaluated all patients on postoperative day 14 with the Korean version of the Short Blessed Test (SBT-K) [21], which was adapted from a six-item Orientation-Memory-Concentration Test [22]. The optimal cutoff point to differentiate patients with dementia from control subjects was 10/11 on the SBT-K.

**Results of single photon emission computed tomography for obsessive-compulsive disorder diagnosis**

The mean image of the OCD group at a threshold probability value of 0.001, with a $Z$ value of 3.09 and a corrected extent threshold probability value of 0.05, showed increased perfusion within the anterior cingulate gyrus, the left basal ganglia, and the front lobe (Fig. 3). Hyperperfusion within the orbitofrontal cortex or the caudate nucleus was not evident; however, diffusely decreased perfusion within the bilateral cerebral and cerebellar cortices, including the inferior frontal gyrus, was seen in the OCD group (Fig. 4). When individual SPECT images of the OCD patients were compared with the mean images of the normal control group, increased perfusion was seen within the anterior cingulate gyrus in five patients and the frontal lobe in two. Increased perfusion within the basal ganglia, the thalamus, and the orbitofrontal cortex was seen in only one patient (Fig. 5).
When the SPM parameters were shifted to the threshold probability value of 0.005, with a Z value of 2.58 and a corrected extent threshold probability value of 0.05, hyperperfusion was seen within the anterior cingulate gyrus in all patients, within the thalamus in five, within the basal ganglia in four, within the caudate nucleus in three, and within the orbitofrontal cortex in three (Table 3).

The OCD group showed increased perfusion within the anterior cingulate gyrus, the bilateral frontal, and the temporo-occipital areas compared with the schizophrenia group (Fig. 6).

**Outcome of anterior bilateral cingulotomy**

All patients demonstrated improvement in their Y-BOCS score after cingulotomy (Table 4). The mean Y-BOCS score was 34.9 ± 4.0 before surgery, whereas those at 6 and 12 months after cingulotomy were reduced significantly to 24.3 ± 7.4 and 21.5 ± 6.6, respectively (P < 0.01). The mean CGI-Severity score was also reduced significantly from 6.9 before surgery to 4.8 and 4.2 at 6 and 12 months, respectively (P < 0.01). The mean CGI score at 12 months was 2.1. All OCD symptoms seemed to respond to surgery, except hoarding behavior.

Most patients experienced an immediate reduction in depression and anxiety after cingulotomy. The mean HAM-D score was also reduced significantly from 27.5 ± 11.8 before surgery to 16.2 ± 10.6 and 10.0 ± 6.0 at 6 and 12 months after cingulotomy, respectively (P < 0.01). Also reduced significantly was the mean HAM-A score from 16.1 ± 7.8 before surgery to 9.2 ± 7.1 and 6.3 ± 5.4 at 6 and 12 months after cingulotomy, respectively (P < 0.01). The mean postoperative SBT-K score was 6.9 ± 2.1. All patients scored below the optimal cutoff point for differentiation of dementia (10/11) on the SBT-K.

The patients tolerated the procedure well, and none experienced serious permanent complications related to the procedure. Three patients...
showed transient disorientation during the postoperative period. One case of wound dehiscence occurred from scratching of the wound as a result of compulsive behavior; however, the wound healed well after reclosure. Several patients experienced minor interference with verbal fluency and minor personality changes; however, these patients recovered from their minor problems within the first operative month.

The neuropsychologic testing demonstrated that cingulotomy did not cause any significant cognitive problems in areas like intelligence, language, visuospatial skills, and frontal executive function. On the contrary, we observed an improvement of intellectual function after cingulotomy in several patients, although it was not statistically significant (mean preoperative IQ = 99, postoperative [Ed-corrected] IQ = 105).

**Single photon emission computed tomography and anterior bilateral cingulotomy**

We performed postoperative SPECT in eight patients after cingulotomy; the other five patients refused for various reasons. After surgery, the OCD patients demonstrated reduced perfusion
within the anterior cingulate gyrus and the right orbitofrontal cortex in the summated and subtracted postoperative SPECT images compared with the preoperative SPECT images ($P < 0.01$) (Fig. 7).

Discussion

**Outcome of bilateral anterior cingulotomy for obsessive-compulsive disorder**

There was an overall significant improvement in the Y-BOCS and HAM-D scores, with no significant change in neuropsychologic testing after stereotactic bilateral anterior cingulotomy.

In general, bilateral anterior cingulotomy is regarded as an important therapeutic option for intractable OCD [23,24]. Studies on the effects of cingulotomy for OCD during the last decade have demonstrated that about one third of patients were improved after cingulotomy [25]. As reported previously [23,24], there was a general delay in the onset of improvements of symptoms. In our series, all patients showed gradual improvement after surgery, and this delayed process may suggest that effects are related not only to
interruption but to reorganization of neural pathways after surgery. Prior reports have claimed that only 39% of patients were considered responders or possible responders on the basis of demonstrating an improvement on the Y-BOCS of more than 35% or a CGI score of 1 or 2 [24].

Our entire group improved significantly in terms of functional status ($P < 0.01$), and no significant adverse effects were encountered after cingulotomy. The responder and possible responder ratios were 30.8% and 30.7%, respectively, on the basis of an improvement on the Y-BOCS of more than 35% or a CGI score of 1 or 2. Our study featured more possible responders than those of previous reports [20,24]. One possible explanation for this is that our lesion is larger than those used in other studies. We did experience minor and transient mental deterioration (subsided within 1 week), described as a nonsponsive/flat affect, minor interference with verbal fluency, lack of spontaneity, and minor personality changes. This transient postoperative complication seemed to occur as a result of temporary perilesional brain edema around the lesions, as evident in Fig. 1. Our neurocognitive/neuropsychologic battery of tests in these patients demonstrated that cingulotomy did not cause any significant cognitive problems in areas like intelligence, language, visuospatial skills, and frontal executive function.

For patients undergoing stereotactic bilateral anterior cingulotomies, it becomes important to have the proper target location and the optimal lesion volume in the anterior cingulate gyrus. We are not recommending that our positive results justify general adoption of the procedure as a routine treatment for OCD, however. As Cohen et al [26] reported, subtle personality and functional changes could remain. We believe that these minor neurobehavioral sequelae do not hinder the performance of cingulotomy as a treatment method for a certain portion of intractable OCD patients so as to improve their quality of life.

### Table 3

<table>
<thead>
<tr>
<th>Case</th>
<th>Other areas</th>
<th>Caudate</th>
<th>Putamen</th>
<th>Thalamus</th>
<th>OFC</th>
<th>Basal ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.01$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.005$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.005$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.005$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.005$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.005$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>$P &lt; 0.005$</td>
<td>+</td>
<td></td>
<td>$P &lt; 0.005$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**: OFC, orbitofrontal cortex; Bilat, bilateral; Lt, left; Rt, right.

A number of neuroimaging studies using PET have determined abnormal activity in the orbitofrontal cortex, the anterior cingulate gyrus, and the head of the caudate nucleus. These areas are interconnected anatomically and are among the regions implicated in the pathophysiology of OCD.

**Single photon emission computed tomography and obsessive-compulsive disorder**

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have demonstrated abnormal activity in the orbitofrontal cortex, the anterior cingulate gyrus, and the head of the caudate nucleus. These areas are interconnected anatomically and are among the regions implicated in the pathophysiology of OCD.
Our brain perfusion study of OCD patients using high-resolution SPECT showed consistently increased perfusion within the anterior cingulate gyrus compared with that of normal controls and other psychiatric patients (drug-naive schizophrenia). Hyperperfusion within the caudate nucleus or the orbitofrontal cortex was less frequently observed. Our results have shown outcomes using SPECT for the first time and have correlated it to clinical improvements as determined by standardized tests. SPECT results demonstrated reduced perfusion within the anterior cingulate gyrus and the right orbitofrontal cortex after surgery.

Functional imaging of OCD with $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET at resting state demonstrated the hyperactivity of various anatomic structures, such as the basal ganglia, the thalamus, and, in particular, the orbitofrontal cortex. In addition to resting PET, comparative studies of the OCD patients before and after surgery showed significant differences in the orbitofrontal cortex.

**Table 4**

<table>
<thead>
<tr>
<th>Evaluation method</th>
<th>Preoperative</th>
<th>Postoperative 6-month</th>
<th>Postoperative 12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-BOCS (mean ± SD)</td>
<td>34.9 ± 4.01</td>
<td>24.3 ± 7.431*</td>
<td>21.5 ± 6.612*</td>
</tr>
<tr>
<td>CGI-S (mean)</td>
<td>6.9</td>
<td>4.83*</td>
<td>4.24*</td>
</tr>
<tr>
<td>CGI</td>
<td>2.4</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>HAM-D (mean ± SD)</td>
<td>27.5 ± 11.75</td>
<td>16.2 ± 10.621*</td>
<td>10.0 ± 5.982*</td>
</tr>
<tr>
<td>HAM-A (mean ± SD)</td>
<td>16.1 ± 7.88</td>
<td>9.2 ± 7.123*</td>
<td>6.3 ± 5.414*</td>
</tr>
</tbody>
</table>

**Abbreviations:** Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; CGI-S, Clinical Global Improvement of Severity Scale; CGI, Clinical Global Improvement.

* $P < 0.01$ (Wilcoxon signed rank test).
treatment have shown a decrease in cerebral glucose metabolism within the caudate nucleus, the orbitofrontal cortex [4,5,10,11], and the anterior cingulate gyrus [27]. This decrease in metabolism was correlated with a significant improvement in OCD symptoms. Despite these findings, however, there are several inconsistencies in the published data. For example, Swedo et al [28,29] showed increased metabolic rates within the orbitofrontal cortex and the anterior cingulate gyrus, whereas Baxter et al [4,5] found increased metabolism in the whole brain, especially in the orbitofrontal cortex and the caudate nucleus but not in the anterior cingulate gyrus. Perani et al [27] described hypermetabolism within the anterior cingulate gyrus, thalamus, and basal ganglia but not in the orbitofrontal cortex. Nordahl et al [30] found no difference in activity within the caudate nucleus. Mindus and Jenike [31] found that orbital and caudate glucose metabolic rates decreased significantly 1 year after bilateral anterior capsulotomy compared with those before surgery.

Regardless of the specific treatment or type of imaging modality used, it is apparent that studies of pretreatment and posttreatment OCD have most consistently shown findings of decreased orbitofrontal cortex and caudate activity after treatment.

The difference between PET and SPECT may stem from several factors. First, the PET studies were conducted using $^{18}$F-FDG, which requires 40 to 60 minutes between injection and imaging. $^{99m}$Tc EDC for brain SPECT, however, is rapidly taken up by the neurons in the brain within a few minutes, proportional to the cerebral blood flow [32]. Therefore, the emotional state and presenting symptoms at the time of injection are important determinants in brain perfusion SPECT but are less critical in PET. In fact, regional cerebral blood flow measured during symptom provocation using oxygen-15–labeled carbon dioxide PET showed increased blood flow within the caudate nucleus, the anterior cingulate gyrus, and the orbitofrontal cortex [33], although resting brain SPECT has demonstrated contradictory findings, such as decreased perfusion in the orbitofrontal cortex [34] and the caudate nucleus [8,35]. Therefore, a SPECT study performed during symptom provocation would be better than resting SPECT to evaluate the pathophysiologic mechanism of OCD.

The spatial resolution of current cameras used may be another important factor, because the orbitofrontal cortex and caudate nucleus are relatively smaller and thinner than the anterior cingulate gyrus, especially on transaxial images. Therefore, small activation sites within these small
areas might be obscured and diluted by the surrounding normal cells or background activity as a result of the poor spatial resolution of SPECT cameras.

The analytic method of measuring radioactivity in terms of ROI or calculation of hemispheric ratio may contribute to false-negative results as well as false-positive results as previously described. In this study, data were analyzed using an SPM method in which relative activity distribution between the subject and control groups was compared and transformed to the unit of normal distribution in terms of z values and then displayed in coronal, axial, and sagittal views showing only those voxels that reach a statistical significance of \( P < 0.001 \) or \( P < 0.005 \). The SPM analysis is known to be more accurate and reliable than semiquantitative measurement [13]. In this study, although five of the seven patients showed hyperperfusion within the anterior cingulate cortex on higher z and probability values (3.09 and 0.001, respectively), all patients showed anterior cingulate hyperperfusion on lower thresholds (z value of 2.58 and \( P < 0.005 \)). In addition, hyperperfusion within the caudate nucleus (\( n = 3 \)), the orbitofrontal cortex (\( n = 3 \)), and the thalamus (\( n = 5 \)) was frequently observed. Therefore, in SPECT or even PET studies without SPM, analysis may be inconsistent and conflicting in cases with slightly increased radioactivity within an activation site.

Although not all studies agree, a review of the OCD functional brain imaging literature reveals a remarkable amount of data suggesting the presence of abnormalities in the orbitofrontal cortex, the anterior cingulate gyrus, the caudate, and the thalamus, all of which are structures linked by well-described neuroanatomic circuits [10].

In our study, the OCD patients exhibited increased perfusion in the anterior cingulate gyrus compared with both the healthy controls and the schizophrenic patients (see Figs. 2 and 3). A more interesting finding was the observation of postoperative hypoperfusion in the anterior cingulate gyrus and the right orbitofrontal cortex in the OCD patients. We assumed that the perfusion in the anterior cingulate gyrus was caused by the cingulotomy itself; however, the reduction of perfusion in the right orbitofrontal cortex was an interesting result. In the literature, there are many reports concerning the role of the orbitofrontal cortex in the genesis of OCD and many PET studies demonstrating a decrease in cerebral glucose metabolism in the orbitofrontal cortex after OCD treatment [4,11,36]. Those reports also showed an increased glucose metabolism in the caudate nucleus and the orbitofrontal cortex before the treatment. In our study, however, there was no observation of any hyperperfusion in the orbitofrontal cortex before the treatment. The only equivalent observation was in the anterior cingulate gyrus.

We suggest two potential explanations for this divergence of results. First, as previously discussed, SPECT has many weaknesses, including poor spatial resolution. The caudate nucleus and the orbitofrontal cortex are relatively smaller and thinner than the anterior cingulate gyrus, especially on transaxial images, allowing the possibility for small activation sites within these small areas to be obscured and diluted by the surrounding normal cells or background activity as a result of poor spatial resolution. Second, the disparity between various studies, including PET and SPECT images, in terms of secondary change of perfusion according to cingulotomy has not been fully elucidated. The SPECT data may correctly demonstrate the major changes of perfusion after cingulotomy. Thus, the anterior cingulate gyrus may be the key center for the genesis of OCD, and the improvement of OCD symptoms may be related to change of the orbitofrontal cortex.

Of special note was the observed decrease of perfusion in the right side of the orbitofrontal cortex. Several studies comparing therapy-related regional cerebral metabolic effects in patients with OCD have demonstrated orbitofrontal hypermetabolism on the right side before treatment [28,29,37]. Right-sided orbitofrontal metabolic reduction was noted in the same reports. Lippitz et al [38] also suggested the crucial role of the right hemisphere in OCD.

The observation that obsessive-compulsive behaviors can be controlled by lesioning at several targets, including the orbitofrontal cortex, internal capsule, and anterior cingulate gyrus, supports the hypothesis that these structures are closely related and involved with the neuronal circuitry of OCD.

Neuroanatomic studies have also shown that the striatum contains a complex system—neurochemically specialized zones called striosomes dispersed within a larger compartment called the matrix [7,39]. The striosomes of the caudate nucleus receive inputs from the orbitofrontal cortex and the anterior cingulate gyrus, and the caudate processes the cortical information in
preparation for an initiation of behavioral responses [10,11]. The imbalance of this neuronal circuit is important for the generation of OCD symptoms. Our findings of reduced perfusion in the right orbitofrontal cortex after cingulotomy may offer an explanation for the improvement of OCD symptoms being related not only to the anterior cingulate gyrus but to the orbitofrontal cortex.

Over the last several decades, many attempts have been made to investigate the outcome of surgery prospectively. Although it is difficult to compare the results because of lack of control groups, the OCD perfusion patterns were distinguished from those of schizophrenia in this study. Because a certain population (reported to be 26% in Porto’s analysis of schizophrenia) has comorbid OCD, and given that schizophrenia also involves the frontostriatal-thalamic circuit [3], we performed a group comparison of SPECT images between OCD and drug-naive cases of schizophrenia using SPM. The results demonstrated that the OCD patient group had a significant increase of blood flow in the anterior cingulate gyrus as well as in the temporo-occipital area. This finding is consistent with the neuropathologic analysis of schizophrenia, which demonstrated cytoarchitectural alteration of the anterior cingulate gyrus and the superior temporal gyrus as well as decreased volume and cell number of the mediodorsal thalamic nucleus [40].

Summary

In conclusion, the present study suggests that SPECT, using a sophisticated SPM analysis method, may be useful as a potential diagnostic tool for OCD and a possible predictor of treatment outcome for OCD patients undergoing bilateral anterior cingulotomy. The anterior cingulate gyrus seems to be an important structure in the pathogenesis of OCD symptoms. Furthermore, our operative technique of anterior cingulotomy, featuring a larger lesion, seems to be effective in ameliorating the symptoms of OCD without causing any serious complications.

References

Neuropsychiatric thalamocortical dysrhythmia:
surgical implications

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Neuropsychiatric surgery has had a long and complex history with examples of less than optimal surgical procedures implemented in wrong settings. Such past errors have raised important philosophic and ethical issues that remain with us for good reasons. Nevertheless, the existence of enormous suffering as a result of chronic therapy-resistant disabling neuropsychiatric disorders compels a search for alternative surgical approaches based on a sound understanding of the underlying physiopathologic mechanisms. We bring evidence from single cell physiology and magnetoencephalography for the existence of a set of neuropsychiatric disorders characterized by localized and protracted low-frequency spontaneous recurrent activation of the thalamocortical system. This condition, labeled thalamocortical dysrhythmia (TCD), underlies certain chronic psychotic, affective, and anxiety disorders as well as obsessive-compulsive disorder (OCD) and impulse control disorder (ICD). Considering the central role of recurrent oscillatory thalamocortical properties in the generation of normal hemispheric functions, we propose a surgical approach that provides re-establishment of normal thalamocortical oscillations without reduction of cortical tissue and its specific thalamic connectivity. It consists of small, strategically placed, pallidal and medial thalamic lesions that serve to make subcritical the increased low-frequency thalamocortical recurrent network activity. This result is attained via reduction of both thalamic overinhibition and low-frequency oversynchronization. Thalamic disinhibition is obtained by a lesion in the anterior medial paralimbic pallidum. The medial thalamic lesion is localized in the posterior part of the central lateral nucleus (CLN), where most cells have been shown to be locked in low-frequency production and to have lost their normal activation patterns. We present here our experience with 11 patients, including clinical follow-ups and pre- and post-surgical magnetoencephalographic (MEG) studies. The evidence speaks for a benign and efficient surgical approach and for the relevance of the patient’s presurgical cognitive and social settings, making them more or less prone to postoperative psychoreactive manifestations on rekindling of personal goals and social re-entry.


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After the questionable and inordinately wide application of the prefrontal lobotomy [1,2] in the first half of the twentieth century, many groups realized the necessity of confining surgical interventions to the paralimbic (or mesocortical) domain [3]. This gave rise to the three main stereotactic operations still in use today in view of their efficiency and limited side effects: (1) the anterior cingulotomy [4], (2) the subcaudate tractotomy [5], and (3) the anterior capsulotomy [6]. These three procedures entail an interruption of the thalamocortical paralimbic frontal network. Such surgical approaches have been efficient against major depression and OCD but not against psychosis. Early on, however, Spiegel and Wycis [7] explored the possibilities of stereotactic interventions in the mediodorsal nucleus of the thalamus and described positive results in psychotic patients.

There are both older and more recent data demonstrating the physiopathologic and histologic involvement of paralimbic cortical areas and their corresponding specific thalamic partner, the mediodorsal nucleus, in the generation of the neuropsychiatric disorders. Indeed, electroencephalographic (EEG) [8–12], positron emission tomographic (PET) [13,14], histologic [15,16], and radiologic [16] studies indicate spiking activities, increased low frequencies, and hypometabolism as well as histopathologic and MRI changes in these domains.

Our surgical approach is based on two premises: the central role of the oscillatory thalamocortical properties in the generation of normal hemispheric functions [17] and the existence as a physiopathologic basis to neuropsychiatric disorders of a TCD as evidenced by thalamic single cell recordings [18,19] and magnetoencephalography [20–23] and characterized by increased low-frequency generation. In this context, we elected to normalize low-frequency production without affecting the anatomic integrity of the functional cognitive thalamocortical network.

The goal of this article is to describe this approach at the surgical, clinical, and MEG levels.

Methods

Patient group

All patients (n=11) suffered from chronic therapy-resistant neuropsychiatric disorders, including at least one, and often several, of the following clinical manifestations: (1) psychotic hallucinatory/delusional disorder (4 patients), (2) OCD (8 patients), (3) major (or endogenous) depression (7 patients) or bipolar mood disorder (2 patients), (4) anxiety disorder (7 patients), and (5) ICD (4 patients). We believe that the presence of a high percentage of complex atypical neuropsychiatric syndromes is a result of the fact that these patients exhibited particularly resistant disease forms related to widespread and strong TCD mechanisms and were thus at the forefront in terms of surgical indication. Available drug treatments were used without success in all of them, and electroconvulsive therapy (ECT) was applied in four patients before they were referred to us. In addition, three patients came to us after prior unsuccessful interventions. One of them had a gamma knife capsulotomy, the second had a gamma knife thalamotomy, and the third had a vagal nerve stimulator. The patients, seven men and four women, ranged in age between 21 and 59 years (with a mean age of 35 years) at the time of the first surgery. The duration of the disease before the first surgery ranged between 6 and 21 years, with a mean of 15 years. Postoperative relief percentages were given by the patients themselves.

Surgical strategy

We have applied the following criteria for surgical indication: (1) a protracted evolution of the disease (many years), (2) resistance to pharmacologic and other conservative therapies, and (3) a major impact of the symptoms on the patient’s quality of life.

Two surgical targets have been developed, the central lateral thalamotomy (CLT) and the anterior medial pallidotomy (AMP). The CLT targets the posterior part of the CLN, and its stereotactic coordinates are located anteroposteriorly 2 mm posterior to the posterior commissure, mediolaterally 6 mm lateral to the border of the third ventricle, and dorsoventrally 2 mm ventral to the intercommissural plane. The target is reached using an anteroposterior angle of 60° and a mediolateral angle of 5° to 10°. The CLT lesion measures 4 mm in diameter over 12 to 14 mm in length.

The AMP, as its name implies, targets the paralimbic anterior and medial pallidum, and its stereotactic coordinates are located anteroposteriorly 4 mm posterior to the anterior commissure, mediolaterally 12 mm lateral to the ventricular border, and dorsoventrally 2 mm ventral to the intercommissural plane. It is reached using an anteroposterior angle of 55° and a mediolateral
angle of 20°. The AMP lesion measures 4 mm in diameter over 6 mm in length.

Physiologic confirmation of target localizations within given geometric confines is provided by microelectrode recording (Fig. 1) as well as by macrostimulation. Figure 2 displays the CLT and AMP lesions as seen on our stereotactic atlas [24] and MRI.

The general surgical goal was a bilateral coupling of CLT and AMP. We report on five patients with such full surgical treatment, two patients operated on only on one side on the basis of the discovery of a unilateral thalamic causal lesion (and, in the absence of evidence to the contrary, considered fully treated), two patients partly operated on (the first with a left CLT/AMP and the other with a bilateral CLT), and two parkinsonian patients displaying endogenous neuropsychiatric manifestations (anxiodepressive episodes and ICD plus depression) and treated by a unilateral AMP.

**Magnetoencephalography**

Pre- and postoperative MEG recordings were performed in three patients. Analyses included power spectra and coherence studies [20,21] as well as magnetic source imaging.

![Fig. 1. Example of a unit activity recorded in the posterior part of the central lateral nucleus of the thalamus. Upper row: the discharge is composed of a series of recurring bursts of action potentials at a frequency of 3.3 Hz. Two of these bursts are shown using a faster time scale, revealing their intrinsic characteristics. Note that (1) the interspike interval (ISI) within a burst increases with each successive interval and that (2) the shorter the first ISI is in a burst, the larger is the number of spikes within this burst. These features are quantified in the two lower histograms. On the left, plotting of the duration of ISIs as a function of their position within the burst illustrates the progressive lengthening of successive intervals within bursts composed of an increasing number of action potentials. On the right, the duration of the first ISI in a burst shows a tight inverse relation to the number of following spikes within this burst (fitting with a logarithmic function). All these properties indicate that these bursts are the consequence of the deinactivation of calcium T-channels as a result of cell membrane hyperpolarization, the so-called low-threshold calcium spike bursts.](image-url)
A whole-head, 148-channel, MEG system (4D Neuroimaging, San Diego, CA) was used for all patients. Spontaneous brain activity was continuously recorded for 5 minutes while the patient reclined and was asked to stay alert with eyes closed or eyes open. The bandpass was 0.1 to 100 Hz, and the sample rate was 508 Hz. The electrocardiogram was simultaneously recorded digitally for off-line heartbeat artifact rejection. Spectral analysis of 5-second windows using the multitaper technique and cross-correlation between spectral amplitudes at different frequencies was performed with in-house software and commercial Matlab 6 (Mathworks, Natick, MA) on a Linux (Red Hat, Raleigh, NC) cluster computer system. Artifacts emanating from cardiac and other distant sources were removed by the software in a channel-specific manner.

As for magnetic source imaging, the Fourier-transformed signals obtained with the multitaper method were expanded with the singular value decomposition for frequencies of interest. A complex space mode for each frequency was composed using the first five singular vectors. A

Fig. 2. Sagittal atlas projections (left column) and 2-day postoperative T1-weighted MRI images (right column) of central lateral thalamotomy (A) and anterior medial pallidotomy (B) lesions. The coordinates of atlas sections are 7.2 mm (A) and 12 mm (B) lateral to the ventricular border, and the crosses indicate the position of the posterior (A) and anterior (B) commissures. In both series, sections are oriented with posterior to the left and the intercommissural plane (represented by an interrupted line in the left panels) horizontal. The lesions represented in atlas sections do not include the edematous area seen on MRI. Stippled areas in the central lateral nucleus represent densocellular clusters. ac = anterior commissure; AV = anteroventral nucleus; Cd = caudate nucleus; CL = central lateral nucleus; CM = centre median nucleus; LD = lateral dorsal nucleus; Li = limitans nucleus; GPl,e = internal and external pallidum; MDPc = mediodorsal nucleus, parvocellular division; Pf = parafascicular nucleus; PuM = medial pulvinar; PuT = putamen; R = reticular nucleus; STh = subthalamic nucleus; VA = ventral anterior nucleus; VAmc = magnocellular division of VA; VLP(d,v) = ventral lateral posterior nucleus, dorsal and ventral divisions; Vla = ventral lateral anterior nucleus; VM = ventral medial nucleus; VPMpc = ventral posterior medial nucleus, parvocellular division; ZI = zona incerta. Scale bars: 2 mm in atlas and 10 mm in MRI.
volumetric source space was constructed using the averaged MRI MNI-152 [25] provided in SPM99. Voxels with a gray matter probability higher than 0.4 were selected. This probabilistic source space was transformed onto a head-centered coordinate system and scaled. The lead field operator was computed using a spherically symmetric volume conductor model. Inverse source imaging of the space modes at frequencies of interest were computed using a recursively weighted minimum-norm algorithm [26]. Noise reduction was performed with Tikhonov regularization using the generalized cross-validation criterion. The current density solutions were smoothed with a three-dimensional gaussian kernel. For visualization, smoothed solutions were linearly interpolated onto the tessellated cortical surfaces of a sealed MRI previously segmented using Free Surfer [27].

Results

Patient descriptions

Patient 1, born in 1970, experienced a 10-year history of a complex neuropsychiatric syndrome, including schizoaffective (delusions and bipolar disorder) and anxiety disorders as well as ICD and OCD. He underwent surgery on the left side only on the basis of the discovery of a small, vascular, probably developmental, inactive abnormality in his left mediodorsal thalamic nucleus. At a follow-up of 1 year after the left-sided CLT/AMP, he presents with 100% relief of the schizoaffective, OCD, and ICD symptomatology but with only 50% relief of his anxiety and hyperactivity. His global improvement estimation is 60%. His drug intake could be markedly reduced. He experienced only one reactive depressive episode in the post-operative phase, caused by the concurrence of multiple acute mental stressors, from which he fully recovered over a few weeks. Independence level and daily activities have increased significantly. His clinical improvements correlate with the MEG recordings shown in Figure 3 before and 1 year after surgery.

Patient 2, born in 1957, had a 20-year history of a schizoaffective disorder characterized by delusional, hallucinatory, and affective bipolar manifestations with a few ICD elements. Over a few weeks after the second CLT/AMP, he experienced progressive and then complete symptom relief, which is still present 2 years after surgery. In the interim period, he presented with two episodes of agitation, anxiety, confusion, and depression resulting from personal and social stressors, with activation of powerful guilt and feelings of self-insufficiency. Medication is being tapered slowly in view of its 20-year use. Figures 3 and 4 display the patient’s MEG findings before and 3 months after surgery.

Patient 3, born in 1956, suffered from a 14-year syndrome characterized by the coupling of an OCD with major depression in addition to anxiety and psychotic elements. Six years after the bilateral CLT/AMP, the patient presents with complete relief of the OCD, anxiety, major depressive, and psychotic manifestations and has redeveloped a social and professional life to a degree inconceivable before surgery. She still experiences moderate to strong episodes of reactive depression based on marked insufficiency feelings, frustrating/disappointing confrontations, and unfulfilled personal wishes.

Patient 4, born in 1980, was affected for 14 years by a complex syndrome with OCD and ICD as well as anxiety and psychotic disorders. At the follow-up 6 months after the bilateral CLT/AMP and with a significant drug reduction, there is relief of the psychotic elements, at least a 50% reduction of the OCD, and only moderate improvement of the anxiety and ICD. Although the patient could never conduct social interaction for more than a few minutes before surgery, after surgery, he can have hour-long discussions with members of the team. Anxiety and impulse control problems are centered on year-long difficulties in social and familial interactions.

Patient 5, born in 1971, suffered from an OCD associated with outspoken vegetative manifestations (ie, sweating, daily vomiting) and anxiety for 6 years before surgery. At a follow-up 2 years after the bilateral CLT/AMP, he enjoys complete relief of his OCD symptoms. In the context of a preexistent substance use disorder, the patient is currently in a withdrawal process from benzodiazepine dependence marked by anxiety.

Patient 6, born in 1973, suffered from a 21-year OCD coupled with major depression. Immediately after the second CLT/AMP, she described complete relief of her obsessive manifestations and was shaken by the emptiness left by their disappearance. One and a half year later, she complains about obsessive ideas that she has great difficulty in describing. She shows signs of an anxiodepressive state and, only recently, motivation for psychotherapeutic treatment. The facts
Fig. 3. Magnetoencephalographic data from three patients in this series. Power spectra (four top panels) and coherence plots (three bottom panels) are displayed. The top left panel shows the power spectra from controls (blue) and thalamocortical dysrhythmia (TCD) patients, including neuropsychiatric as well as parkinsonian, neurogenic pain, and tinnitus patients. A peak shift into the theta domain and power increase in the theta and beta bands are demonstrated for TCD patients in comparison to controls. The top right panel presents the power spectrum of Patient 2, with a postoperative (blue) curve demonstrating the reappearance of the alpha peak and the power decrease in the theta and beta bands. The postoperative power spectra of Patient 7 (middle left) and Patient 1 (middle right) are mainly characterized by a reduction in theta and beta power, allowing reappearance (Patient 7) or better visualization (Patient 1) of the alpha peak. Coherence was analyzed applying a cross-correlation analysis of the variation along time of the spectral power for frequencies between 0 and 40 Hz. The bottom left panel shows such coherence for controls, the middle panel shows coherence for Patient 2 before surgery, and the right panel shows coherence for the same patient after surgery. (See also Color Plate 1.)
that she has no memories, even as a child, of obsession-free moments and that several first-degree relatives also suffer from neuropsychiatric disorders provide a formidable barrier to adjustment of her perspective toward a disease-free existence. Given this context, a drug reduction has not yet been possible.

Patient 7, born in 1970, suffered from a 20-year neuropsychiatric syndrome characterized by obsessive, anxiety, and depressive disorders associated with anger, pain, tinnitus, and dyskinetic elements. MRI examinations showed the presence of an inactive, probably old, vascular anomaly in the left mediodorsal nucleus, which was submitted to gamma knife surgery with no change in symptomatology. Multiple ECT sessions were applied without results, and a vagal nerve stimulator brought no relief but only an increase in anxiety. A unilateral left-sided CLT/AMP (considered in principle to be sufficient) as for Patient 1) was performed. One year and a half later, the patient describes an at least 50% improvement of his OCD, 90% relief of anxiety, 70% relief of depression and pain, 20% relief of tinnitus, 80% relief of dyskinesias, but only a slight (30%) improvement of anger. The global improvement rate is 70%. The patient’s evolution is colored by (1) the fear that something still may progress in his brain and jeopardize his improvements and future, and (2) the mismatch between what is/has been and what should be, associated with marked feelings of self-insufficiency. There is a clear-cut increase of independence and 60% improvement of daily activities (the patient traveled two times on his own from the Midwest to New York City and found the office of one of the authors, an activity that would have been impossible before surgery without his parents). He is presently on one antidepressant drug at a low dose only and is undergoing psychotherapy. His MEG recordings before and a year and a half after surgery correlate well with these clinical results and are shown in Figure 3.

Patient 8, born in 1970, suffered from an 18-year OCD associated with an anxiety disorder and depression. Repeated ECT and a gamma knife bilateral capsulotomy did not improve the symptomatology and may have triggered anxiodepressive manifestations. At a follow-up of 9 months after the first left-sided CLT/AMP, a differentiated result is observed, with strong improvement of one OCD element (obsessive social component) but lack of improvement of another (obsessive cleanliness). There have been variable but overall significant improvements in daily activities and independence. A second CLT/AMP is being considered.

Patient 9, born in 1971, suffered from a 13-year OCD associated with major depressive episodes. During the 2 years after the bilateral CLT, there have been fluctuating degrees of response of the OCD symptoms, ranging between 50% and 100% improvement. There were no postoperative major depressive episodes. The acute postoperative evolution was characterized by total control of the OCD symptomatology, resulting in a state of massive anxiety as a result of the emptiness after suppression of the constant obsessive ideas. The patient’s spontaneous interpretation concerning the fluctuating reappearance of obsessions was that her anxiety was so severe that she herself reactivated some of them to relieve her inner tension. This psychodynamic context was complicated by the presence of an excess in self-demands so as to comply with a strict and perfectionist picture of herself. At the moment, we await complementary evidence to ascertain better the necessity of a bilateral AMP.

Patient 10, born in 1937, suffered in the context of a parkinsonian disease from a 16-year neuropsychiatric depressive disorder and ICD. For 5 years after a right-sided AMP coupled to a subthalamotomy to alleviate his motor syndrome, the patient presented with complete relief of both motor and neuropsychiatric symptoms. Recently, disease progression at both motor and neuropsychiatric levels poses the question of surgical restabilization of the other hemisphere.

Patient 11, born in 1944, suffered in the context of a parkinsonian disease from a 13-year major depressive disorder characterized by unmotivated abrupt anxiodepressive episodes. He presented 80% to 100% relief of this disorder during a year and a half after a left-sided CLT/AMP coupled to a pallidothalamic tractotomy [19]. As for the previous patient, disease progression at both motor and neuropsychiatric levels raises the possibility of a right-sided intervention.

Summarizing (Table 1), all patients demonstrated significant to complete relief from their neuropsychiatric ailments. We observed the following postoperative reactive manifestations: (1) anxiety (1 patient), (2) anxiodepressive state (3 patients), (3) anxiety and nonacceptance/frustration (3 patients), and (4) frustration and depression (1 patient). A conceptual rigidity with lack of adaptation to the new situation was seen in two patients.
## Table 1
Overview of patient data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>ECT</th>
<th>GK</th>
<th>VNS</th>
<th>Causal lesion</th>
<th>Symptoms</th>
<th>Operation</th>
<th>Relief (%)</th>
</tr>
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<td>10</td>
<td></td>
<td></td>
<td></td>
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<td>PSY/BIP/ANX/OCD/ICD</td>
<td>L CLT/AMP</td>
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<td></td>
<td>+</td>
<td></td>
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<td>Bilateral CLT/AMP</td>
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<tr>
<td>3</td>
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<td>14</td>
<td>+</td>
<td></td>
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<td>OCD/DEP/ANX/PSY</td>
<td>Bilateral CLT/AMP</td>
<td>100 100 100 100</td>
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<td>14</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>OCD/ICD/ANX/PSY</td>
<td>Bilateral CLT/AMP</td>
<td>100 50 &lt;50 &lt;50</td>
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<td>5</td>
<td>28</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<td>Bilateral CLT/AMP</td>
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</tr>
<tr>
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<td>27</td>
<td>21</td>
<td></td>
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<td>Bilateral CLT/AMP</td>
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</tr>
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<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>L Thal/MD</td>
<td>OCD/ANX/DEP</td>
<td>L CLT/AMP</td>
<td>70 &gt;50 90</td>
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<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>L Thal/MD</td>
<td>OCD/ANX/DEP</td>
<td>L CLT/AMP</td>
<td>&lt;50 &lt;50</td>
</tr>
<tr>
<td>9</td>
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<td>R AMP</td>
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<td>13</td>
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<td></td>
<td>ANX/DEP</td>
<td>L CLT/AMP</td>
<td>90 90</td>
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</tbody>
</table>

**Abbreviations:**
- ECT: Electroconvulsive therapy
- GK: Gamma knife
- VNS: Vagal nerve stimulator
- PSY: Psychotic disorder
- BIP: Bipolar affective disorder
- ANX: Anxiety disorder
- OCD: Obsessive-compulsive disorder
- ICD: Impulse control disorder
- DEP: Major depression
- L: Left
- Thal: Thalamus
- MD: Mediodorsal nucleus of the thalamus
- CLT: Central lateral thalamotomy
- AMP: Anterior medial pallidotomy
- CLT/AMP: Central lateral thalamotomy and anterior medial pallidotomy

Percentages correspond to relief estimation by the patients.
Magnetoencephalographic data

Preoperative MEG recordings demonstrated a marked increase of power in the theta domain (4–8 Hz), with the presence of a variable number of identifiable peaks (see Fig. 3). In addition, there was an increase of beta power and of the coherence between the theta domain and the alpha and beta (9–13 Hz and 13–30 Hz) ranges. After surgery, we observed a clear-cut decrease in theta power down to values comparable with those of controls and the reappearance of a normal alpha peak at or above 10 Hz. There was also a reduction of beta power. Interfrequency coherence came down close to that of controls. In terms of source localization, Fig. 4 displays in Patient 2 the presence of a domain of increased theta activity (selected according to his power spectrum between 4 and 10 Hz) in the right-sided medial and lateral temporopolar, anterior parahippocampal, orbitofrontal, and basal medial prefrontal cortices. After surgery, this paralimbic theta focus disappeared. There was maintenance of well-defined bilateral mu Rolandic activity as well as discrete temporal and occipital, probably normal, slow rhythmicity. The Rolandic mu rhythm, which is considered a normal EEG component, was also described in individuals with mild to moderate anxiety, irritability, and emotional instability [28].

Discussion

The neuropsychiatric thalamocortical dysrhythmia

Evidence is presented both at the single cell and MEG levels that a TCD, as previously defined [18–23], underlies certain of the main neuropsychiatric disorders, namely, psychotic and affective disorders as well as ICD and ICD. This TCD is characterized by the following sequential set of events (Fig. 5):

1. Hyperpolarization through disfacilitation and/or overinhibition of thalamic relay and/or reticular cells by the disease source. In psychotic disorders, such a source anomaly may be found in the paralimbic cortical domain or in the paralimbic striatum [16,29,30], with the cortical anomaly providing corticothalamic disfacilitation and the striatal anomaly providing pallidothalamic overinhibition. The possibility of the alternative triggering of a neuropsychiatric disorder by a chronic dysfunction of the cognitive network (comprising conceptual, emotional, mnemonic, and attentional functions) is discussed later in this article.

2. This hyperpolarized state is the source of calcium T-channel deinactivation [31], causing the production of low-threshold calcium spike (LTS) bursts by thalamic (see Fig. 1) and/or reticular neurones.

3. Neurones in such a state impose a slow rhythmicity to the thalamocortical loops they are part of, being locked in the theta low-frequency domain by their ionic properties. Recurrent divergent corticothalamic and reticulothalamic projections back to the thalamus provide the necessary coherent diffusion of these frequencies to various related cortical areas. Our MEG recordings (see Fig. 3) indeed demonstrate increased theta power. Its existence has also been revealed by EEG studies [9,12] and may be directly correlated with cortical [14] and thalamic [13] hypometabolism in PET studies.

4. The final step in the description of this syndrome is the proposed existence of activation of high-frequency (beta and gamma) cortical domains as the result of an asymmetric corticocortical GABA-ergic collateral inhibition [20,21]. The proposed mechanism, an “edge effect” as observed in the retina as a result of lateral inhibition, would result from the asymmetric inhibition between a low-frequency cortical area and neighboring high-frequency domains, providing a ring of reduced inhibition onto, and thus activation of, the cortex surrounding this low-frequency area. Our coherence studies [20,21] support the proposition of such an edge effect, as evidenced by an increased multifrequency coherence between theta and beta domains, which is an event seen with much less prominence in the normal brain. This activation of high-frequency areas might express itself through abnormal EEG spiking activity, as demonstrated in psychotic patients [8,11].

Surgical control of the thalamocortical dysrhythmia

Considering the central role of resonant oscillatory thalamocortical properties in the generation of normal hemispheric functions, we propose a surgical approach that does not imply a reduction of functional thalamocortical loops and is based on regulation toward normality of
dysrhythmic thalamocortical oscillations as documented by our MEG data. For this purpose, we use small pallidal and medial thalamic lesions, the goal of which is to make subcritical the increased low-frequency thalamocortical generation, in other words, to move the dynamic properties of the system away from the increased low-frequency coherent activity. The CLT has as a goal a reduction of low-frequency overamplification and oversynchronization, which can be accomplished by a carefully placed and restricted lesion in the medial thalamus. A similar if less well-defined procedure has been known as medial thalamotomy since the dawn of stereotactic neurosurgery [32]. The rationale and general results of this operation are in full accordance with long-standing electrophysiologic studies [33] demonstrating the progressive spread of the
cortical recruiting response during low-frequency stimulation of the medial thalamus. In addition, the thalamic nonspecific system has been shown to serve as a temporal coincidence activator when summed with the thalamic specific input to the same cortical site [34]. We have taken advantage of physiopathologic data to focus our medial thalamotomy target on the posterior part of the CLN, where more than 95% of the cells produced spontaneous LTS bursts (see Fig. 1) and/or were unresponsive to stimuli [18]. By doing so, we restrict the lesion to the affected site and spare the other medial thalamic subnuclei, which, over time, seem to have taken over the function originally fulfilled by the CLT. This is a reasonable conjecture given the fact that patients experience no obvious reduction in sensory, motor, or cognitive abilities after CLT. The second target, the AMP, addresses the issue of reducing thalamic excess inhibition. In the case of neuropsychiatric disorders, this reduction in inhibition (or disinhibition) is attained by targeting the paralimbic anterior internal pallidum [30].

The results presented here for 11 patients unequivocally demonstrate that this surgical approach has significant therapeutic value against symptoms pertaining to psychotic, major depressive, and bipolar disorders as well as OCD and ICD. There is, however, a clear-cut limit concerning reactive, as opposed to endogenous, symptoms in the domains of anxiety, depression, and frustration. Postoperative reactive decompensations are understandable by the fact that the disinhibitory approach presented here may result in a momentary hyperactive phase during the acute postoperative period. This condition serves to emphasize the fundamental difference between the procedure described here and the other available surgical approaches, such as capsulotomies, cingulotomies, and subcaudate tractotomies, in which the goal is a reduction of cortical activity through thalamocortical disconnection.

As expected given the nature of the lesions, we did not observe permanent classical postoperative prefrontal deficits. Patient 6 presented with neuropsychologic impairments in the executive and memory domains, which were fully compatible with her anxiodepressive postoperative reactive profile [35] and happened in the context of a maintained general cognitive performance and improved general IQ. Patient 3 presented with clear-cut neuropsychologic improvements in a large number of domains, including prefrontal and perceptual functions. The neuropsychologic-sparing quality of CLT has been documented in a large group of patients suffering from other TCDs (manuscript in preparation). A future systematic study will address this issue concerning the coupling of CLT and AMP lesions. The observed patient histories already dispel the possibility of adverse postoperative prefrontal abulic manifestations or personality changes, however, and neither patients nor families complained about a personality reduction or alteration.

**Thalamocortical slow burn**

Evidence of progressive cortical [36] and thalamic [16] atrophy has been documented in patients suffering from neuropsychiatric disorders. This phenomenon leads to thalamocortical self-destruction. One likely mechanism for such morbidity is a persistent increase in calcium entry into the thalamic cells generating LTS bursts, which may cause long-term deleterious effects (eg, via calcium-triggered apoptosis). Furthermore, the continuous high-frequency cortical activation caused by the edge effect provides a framework for the development of excitotoxicity of cortical cells. Under these conditions, the system may fall into a self-reduction mode, a sort of “slow burn” with loss of neuronal substrate. This process serves to reinforce the TCD, however, as the level of thalamocortical and corticothalamic activation decreases and exposes thalamic cells to more disfacilitation and, consequently, to more LTS burst generation and more low-frequency production. If this is confirmed, the surgical treatment of a TCD would not only provide symptom relief and disease control but would additionally acquire a protective role.

**The cognitive factor**

By cognitive, we mean conceptual, emotional, mnemonic, and attentional functions, which are supported by the activation of the widespread paralimbic (or mesocortical) and association networks [3] located in dorsolateral and medial prefrontal, orbitofrontal, cingulate, posterior parietal, insular, and medial temporal areas. Accumulating evidence from EEG and MEG studies underscores the fact that conceptual and mnemonic [10,37–39] as well as emotional [40] activation in human beings increases low-frequency theta activity. A low-frequency increase may thus arise either on the basis of a disease-related or endogenous abnormal input to the thalamus (as the result of a micro- or macroscopic brain anomaly) or via
a “top-down” mechanism driven by mental activity and generating low frequencies on a reactive basis. This finding provides a substratum for (1) the appearance of reactive phenomena in the postoperative period, (2) the genesis of chronic reactive psychiatric disorders with a long-term unsolved mental conflict at their source, and (3) the grouping of many if not all neuropsychiatric disorders into a dynamic realm of thalamocortical dysfunction. Indeed, whether their triggering mechanism is endogenous or reactive, they may be regarded as mirroring an uninterrupted continuum of uncontrollable and thus disturbing low-frequency distortions of the cognitive network. In this sense, the loss of control that may occur in any healthy human brain during strong stimulus-bound transitory emotional reactions may be viewed as a short-lived and in this sense not unhealthy (although sometimes quite undesirable) TCD phenomenon.

Our clinical observations show that surgery can provide marked reduction or even suppression of the disease-related TCD but does not address the cognitive reactive manifestations of the patient to her/his new postoperative situation. Fear, expectations, despair, and frustration may even increase for a time after surgery, representing a powerful cognitive source for increased low-frequency activity necessitating intensive psychotherapeutic support. Our experience has shown that this situation provides a new chance to approach and solve long-standing resistant emotional conflicts by psychotherapy, however.

Such postoperative reactive manifestations are represented by anxious or anxiodepressive states and are also characterized by nonacceptance/frustration postures possibly leading to depression or by lack of adaptation to the new situation. Distinctive characteristics indicating a reactive basis to these observations are (1) symptomatology not present before surgery in relation to the new postoperative situation (eg, Patient 9), (2) large variations across time and according to situations (eg, Patients 4, 6, and 7), (3) difficulties in describing the symptoms (eg, Patient 6), and (4) symptoms fitting well with the personal internal and situational profile (eg, Patients 1, 2, 3, 4, 6, and 7).

Psychotic and affective (bipolar and major depressive) disorders described are viewed here as having an endogenous origin and are well controlled by the CLT/AMP. OCD and ICD manifestations also receded after surgery, but the issue of the endogenous or reactive origin of these disease entities remains as yet unresolved. As for the postoperative anxiodepressive and frustration-related manifestations, the question may be raised as to their origin and their resistance to surgery in view of the fact that anxious and depressive symptoms on the other side may respond to surgery. One possibility is that these manifestations may be responsive to surgery in the measure in which they are endogenous. Another way of viewing this is that whereas all anxiodepressive and frustration-related disorders are of reactive origin, some of them may be self-entertained, thus presenting the observed resistance to surgery. Along this line, postoperative anxiety reactions may be initially strong but amenable to external and internal relieving factors and may thus subside relatively quickly and easily (Patients 1 and 2). To the contrary, frustration/anger and conceptual rigidity do not cause direct suffering, and frustration is even self-entertained. Nonacceptance of a given situation recedes only when the person has decided that it should indeed recede. This mental profile may thus represent a stronger challenge for the relevant network and correlate with more difficult and protracted postoperative evolutions (Patients 3, 4, 6, and 7).

**Summary**

Clearly, more clinical experience must be amassed to define in detail the possibilities of this surgical approach in disabling neuropsychiatric disorders. We propose, however, that the evidence for benign and efficient surgical intervention against the neuropsychiatric TCD syndrome is already compelling. The potential appearance of strong postoperative reactive manifestations requires a close association between surgery and psychotherapy, with the latter providing support for the integration of the new situation as well as the resolution of old unresolved issues.

**Acknowledgments**

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**References**


Electrical stimulation of the anterior limbs of the internal capsules in patients with severe obsessive-compulsive disorder: anecdotal reports

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Electric stimulation of the anterior limbs of the internal capsule was introduced as a treatment for patients with severe incapacitating and treatment-resistant obsessive-compulsive disorder (OCD) by two groups that collaborated closely: the Belgian group, which consisted of a psychiatric branch at the University of Antwerp and a neurosurgical branch at the Katholieke Universiteit Leuven, and the Swedish group at the Karolinska Institute in Stockholm [1,2]. Although it was clearly shown that anterior capsular stimulation induces beneficial effects in patients with severe OCD, some unpublished psychiatric and neurosurgical clinical observations may enlighten and document certain effects of this kind of brain modulation.

Materials and methods

In six patients with severe incapacitating and treatment-resistant OCD, two quadripolar electrodes (Model 3887 [4-mm contact spacing, 3-mm contact length], Pisces Quad Compact; Medtronic (Medtronic Inc., Minneapolis, MN) were implanted into the anterior limbs of the internal capsules by one of the authors (B.N.). Using strict selection criteria, the patients were screened by a committee for neurosurgery for psychiatric disorders, an ethical review board, and an expert committee [3]. The investigational treatment was approved by the Leuven and Antwerp local hospital ethical standards committees on human experimentation and was in accordance with the declaration of Helsinki of 1975 (1983 revision and subsequent revisions). Patients gave written and witnessed informed consent. The stimulation targets were similar to those aimed for in the anterior capsulotomy [1,3]. The electrodes were placed 3 mm anterior to the anterior border of the anterior commissure and entered the brain via precoronal burr holes. The three most ventral stimulating contacts were placed in the internal capsule, and the fourth one was sited dorsal to the internal capsule. Although psychiatrists and psychologists blindly evaluated obsessions, compulsions, anxiety, depression, and several other relevant parameters using validated psychiatric and neuropsychologic scales, we only report here on some observations that interested the authors.

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The authors (B.N., L.G., and P.C.) have been previously involved in research and/or education that was in part sponsored by Medtronic. One author (B.N.) is also filing a patent together with Medtronic.
and on responses to stimulation subjectively re-
ported by the patients. Unless otherwise defined
in the text, one author (B.N.) changed the stim-
ulation parameters (amplitude varying between
0 and 10.5 V, frequency varying between 5 and
130 Hz, and pulse width varying between 60 and
450 microseconds) and the stimulation contacts
of the quadrupolar electrodes. Two other authors
(L.G. and P.C.) evaluated the patients. During
all evaluation sessions, these authors as well
as the patients and their families were blinded
for stimulation condition. In some conditions, the
patients may have guessed that the stimulator
was on because of the stimulation-induced effects.
If the patients received a programming device,
they were not blinded. In that condition, how-
ever, the patients still did not know when the
stimulator was automatically switched on or off.

Subjects

The first patient (Patient 1) was a 35-year-old
man who suffered from many different obsessions
and compulsions, including washing, counting,
and rereading-rewriting-recalculating rituals as
well as concerns with dirt, germs, and household
items (white-spirit). His “major” current obsession
was “the sound of silence.” He avoided being in
a quiet environment and listened to loud beat
music whenever he could. He had an exces-
sive fear of hair growth and detested aging. A
comorbid undifferentiated somatoform disorder
was present with persistent complaints of vertigo,
hypersomnolence, and loss of energy.

Patient 2, a 52-year-old woman, suffered from
excessive concerns with urine and feces and ob-
sessive thoughts about harming others after hav-
ing touched herbs and plants. Compulsive hand
washing, checking, and a compelling urge to ask
questions were omnipresent.

Patient 3 was a 38-year-old woman who had
excessive toilet, washing, and counting rituals;
buying compulsions; and the compelling urge
to touch. The thought that persons, objects, and
things might not be real preoccupied her, and
she developed a whole range of compulsions to
prove their existence and reality. Her parents
always had to stay within eyesight or, when this
was not possible, had to talk to her continuously
to reassure her.

Patient 4 was a 35-year-old man who had
strong fears of harming others by not being
careful enough and obsessions about poisoning
others by contamination with nicotine, tar, or any
harmful household product. He had strong ideas
that a road accident or drowning could have hap-
pened to someone and that he would not have
given the necessary assistance or would not have
alerted the emergency services. He contacted his
sister (or the police) several times a day to check
that no accidents had taken place where he had
passed. He could not take a bus, and when in
a car, he laid on the back seat with his eyes closed
and a towel covering his face.

Patient 5, a 40-year-old woman, had severe
contamination obsessions and was overly con-
cerned with bodily waste and secretions. Going to
the toilet took an hour (two or three times per
day) and required assistance from her mother
both day and night. Washing herself had become
impossible, and a nurse came daily to help her
with this routine. She had excessive and intrusive
sexual thoughts about masturbating. She had
an urgent need to ask for reassurance and to
repeat sentences and statements for herself. She
also hoarded old magazines and empty cigarette
packs.

Patient 6 was a 37-year-old man who suffered
from mostly aggressive obsessions. He had con-
tinuous intrusive thoughts and flashing images
of harming others by poisoning, strangling,
stabbing, or drowning. He also had a fear of
writing compromising things. He avoided having
pens and paper in the same room and could only
read the newspaper when no ballpoint pen was
near. He had excessive checking compulsions and
cognitive escapes (rationalizing) to counter these
aggressive thoughts. He could not drive a car
anymore, because his habit of always checking in
the back mirror made driving dangerous.

Observations and subjective reports

Acute changes with stimulation in the early
postoperative period

Bilateral square wave pulse stimulation was
started immediately after surgery. Effects that
appeared immediately after starting anterior capsu-
lar stimulation are presented in the following
list. We never started chronic stimulation if
these effects were interpreted as side effects and if
they persisted longer than 1 minute.

Subjective feelings reported by the patient

- Anxiety: the patient may be tense or may be
so anxious that he/she experiences an im-
pression of death
• Relief of anxiety
• Feeling of happiness
• Sadness
• Nausea
• General unpleasant feeling
• Strange feeling
• Feeling of fainting
• Feels something in the head
• Sensation of warmth (in the face, chest, throat, feet, and/or legs)
• Tingling sensation (in the face or chest)
• Feels something in the throat
• Difficulty in swallowing
• Headache
• Sleepiness
• Peculiar thoughts (eg, patient wants french fries, patient feels that the stimulator is working like a compact disk that is turning, patient thinks about tennis)
• Visual symptoms and visual hallucinations (eg, patient sees black pieces of dust everywhere, patient has a black visual field on the left side and a white one on the right side, everything becomes darker, the wall seems to come closer, everything becomes smaller, patient has an impression that the room moves, patient sees fog, patient sees a certain person he/she has heard about but has never seen sitting beside her/him, patient has an impression of being in a tunnel, patient has an impression that the ceiling is dirty)
• Feels difficulty in breathing
• Becomes nervous and has the impression that time passes quickly
• Feeling of heavy legs
• Frontal pain
• One patient reported vaginal contractions on three occasions

Objective signs noted by the observer
• Patient makes a deep sigh
• Skin of the face turns red
• Sweating in the face and hands
• Patient says meaningless words during 20 seconds
• Patient repeats words or sentences continuously
• Repetitive movements with the hands
• Laughing or crying
• Yawning
• Patient speaks louder
• Orofacial or total body dyskinesias
• Dysarthria

The list includes subjective feelings and objective signs that appeared immediately after starting anterior capsular stimulation and may have disappeared within 10 to 30 seconds, although some of these effects remained during continuous stimulation. These effects were sometimes reproducible with similar amplitudes and sometimes not reproducible. Apart from the feelings and signs mentioned here, there were also occasions when the patient did not report anything when being stimulated at 10.5 V, 200 microseconds, and 100 Hz or that the reaction was unclear.

Patient 1 reported paresthesias in his face. At higher amplitudes, he felt uncomfortable, as if he was going to pass out. An improvement in mood was induced by using the three most ventral contacts as cathodes and the uppermost contact as an anode with an amplitude of 3 V and with the pulse lasting for 210 microseconds at a frequency of 100 Hz. The patient himself did not feel any improvements in his obsessive thoughts during this first stimulation episode, but a friend and his mother both remarked that he seemed less tense. When the stimulator was switched off for 3 days, Patient 1 started to comment on his noise obsession and felt worse.

At first, the therapeutic effects were not at all pronounced in either Patient 1 or Patient 2. It was only in Patient 3 that the authors saw marked acute changes as have been described elsewhere [1]. She was stimulated with either the three most ventral contacts programmed as cathodes and the uppermost contact as an anode or with all four contacts programmed as cathodes and the stimulator as an anode at 4 V using pulses of 210 microseconds at a frequency of 100 Hz. Clear improvements in obsession, compulsion, depression, and anxiety were noted. Gradually, the amplitude necessary to induce those beneficial effects rose to 6.5 V. Similar high voltages applied in Patient 1 and Patient 2 also induced more pronounced beneficial effects in those patients. The same stimulation parameters were used in Patient 4, Patient 5, and Patient 6 with similar beneficial effects as in Patient 2 and Patient 3.

Immediately after stimulation with these parameters, Patient 4 and Patient 6 uttered verbal perseverations for about 10 to 15 seconds (perhaps the equivalent of recurrent obsessive thoughts and repetitive compulsive acts). Patient 4 reported feeling happy and inclined to laugh, although he could state no reason for this cheerfulness. He once reported seeing a beautiful woman exactly at the moment the stimulator was switched on.
When prompted to elaborate on this, he said it was only a brief flash in his mind that had immediately disappeared.

Patient 5’s sister kept a diary during the patient’s postsurgical hospitalization. “No change” was noted during visits when stimulators were turned off. On days with stimulation, she noted that Patient 5 was in the best of spirits, had more energy, talked, and laughed a lot. She demanded much less reassurance than usual.

When stimulation was first turned on, Patient 6 heaved several deep sighs before starting his perseverative sentences. He felt more light-hearted and stated that he did not see a reason why he would make his life so difficult. He felt casual but not indifferent. He talked a lot more and faster than before. With higher amplitudes, he felt restless and worked up, he felt his heart beating, and he had difficulty in falling asleep.

**Manipulation of stimulation parameters**

The amplitudes necessary to induce symptom reduction rose to between 6.5 and 10.5 V in all six patients 3 to 5 months after the intervention. To reduce battery consumption, a programming device was given to Patient 2 and Patient 3 as one of the strategies. The patients themselves were given the capacity to use high amplitudes and pulse widths only when they felt they needed it. They were allowed to change amplitude and pulse width, whereas frequency was kept constant at 100 Hz. The upper amplitude and pulse width thresholds were determined by one of the authors (B.N.) after ensuring that these parameters did not cause side effects in an acute setting. Patient 3 used 6.5 V when she was at home, 7.5 V when she visited someone, and 8.5 V when she was in a crowd. She told us that if she programmed the amplitude to 9 V, she would start dancing on the table. This higher amplitude immediately induced palpitations and an excessive need for sleep, a condition that she disliked. Decreasing the amplitude to 6.5 V for the sake of saving battery time made her a bit more anxious and worried, a feeling she described “as if she loses something.” She chose 330 microseconds as the optimal pulse width and has been using this pulse width for more than 3 years now. Patient 2 never wanted to use the programming device.

To decrease battery consumption even more, the stimulator was programmed so that it was automatically switched off at night and switched on at 6:00 AM in Patient 2 and Patient 3, again without the patient knowing. Both patients awoke at night about 1 minute after the stimulator was switched off; could not continue sleeping; were anxious, tense and depressed; and were trapped in obsessional thoughts and mental compulsions (constructing and repeating sentences or counting to decrease restlessness) as severe as before surgery. They could only continue sleeping after 6:00 AM, when battery power resumed. During the day, they felt better, as with the continuous stimulation regimen, but were tired as a result of the loss of sleep at night. They both asked to get another stimulation paradigm after some days.

Programming the stimulators for 1 minute on and for 1 minute off induced a happy face for 1 minute with a smile and a sad face during the following minute, and this was tested for 30 minutes in two patients. The patients did not like this kind of stimulation algorithm because they never felt continued relief of anxiety and the sudden mood switches made them feel completely unnatural. Unilateral right-sided stimulation for 2 weeks with the stimulator on during 1 minute and off during the following minute did not improve symptoms as compared to the preoperative condition.

Many contact combinations were tried out. As an example, using the three most ventral contacts as cathodes and the uppermost contact as an anode, the symptoms were reduced in Patient 1 and Patient 3. Conversely, doing the opposite in the same patients, programming the three most caudal contacts as anodes and the uppermost contact as a cathode, symptoms were comparable to the prestimulation level.

Stimulation at 100 Hz or 130 Hz and stimulation at higher pulse widths (210 microseconds up to 450 microseconds) induced better symptom reduction than stimulation at 5 Hz or at a pulse width of 60 microseconds.

**Effects of continuous stimulation**

We evaluated the six patients on a regular basis and asked peers and family about each patient’s condition. Respective follow-up times are 50 months (Patient 1), 49 months (Patient 2), 47 months (Patient 3), 28 months (Patient 4), 9 months (Patient 5), and 3 months (Patient 6). Patients 2 through 6 reported spontaneously that several symptoms had improved during the period that stimulation actually took place. Patient 1 stated that he experienced only marginal or temporal benefit, but both his friend and the
authors observed a slight but definite improvement in mood. His friend also noted that he seemed more peaceful and less preoccupied by his obsessions. He certainly talked less about them and was less self-centered, as if the noise obsession was still there but had become less intrusive.

Patient 2 asked fewer questions and started to do part of the housekeeping (cleaning, laundry, ironing, and cooking) again. She still felt the urge to ask for reassurance but could control it most of the time. She could again enter rooms at home where she did not dare to go before surgery.

Patient 3 reported a 90% decrease in obsessions and compulsions, felt much happier, was much less anxious, and was not depressed. She started listening to music again and enjoyed watching television, whereas before stimulation, she complained loudly each time someone switched the television on. She could re-enter her former bedroom, which had been impossible previously because she became obsessed with thoughts of death and mortality. She used clothes she had not dared to wear for many years, and she also dared to touch a cleaning towel, which was previously impossible. She was a lot more dynamic, attended cultural events, and regained her interest in art history. She actually started to read the books she formerly collected and stored in the cellophane packing in which they came. She stopped hiding for family meetings. She accompanied her mother to the cemetery on All Souls’ Day. This was unthinkable before, because she would have become trapped in ideas of nonexistence.

Patient 4 reported being more relaxed, was happier, and controlled less. He realized that he could resist the urge to control for accidents, that his obsessions and compulsions were only products of his mind, and that there was no real need to act on them. He could postpone checking the parking lot and make short walks.

Patient 5 was less anxious and less tense. Going to the toilet was less time-consuming, and she did not insist on her mother’s assistance during the night anymore. After some weeks of stimulation, the nurse who came to wash her before surgery only paid short reassuring visits but did not need to assist her anymore. She experienced overall a 50% reduction in contamination fears and washing compulsions. She continued to ask many questions, but she took more initiative, read newspapers, and watched television more frequently. She was in a better mood.

Patient 6, in whom follow-up is only 3 months, felt a lot more relaxed with stimulation. He again enjoyed going with his children to a playground or amusement park, where he had formerly dreaded the thought of having strangled or hurt one of the other children. He joined his family in a barbecue party without fear of burning others. He readily finished his “to do” list of chores that he had always postponed before surgery and felt the need for new interests.

It is clear that anterior capsular stimulation may improve some of the symptoms of OCD patients. Validated tests using strict research paradigms have been submitted for publication elsewhere. A disequilibrium in the systemic environment of the patient in reaction to the changes attributable to stimulation has to be taken into account, however. When Patient 2 became able to do some of the housekeeping again, she was expected to take up part of the responsibilities and regain some independence. She found it difficult to develop interests of her own and longed for the continuous closeness of her husband. He had been taking care of his wife and children for so long that he felt he deserved some relief and the right to engage in activities he had had to give up because of her disorder. Patient 3 became more independent and started traveling alone and abroad. She continued to live with her parents because this was comfortable, but she sometimes wondered if she wanted to care for them when they became older and in need of help. She was also sad because she realized that she had missed a large part of her young life as a result of the continuous severity of her OCD. Always being amid older people, she also had trouble in building meaningful relationships with people of her own age. Patient 5 felt much more self-confident and assertive during stimulation. She had been subdued and lived with her parents, who, together with her two sisters, had taken care of her for many years. After stimulation, she wanted to decide for herself at what time she would come home at night. She also could not stand the fact that her sisters were sharing their deepest feelings with each other and wanted to take part in this. She no longer accepted any authoritarian behavior from her father or dominance by her sisters. She started to go to school and wanted to live on her own. Conversely, she was not symptom-free and thus claimed that she could not accept full responsibility for herself and still needed help. She was living on disability benefits and controlled her own finances. She realized that living in her own apartment was financially unacceptable for the
moment. This caused numerous discussions within the family.

A similar form of increased independence as a result of stimulation could be noted in Patient 1. He was a successful artist. After he started being stimulated, he dared to try out new ways of painting, although he never thought about this before surgery. He painted more of his own ideas and developed a style of his own. He received critical acclaim, and art connoisseurs stated that he painted better and more balanced than before implantation of the electrodes. During stimulation, he felt lots of energy, which made him produce many paintings per day. His success placed social demands on him, and he tended to experience more fear of failure and an extreme need for endorsement.

Impact of stimulation on quality of life

Quality of life (QoL) in patients considering neurosurgery for treatment-refractory OCD is low. Severe OCD interferes with the ability to work and to do the housekeeping and with education, family relationships, and social life; beyond that, physical and psychologic well-being is low. After 1 year of stimulation, all six patients remain defective in several domains of health-related QoL. Patient 1 was more successful in his work. Patients 2 through 5 were unemployed at the time of surgery and did not start to work afterward. Patient 2 became more active in housekeeping tasks, whereas she had been hospitalized almost continuously for several years before surgery. Patient 3 was much less dependent on her parents, and her family relationships improved tremendously. Patient 4 went through a divorce at the time of surgery. He has recently started to go out again on Saturday nights and is meeting new people. He also started some volunteer work at a library (part-time). Patient 5 started adult education classes and devotes serious energy to her studies.

Medication, additional treatment, and counseling

In the opinion of the authors, the follow-up of electrically stimulated OCD patients is comparable to the follow-up of electrically stimulated parkinsonian patients. As parkinsonian patients are still followed by a neurologist, OCD patients need follow-up with their psychiatrist. Until now and for the sake of scientific methodology, medication was tapered off to a minimum before surgical intervention and kept stable throughout the first year of stimulation. No additional psychotherapy specifically aimed at improving OCD (eg, exposure and response prevention [ERP]) was given during this period. Patients were asked to remain under the care of their treating psychiatrist for treatment “as usual” and to come to our centers only as part of the research evaluation. It seems likely, although not yet studied in detail, that the stimulated patients respond better to drug treatment and behavioral therapy than when not stimulated. Only the first four patients have completed their first year of stimulation to date. Patient 1 is still taking the same medication, but the dose of benzodiazepine (BZD) could be slightly reduced for Patient 2 and Patient 3. For Patient 4, medication was completely changed 2 years after surgery by the treating psychiatrist. None of the patients engage in ERP treatment, but they avoid less and seem to involve themselves more in everyday life.

Replacement of batteries

When batteries wore out, patients started to feel worse again and OCD symptoms resumed at their former intensity over the course of a few days. All patients immediately contacted one of the authors (B.N.) when they thought the battery was empty, although only two of them had a programmer by which they could really check whether the battery had run low. Stimulation was always performed with a symmetric voltage supply, but because impedances differed somewhat between the left and right sides, the battery of one stimulator was usually empty earlier than that of the other. Usually, only one of the stimulators (either right or left side) had run low when patients requested a check on battery status for sudden worsening, implying that unilateral stimulation is less effective than bilateral stimulation. Similarly, in observing acute reactions (minutes) when changing stimulation parameters, it was almost always clearly noticeable that the effects of bilateral stimulation were more pronounced than those of unilateral stimulation, whether it was right-sided or left-sided stimulation. The patients’ urge to ask for renewal of the stimulators was comparable to that of some parkinsonian patients, who are electrically stimulated in either subthalamic nuclei or ventral intermediate nuclei, to request this when their battery runs low. Their condition changed dramatically after stimulator renewal, even on the operating table, straightaway after the stimulators
were switched on. In Patient 2, the degree of this change fluctuated. The beneficial effects were sometimes only seen after several days, but the husband once said that we had suddenly altered his wife into a lovely young flower. He was not used to this appeal, and he felt uneasy about it. These sudden changes required adaptations in their relationship that were not easy to attain. All patients reacted strongly when the batteries ran down. They felt bad again, and although after a few battery replacements, they knew that these bad feelings were caused by technical reasons, it was difficult to accept this and to put it into perspective. Patient 4 twice experienced a brief hypomanic state (2–3 days) after placement of new batteries. His family reported that he was overactive and could not sleep at all for 36 hours. He tried to impress others and even threatened violence if others did not accept him as “the man who could do it all.” He felt good about himself and regretted that his brother (who also had severe OCD and had committed suicide several years before) could not have benefited from stimulation. He also made some sexual insinuations and passes directed at some acquaintances, and he suddenly demanded a paternity test for his 8-year-old son. When questioned about these episodes in a psychiatric interview some time later, he remembered the hyperactive state but not the showing off and swaggering behavior. He explained that during an argument years earlier, his former wife had told him he could never be sure that he was his son’s father and that this had come into his mind and obsessed him for a few days. He did not persist in demanding the paternity test.

Complications

Technical problems and hardware failures

The most important inconvenience was definitely the high current amplitude needed to maintain acceptable results in the years after the surgery. Stimulators had to be replaced every 5 to 12 months in all patients. This makes the therapy difficult to use as standard therapy, but one can think of strategies either to improve battery technology (eg, rechargeable batteries) or to reduce battery consumption. The stimulators could be replaced under local anesthesia and in an ambulatory setting.

Severe weight loss as a result of severe pyelonephritis in Patient 2 caused the left stimulator, which was implanted in the left hemiabdo-

ments, to migrate more caudally, which induced traction on the extension cable and thus on the electrode. This traction led to fracture of the left electrode and worsening of the OCD symptoms 44 months after surgery. The electrode was replaced, and the patient improved again.

In Patient 5, the impedance of the uppermost contact increased to more than 4000 Ω shortly after implantation, which suggests a broken contact. Therefore, we could only stimulate with three of the four contacts on the left side, but clear beneficial effects on OCD symptoms were still seen.

Side effects

Possible side effects were a major concern when starting this new kind of therapy. There were no intracranial hemorrhages, epileptic fits, or infections, although there was a more than usual swelling of the face in Patient 5 during the first 4 days after surgery, which was prophylactically treated with antibiotics for 1 week even though cultures of aspirated subcutaneous fluid remained sterile.

On some days, Patient 1 felt the leads and the stimulator and wanted to take the system out. During most of the time, however, he wanted to continue the stimulation. He found the advantages of the capsular stimulation not comparable to the disadvantage of needing to have the stimulators replaced every 8 months. Apart from severe OCD, he also suffered from undifferentiated somatoform disorder. For those reasons, his electrodes were removed, and he underwent a bilateral anterior capsulotomy. Other patients complained less about the presence of the stimulators.

Fatigue lasting for several months was a major complaint of Patient 3. When she was given the option of decreasing the amplitude to get immediate relief of her fatigue, she chose to continue stimulation because she appreciated the fact that the benefits of the stimulation were so much greater than the disadvantage of the fatigue. Paradoxically, she showed more energy during the daytime and took much more initiative than before surgery. All patients reported better sleep at night.

Although Patient 3 once reported that one of the authors resembled her previous lover, no frontal signs were noted during subsequent neuropsychologic testing. Also, no permanent pathologic frontal signs were observed in the other patients. Patient 3 complained of a worsening of
memory, but neuropsychologic tests before and 1 year after surgery could not document any difference. Patient 2 was treated for pyelonephritis, which was interpreted as being unrelated to the stimulation. Patient 2 lost weight, and Patients 3 through 5 gained weight to different degrees.

Summary

Anterior capsular stimulation induces some improvement in severe treatment-resistant OCD patients. At this stage, not all stimulation-induced effects can be explained. The effects are a valuable source for further neurophysiologic and neuroanatomic research. It was reassuring that when the group of Drs Rasmussen, Greenberg, and Friehs in Providence and the group of Drs Rezai, Montgomery, and Malone in Cleveland started to operate on OCD patients using exactly the same technique, similar effects were seen in the patients. The authors still want to stress that anterior capsular stimulation remains investigational and needs optimization, especially to try to solve the problem of the short battery life of the stimulators.

References

Cervical vagus nerve stimulation for
treatment-resistant depression

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Intermittent electric stimulation of cranial nerve X (called the “vagus,” Latin for “wandering”) via a surgically implanted programmable prosthesis was approved by the US Food and Drug Administration (FDA) for medically refractory partial-onset seizures in 1997. Only 4 years later, and without the benefit of controlled data to establish its efficacy, the VNS Therapy system (Cyberonics, Houston, TX) for delivery of cervical vagus nerve stimulation (VNS) had become an approved treatment for medication-resistant or -intolerant depression or bipolar disorder in Europe and Canada. That VNS has come to be regarded as one of the most promising new forms of therapeutic brain stimulation reflects a tremendous need for better long-term treatments of disabling depression as well as great expectations for the application of new technologies in treating mental illness. The history of its development and practical considerations for its application in psychiatric disorders are reviewed in this article.

Anatomy of the vagus nerve

The vagus nerve, best known for its parasympathetic efferent functions, such as autonomic control and regulation of heart and gut viscera, is actually a mixed sensory and motor nerve. Approximately 80% of the vagus is sensory afferent fibers, carrying information to the brain from the head, neck, thorax, and abdomen [1]. Through sensory afferent connections in the nucleus tractus solitarius (NTS), the vagus has extensive projections to brain regions that are thought to modulate activity in the limbic system and higher cortex [2–4]. Pathways connecting the NTS with the parabrachial nucleus and the locus ceruleus (LC) carry afferent vagal input to noradrenaline-containing neurons, which reach the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic structures [5].

Preclinical investigations of vagus nerve stimulation

The first published report suggesting that VNS directly affected central function appeared in 1938, when Bailey and Bremner [2] described synchronized activity of the orbital cortex produced by VNS in cats. Slow-wave response in the anterior rhinal sulcus and amygdala to VNS was noted in awake cats with high cervical spinal section [3]. Further evidence of VNS effects on the basal limbic structures, thalamus, and cingulate was generated by a study in monkeys [4]. A synthesis of this preclinical literature led Zabara [6, 7] to hypothesize and further investigate in dogs the notion that VNS would have anticonvulsant action. Zabara observed VNS-induced cortical electroencephalographic (EEG) changes and seizure cessation in dogs, leading him to postulate...
that the antiepileptic mechanisms of action of VNS would involve direct termination of an ongoing seizure as well as seizure prevention [8]. In preclinical investigations, access to the vagus was achieved through an abdominal or diaphragmatic approach.

**Clinical trials of vagus nerve stimulation for epilepsy**

In 1988, the first human implants were performed for a pilot study of cervical VNS in patients with medication-resistant epilepsy who were not candidates for neurosurgery [9]. The VNS Therapy system commercially manufactured by Cyberonics includes a pocket watch-sized generator that is implanted subcutaneously in the left chest wall in a fashion similar to placement of a cardiac pacemaker [10]. Bipolar electrode coils are wrapped around the left vagus nerve near the carotid artery in a separate neck incision (Fig. 1). The leads are subsequently tunneled under the skin for connection with the programmable generator. A telemetric wand connected to a portable computer is held to the chest (over the patient’s clothing) to assess and control the stimulation parameters in a noninvasive office procedure.

By 1990, the first multicenter pivotal VNS trial was being conducted in the United States and Europe to investigate its role in medically refractory epilepsy [11]. Results from three open trials and two double-blind studies [11,12] indicated a 25% to 30% mean decline in seizure frequency and suggested a tendency for anticonvulsant benefits to be sustained or improved over time with continuing VNS [13,14]. Collective data from the epilepsy trials showed that after 2 years of continuous VNS, the categorical response rate (defined as a 50% or greater reduction in seizure frequency) reached 43% and was maintained at the 3-year mark [13]. Although few epilepsy patients receiving VNS have achieved full remission and become free of anticonvulsant medications, data from these studies supported the use of cervical VNS as a safe and effective adjunct treatment for difficult-to-treat epilepsy [15]. Perhaps more important to the future development of clinical VNS applications, the epilepsy studies demonstrated that cervical VNS was well tolerated, with adverse events (AEs) rarely leading to discontinuation of VNS therapy [16]. Pooled data from epilepsy clinical studies (n = 454) show minimal surgical complications associated with implantation: infection without explantation of the device (1.8%), infection with subsequent explantation (1.1%), hoarseness or temporary vocal cord paralysis (0.7%), and hypesthesia or lower left facial paresis (0.7%) [17]. Side effects related to the intermittent stimulation itself (ie, voice alteration or hoarseness, cough, paresthesia, dyspepsia) were judged to be mild or moderate most of the time and were noted to decrease over time with ongoing VNS at the same “dosage.” Stimulation-related AEs could be diminished by reprogramming the device to deliver a lower level of output current. Alternatively, a patient can completely abort a stimulation-induced AE by holding or taping a small magnet over the pulse generator. High continuation rates (72% at 3 years), lack of compliance issues or drug-interactions, and favorable practice and reimbursement economics have all contributed to the success of VNS in the treatment of patients with severe epilepsy. At the time of this publication, more than 20,000 epilepsy patients worldwide have received cervical VNS (S. Perkins, Cyberonics, personal communication 2003), and the treatment has been judged by the American Academy of Neurology’s Technology and Therapeutics Committee as having “sufficient evidence...to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence” [15].
Anticonvulsant mechanism of action research

Ascending projections from the NTS to the midline raphe and LC are hypothesized to be the pathways through which VNS exerts antiseizure and neuropsychiatric effects. Studies in rats during VNS reveal increases in cellular activity as measured through the oncogene C-fos in the amygdala, cingulate, LC, and hypothalamus [18]. Further support for a role of noradrenergic neurotransmission comes from a report of suppression of the antiseizure effects of VNS in animals after lesions of the LC [19]. Although the basic mechanisms of action are unknown, a theoretic VNS-induced increase in NTS concentration of γ-aminobutyric acid (GABA) and/or a decrease in NTS glutamate level could explain the antiseizure activity of VNS [20]. Consistent with this hypothesis, a study of lumbar cerebrospinal fluid (CSF) components in epilepsy patients sampled before and after 3 months of VNS showed significant increases in CSF concentrations of GABA and trend-level decreases in glutamate [21]. Other provocative findings from the CSF study were trends toward VNS-induced increases in levels of the major metabolite of dopamine, homovanillic acid (HVA), and the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). A positron emission tomography (PET) study in epilepsy patients demonstrated significant VNS-induced modulation of blood flow in key brain structures thought to be involved in seizures and emotion regulation [22]. Blood flow increases were seen in the rostral medulla, thalamus, hypothalamus, insula, and postcentral gyrus, all with greater activation on the right side. Bilateral decreases were seen in the hippocampus, amygdala, and cingulate gyrus.

Vagus nerve stimulation as a potential treatment for depression

During the early epilepsy trials of VNS, patients frequently stayed in the same hotel in Gainesville, Florida, during follow-up visits at the study site. An astute observation made by a hotel clerk and reported to VNS investigator B.J. Wilder was that the VNS patients seemed to be in better spirits as time passed. Anecdotal reports of mood improvements apparently unrelated to reduction in seizure frequency further inspired the VNS investigators to systematically assess mood and anxiety symptoms [11,12]. Both retrospective data analysis [23] and prospective assessments during epilepsy trials [24] suggested that VNS was associated with a reduction in depressive symptoms, even in the absence of improvement in seizures.

Incidental findings of psychiatric improvements during clinical trials of anticonvulsant therapies have provided the rationale for further investigation into the potential utility of other drugs like carbamazepine in the management of bipolar disorder [25]. In light of the growing number of modern anticonvulsant agents (eg, carbamazepine, valproic acid, lamotrigine) that have demonstrated beneficial effects in mood-disordered patients, a possible role for VNS in the treatment of depression seemed worthy of investigation. The similarities between VNS and electroconvulsive therapy (ECT), considered to be the most effective available antidepressant treatment, also supported the hypothesis that VNS may have primary antidepressant properties. These considerations, together with the known anatomic projections of the vagus to regions of the brain involved in mood regulation and the preclinical and human CSF data suggesting that VNS altered major neurotransmitter systems implicated in depression, provided a rationale for studying VNS in a new population of subjects.

Open-label study of vagus nerve stimulation for treatment-resistant depression (D-01)

The safety and efficacy of VNS for non-psychotic, chronic, or recurrent treatment-resistant depression was first studied in an open-label fashion in 30 patients at four academic sites in the United States [26]. Patients enrolled in the study, called “D-01,” had either bipolar or unipolar forms of affective illness and continued to be severely symptomatic despite exposure to an average of 16 different clinically administered treatments (including an average of five strictly defined adequate antidepressant trials) for the current major depressive episode. The majority (66%) had undergone a course of ECT for the index depressive episode before enrolling in the VNS study and undergoing surgical implantation of the VNS Therapy system. After a 2-week single-blind period for recovery from surgery, the patients began active VNS with an initial 2-week period of stimulation adjustment (consistently programmed to take place in cycles of 30 seconds “on” and 5 minutes “off” but variable in intensity of output current) and a subsequent 8-week
period of fixed-dose VNS. All patients continued on stable psychotropic medication regimens. The categoric response rate (50% or greater decrease in total score on the 28-item Hamilton Rating Scale for Depression [HRSD]) after 10 weeks of adjunctive VNS was 40% for the first 30 patients. Substantial functional improvement was also seen, suggesting acute antidepressant efficacy in a difficult-to-treat depressed population. A second cohort of 30 patients with treatment-resistant depression meeting similar inclusion and exclusion criteria was added to the open-label study. A somewhat less robust response rate of 21% was seen at the end of the “acute phase” (10 weeks of active VNS) for this second cohort. The overall acute response of 30.5% for the combined cohorts (n = 60), with 15% meeting criteria for full remission of the depressive episode, was still much higher than what might be expected in such a severely ill and treatment-resistant population, however.

Quality of life assessments suggested that VNS was associated with improvements in vitality, social function, and mental health domains even among patients who were considered VNS acute-phase nonresponders [27]. Safety data from the D-01 open-label depression study mirrored that of the epilepsy trials, as most side effects were experienced only during stimulation and were considered mild. No dose-response relationship was detected when final output current data were examined. Neuropsychologic tests indicated neurocognitive improvements after VNS relative to baseline, especially in those who experienced decreased depressive symptoms [27]. The only identifiable predictor of response was degree of treatment resistance as measured by the number of failed antidepressant trials in the index depressive episode. More severely refractory patients experienced poorer responses to the 10-week VNS therapy.

Longer term follow-up results: open-label study of vagus nerve stimulation for depression (D-01)

Although the short-term results were considered encouraging, the longer term data generated even more enthusiasm for VNS in treatment-resistant depression. After 1 year of VNS, 91% (10/11) of the first cohort of acute-phase study responders had maintained their response and 18% (3/17) of the initial nonresponders had achieved a reduction of depressive symptoms sufficient to meet “responder” criteria [28]. When the entire sample (n = 59) participating in the open-label (D-01) study was followed to the 1-year mark, the response rate was 45% and the remission rate was 27%. For those who had reached the 2-year mark, there continued to be evidence of sustained or even enhanced response to VNS (13/24 responders [54%]) [29]. It is worth noting that changes in dose or type of psychotropic medication and VNS stimulation parameters were not controlled after exit from the acute-phase study, introducing the possibility that the observed improvements were not entirely attributable to the ongoing VNS. Nevertheless, the association of adjunct VNS with sustained depressive symptom reduction and improved functional status after 2 years is suggestive of antidepressant efficacy in a naturalistic setting.

Pivotal, placebo-controlled study of vagus nerve stimulation for depression (D-02)

Encouraging results from the open-label studies clearly indicated a need for a placebo-controlled investigation of the antidepressant efficacy of VNS. A large-scale pivotal study was thus designed to be almost identical to the open-label study that preceded it, with the exception of double-blind randomization to either active VNS or a sham condition. Additionally, the protocol exclusion criteria were revised to exclude those with the highest levels of treatment resistance (six or more failed adequate trials in the index depressive episode), because they did not appear to benefit from VNS in the open-label study. After completing the 12-week acute study, patients in the sham condition who continued depressed would cross over to active stimulation, and long-term data would be collected on all patients.

Results of the randomized controlled study, called “D-02,” were released to the press in early 2002. Two hundred twenty-five patients received VNS (2 weeks of VNS stimulation parameter adjustments and 8 weeks of fixed-dose VNS) in an “add-on” study design. Acute safety and tolerability of VNS were demonstrated. The placebo (sham) response rate was low at 10%, but only 15% responded to active VNS, which failed to confirm the short-term antidepressant efficacy of the adjunct therapy statistically [30].

Speculation about why the D-02 treatment group response was inconsistent with the open-label study results included hypotheses about inadequate dosing of VNS stimulation. A preliminary comparison of the output current
delivered in the D-02 depression study with that used in the initial open-label depression study and in epilepsy studies suggests that stimulation set at 1.0 mA or higher is associated with higher rates of clinical response. Stimulation parameters were at lower settings in the D-02 study compared with those used in the initial open-label D-01 depression studies and epilepsy trials. At present, systematic efforts are underway to “ramp up” or increase the dose of VNS in pivotal study patients who have not yet remitted in hopes of generating data that will better address the possibility of a dose-response relationship for VNS in depression.

**Longer term results in the pivotal study (D-02)**

In light of the apparent gradual accumulation of more VNS responders over time in the D-01 open-label study, there has been considerable interest in the clinical course and longer term outcomes experienced by the depressed patients who continue to receive VNS after finishing the acute-phase trial. In a preliminary look at data from the first 36 patients to have completed a full year of VNS in the D-02 pivotal study [30], the response rate at the 1-year mark was 44%, which is consistent with 1-year outcomes measured from subjects in the open-label study. Although this finding raises the provocative possibility that VNS simply takes longer (ie, longer than the 10 weeks of acute-phase therapy) to exert its antidepressant effects, the longer term data do not reflect response under continued controlled conditions. It is possible that changes in antidepressant therapies or VNS stimulation parameters account for the growing percentage of patients meeting categorical criteria for antidepressant response over time. More extensive evaluation of follow-up data, with larger sample sizes and over longer periods of exposure to VNS, will eventually be available. Nevertheless, it will remain difficult, if not impossible, to parse out the effects of antidepressant medications or spontaneous remissions in this large cohort and to demonstrate antidepressant effects that can be clearly attributed to adjunct VNS.

Interestingly, recent device regulatory precedents suggest that statistically significant long-term longitudinal results may be appropriate to support FDA approval, particularly in light of the pressing need for safe, tolerable, and effective maintenance treatments for patients with severe chronic and/or recurrent depressions. In summary, it seems premature to conclude either that more placebo-controlled trials of VNS will be needed or that the present data set will be adequate to demonstrate an adequate level of antidepressant efficacy.

**“Mechanisms of action” research in depression**

One of the most compelling aspects of the VNS development “story” is the growing body of clinical neurobiologic research findings that speak to its direct actions on the brain and central nervous system. Because antidepressant action of VNS has yet to be empirically established, it is not appropriate to interpret dynamic brain imaging results and other biologic correlates of VNS in depressed patients as evidence of its mechanism of antidepressant action. That qualification notwithstanding, such data seem to provide converging lines of evidence that VNS exerts measurable effects in brain regions and neurotransmitter systems implicated in mood disorders.

A single-photon emission computerized tomography (SPECT) imaging study conducted in six depressed patients receiving VNS in the open-label study found that compared with normal controls, patients had reduced regional cerebral blood flow (rCBF) to left dorsolateral prefrontal, anterolateral temporal, and perisylvian temporal structures, including the posterior insula, at baseline [31]. After 10 weeks of VNS, these depressed patients showed increased rCBF in the superior frontal gyrus and right mesial (posterior hippocampus) and lateral temporal cortex. The 10-week trial of VNS seemed to produce resolution of classic rCBF abnormalities in depressed patients, especially among those showing a favorable clinical response.

A method for synchronized blood oxygenation level-dependent (BOLD) functional MRI (fMRI) was developed to detect signal from the implanted device and link it to fMRI image acquisition [32]. In depressed patients, a BOLD fMRI response to VNS was shown in areas regulated by the vagus nerve: orbitofrontal and parieto-occipital cortex bilaterally, left temporal cortex, hypothalamus, and left amygdala. This newly developed fMRI technique was also used to examine whether BOLD signal changes depend on the frequency of VNS [33]. Results confirmed that acute immediate regional brain activity changes vary with the frequency or total dose of stimulation. Additionally, results suggested that VNS exerts a dose-dependent modulatory effect on other brain activities, such as hearing a tone.
Sleep EEG studies have also measured apparent VNS-induced improvement in indices of sleep macro- and microarchitecture in patients with treatment-resistant depression [34]. After 10 weeks of VNS, the amplitude of sleep EEG rhythms was restored to near-normal levels, and patients manifested significantly less awake time and “light sleep” and significantly more stage 2 (deep) sleep.

Lumbar CSF samples were collected in 18 patients both before and after VNS therapy, in the pivotal study (D-02) [35]. Consistent with CSF findings reported for a group of seizure patients receiving 3 months of VNS, the depressed group showed a significant VNS-associated increase in CSF concentrations of HVA, the major dopamine metabolite. Unlike the CSF results obtained during the epilepsy trials, however, no changes in CSF GABA were detected. Although categorical clinical response rates were low, the data suggested that an increase in CSF level of norepinephrine during VNS was correlated with better clinical outcome. This norepinephrine finding is of interest in light of known anatomic connections and animal studies demonstrating that VNS exerts effects on higher brain regions via actions at the LC, the major noradrenergic nucleus in the brain.

Several other types of biologic measures of VNS are currently being investigated to evaluate the effects of VNS in treatment-resistant depression, including evoked response potential (ERP) recordings and provocative neuroendocrine challenge responses. The biologic data thus far suggest that VNS has acute and chronic effects on various key indices of brain activity and neurotransmitter regulation that have also been implicated in mood regulation. As is still the case with most available pharmacotherapies, however, the direct mechanism of therapeutic action of VNS is still not known.

Other potential clinical applications of vagus nerve stimulation

In addition to the use of VNS for treating medication-refractory epilepsy and depression, a number of potential new indications for VNS are being explored. Based on clinical observations from epilepsy and depression studies, results from preclinical and clinical mechanisms of action research, neuroanatomic knowledge, and market opportunities, Cyberonics, Inc. has patents for “application of pulsed electrical signal” in the treatment of movement disorders, eating disorders/obesity, anxiety disorders, dementia and Alzheimer’s disease, chronic pain, migraine headache, and cardiac disease. Several of these areas are under current clinical investigation, including an open-label study of bilateral diaphragmatic VNS (using higher output currents than used in cervical VNS applications) for morbid obesity. Multicenter trials of cervical VNS for panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and rapid-cycling bipolar disorder are also underway.

Practical considerations in the use of vagus nerve stimulation for psychiatric disorders

Surgical implantation of the VNS Therapy system is considered a procedure of low technical complexity for a surgeon with experience in the head and neck area. The surgery typically takes from 30 minutes to 1 hour in the operating room and is usually performed on an outpatient or day surgery basis, without subsequent admission to the hospital for routine postsurgical recovery or monitoring. General anesthesia is used in most cases, but regional or local anesthesia has been used in some centers. A device “programmer” who is knowledgeable about the operation of the VNS Therapy system must be present but not sterile in the operating room to perform lead testing before surgical incisions are closed. A 4- to 5-cm incision is made in the neck for placement of the two stimulating electrodes, which coil around the vagus nerve (see Fig. 1). A second incision similar in size is made in the chest wall (or alternatively in the axillary region for a superior cosmetic result) for insertion of the pacemaker-like pulse generator. A tunneling tool subcutaneously passes the electrodes to the site connection with the pulse generator. The battery life of the currently available pulse generator model is approximately 8 to 12 years. A single surgical incision is needed in the chest wall to replace the entire pulse generator once the battery has expired.

Because of the potential for heating of the electric leads, whole-body MRI is contraindicated in patients who have the VNS pulse generator implanted. Special “send-receive coils” have been used to concentrate magnetic fields away from the neck area when MRI of the brain is necessary. Patients with the VNS Therapy system are asked
to carry identification cards and are educated about risks related to being in close proximity to strong magnetic fields.

The cost of the VNS Therapy system and surgical implantation for cervical VNS is approximately $20,000, making it to roughly comparable to the cost of a course of ECT for depression in an inpatient setting. If the generator battery life is 10 years, VNS costs can be calculated at about $2000 per year. Early success in establishing adequate terms of coverage and reimbursement by third-party payers has contributed to the wide-scale availability of VNS for patients with epilepsy in the United States. At present, VNS as a treatment for depression remains investigational in the United States; as such, it can be offered only at academic centers conducting approved research protocols. Data regarding the optimal stimulation parameters for antidepressant effects are extremely limited. Because there is much yet to be learned about the effects of various stimulation “doses” and patterns of electric pulse delivery, off-label use of VNS is discouraged at this time. Although it is tempting to imagine that VNS may replace psychotropic medications and the many undesirable side effects that accompany them, it is important to bear in mind that VNS has been investigated as an adjunct therapy rather than as a monotherapy in most cases to date. Patients’ expectations for dramatic symptom recovery or even cure from severe psychiatric illness may be fueled by the introduction of new technology and the highly interventional nature of the device implantation surgery. Management of such expectations should be undertaken with great care, particularly in depressed patients, who are at heightened risk for acting impulsively and self-destructively on feelings of disappointment and hopelessness.

With those caveats in mind, it is useful to consider the relation of VNS to other somatic methods of therapeutic brain stimulation, such as ablative neurosurgery, gamma knife neurosurgery, deep brain stimulation (DBS), ECT, MR spectroscopy (MRS), and transcranial magnetic stimulation (TMS). On a spectrum of relative invasiveness of the procedure, with ablative surgery at one end and TMS at the other, VNS might be ranked in the middle [36]. Future applications of VNS may include combining it with brain imaging techniques to evaluate immediate dynamic effects and, possibly, to influence regional focus through adjustment of the stimulation parameters [36].

Summary

Therapeutic brain stimulation through left cervical VNS now has established safety and efficacy as a long-term adjunct treatment for medication-resistant epilepsy. There is considerable evidence from both animal and human studies that the vagus nerve carries afferent signals to limbic and higher cortical brain regions, providing a rationale for its possible role in the treatment of psychiatric disorders. Open-label studies in patients with treatment-resistant depression have produced promising results, especially when response rates at longer term (1 year and 2 years) follow-up time points are considered. Short-term (10 weeks) treatment with VNS failed to demonstrate statistical superiority over sham treatment in a recently completed double-blind study, so antidepressant efficacy has not yet been established. Longer-term data on VNS in depressed patients as well as further information regarding the possible dose-response relation will help to determine the place of VNS in the armament of therapeutic modalities available for major depression.

References


Transcranial magnetic stimulation

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The ability to stimulate the brain in awake alert adults without the need for anesthesia or open craniotomy is a significant advance that has long been a dream of clinicians and neuroscientists. The pioneering work of the neurosurgeons Penfield and Perot demonstrated the behavioral results of direct electric stimulation of epilepsy patients during open craniotomy. This work demonstrated how powerful and important direct brain electric stimulation might be for advancing understanding of the brain [1,2]. Their results were confined to epilepsy patients, however, and the testing was done during open craniotomy.

Transcranial magnetic stimulation (TMS) is the answer to this dream of noninvasive stimulation in awake individuals. TMS produces noninvasive direct cortical brain stimulation by creating a powerful transient magnetic field [3,4], which then induces electric currents in the brain. Because of its noninvasiveness, TMS has considerable promise as a research tool to understand brain–behavior relations. Although TMS is not limited to use by neurosurgeons and does not involve surgery, it is important for neurosurgeons to be familiar with this most powerful new tool for causing “electrodeless electric stimulation.” Advances made with TMS promise to set the stage for other brain stimulation advances in neurosurgery. Moreover, information gleaned from TMS studies will likely inform us about the mechanisms of action of classic neurosurgical techniques like deep brain stimulation (DBS).

Despite TMS’s promise and widespread use, there is still inadequate understanding of the exact mechanisms by which TMS affects the brain and...
how these effects change as a function of different TMS use parameters, such as intensity and frequency. Progress in this area is occurring by performing TMS in animal models and by combining TMS with functional neuroimaging. There has been much interest in using repeated daily administration of TMS as a potential treatment in a variety of neuropsychiatric disorders. The largest body of work has been done in the treatment of major depression. Although several meta-analyses of these antidepressant studies show that TMS has statistically significant effects greater than those of placebo, larger sample studies are still needed to clarify its clinical role. Additionally, TMS as a treatment for depression has not yet been approved by the US Food and Drug Administration (FDA), although pivotal trials geared for eventual FDA approval are currently underway. This article succinctly summarizes basic TMS physics and mechanisms and then critically reviews the potential clinical uses of TMS, particularly in the treatment of depression and other neuropsychiatric conditions.

Description of transcranial magnetic stimulation and mechanisms of action

TMS uses a powerful handheld magnet to create a time-varying magnetic field, where a localized pulsed magnetic field over the surface of the head depolarizes underlying superficial neurons [3–5]. High-intensity current is rapidly turned on and off in the electromagnetic coil through the discharge of capacitors (Fig. 1). It is important to realize that TMS, which produces powerful but brief magnetic fields that, in turn, induce electric currents in the brain, radically differs from the currently popular use of low-level static magnetic fields as alternative therapies. Constant exposure to static magnetic fields can have biologic effects [6]. TMS does not produce magnetic fields for long (microseconds), however, and they are relatively weak, except directly under the TMS coil. It is thus assumed that TMS produces its behavioral effects solely through the production of electric currents in the cortex of the brain. This assumption has not been proved, however. If TMS pulses are delivered repetitively and rhythmically, the process is called repetitive TMS (rTMS) [7]. rTMS can be modified by the term fast if the frequency is greater than 1 Hz [8]. Fast rTMS is currently limited to brief runs of approximately 25 to 30 Hz. Stimulation frequencies faster than this have an increased seizure risk, and most modern capacitors cannot keep delivering the needed energy before depleting. Thus, fast TMS is performed at frequencies that would be considered slow for DBS, where stimulation frequencies sometimes exceed 150 Hz.

The magnetic field induced by TMS declines rapidly with distance away from the coil. Thus, with current technology, TMS coils are directly and electrically only able to stimulate the superficial cortex and are not able to produce direct electric stimulation deep in the brain [9]. Although this limited depth of penetration is a limitation of the present technology, deeper brain structures can be influenced by cortical TMS because of the cortex’s

Fig. 1. Diagram of events leading to transcranial magnetic stimulation excitation. (From George MS, Belmaker RH. Transcranial magnetic stimulation in neuropsychiatry. Washington (DC): American Psychiatric Press; 2000; with permission).
massive interconnections and redundant cortical-subcortical loops [10]. Moreover, there are several groups working on novel TMS coil designs that might be able to reach deeper into the brain without overwhelming superficial cortical structures.

The amount of electricity needed to cause changes in the cortex varies from person to person and also from one brain region to the next [11]. One commonly used method for standardizing and adjusting the amount of electricity delivered and induced by TMS across different individuals is to determine each person’s motor threshold (MT). The MT is commonly defined as the minimum amount of electricity needed to produce movement in the contralateral thumb when the coil is placed optimally over the primary motor cortex. MT can be determined either by using electromyographic (EMG) recordings [12] or, with less precision, by using visible movement [13].

TMS has been shown to produce immediate effects (within seconds), such as the movement of the thumb or direct inhibition of another TMS pulse followed shortly in time. These immediate effects are thought to result from direct excitation of inhibitory or excitatory neurons. There is some evidence to suggest that TMS at different intensities, frequencies, and coil angles excites different elements (eg, cell bodies, axons) of different neuronal groups (eg, interneurons, neurons projecting to other parts of the cortex, U fibers) [8,14–17]. This is further complicated by the complex six-layer arrangement of human neocortex along with the varying gyral folds, which places some aspects of the brain close to the surface and others far away in sulcal folds.

Another example of immediate TMS effects is called paired-pulse TMS. This technique involves delivering two TMS pulses to the same region with varying interpulse intervals (usually milliseconds long) and intensities [12]. Depending on the relative strength of the first pulse to the second and the interpulse interval, the first pulse can either inhibit or enhance the second pulse. Paired-pulse TMS over the motor area can be used to assess natural brain inhibitory and excitatory systems at rest in individuals with different disorders [18,19] as well as after the administration of different centrally active compounds or other treatments [20]. The different TMS use parameters (eg, frequency, intensity, length of stimulation, intertrain interval) are most certainly all biologically relevant and likely important. Particular attention has been focused on whether and to what degree different frequencies of TMS might have divergent biologic effects. For example, repeated stimulation of a single neuron at low frequency in culture produces long-lasting inhibition of cell-cell communications (called long-term depression [LTD]) [21–24]. Conversely, repeated high-frequency stimulation can improve cell-cell communication (called long-term potentiation [LTP]) [25]. With these cellular data on LTD and LTP as a background, there has been much interest in whether TMS, exciting hundreds or thousands of neurons in a pulse, can produce sustained inhibitory or excitatory effects [26,27]. Several studies have now shown that chronic low-frequency stimulation of the motor cortex can produce inhibitory intermediate-term effects (lasting for several minutes) after stimulation [28,29]. There is also some evidence that high-frequency stimulation can produce intermediate-term excitatory effects [30]. One of the most easily demonstrated immediate effects of TMS is speech arrest, where high-frequency TMS placed precisely over the Broca’s area can immediately and transiently block fluent speech [31]. TMS used in studies like this can produce what are sometimes referred to as “virtual lesions.” Importantly, none of these temporary lesion effects were demonstrated to persist beyond the time of active TMS administration. Thus, the lesions are truly virtual and temporary. This contrasts with observations that a train of repeated high-frequency stimulation can excite the brain so much that it results in seizure activity [32]. With knowledge of the appropriate limits of stimulation, seizures can be avoided safely.

Safety issues

Although there is minimal risk of a seizure when TMS is performed within the published safety guidelines, the most well-known critical safety concern with TMS is inadvertently causing a seizure [7]. It is important to realize that this TMS safety table was developed in a small subject sample using a surrogate end point for a seizure—spread of TMS-induced motor-evoked potentials (MEPs) beyond the target area of stimulation. Thus, the safety table exists only for stimulation of motor cortex and cannot readily be applied to using TMS over other brain regions. Finally, although the intensity and frequency of stimulation were examined, the intertrain interval was not. One of the inadvertent seizures was induced with stimulation trains that were within the safety guidelines but that were administered with an excessively short intertrain interval [33]. A general rule of thumb is
that one should have an intertrain interval at least as long as the period of stimulation. A known seizure disorder, history of epilepsy, or intracranial abnormality, such as a prior stroke, can all increase the risk of a TMS-induced seizure [34]. Although an inadvertent seizure is the main safety hazard associated with TMS, there have been only 12 reported cases since 1985 when cranial TMS began. It is, in fact, not easy to intentionally use TMS to produce a seizure, even in patients with epilepsy [35]. For example, an attempt to use TMS to produce a seizure intentionally in a patient with a focal epilepsy was not successful [35]. In addition, in a study exploring rTMS as a method to induce therapeutic seizures, stimulation parameters far above the published safety thresholds had to be used to reliably induce seizures [36].

A muscle tension type headache and discomfort at the site of stimulation are less serious but relatively common side effects of TMS. In contrast to electroconvulsive therapy (ECT), no deleterious cognitive effects of 2 weeks of slow or fast rTMS have been found [37,38]. This is not surprising, because ECT induces a generalized seizure, whereas rTMS is being used at subconvulsive levels. Like MRI, TMS could cause the movement of paramagnetic objects in or around the head. For this reason, subjects with paramagnetic metal objects in the head or eye are generally excluded from TMS studies. TMS can cause heating of metallic implants and the inactivation of a pacemaker, medication pumps, or cochlear devices. In the United States, rTMS is an experimental procedure that requires an investigational device exemption (IDE) from the FDA for research. It should be kept in mind that modern TMS did not begin until 1985 [39] and that the total number of subjects or patients to receive TMS is likely still less than 10,000. Nevertheless, substantial experience to date suggests that at least in the short term (<10 years), TMS at moderate intensity has no other evident lasting adverse effects in adults.

Overview of research uses relevant to neurosurgery

As a research tool, TMS has been used to influence many brain functions, including movement [40], visual perception [41,42], memory [43,44], attention, speech [31,45], and mood [46–48]. A full review is beyond the scope of this article [49,50]. We discuss below the TMS uses germane to neurosurgery.

Interestingly, in light of the initial pioneering results of Penfield, stimulation with TMS has never evoked the type of complex behavioral symptoms reported with direct electric stimulation in human beings. TMS has never been reported to provoke a memory, smell, or song as reported by Penfield [1,2,51]. There may be several explanations for this difference between TMS and direct cortical stimulation. First, most TMS studies are in healthy subjects, whereas the Penfield results were from patients with refractory epilepsy requiring surgery. Complex behaviors have not been provoked by TMS, even when it has been used in epilepsy patients [35,52]. This area has not been systematically explored, however. Second, Penfield and Perot used high-intensity electric stimulation that even caused seizures in some instances. In other words, the initial electric stimulation likely spread to other regions through pathologically kindled neuronal circuits. Stimulation of these circuits led to the expression of auras. Thus, most importantly, all the complex behaviors reported by Penfield and Perot were actually auras commonly experienced by the patients. This fact is underappreciated but was recently confirmed by Perot (P. Perot, personal communication, 2002). Thus, it is likely that TMS does not produce complex behaviors like historic accounts of direct cortical electric stimulation because TMS has not been delivered in intensities high enough to cause spreading of a seizure discharge and elicitation of auras.

Use of transcranial magnetic stimulation and speech arrest to determine eloquent cortex

TMS delivered over the motor speech area can produce transient speech arrest. There was initial interest in whether TMS might be used to determine eloquent cortex. This information could be useful in patients about to undergo surgical resection of tumors or seizure foci. Initial reports found that TMS needed to be delivered at frequencies around 20 Hz, which was painful and might induce a seizure in a patient with a focal lesion or epilepsy [52–54]. A later study showed that TMS could be performed at lower frequencies, sometimes as low as 4 Hz [31]. There has not been a formal comparison of TMS speech arrest with the Wada test or functional MRI (fMRI) presurgical mapping. Some studies have found that the TMS-indicated region for motor cortex correlates well with fMRI-predicted motor cortex and later direct neurosurgical stimulation [55]. Further work
using TMS to help with presurgical planning for motor or speech areas is warranted [56].

**Use parameter effects in animal models**

Although TMS has been used quite effectively as a tool to investigate normal and pathologic brain function, its full and proper uses as a research tool and clinical treatment are still hampered by incomplete knowledge of the neurobiologic cascade of events triggered by TMS at different settings. Numerous animal studies have been important in trying to bridge this knowledge gap and improve our understanding of the modes of action of TMS.

TMS studies with intracranial electrodes in rhesus monkeys have provided information about the nature and spatial extent of the rTMS-induced electric field [57,58]. Corticospinal tract development, aspects of motor control, and medication effects on corticospinal excitability have been studied fairly extensively in nonhuman primates using single-pulse TMS [59–67]. Such work has yielded information about TMS neurophysiologic effects, such as the observation that TMS-evoked motor responses result from direct excitation of corticospinal neurons at or close to the axon hillock [67].

Rodent rTMS studies have reported antidepressant-like behavioral and neurochemical effects. In particular, rTMS enhances apomorphine-induced stereotypy and reduces immobility in the Porsolt swim test [68,69]. rTMS has been reported to induce electroconvulsive shock (ECS)-like changes in rodent brain monoamines, β-adrenergic receptor binding, and immediate early gene induction [69–71]. The effects of rTMS on seizure threshold are variable and may depend on the parameters and chronicity of stimulation [26,72]. Within the past year, Pope and Keck [73] have completed a series of studies using more focal TMS in rat models. They have largely replicated earlier TMS animal studies using less focal coils. Even with the attempt at focal rat stimulation, the effects involve an entire hemisphere and cannot readily be extrapolated to what is happening in human TMS using focal coils [74].

**Combining transcranial magnetic stimulation with functional imaging**

A critically important area that will ultimately guide clinical parameters is to combine TMS with functional imaging to monitor TMS effects on the brain directly and to thus understand the varying effects of different TMS use parameters on brain function. Because it seems that TMS at different frequencies has divergent effects on brain activity, combining TMS with functional brain imaging will better delineate not only the behavioral neuro-psychology of various psychiatric syndromes but some of the pathophysiologic circuits in the brain. In contrast to imaging studies with ECT, which have found that ECT shuts off global and regional activity [75], most studies using serial scans in depressed patients undergoing TMS have found increased activity in the cingulate and other limbic regions [76–78]. However, two studies have now found divergent effects of TMS on regional activity in depressed patients, determined both by the frequency of stimulation and the baseline state of the patient [79,80]. In other words, for patients with global or focal hypometabolism, high-frequency prefrontal stimulation has been found to increase brain activity over time, with the opposite happening as well. Conversely, patients with focal hyperactivity have been shown to have reduced activity over time after chronic daily low-frequency stimulation. These two small sample studies have numerous flaws, however. They simultaneously show the potential and the complexity surrounding the issue of how to use TMS to change activity in defined circuits. They also point out an obvious difference from ECT, where the net effect of the ECT is to decrease prefrontal and global activity [75].

Over the past year, several studies combining TMS with other neurophysiologic and neuroimaging techniques have helped to elucidate how TMS achieves its effects. The Medical University of South Carolina (MUSC) group has pioneered and perfected the technique of interleaving TMS with blood oxygen level–dependent (BOLD) fMRI, allowing for direct imaging of TMS effects with high spatial (1–2 mm) and temporal (2–3 seconds) resolution [81–83] (Fig. 2). Another group in Germany has now succeeded in interleaving TMS and fMRI in this manner, replicating some of the earlier MUSC work [84]. Work with this technology has shown that prefrontal TMS at 80% MT produces much less local and remote blood flow changes than does 120% MT TMS [85]. Strafella et al [86] used positron emission tomography (PET) to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus, and Paus et al [87] used the same modality to show that prefrontal cortex TMS has reciprocal activity with the anterior cingulate gyrus. Our group at the MUSC [76,77,88] as well as investigators in Scotland (K. Ebmeier, personal communication 2002) and Australia [80]...
have all shown that lateral prefrontal TMS can cause changes in the anterior cingulate gyrus and other limbic regions in depressed patients.

It is thus clear that TMS delivered over the prefrontal cortex has immediate effects in important subcortical limbic regions. The initial TMS effect on cortex and the secondary synaptic changes in other regions likely differ as a function of mood state, cortical excitability, and other factors that would change resting brain activity. The MUSC group thus wondered whether these TMS-induced limbic effects might be modified by medications that are known to treat or stabilize mood. Would a medication that inhibits cortical spreading of electric stimulation change the TMS-induced limbic effects? To answer this, we recently designed and completed a study in 12 healthy young men, where we measured the TMS MT as well as performed TMS/fMRI on 2 separate days [89]. On the first day, subjects received one single oral dose of 325 mg of lamotrigine or placebo. On the other day 1 week later, in a randomized fashion, they received whatever they did not receive during the first session. Lamotrigine is a use-dependent sodium channel inhibitor with broad-spectrum anticonvulsant, antidepressant, and mood-stabilizing effects. As with many central nervous system (CNS) active compounds, particularly those with inhibitory mechanisms. Further studies are needed to determine if this technique is useful in new compound development or in monitoring or predicting clinical efficacy.

Uses of transcranial magnetic stimulation as therapy

Depression

Although the functional anatomy of mood regulation is not nearly as well understood as the

Fig. 2. Image of blood oxygen level-dependent (BOLD) functional MRI (fMRI) data from healthy adults, where transcranial magnetic stimulation (TMS) has been applied at 120% motor threshold over the prefrontal cortex. Note that although TMS initially affects only superficial cortex, cortical-subcortical connections cause changes in deeper limbic regions (8 individuals, \( P < 0.001 \), extent \( P < 0.05 \) for display on Talairach normalized MRI template). (From Nahas Z, Lomarev M, Roberts DR, et al. Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry 2001;50:712–720; with permission).
circuitry of the visual or motor systems, most scientists agree that certain brain regions are consistently affected in depression and, to a lesser extent, mania. Although there is controversy and much more work is needed, certain regions have consistently been implicated in the pathogenesis of depression and mood regulation [90–99]. These include the medial and dorsolateral prefrontal cortex, the cingulate gyrus, and other regions commonly referred to as limbic (ie, amygdala, hippocampus, parahippocampus, septum, hypothalamus, limbic thalamus, insula) and paralimbic (ie, anterior temporal pole, orbitofrontal cortex).

The notion of using something like TMS as an antidepressant dates back at least to the turn of the century, when a patent was filed in Vienna in 1902 [100]. In more modern times, there were two open studies in Europe in the early 1990s using nonfocal round coils centered over the vertex to deliver TMS to broad frontal and parietal regions in an attempt to treat depression [101,102]. Reasoning that prefrontal and limbic regions were more important for mood regulation than the brain regions near the vertex and that theories of ECT action emphasize the role of prefrontal cortex effects [103], one of us (M.S.G.) performed the first open trial of prefrontal TMS as an antidepressant in 1995 [104], followed immediately by a cross-over double-blind study [105]. The theory behind this work was that chronic, frequent, subconvulsive stimulation of the prefrontal cortex over several weeks might initiate a therapeutic cascade of events in the prefrontal cortex as well as in connected limbic regions. Thus, beginning with these prefrontal studies, modern TMS was specifically designed as a focal, nonconvulsive, circuit-based approach to therapy. TMS was conceived of and launched to serve as a bridge from functional neuroimaging advances in circuit knowledge to the bedside as a focal non-invasive treatment.

Since the initial studies, there has been continued high interest in TMS as an antidepressant. Multiple trials have been conducted by researchers around the world. In general, there is not a large industry sponsoring or promoting TMS as an antidepressant (or therapy for other disorders), and the funding for these trials has largely come from foundations and governments. The samples sizes in these antidepressant trials are thus small (in all, less than 100 subjects per trial) compared with industry-sponsored pharmaceutic trials of antidepressants. A thorough review of all of these trials is beyond the scope of this article.

An initial study from Spain from a group not involving a psychiatrist and without prior treatment trial experience in depression found profound antidepressant effects in psychotically depressed patients with only 1 week of left prefrontal treatment [106]. The design of this trial was unorthodox for studying depression, involving 1 week of therapy per month repeated over 6 months. Nevertheless, it generated much interest in the field. The findings of rapid response after only 1 week have not been replicated despite numerous attempts, and many early TMS trials were designed using this study to determine the sample size and treatment algorithms, leading to small underpowered studies using an inadequate stimulation intensity (80% of MT). Since then, most of approximately 20 studies have found modest antidepressant effects that take several weeks to build. Not all TMS antidepressant treatment studies have been positive, however [107].

Meta-analyses of transcranial magnetic stimulation antidepressant effect

There have now been five independent meta-analyses of the published or public TMS antidepressant literature (Table 1). Each of these meta-analyses has used different methods of selecting studies as well as different methods of performing the statistical analysis of the literature. Their different approaches are summarized in Table 1. Their results are the same: daily prefrontal TMS delivered over several weeks has antidepressant effects greater than sham treatment. An initial meta-analysis by McNamara et al [108] of 5 sham-controlled studies found that TMS was statistically significantly superior to sham TMS and that this difference was robust. In a different meta-analysis, Burt et al [109] examined 23 published comparisons for controlled TMS prefrontal antidepressant trials and found that TMS had a combined effect size of 0.67, indicating a moderate to large antidepressant effect. A subanalysis was done on those studies directly comparing TMS with ECT. The effect size for TMS in these studies was greater than in the studies comparing TMS with sham, perhaps reflecting subject selection bias. The authors suggested that perhaps TMS works best in patients who are also clinical candidates for ECT. Holtzheimer et al [110] analyzed both published and some unpublished sham-controlled studies and concluded that, overall, prefrontal TMS was superior to sham and that...
left-sided treatment had a nonsignificantly greater effect size. Yet another meta-analysis was recently conducted by Kozel and George [111]. This analysis was confined to published double-blind studies with individual data using TMS over the left prefrontal cortex. The summary analysis using all 10 studies that met criteria revealed a cumulative effect size of 0.53 (Cohen's D) (range: 0.31–0.97), with the total number of subjects studied being 230. The authors used a funnel plot technique to assess whether there was a publication bias in the literature to date and whether this bias might affect the results of the meta-analysis. This technique assumes that with small sample studies, there is a large chance of both erroneous positive and negative results. As the sample size of studies increases, the effect sizes should begin to converge, resembling a funnel. The funnel plot (Fig. 3) indicates that a publication bias is likely and that there are more positive small sample studies in the TMS antidepressant literature than should occur by chance. These authors then used techniques to determine how large this publication bias would have to be to change the results of the meta-analysis. The fail-safe results indicated that there would have to be 56 nonsignificant unpublished studies of approximately the same average sample size as the published studies to change the cumulative meta-analysis effect to a nonsignificant result (56 studies with Rosenthal's method, 22 studies with Orwin’s method). The most critical meta-analysis of the TMS antidepressant field was recently conducted using the guidelines put forth in the Cochrane Library [112]. This study cannot be compared directly with the other meta-analyses because it looks at the field from a completely different angle. Cochrane reviews typically try to establish the clinical value of a given therapy using stringent guidelines. The method is not well suited to look at small effects, which are scientifically important but are of lesser value in establishing clinical significance. In addition, Cochrane study

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection method</th>
<th>No. studies</th>
<th>No. subjects</th>
<th>TMS effect size</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>McNamara et al, 2001</td>
<td>R and L PFCX, DB</td>
<td>5</td>
<td>81</td>
<td>Active 43% greater than sham</td>
<td></td>
</tr>
<tr>
<td>Holtzheiser et al, 2001</td>
<td>R and L PFCX, DB, published and unpublished</td>
<td>12</td>
<td>210</td>
<td>Overall, Cohen’s D = 0.81</td>
<td>Left, Cohen’s D = 0.9, right = 0.7</td>
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<td></td>
<td>Compare with ECT, published</td>
<td>16</td>
<td>432</td>
<td>Cohen’s D = 0.67</td>
<td></td>
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<tr>
<td>Kozel and George, 2002</td>
<td>Left PFCX, DB, data available</td>
<td>12</td>
<td>230</td>
<td>Hedge’s D = 0.53</td>
<td>Funnel plot shows publication bias, 25–50 negative studies needed to change results</td>
</tr>
<tr>
<td>Martin et al, 2002</td>
<td>DB, published and unpublished</td>
<td>14 overall</td>
<td></td>
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<td></td>
<td>Left PFCX</td>
<td>9</td>
<td>197</td>
<td>2 weeks, TMS WMD-0.35 greater than sham</td>
<td>Does not allow for adjustment for difference</td>
</tr>
<tr>
<td></td>
<td>Right PFCX</td>
<td>1</td>
<td></td>
<td>2 weeks, TMS WMD-6.0 greater than sham</td>
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<tr>
<td></td>
<td>Compare ECT</td>
<td>1</td>
<td>40</td>
<td>2 weeks, ECT WMD 1.7 greater than TMS</td>
<td></td>
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*Abbreviations: TMS, transcranial magnetic stimulation; DB, double-blind; PFCX, prefrontal cortex; R, right; L, left; ECT, electroconvulsive therapy; WMD, weighted mean difference.*
groups try to include unpublished negative data to correct, at least in part, for publication bias. Moreover, the Cochrane method does not allow for within-study adjustments for between-group differences in illness baseline and instead uses raw illness variables. Thus, unequal initial distribution of illness severity, especially in small studies, can introduce significant bias into the results and conclusions. Even this stringent meta-analysis included 14 trials suitable for analysis, however [112]. Importantly, these investigators found “No difference...between rTMS and sham TMS using the Beck Depression Inventory or the Hamilton Depression Rating Scale, except for one time period (after 2 weeks of treatment) for left dorsolateral prefrontal cortex and high frequency; and also for right dorsolateral prefrontal cortex and low frequency, both in favor of rTMS and both using the Hamilton scale” [112]. In summary, all five meta-analyses of the TMS published literature concur that repeated daily prefrontal TMS for 2 weeks has antidepressant effects greater than those of sham.

Although there is general consensus that TMS has statistically significant antidepressant effects, a more important question is whether these effects are clinically significant. The meta-analyses discussed previously concur on an effect size of Cohen’s D of 0.65, which is a moderate effect in the same range as the effects of antidepressant medications. For example, small to medium effect sizes (0.31–0.40) are common in randomized controlled trials of novel antidepressants [113,114]. Thus, with respect to whether or not TMS has clinical significance, an important clinical issue is whether TMS would be clinically effective in patients referred for ECT. This question has been addressed in a series of studies in which ECT referrals were randomized to receive either ECT or rTMS. In an initial study, Grunhaus et al [115] compared 40 patients who presented for ECT treatment and were randomized to receive either ECT or TMS. ECT was superior to TMS in patients with psychotic depression, but the two treatments were not statistically different in patients without psychotic depression. This same group recently replicated this finding in a larger and independent cohort with an improved design (L. Grunhaus, personal communication, 2001). Recently, Janicak and colleagues [116] reported a similar small series finding near equivalence between TMS and ECT. The major differences between these studies and the rest of the controlled studies of TMS efficacy are the
patient selection (suitable for ECT), length of treatment (3–4 weeks), lack of blinding, and lack of a sham control. Unfortunately, none of the studies explicitly measured differences in cognitive side effects, although, presumably, TMS has no measurable cognitive side effects, whereas ECT has several. In a similar but slightly modified design, Pridmore [117] recently reported on a study comparing the antidepressant effects of standard ECT (three times per week) and ECT given one time per week followed by TMS on the other 4 weekdays. At 3 weeks, he found that both regimens produced similar antidepressant effects. Unfortunately, detailed neuropsychologic testing was not performed, but one would assume that the TMS and ECT group had less cognitive side effects than the pure ECT group. Finally, an Israeli group recently published their finding that relapse rates in the 6 months after ECT or rTMS were similar [118]. For both treatments to maintain maximal benefit, some form of maintenance therapy is recommended. In sum, TMS clinical antidepressant effects are in the range of those of other antidepressants and persist as long as the clinical effects after ECT.

Although the literature suggests that prefrontal TMS has an antidepressant effect greater than that of sham and that the magnitude of this effect is at least as large as that of other antidepressants, many issues are not resolved. For example, it is unclear how best to deliver TMS. Most but not all [119] studies have used focal coils positioned over the left prefrontal cortex. It is still not known whether TMS over one hemisphere is better than that over another hemisphere or whether there are better methods for placing the coil. For the most part, the coil has been positioned using a rule-based algorithm to find the prefrontal cortex, which was adopted in the early studies [46,104–106]. This method was shown to be imprecise in the particular prefrontal regions stimulated directly underneath the coil, depending largely on the subject’s head size [120]. Additionally, most studies have stimulated with the intensity needed to cause movement in the thumb (MT). There is now increasing recognition that higher intensities of stimulation might be needed to reach the prefrontal cortex, especially in elderly patients, where prefrontal atrophy may outpace that of motor cortex, where MTs are measured [121–123]. There are also emerging data that TMS therapeutic effects likely take several weeks to build. Consequently, many of the initial trials, which lasted only 1 to 2 weeks, were likely too brief to generate maximum clinical antidepressant effects.

Maintenance transcranial magnetic stimulation to prevent depression relapse after recovery

Because of its noninvasiveness and positive safety and cognitive profile, TMS is potentially attractive as a maintenance treatment. At MUSC recently, seven treatment-resistant bipolar depressed patients who had responded to an acute TMS trial were offered admission into a 1-year maintenance therapy of weekly TMS [124]. TMS was performed 1 day per week over the left prefrontal cortex at 110% MT and 5 Hz for 8 seconds for 40 trains. During this follow-up period, four subjects dropped out of the maintenance study and were labeled nonresponders (average of 25 weeks of treatment). Three subjects completed 1 full year of weekly TMS without a depression relapse. These data suggest that TMS might eventually be used as a maintenance tool in depression and that one treatment per week might be a good first attempt at a maintenance schedule. Much more work is needed, however.

Transcranial magnetic stimulation to treat mania

Grisaru and his colleagues in Israel [125,126] reported on an interesting study using either right or left prefrontal TMS in bipolar affective disorder (BPAD) manic patients admitted to their hospital for mania. TMS was given daily in addition to the standard treatment for mania. After 2 weeks, the group receiving right-sided TMS was significantly more improved than the group that had received left-sided TMS. The authors concluded that TMS might be useful as an antimanic agent. This same group has attempted to replicate these findings but has not found similar results (N. Grisaru, personal communication, 2001). Additionally, although subjects were assigned to the two groups at random, the left-sided group was more ill than the right-sided group on several measures. Further work is needed.

Current state of transcranial magnetic stimulation clinical practice for depression

In summary, TMS is a promising tool for treating depression acutely. It likely can also induce mania or hypomania in BPAD patients or susceptible patients. Its antimanic properties remain to be explored. Although it is approved in Canada and Israel as a treatment, it is still considered investigational in the United States by the FDA. Much work remains to understand the optimum
dosing strategy for the antidepressant effect of TMS. It is unlikely that the initial combinations of intensity, frequency, coil shape, scalp location, number of stimuli, or dosing strategy (daily, twice daily) are the most effective for treating depression. Some US and European psychiatrists are using TMS in clinical practice to treat depression under their general license to practice.

**Important unanswered clinical questions**

It is not clear which, if any, medications work well with TMS or interfere with its therapeutic effects. Despite these major unanswered questions, since the first use of prefrontal TMS as an antidepressant in 1995, this tool has clearly opened up new possibilities for clinical exploration and treatment of depression. Many parameters, such as intensity, location, frequency, pulse width, intertrain interval, coil type, duration, numbers of sessions, interval between sessions, and time of day, remain to be systematically explored. Although there are suggestions of antidepressant effects of TMS, there are questions about how it might be used in treatment algorithms. It will perhaps always be easier to see a clinician occasionally and take daily medication rather than traveling to a treatment facility for TMS on a daily basis. Thus, the ultimate clinical role of TMS in treating depression may be in medication-refractory cases, those who would otherwise receive ECT, or in patients who are unable to tolerate systemic therapy because of pregnancy [127] or a medical condition.

**Other conditions**

TMS has also been investigated as a possible treatment for a variety of neuropsychiatric disorders. In general, the published literature on these conditions is much less extensive than for TMS as an antidepressant; therefore, conclusions about the clinical significance of effects must remain tentative until large sample studies are conducted.

**Movement disorders**

Some initial studies found positive effects in Parkinson’s disease [128]; however, one of these early results could not be replicated [129], and some of the methods described were actually not credible. Moreover, a recent study found that TMS delivered over the supplementary motor area (SMA) actually worsened Parkinson’s disease symptoms [130].

Three other recent studies [131–133], however, as well as a study from Japan using TMS over the prefrontal cortex at low frequencies and doses [134,135] report that TMS may improve effects in Parkinson’s disease. Further studies are needed. It should be remembered that only a small portion of the combinations of use parameters, brain regions, and dosing schedules have been tried.

There are two small positive studies showing that TMS can benefit writer’s cramp, a form of focal dystonia [136]. After publication of a positive small abstract, two groups have used TMS to investigate and possibly treat Gilles de la Tourette syndrome [137]. One study found modest and transient beneficial effects on tics when applied over prefrontal cortex (M. Trimble, personal communication 2002). Another study at MUSC also found positive effects on tics and obsessive-compulsive disorder (OCD) symptoms [137]. Further work is needed in this promising area.

The TMS MT is reduced in patients with untreated epilepsy [138], hinting at widespread problems in cortical excitability. Therapeutically, there is one report of potential beneficial effects of slow rTMS in action myoclonus [139]. Additionally, TMS has been used to examine cortical excitability and inhibition in Tourette’s syndrome, dystonia, and OCD [18,19]. Reduced intracortical inhibition has been reported in all three illnesses.

**Schizophrenia**

Several studies have used TMS to investigate schizophrenia without consistent replication of early findings, which were compounded by medication issues [140,141]. A 1-day prefrontal TMS challenge study by Nahas and colleagues [142] at MUSC failed to find significant effects on negative symptoms. Hoffman and colleagues [143,144] have used low-frequency TMS over the temporal lobes to treat hallucinations in patients with schizophrenia. Although they have replicated their earlier study, another group has tried to replicate this effect without success (K. Ebmeier, personal communication 2002).

**Anxiety disorders**

In a randomized trial of left and right prefrontal and midoccipital 20-Hz stimulation in 12 patients with OCD, Greenberg et al [145] found that a single session of right prefrontal rTMS decreased compulsive urges for 8 hours. Mood was also transiently improved, but there was no effect on anxiety or obsessions. Using TMS probes, the
same group reported decreased intracortical inhibition in patients with OCD [146], which has also been noted in patients with Tourette’s syndrome [19]. Somewhat surprisingly, OCD patients had a lowered MEP threshold in one study [147], which was unrelated to intracortical inhibition and seems to replicate (E.M. Wassermann, personal communication 2002). Only two other studies have examined possible therapeutic effects of rTMS in OCD. A double-blind study using right prefrontal slow (1 Hz) rTMS and a less focal coil failed to find statistically significant effects greater than those of sham [148]. In contrast, a recent open study in a group of 12 OCD patients refractory to standard treatments, who were randomly assigned to right or left prefrontal fast rTMS, found that clinically significant and sustained improvement was observed in one third of patients [149]. Clearly, further work is warranted testing TMS as a potential treatment for OCD.

McCann et al [150] reported that 2 patients with posttraumatic stress disorder (PTSD) improved during open treatment with 1 Hz of rTMS over the right frontal cortex. Grisaru et al [151] similarly stimulated 10 PTSD patients over motor cortex and found decreased anxiety. Grisaru and colleagues also reported a positive TMS study in PTSD patients (N. Grisaru, personal communication, 2001). Further work is needed.

A potential new way of using transcranial magnetic stimulation–magnetic seizure therapy as an antidepressant

The discussion throughout this article has focused on using TMS to change brain function without inadvertently causing a seizure. As mentioned previously, TMS at high frequencies and intensities can cause seizures. ECT produces a seizure through direct electric stimulation, under anesthesia, of the scalp and skull. Although ECT is the most effective antidepressant, it has cognitive side effects and does not work in up to half of treatment-resistant patients. If one used TMS to induce an ECT-like seizure, one might be able to focus the point of origin of the seizure and thus spare some brain regions from unnecessary exposure to electric currents and to seizure spread. This is possible with TMS, because magnetic fields pass through the scalp and skull unimpeded, whereas the direct application of electricity to the scalp with ECT loses focality and power as a result of the impedance of the overlying tissue. After a proof of concept demonstration in primates [152], Lisanby et al [36] used an enhanced device with four times the usual number of charging modules to induce seizures in depressed patients referred for ECT. Further clinical and preclinical work with this exciting technique called magnetic seizure therapy (MST) has proceeded. An initial safety study found that MST seizures were briefer in duration than ECT seizures, that patients awoke from anesthesia much faster with MST, and that their acute cognitive side effects were much less with MST [153]. Further work is underway to determine whether this technique has antidepressant effects. Because MST induces a seizure, it still requires repeated episodes of general anesthesia.

The long-held dogma in the field of convulsive therapy was that a seizure was necessary and sufficient to constitute an effective treatment for depression. Recent research in ECT and new work in TMS have challenged both aspects of that theory with respect to the antidepressant potential of brain stimulation. First, it was demonstrated that it was possible to generate seizures with ECT that lacked efficacy; thus, a seizure cannot be sufficient [154,155]. What we have learned about the features that distinguish effective from ineffective seizures has guided the development of MST as a more targeted way of producing an effective treatment that should be less contaminated by the consequences of generalization to regions of the brain linked to cognitive side effects (medial temporal structures). Because MST offers a focal means of inducing seizures, it is possible to use MST to examine the roles of the location of seizure onset and patterns of seizure spread in the antidepressant effects and cognitive side effects more precisely than one could do with ECT.

In addition to not being sufficient, recent work with TMS has challenged the theory that a seizure is necessary at all [156]. This radical notion was not easily accepted by the field as recently as 8 years ago, because it challenged the then widely held dogma that a seizure was needed for ECT, and by extension, any form of transcranial stimulation to be effective in treating depression. The recent suggestions of antidepressant effects of vagus nerve stimulation (VNS) in treatment-resistant depressed patients [157–159] as well as in comorbid epilepsy and depression patients [160,161] add weight to the notion that somatic treatments can improve mood without causing a seizure (VNS does not cause seizures and is, in fact, an anticonvulsant treatment method). Additionally, the recent reports of mood effects with DBS also underline the point that nonconvulsive
stimulation can powerfully change mood [162]. The recent studies with MST, although perhaps a radical improvement over the current methods of inducing seizures, still work within the paradigm that a seizure is needed for antidepressant effects. If MST has clinically significant antidepressant effects that are not associated with side effects, one could imagine eventually doing a direct comparison of MST versus TMS over the same region and finally settling the argument over the necessity of the seizure to treat depression. While debating the theory can be useful in refining our perspective on the modes of action of antidepressant treatment, it is important to recognize that these various brain stimulation techniques for depression are not in competition; rather, each may be helpful for specific subpopulations of depressed patients. Demonstrating that a subconvulsive form of stimulation can be effective in depression does not necessarily make convulsive forms of treatment obsolete. The goal has been to expand our therapeutic options for severely ill and resistant patients and, in the process, to illuminate the brain circuitry and common mechanisms underlying antidepressant action.

Summary

TMS is a powerful new tool with extremely interesting research and therapeutic potentials. Further understanding of the ways by which TMS changes neuronal function, especially as a function of its use parameters, will improve its ability to answer neuroscience questions as well as to treat diseases. Because of its noninvasiveness, it does not readily fit under the umbrella of neurosurgery. Nevertheless, it is important for neurosurgeons to be aware of TMS, because findings from TMS studies will have implications for neurosurgical approaches like DBS and VNS. Indeed, it is possible to think of using TMS as a potential noninvasive initial screening tool to identify whether perturbation of a circuit has short-term clinical effects. In the example of chronic refractory depression or OCD, which is generally a chronic illness, it might then follow that rather than having daily or weekly TMS for the rest of their lives, patients would have DBS electrodes implanted in the same circuit.

Whatever road the future takes, TMS is an important new tool that will likely be of interest to neurosurgeons over the next 20 years and perhaps even longer.

Acknowledgment

The authors dedicate this article to Marty Szuba, MD, from the University of Pennsylvania.

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From psychosurgery to neuromodulation and palliation: history’s lessons for the ethical conduct and regulation of neuropsychiatric research

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We are certain that these experiments shall stir up keen discussions in the medical, psychiatric, psychological, philosophical, social and other fields. We expect that, but hope at the same time that this discussion shall promote the progress of science and above all the benefit of mental patients [1].

Egas Moniz, 1936

...We, the doctors, are so fallible, ever beset with the common and fatal facility of reaching conclusions from superficial observations, and constantly misled by the ease with which our minds fall into the rut of one or two experiences [2].

William Osler, 1903

Optimism tempered by history

As we contemplate the emerging era of neuromodulation and imagine the utility of deep brain stimulation for disease entities in neurology and psychiatry, our enthusiasm is immediately tempered by history. Just a generation ago, other confident investigators were heralding invasive somatic therapies like prefrontal lobotomy to treat psychiatric illness. That era of psychosurgery ended with widespread condemnation, congressional calls for a ban [3], and a vow that history should never repeat itself. Now, just 30 years later, neurologists, neurosurgeons, and psychiatrists are implanting deep brain stimulators for the treatment of Parkinson’s disease and contemplating their use for severe psychiatric illnesses, such as obsessive-compulsive disorder (OCD) [4,5] and the modulation of consciousness in traumatic brain injury [6–8].

Any student of medical history would have to ask if these developments are ethically appropriate and whether the promise of neuromodulation will be able to transcend the potential peril associated with the manipulation of motor, psychiatric, or cognitive function. Can today’s investigators avoid the moral blindness of their predecessors? Will society tolerate this new foray into somatic therapy and seek to regulate it as legitimate science, or will a lingering memory of psychosurgery be so overwhelming as to make this impossible?

Lay journalists covering the most exciting developments associated with deep brain stimulation often ask these questions [9]. A recent editorial in The Economist, for example, asserted that these new developments in neurobiology pose a “greater threat to human dignity” than the debate over cloning [10]. Editorialists like William Safire have raised questions about the world of “neuroethics” [11], and The Washington Post Magazine featured a story on the lobotomist Walter Freeman in response to the excitement over deep brain stimulators [12]. In the lay press, the link between psychosurgery and present efforts in neuromodulation is clear, and the message has been cautionary [13].

Historical analogies are important, but they only tell part of the story. From a scientific
standpoint, there are critically important differences between psychosurgery and neuromodulation. Although both are somatic therapies, deep brain stimulation seeks to modulate brain function through the insertion of electrodes. In contrast, psychosurgery destroyed vital brain tissue through lesioning. These lesions were also permanent, whereas the presently known effects of neuromodulation are reversible. In addition, the permanent cognitive impairment seen with psychosurgical ablation does not occur with deep brain stimulation.

There are also important differences between Freeman’s prefrontal lobotomy and psychosurgical procedures performed today. Psychosurgical operations of the past were crude and their rationale was based on a mix of anecdotal experience and supposition [14,15]. Current psychosurgical procedures utilize modern neuroimaging techniques and are more precise and procedurally diverse. They have a more benign side effect profile and demonstrate evidence of efficacy for some refractory neuropsychiatric conditions [16].

Modern neuromodulation’s knowledge base, although still a nascent area of investigation, far exceeds what was known to psychosurgeons at midcentury [17]. Today, clinical investigators are supported by an extensive platform of structural and functional neuroimaging and detailed anatomic and electrophysiologic studies that allow for more precise hypotheses concerning neural systems underlying disease states.

These improvements have led to greater procedural precision and better diagnostic capacity to identify mechanisms of action, efficacy, and lack of therapeutic response. In the treatment of Parkinson’s disease, these advances have coalesced so that neuromodulation is now a mature and established therapy for refractory disease [18,19]. Deep brain stimulation procedures for movement disorders are covered in the United States by Medicare and have become the standard of care for refractory disease.

Although these scientific differences are significant, a more salient distinction is the respective historical and cultural contexts of psychosurgery and neuromodulation. Historically, psychosurgery developed before the rise of modern bioethics. Neuromodulation, today, is emerging both against the historical backdrop of psychosurgery and within an ethical and regulatory context that should be far more attentive to human subject protections.

By reviewing the history of the psychosurgery movement, I will demonstrate that this work continued in an unregulated and ethically disproportionate fashion despite well-articulated and early criticism. I will maintain that this was possible because there was no mechanism to regulate the conduct of these practices until the advent of modern bioethics in the late 1960s and early 1970s as a scholarly discipline able to influence clinical practice and public policy.

Earlier critiques, although often cogent and well informed, were unable to influence clinical or research practice because they were made in a practice environment that had yet to overcome the prerogative of the physician to direct care without additional oversight. As we shall see, individuals who criticized their colleagues’ practice of psychosurgery in the literature or at national meetings were powerless to ensure that their concerns were heard at the psychosurgeon’s home institution. There was no mechanism to collect these arguments and regulate these activities. It would take broader societal changes, such as the decline of physician paternalism and the emergence of civil and patient rights [20] reflected in the establishment of bioethics think-tanks like the Hastings Center and the regulatory efforts of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, before broader regulations governing clinical research were put into place.

Sadly, much of this history has already been forgotten or deemed irrelevant. In an oddly analogous way, the debate over lobotomy and psychosurgery has gone the way of a Tommy Dorsey long-playing record or a Led Zeppelin eight-track tape. As we shall see, many of the regulatory recommendations made by the National Commission, such as the proposed National Psychosurgery Advisory Board or recommendations on research involving the institutionalized mentally infirmed, never went into law. This lacuna in the law necessitated the Clinton era 1998 National Bioethics Advisory Commission’s “Report on Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity” [21]. Ironically, this is yet another set of recommendations that have yet to be ensconced in Federal regulations.

The emergence of neuromodulation as a credible science with real and potential clinical applications, however, makes it essential that we revisit these earlier ethical and clinical debates so that the hard-won wisdom and scholarship of earlier eras
can help to navigate what will be demonstrated as recurrent ethical challenges. Many familiar questions about consent, coercion, and personhood are now resurfacing in the debate over applying neuromodulation techniques, *né psychosurgery*, to OCD, the first of many psychiatric entities to which this modality may be applied.

It is my hope that a reconsideration of this rich history in light of these promising scientific developments will deepen the insight of a new generation of psychiatrists, neurologists, and neurosurgeons who are destined to face challenges that their forbears could only have imagined.

**When psychosurgery was therapy**

It is one of those strange paradoxes in history that 2 years after the articulation of the Nuremberg Code and the development of the stereotactic technique, Egas Moniz won the Nobel Prize for the development of the prefrontal leukotomy [22,23]. He began his work in 1935 [24], just 3 years after the initiation of the Tuskegee Syphilis Study [25]. Both the Tuskegee Syphilis Study and psychosurgery would be criticized decades later as an abrogation of patient rights invoking the same ethical principles articulated in the Nuremberg Code. In 1949, however, the Nobel Prize celebrated Moniz’s work in medicine and physiology.

Although some have maintained that the Nobel Prize was really meant for Moniz’s more enduring discovery of cerebral angiography [26], the citation on his medal read simply, “For his discovery of the therapeutic value of prefrontal leucotomy in certain psychoses” [27]. The understatement in this inscription fails to capture the lack of effective therapy for severe mental illness and the desperation of patients and the frustration of their families and caregivers. When Moniz was given the prize, his work was hailed as being at the vanguard of therapeutics for severe mental illness [28]. In the era before the introduction of antipsychotics, prefrontal lobotomy offered a potential therapy for the severely and persistently mentally ill who otherwise would require institutionalization. It was viewed as a therapy of last resort and positively portrayed in the American media, at least in the early years after its introduction [29].

All was not sanguine in professional circles, however. As early as 1938, Oskar Diethelm, a contemporary of Freeman and Watts in the United States, poignantly warned about the emerging somatic therapies in psychiatry [30]. In an address at the Annual Meeting of the American Psychiatric Association in San Francisco, the New York psychiatrist urged professional humility. He cautioned investigators to have some humility in their speculations and an awareness of the investment that they have in their own theoretic speculations. To mitigate against these excesses, he urged investigators to assume as “an inflexible duty” to gain knowledge of the mechanism of any proposed therapy [30]. Specifically, he observed:

> In any scientific treatment which is not fully understood there is the serious danger of not being able to predict possible damage. It should be an inflexible duty to become thoroughly familiar with the drug or procedure to be employed. This implies a thorough understanding of the physiological and psychobiological functions which may have a bearing on the proposed treatment. No one has the right to invent theories to suit his desires without having given full consideration to what has been established or found plausible [30].

In the same address, Diethelm implicitly commented on issues that would later inform the literature on informed consent. He warned of the vulnerability of lay people to the latest scientific trend and the powerlessness of patients, “who are forced to follow”:

> ...it is important in medicine to recognize fully the responsibility with regard to those who follow voluntarily that is the physicians; to those who follow blindly, that is lay people; and to those who are forced to follow, that is the patients. The pleasure of being an inventor and pathfinder is alluring but leads to all the dangers of adventure [30].

In these comments, Diethelm anticipates the Nuremberg Code with its emphasis on the scientific basis of human experimentation and the centrality of informed consent and voluntariness [31].

A young psychiatrist attending the same meeting tells us that, as yet, there was no mention of Moniz’s work at the conference and that Diethelm did not mention lobotomy specifically in his address [32]. His comments were more generic and directed toward the growing place of somatic therapy in psychiatry, a subdiscipline of the field of which psychosurgery would become a part.

Diethelm’s warnings would be applicable to the leading proponents of psychosurgery as illustrated by the hubris of both Freeman and Moniz.
Moniz himself was smug and overly optimistic about his work and methods. In an early summary article originally published in the *American Journal of Psychiatry* in 1937, he summarily dismissed any discussion of the risks and benefits of his prefrontal leukotomy. He simply concluded by asserting:

> Following this exposition I do not wish to make any comment since the facts speak for themselves. These were hospital patients who were well studied and well followed. The recoveries have been maintained. I cannot believe that the recoveries can be explained upon simple coincidence. Prefrontal leucotomy is a simple operation, always safe, which may prove to be an effective surgical treatment in certain cases of mental disorder [33].

Freeman, too, was overly confident. Just months before the American Psychiatric Association meeting, he demonstrated the traits that Diethelm believed were so dangerous in a clinical investigator. Lawrence M. Weinberger recalls that as a young physician, he met Freeman in the spring of 1938. Weinberger was a second-year fellow in neurologic surgery at the University of Pennsylvania and had traveled to the Delaware State Hospital to meet Freeman and to learn how to perform the novel procedure. Freeman’s method of patient selection and his “purely observational” technique of determining who might be a suitable candidate for surgery mortified Weinberger. He asked Freeman about his selection criteria and “...was answered with a prolonged silent stare and finally one word: ‘Experience!’” [34]. Weinberger reported being “squelched” and saying no more [34].

Concerns were not limited to junior trainees. Roy Grinker publicly questioned Walter Freeman at a panel discussion before the Section on Nervous and Mental Diseases at the annual session of the American Medical Association held in Cleveland in 1941 [35]. At that time, Grinker was Chief of the Division of Neuropsychiatry at Michael Reese Hospital in Chicago. He would later become a training analyst and Editor-in-Chief of the *Archives of General Psychiatry* [36].

Grinker sought to moderate attitudes toward lobotomy, about which he acknowledged “...a great deal of preconception and emotional bias.” He acknowledged that there was controversy between those who believed that the psychoses had an organic basis and might be amenable to “physical therapy in psychiatry” and those opposed to a “...mutilating operation that destroys brain tissue.”

Ultimately, Grinker questioned Freeman’s methodology because “...once one cuts, there is no return.” Given the irreversibility of the procedure, he voiced concern about how patients were selected for the procedure and the vagueness of entry criteria that required the patient to have failed “conservative measures.” He was particularly aware of the vulnerability of most of the patients who came from state facilities and whose preoperative assessment was suspect:

> ...We are dealing with a large number of patients who have been chosen from state hospital populations. There have been some private cases, it is true, but when one thinks of what conservative treatment means, of what actual, thoroughgoing psychologic study and treatment means, it is difficult to imagine that the patients who come from state hospital populations are getting the benefit of that type of treatment [35].

He expressed his “surprise” that patients were lobotomized after only a few months of mental illness before a spontaneous remission might occur and in young patients in their 30s. He also questioned the application of the procedure to a wide range of diagnoses and was concerned about the postoperative defects and the means to assess their impact on intelligence.

Addressing the risks of the procedure, he suggested that more attention needed to be paid to cognitive impairment and the late effects of scarring, which might lead to the development of seizure disorders. He also noted the vague way in which cognitive defects were described noting, “There must be developed a technique of measuring very carefully both the existing function and the defect in the individuals before and after the operation” [35]. Grinker also observed that a technologic solution to psychic problems was not always in order, although the alternatives were often more time-consuming and taxing:

> It is obvious that if the anxiety and suffering, the things which one wants to relieve, are based on conflict, the rational basis of treatment is a psychological therapy. This can not always be done. It is sometimes very tedious and very costly, but if it were more possible we would not hesitate to ask for more psychologic work in state hospitals rather than more operating rooms [35].
Building on a therapeutic approach that was broader than the merely surgical, Grinker also outlined the professional responsibilities of the surgeon and his obligation to ensure that adequate assessment occurred before any procedure was performed. Without equivocation, he asserted that:

I do not believe that the surgeon can assume the responsibility of being the operator at the behest of his neurologic and psychiatric friends and say “I did it because they told me to.” He must assume the responsibility of insisting that before such operations are done all conservative means—and by “conservative means” I mean thorough going psychological treatment—have been employed [35].

Grinker’s criticisms are all the more credible because he did not categorically condemn the procedure. Instead, he saw it not as a therapy but “still an experiment.” Amid proponents and critics of psychosurgery, he confessed that his point of view, “…perhaps might disappoint some, as I am not iconoclastic about the operation.” He believed that the operation had a “usefulness” but that “the delimitations of its usefulness have not been clarified.” Until those limitations became better understood, he cautioned that “…I do not think this is the time to disseminate it widely to the profession or to the public…”

Unfortunately, Grinker’s pointed—and balanced-criticism of the lobotomy in 1941 had little impact. Although he urged restraint and viewed lobotomy as experimental, the procedure was widely disseminated as therapy over the next 10 years. It is estimated that by 1951, 19,000 to 20,000 Americans were lobotomized, with many of those subjected to the procedure being returning veterans [37]. In spite of growing professional uncertainty about the effectiveness of the procedure and its safety, public sentiment was positive enough to compel the Veterans Administration and state hospitals to introduce the procedure [38]. It is estimated that nearly 3000 returning veterans underwent psychosurgery [39].

Although Grinker’s early criticism did little to stem the tide of lobotomy, his well-considered concerns about methodology, patient selection, outcome data, and the morbidity associated with the procedure would be revisited by the First Research Conference on Psychosurgery convened by the National Institute of Mental Health in 1949 [40]. During this meeting, although lobotomy was being used as a therapy in the community, the editor observed that, “although we seem well warranted to continue the procedure, it is not even clear that psychosurgery, as performed now, is more beneficial than harmful” [40]. Experts were unable to reach a consensus except to conclude that “…an enormous amount of further research is an imperative need in nearly every aspect of the field” [40].

Among these needs was greater clarity about whom the procedure was being performed on and how patients fared. Eleven years after Weinberger personally questioned Freeman about his method of selecting patients and evaluating outcomes, methodologic issues remained a concern. One thoughtful commentator on that era has maintained that the patient’s diagnosis was less relevant than the severity of the patient’s symptoms in determining whether or not he or she would be a surgical candidate [41]. It was against this imprecision that experts agreed that there was a need for a comprehensive means of engaging in outcome measures to discern whether the procedure was efficacious and on which subjects. Efforts to introduce quantitative analysis were complicated, however, because markers of improvement, such as hospital discharge, could be a result of the patient’s family situation [42]. Indeed, if any consensus was achieved at the First Research Conference on Psychosurgery, it was that a majority of assembled experts urged the adoption of a “…universally accepted rating scale, with patients individualized by diagnosis or other category…[to] provide an effective method for both case-selection and evaluation of operative results” [40].

In the second edition of his comprehensive textbook on psychiatric treatment, Diethelm noted that the operative procedures under consideration had “undergone considerable modification” [43]. He viewed these modifications as evidence of what he described as “therapeutic insecurity which should exert a strong critical hesitancy on the part of the clinician who is considering surgical procedure” [43].

Despite growing controversy about the safety and efficacy of psychosurgery at subsequent national conferences [40,44] and concerns about the side effects of the procedure [45], these concerns did not decrease the incidence or popularity of the procedure. Although articulated at conferences or in journals, these criticisms had little impact on the incidence of psychosurgery in the
United States. Between 1936 and 1946, some 6000 patients were operated on in the United States alone [46]. By the late 1950s, 40,000 to 50,000 procedures had been performed in the United States, with some 4000 estimated by Freeman to have been done or directed by him in 30 hospitals in 15 states nationwide [47]. Rosemary Kennedy, the sister of President Kennedy, was among those operated on.

The popularity of the procedure needs to be contextualized against the dismal condition of state mental hospitals and the absolute lack of effective treatment for the persistently and chronically mentally ill. One representative report from a state hospital during that era describes lobotomy as a “fruitful method in the treatment of chronic mental illness,” with 37.4% of patients being able to be discharged from hospital after the procedure [48]. The authors of this study, which mostly involved patients with schizophrenia, maintained that:

...While there are many limitations and failures with this treatment, they are overshadowed by the generally satisfactory and not infrequently brilliant results. It is still difficult to assess the extent to which technical difficulties or inherent resistance of the disease process contribute to operative failures. However, it is truly gratifying to observe a patient who was previously a tremendous problem in management—secluded, untidy, aggressive, destructive, and combative to the point of requiring half a dozen attendants to carry out the basic necessities of personal care—become a quiet cooperative individual, taking pride in her personal appearance, assisting with various ward tasks, and finally returning to her own home. Possibly only those who have served in a state hospital can appreciate fully these problems. The comments we have heard occasionally to the effect that postlobotomy patients lack judgment, and cannot, for example, plan a meal or play a good game of bridge seem to lack satisfactory perspective when one regards the level from which these individuals were plucked. Lobotomy is not a cure-all but it can well be regarded as an encouraging therapeutic weapon for a very malignant disease [48].

Although studies like this one failed to take into account a potential placebo effect or the possibility of spontaneous remission, criticism of lobotomy hinged on the question of side effects and not on the important issue of efficacy. The question was not whether lobotomy altered the status of the patient’s symptoms but whether the cognitive side effects were justified [49]. Nolan Lewis, Director of the New York Psychiatric Institute, asked whether “the quieting of a patient” was indeed a “cure” and worried about the number of “zombies” and “mental invalids” produced as a consequence of the procedure [50].

The decline of psychosurgery was not prompted by ethical concerns but rather by the advent of modern psychopharmacology and effective therapy for psychoses with the major tranquilizers, such as chlorpromazine in 1954. Indeed, two commentators have opined that even with the growing backlash against psychosurgery in the early 1950s, the lack of an effective alternative would have been sufficient to keep the procedure in “common use” [51].

Psychosurgery and the body politic

Not even chlorpromazine was enough of an advance to remove psychosurgery entirely from therapeutic consideration in the 1960s and early 1970s. Some physicians, such as the Harvard neurosurgeon H. Thomas Ballantine, Jr, maintained that psychosurgical procedures like cingulotomy retained a role in conjunction with standard psychiatric care for refractory patients. He articulated guidelines to regulate the judicious use of the procedure for the relief of the patient’s suffering and improvement of functioning in society. Procedures were to be reserved for patients who failed all other methods of treatment. Decisions to operate were to be made in conjunction with a psychiatrist, who would also make psychiatric follow-up available, and patients and family were to be informed of potential risks and benefits. Most critically, he condemned the use of psychosurgery for political or social purposes, articulating instead a solely patient-centered rationale for the procedure [52].

It was the social uses of psychosurgery for what was called behavior control that, which Ballantine and others condemned, that caused a furor during that era. As distinct from its earlier iteration as a means to address a patient’s depression or schizophrenia, this more modern dimension of psychosurgery sought to modify behavior. Amid the social turmoil of that era, sociobiologists began to suggest that psychosurgery might have a role in addressing problems like violence or civil unrest. It is perhaps hard to
imagine today that there could be serious concerns about such futuristic attempts at social control, but they were quite real. One news report in the Medical News column in the *Journal of the American Medical Association* sought to reassure the wary reader that “Logistically, psychosurgery for social control is highly unlikely, simply because there are not enough neurosurgeons” [53].

This second period in the history of psychosurgery could be said to have begun through the work of Jose M.R. Delgado. Coupling psychosurgery with burgeoning efforts in computer technology and solid state electronics, Delgado advanced the idea of “psychocivilizing society” using an implantable brain implant that could be operated by remote control [54]. Delgado came to international attention in 1965 when he returned to his native Spain for a now famous publicity stunt in which he demonstrated the potential of his work by stopping a charging bull in Cordoba’s bullring using a “stimociever” he had developed [55].

Delgado’s work raised concerns about the possibilities of mind control, and his legacy remains a lingering question for the current era of neuromodulation. Recent reports in the lay press describing a remotely controlled “cyborg” rat with a brain implant [56] alluded to Delgado’s work [57,58], thus resurfacing the question of mind control, which had explosive political consequences when first introduced.

A physician and physiologist working in the Department of Psychiatry at Yale University, Delgado studied aggression in primates and then manipulated their response through the use of implantable electrodes, arguing that “a better understanding of the neurophysiological mechanisms responsible for aggressive and destructive reactions may provide man with greater capacity to educate and direct his own behavior” [59]. Delgado, some of whose work was funded by the United States Public Health Service, the Office of Naval Research, and the Department of the Air Force [60,61], argued that society was on the cusp of a new era in which the human mind could influence its own evolution through the use of technology. Using notions of self-dominion, he envisioned an escape from the blind chance of normal evolution to one where man and technology would alter human history, ultimately leading to a “...future man with greater personal freedom and originality, a member of a psychocivilized society, happier, less destructive, and better balanced than present man” [54].

Delgado analogized cerebral pacemaking to the growing role of cardiac pacemakers as a means to suggest the utility of brain pacemaking in the future. He acknowledged concerns about the ethical implications of his work and urged “intelligent collaboration of the best minds” to address the field’s “fundamental medical, social, and even philosophical implications.” Nonetheless, he urged continued scientific progress, noting that “We are certainly facing ethical, philosophic, and practical problems not exempt from risks, but we should also expect important medical application of the new methods to epilepsy, intractable pain, involuntary movements, and mental disorders” [62]. His position might be best summed up by his observation that “Fears have been expressed that this new technology brings with it the threat of possible unwanted and ethical remote control of the cerebral activities of man by other men, but this danger is quite improbable and is outweighed by the expected clinical and scientific usefulness of the method” [63].

Leading proponents of psychosurgery for the control of violence were Frank R. Ervin, a psychiatrist at the Neuropsychiatric Institute at the University of California at Los Angeles, and Vernon H. Mark, a Harvard neurosurgeon, who together coauthored *Violence and the Brain* [64]. Much of their work hinged on seeking to demonstrate the relation between organic brain disorders, such as temporal lobe epilepsy (TLE), and violent or aggressive behavior. In one early case, they were able to demonstrate a left temporal horn lesion by means of a pneumoencephalogram in a young woman with TLE in whom violent outbursts were inducible using implantable electrodes and telemetric equipment supplied “through the courtesy and assistance of Dr Delgado” [65].

Echoing Delgado’s notion of “greater personal freedom,” Mark maintained that “I believe the correction of that organic condition gives the patient more rather than less, control over his own behavior. It enhances, and does not diminish, his dignity. It adds to, and does not detract from, his human qualities” [66]. Although many of Mark’s aspirations for psychosurgery seem overly optimistic, he did foreshadow developments in psychiatry, moving that field from being dominated by psychoanalysis and “political psychiatrists” toward those having an interest in the organic basis of disease [67].

He wrote about the “absurd split” and the:
...historical dichotomy between 'purely organic' and 'purely social' abnormalities. Specifically, physicians tend to categorize a few abnormal behaviors, such as paralysis, blindness and dementia as neurological problems. At the same time, certain other abnormalities, such as depression and aggression, have found a hard niche within the domain of the psychiatrists, sociologists and criminologists. Many of them view these behaviors as nothing but the reflections of particular environments. They tend to believe that brain function or dysfunction is not an important determinant of abnormal behavior [68].

As much as his work in psychosurgery, these views seemed to have engendered a backlash from the more purely socially oriented practitioners who saw psychiatry in political or sociologic terms [69]. This schism made Mark the target of what he described as an “anti-psychiatry campaign” [70]. Reacting to a brief letter he wrote with colleagues to the Journal of the American Medical Association in 1967 on the potential relation between brain disease and urban riots [71], Mark was accused of racism by proponents of social psychiatry [72].

This assault on psychosurgery was led by Peter Roger Breggin, a Washington social psychiatrist. A self-described political conservative and civil libertarian [73], Breggin sought to characterize psychotherapy and on a continuum of a totalitarian-libertarian axis in which a “high degree of autonomy and personal freedom characterizes more libertarian therapies” [74]. In this context, public psychiatric hospitals and psychosurgery were seen as vectors of social control and described as “custodial concentration camps” and “powerful totalitarian technologies,” respectively.

In Congressional hearings before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, Breggin charged that psychosurgeons were unethical because of how they obtained consent for the procedures they performed. He was deeply suspicious of how psychosurgeons sought to regulate their activities through review committees that relied on “professional ethics and medical control” to maintain physician control of the situation. Ultimately, Breggin said, “It creates for themselves an elitist power over the human mind and spirit. If America ever falls to totalitarianism, the dictator will be a behavioral scientist and the secret police will be armed with lobotomy and psychosurgery. And by the way, lobotomy and psychosurgery is an ethical, political and spiritual crime. It should be made illegal” [75].

Breggin's accusations seem more suited to the clinical work of Freeman than to the positions taken by Mark, who was opposed to any social application of his work. In a talk delivered at the Hastings Center's Institute of Society, Ethics and Life Science's Working Group on Behavior Control, he sought to refute the charge of racism lodged against the neurosurgical treatment of violent epileptics [76]. He asked, “Does the theory that some violence is caused by brain disease lead us to expect it is a characteristic mainly of black people? Certainly not. On the other hand the theory that personal violence is caused exclusively by social conditions might very well lead us to look at the black ghettos. The environmental cues to personal violence may very well cluster around racially differentiated areas” [76]. Citing the prevalence of domestic violence across all demographics, both rich and poor as well as black and white, he asserted that “From this perspective, claret is the predominant color [of violence], not black or white” [76]. He would consistently maintain that violence was colorblind in both domestic and international contexts [77].

Indeed, he was one of the first to advocate an “integrated approach” to psychosurgical care. At Boston City Hospital, where he was Director of Neurosurgery, he sought to overcome the dichotomous practices of his neurologic and psychiatric colleagues and to develop a “holistic” therapy in which “...treatment of a patient should involve not only his brain but his family, living conditions, job and role in society. It is very important, therefore, to imbue a neurological diagnosis of problems of violence into a larger integrated approach to human behavior.” Along these lines of comprehensive care, he also advocated a “committee of some sort” that would oversee consent while not accepting patients who do not want therapy.

In retrospect, Mark’s attempt to address organic illness with due attention to the patient's voluntary consent comes across as moderate during inmoderate times prone to hyperbole, overreaction, and suspicion. There was a prevailing sense of alarm that psychosurgery was being broadly applied in law enforcement. Contemporary accounts of that era observed that one of the “appeals” of psychosurgery was viewed as the willingness of law enforcement agencies to embrace this technology for the purpose of addressing seemingly intractable problems. One international
Still another cultural aspect which adds to the appeal of psychosurgery is the readiness of the American government to seek solutions to its domestic problems which hide the causes of the problems. Psychosurgery can be one such solution if used to “cure” the nation’s social problems. The Justice Department and several state departments of correction (notably California’s) have shown great interest both in establishing that black rioters and aggressive inmates are suffering from brain dysfunction and in curing them through psychosurgery. Three leading proponents of psychosurgery have advanced the view that many of those involved in ghetto rebellions acted violently because of brain dysfunction. The accumulated results of racism and poverty were discounted as causal factors since not everyone rioted [78].

Although this citation would suggest widespread use of psychosurgery for social control, the data suggest that it was otherwise. A 1974 study conducted by the Behavioral Control Research Group of the Hastings Institute surveyed the Commissioners of Corrections for all 50 states to ascertain the prevalence of behavior control in the nation’s prisons [79]. Forty-seven states and the District of Columbia responded. If behavior modification was done at all, the least coercive treatments, such as group therapy or token economy systems, were employed. None of the respondents used psychosurgery as a treatment procedure, although one added, “not at this time.” Although these data would suggest that things were better than feared, the author of the report cautioned the reader to be wary of the results. Perhaps reflecting the distrust prevalent during the end of the Nixon administration and the Watergate scandal, she notes that “In dealing with prisons, however, the publicly announced programs may be only a small percentage of what is actually occurring” [79].

This prevalence data concerning psychosurgery for nonmedical purposes was corroborated by a study conducted by the American Psychiatric Association Task Force on Psychosurgery and by the work of the National Commission. As the American Psychiatric Association report put it, “Both reports concluded that there is no reliable evidence that psychosurgery has been used for political purposes, social control or as an instrument for racist repression” [80]. The National Commission report would later confirm this finding. In a review of 600 psychosurgery procedures performed in 1974, only six Hispanics and one black patient were identified. The Commission noted that “The fact that so few patients from minority groups have undergone psychosurgery...is due not to discrimination on the part of surgeons but to the economic realities and public policy” [81].

Furthermore, although minority communities were indeed fearful of these procedures, not all were in opposition. Two black neurosurgeons speaking at the 1976 National Minority Conference on Human Experimentation in Reston, Virginia, urged limited use of psychosurgery with appropriate oversight and review boards [82]. Dr. Jesse Barber, Chief of Neurosurgery at Howard University, observed, “I personally feel guilty about not developing a program (of psychosurgery) at Howard University.” He added that “When it was considered we were reluctant to face the opposition and destroy our image in the black community.”

Although there was little evidence for the use of psychosurgery for law enforcement purposes, the issue of behavior control dominated the deliberations of advocates of all stripes whether they were physicians, philosophers, attorneys, or nascent bioethicists. In the political climate of that era, there was, it seemed, a fine line between scientific fact and science fiction [83]. In contrast to the media’s favorable—and distorted—depiction of psychosurgery in the early years of lobotomy [84], the popular culture of the 1970s heightened fears of abuse. Works like Crichton’s The Terminal Man depicted the “treatment” of a violent criminal with implantation of electrodes. The setting for the procedure was a fictitious neuro-psychiatric institute located in Los Angeles, which, not so coincidentally, borrowed the name of Ervin’s own institution [85].

In this broader cultural context, fears of psychosurgery transcended the internecine battles of psychiatric subdisciplines, as exemplified by Breggin’s less than restrained ideologic attacks. More balanced criticism came from individuals like Edward Mearns, a professor of law at Case Western Reserve University, who observed that:

There is something promising about the notion that the effort to cure sick individuals may result in considerable social
benefit as well. But there is something disturbing about the conscious effort to use medicine and medical men institutions to cure a “sick” society. For it is one thing to use medicine as an instrument of healing and quite another to use it as an instrument for social control [86].

The philosopher Robert Neville, who directed the Hastings Center Working Group on Psychosurgery, echoed this sentiment. Neville asserted that “The ethics of good medicine isn’t easily transferred to good social control, so there is a danger of having the appearance of therapy, when the real purpose is punishment” [87]. Hal Edgar of Columbia Law School pointed out that although procedures on the brain are justifiable if they result in a cure of a physical illness like Parkinson’s disease without undue side effects, it becomes more complex when the focus of the intervention is mental illness which is “...a concept which is heavily influenced by social norms, and a label which is often imposed in a particular case because people engage in ‘strange’ behavior of one sort or another” [88]. Echoing the sentiments of the times about questioning authority, he asked, “...how does one know whether the sick are being cured or whether medicine is being used as yet another tool in society’s ever present effort to secure comfort through conformity” [88].

Much of the resistance to psychosurgery—and the broader issue of behavior control—was closely related to emerging concerns about the use of the procedure on prisoners, who might be coerced or unable to give appropriate consent to experimental procedures [89]. Some of this was related to a fear of somehow legitimizing a deeply flawed penal system through an affiliation with medicine [90], but much of it was a central concern about the ability of inmates to give voluntary and informed consent.

This issue came to national prominence in the 1973 case of Kaimowitz v. Department of Mental Health, in which a three-judge panel in Michigan sought to determine whether a confined prisoner could voluntarily consent to an experimental procedure that might temper his aggressive and criminal behavior [91]. The court opined that there was no scientific basis to suggest that psychosurgery would be therapeutic in the absence of a discernible disorder like epilepsy and that the risk-benefit ratio was disproportionate given the current state of knowledge and the known risks of the procedure. More critically, the court went on to cite the entirety of the Nuremberg Code to argue that reasoned and voluntary consent in prison was so greatly impaired as to make lawful consent in that setting impossible [92,93]. Indeed, one of his attorneys, Professor Robert A. Burt, pointed out that the prisoner himself illustrated the coercive nature of incarceration when his confinement was declared unconstitutional and he had the opportunity to revisit his decision after initially consenting to psychosurgery. When these new developments allowed him to imagine being set free, he suspended his consent to reconsider surgery given his new circumstances [94].

**Regulatory bioethics: the National Commission’s report on psychosurgery**

Elliot S. Valenstein, commenting on this period, observed that “The coalition of civil-rights, anti-psychiatry, and minority groups opposed to psychosurgery proved to be much more effective politically than the earlier opposition to psychosurgery from within the medical profession had been” [95]. Indeed, public sentiment, catalyzed in part by an organized and growing scholarly bioethics movement, led the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to issue a report on psychosurgery in 1977 [81]. As such, the report was a political compromise in lieu of a moratorium or an outright ban as proposed, most prominently, by Senator J. Glenn Beall, a Republican from Maryland [96].

The National Commission was created by the National Research Act of 1974 [97] in the wake of revelations about the Tuskegee Syphilis Study and other research ethics abuses. The National Commission was constituted and staffed by a number of prominent bioethicists, and their work was prolific. They issued a number of reports in addition to the one on the ethics of psychosurgery, although they were specifically mandated to address this issue by Congress. Concerns about psychosurgery were prominent in testimony leading up to the passage of the act. Willard Gaylin, President of the Hastings Center, warned of the dangers of psychosurgery during 1973 Senate hearings [98].

It is somewhat ironic, given the public origins of the report, that it failed to reach the conclusion that most of the public wanted. Instead of adopting the more politically correct position, to invoke a more modern phrase, the National
The Commission found sufficient evidence of efficacy of the modern procedures like cingulotomy and not the prefrontal leukotomies of Freeman’s day to endorse continued experimental work in psychosurgery as long as strict regulatory guidelines and limitations were in place. As Chairman of the National Commission, J. Kenneth Ryan of Harvard Medical School told a Science correspondent:

We looked at the data and saw 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, and that it did not destroy their intelligence or rob them of their feelings. Their marriages were intact. They were able to work. The operation shouldn’t be banned [96].

The National Commission’s view of psychosurgery was tempered, however, by the endorsement of stringent regulatory guidelines and procedural safeguards that would prohibit psychosurgery for anything other than a patient-centered application:

The Commission affirms that the use of psychosurgery for any purpose other than to provide treatment to individual patients would be inappropriate and should be prohibited. Accordingly, the Commission is recommending safeguards that should prevent the performance of psychosurgery for purposes of social or institutional control or other such misuse [81].

Furthermore, although the National Commission decided not to recommend a ban of psychosurgery, it was careful to note that it did not recognize psychosurgery as “accepted practice.” This addressed a lingering question since the 1940s, posed most eloquently by Professor Mearns of Case Western Reserve Law School in 1975:

...Moreover, psychosurgeons do not submit research protocols to review committees for another reason. They simply do not perceive their operations to be experiments. They view them as therapy... They see the patient as ill with a condition that requires specific treatment geared to his particular illness. This need for treatment suggests speed or at least the avoidance of cumbersome review procedures... Somehow, the inconsistency of characterizing psychosurgery as therapy at the time it is performed and as experimentation at the time of publication seems to escape them... The inconsistency results from characterizing psychosurgery at either point in time as solely therapy or solely experimentation. It is clearly both [86].

The ambiguity over psychosurgery’s status as experimental or therapy is also implicit in the report. Psychosurgery is generally viewed as investigational, although the National Commission does acknowledge that some patients had been helped by these interventions.

For the purposes of the report, psychosurgery was defined as surgery whose “primary object of the performance... is to control, change, or affect any behavioral or emotional disturbance...” and included both classic psychosurgeries like ablation as well as its more modern iteration of electric stimulation: “Psychosurgery includes the implantation of electrodes, destruction or direct stimulation of the brain by any means...” [81]. It is interesting to note that brain surgery for the treatment of movement disorders like Parkinson’s disease or for epilepsy and pain management was excluded from this definition.

Given the investigational nature of psychosurgery, the National Commission recommended strict oversight by specially constituted institutional review boards (IRBs) with a subcommittee of Department of Health, Education, and Welfare (DHEW)-sanctioned experts or consultants in neurology, neurosurgery, psychology, and psychiatry to review the technical aspects of the surgery. IRB review was recommended until the “safety and efficacy of any psychosurgical procedure have been demonstrated.” The IRB was charged with assessing the competence of the surgeon, the appropriateness of the procedure for a selected patient, and the adequacy of the patient’s informed consent. In addition, harkening back to historical concerns about the evaluation of procedural efficacy, the National Commission recommended that the IRB ensure adequate pre- and postoperative evaluations.

Addressing concerns about regulatory oversight, informed consent, and the risks of coercion for the voluntarily institutionalized psychiatric inpatient, the National Commission recommended the establishment of a National Psychosurgery Advisory Board that would determine whether the “specific psychosurgical procedure has demonstrated benefit for the treatment of the psychiatric symptom or disorder of the patient.” If the procedure was part of a research study, the advisory board would determine whether enrollment was in compliance with the National Commission’s
recommendations on research involving the institutionalized mentally infirmed [81,99].

The report set even more stringent guidelines for prisoners and those who were involuntarily committed, had a legal guardian, or were believed to be unable to give informed consent because of impaired decision-making capacity. Attempting to balance “access to potentially beneficial therapy” against the coercion or a breach of voluntariness, the National Commission outlined a complex regulatory approach requiring, among other strictures, that the proposed National Psychosurgery Advisory Board determine whether the specified psychosurgical procedure had a demonstrable benefit for the patient’s condition and if the operation were to be performed as an element of a research protocol, whether these efforts would be in compliance with the recommendations on research involving the institutionalized mentally infirmed [81].

To engage in some rudimentary health services research, the National Commission also suggested the establishment of a national data collection registry to assess the safety and efficacy of these procedures. This fundamental issue remained an open question given the small sample of cases reviewed by National Commission consultants. In addition to this data, the National Commission recommended that this registry note the indications for procedures and the demographics of those who underwent psychosurgery.

In addition, with one abstention, the National Commission actually encouraged (their word) the Secretary of the DHEW “…to conduct and support studies to evaluate the safety of specific psychosurgical procedures and the efficacy of such procedures in relieving specific psychiatric symptoms and disorders, provided that the psychosurgery is performed in accordance with these recommendations” [81].

Finally, the National Commission recommended to Congress the imposition of strict sanctions and the threat of Federal defunding if these recommendations were violated and the exclusion of Federal agencies from psychosurgery funding “unless such agencies or components are primarily concerned with health care or the conduct of biomedical and behavioral research” [81].

Not all the National Commission’s recommendations were accepted by DHEW Secretary Joseph Califano in his determination [100]. He decided to promulgate regulations that would limit psychosurgery to those individuals who could provide informed and voluntary consent. Thus, he determined to ban psychosurgery for prisoners, children, the involuntarily confined mentally ill, and those who were decisionally or legally incompetent and unable to provide consent. Furthermore, he endorsed the establishment of a joint committee on psychosurgery, composed of leading professional organizations, “to establish mechanisms for the voluntary regulation and reporting of psychosurgical procedures.” This was a position he later reversed.

Despite Califano’s narrowing of the National Commission’s broader recommendations regarding whom psychosurgery might be performed on, he and the report were still criticized liberally. One of the more strident columns was by William Raspberry of The Washington Post. In an Op-Ed written after Califano’s determination, he said that he wished the Commission had called psychosurgery “…by its right name: making holes in people’s heads and slicing their brains in a hit-or-miss attempt to make them behave themselves” [101]. He criticized Califano’s about-face on the National Psychosurgery Advisory Board and urged the “immediate cessation of butchery-in-the name of medicine.” He concluded by suggesting that someone take Califano to see “One Flew Over the Cuckoo’s Nest” [101]. Despite this response, progressive commentators like George Annas viewed the report, as submitted to the Secretary, as balanced. He observed that “Certain provisions are unlikely to please either avid promoters of psychosurgery or those favoring a complete ban; nonetheless, it is a reasonable response to a highly complex problem, and its basic approach is likely to gain general acceptance” [102].

Professor Annas was right to appreciate the complexity of these issues and the report’s balanced approach to them. He was, however, overly optimistic that the National Commission’s recommendations would eventually be accepted. Three years after the report was issued, Califano’s successor, Health and Human Services (HHS) Secretary Patricia Harris, still had failed to make a determination over proposed regulations [103].

Today, we still have failed to reach a national consensus on research on subjects whose medical, psychiatric, or neurologic conditions make it impossible for them to provide voluntary consent. The 1998 National Bioethics Advisory Commission report on “Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity” attempted to address aspects of this question, but it too remains in
bureaucratic limbo [21,104,105]. The proposed Psychosurgery National Advisory Board would have been empowered to adjudicate these morally complex decisions in the context of psychosurgery or neuromodulation. Because this body never came into being, we have been left without both a regulatory framework and a national locus for a debate about the ethical implications of neuromodulation.

Recent history suggests that there remains a need for such a dialogue as well as a national body empowered to review the science behind proposed clinical trials to ensure that our ethical sensibilities are not offended. In the United States, there is no such body to provide this oversight or catalyze this discussion. The most evolved forums for such deliberations are local bodies like the Cingulotomy Committee at the Massachusetts General Hospital, which provides oversight for therapeutic interventions for patients who are able to provide consent themselves [106]. Professional groups are also evolving to articulate ethical principles for the conduct of neuromodulation research as in the case of the Obsessive-Compulsive Disorder Working Group [107].

In France, the neurosurgeon Alim Benabid voluntarily sought the approval of the French National Bioethics Commission for approval of a clinical trial of deep brain stimulation in refractory OCD, the first of many psychiatric maladies for which neuromodulation is likely to be investigated [108,109]. Benabid’s actions suggests a continued need for extramural oversight of these still contentious interventions along the lines of the proposed National Psychosurgery Advisory Body.

Summary: fairness, palliation, and psychosurgery

Moving forward, we need to create regulatory mechanisms that will balance human subject protections for individuals with intractable neurologic and psychiatric disorders against scientific progress and access to potentially beneficial interventions. This fiduciary obligation of practitioners, clinical investigators, and public policy makers can be facilitated by building on the yet uncompleted efforts of the 1977 National Commission Report on Psychosurgery. This report should serve as a foundation on which additional analysis could be built.

In the spirit of this evolution, I would like to anticipate some of this analytic work in the context of OCD. OCD has already been the object of sophisticated psychosurgical interventions, most notably the cingulotomy as currently performed by Cosgrove’s group [110] and the closed radioablation techniques employing the gamma knife as studied by Greenberg et al [111].

If we begin with definitional issues, we will immediately realize that the distinction between somatic and psychiatric interventions is no longer as neatly sequestered as in the report. Increasingly, the line between mind and brain—and neurology and psychiatry—has become blurred, and it becomes increasingly problematic to treat one brain condition differently than another. For example, although the National Commission distinguished treatment of Parkinson’s disease from psychosurgery, we now know that treatment of the movement disorders of Parkinson’s disease with deep brain stimulation can affect the patient’s emotions. As was described in the New England Journal of Medicine, French investigators have demonstrated that deep brain stimulation has the unrecognized potential to alter a mood state and induce a reversible but acute depression [112]. What is the boundary between modulating a movement disorder and potentially altering emotions? Is one intervention a neurologic procedure and the other psychosurgery, or are both neuromodulation?

This overlap phenomenon is especially confusing if the mechanisms of Parkinson’s disease are compared with those of severe OCD. They share mechanistic similarities and are characterized by hypersynchronous activity. The pathophysiology and neural circuits of both diseases share cortico-basal gangliothalamic interactions [18] and both could be construed as tremors. In the case of Parkinson’s disease, it is a motor tremor. In OCD, it is a limbic-thought tremor.

Although this analogy is not airtight, it is reminiscent of Vernon Mark’s prescient anticipation of a time when the mind-brain dichotomy would be less tenable as an ethical demarcation, justifying treatment for one disorder but proscribing another. This categorization should be disconcerting to those who embrace equity in the treatment of mental and physical disease as a value, especially when the distinction is predicated on a Cartesian dualism unsubstantiated by modern neuroscience. This regard for fairness becomes even more troubling if we recall Surgeon General David Satcher’s call for parity in the treatment of physical and mental illness [113].
A second analytic issue, in my view, will be to move beyond viewing psychosurgery or neuro-modulation as either research or therapy and consider it instead as a form of palliative care. The ethos of pain and symptom management articulated in the palliative care community is applicable to this work. These interventions are not directed toward cure but rather at the masking of intractable symptoms [114] and the alleviation of suffering, a strategy consistent with palliative care [115].

I believe the National Commission may have anticipated the relationship between psychosurgery and neuromodulation and palliation in its willingness to endorse surrogate consent. Justification for surrogate authorization may have been linked to an implicit view of psychosurgery as palliation when it was being applied to intractable psychiatric suffering. Viewing the relief of suffering as an ethical mandate, the National Commission may have been willing to allow surrogates to provide authorization even when the intervention was yet unproven to be therapeutic. Whether notions of palliation entered into the National Commission’s balancing and specification of ethical principles is a question that merits additional study. Although the recommendation regarding surrogate consent was reversed by Secretary Califano, the National Commission’s thinking might suggest an alternative analytic framework than that offered by the more restrictive National Bioethics Advisory Commission report [106].

The analogy to palliative care may also be helpful in fostering a collaborative and patient-centered model of care. In this regard, I offer an analogy to patient-controlled analgesia (PCA). In PCA, the patient is given the ability to determine the frequency of dosing of pain medication to address his/her perception of pain and level of suffering within preset and safe limits. This precedent for joint patient and physician control has important implications for deep brain stimulators given the history of “behavior control.” The still present fear of mind control by the modern equivalent of Delgado’s stimoceiver makes it critical that patients have an appropriate opportunity to adjust the frequencies of their stimulators within safe and monitored parameters. This will allow for a sharing of power and help ameliorate fears of co-optation of personhood.

This is more than a hypothetic issue, because investigators have begun to recognize that subjects with OCD have affective changes depending on the setting of their stimulator. This is not entirely unexpected because of the downstream effects of the stimulation target, the frontal lobe’s cingulum gyrus, which is a site often ablated in the classic prefrontal leukotomy of Moniz and Freeman. These affective changes can range from euthymia to varying degrees of blunting or hypomania. Either extreme should be avoided, especially the blunting end of the spectrum, which is reminiscent of Nolan Lewis’s concerns about the “the quieting of a patient” after the primitive lobotomy [50].

These affective changes may unsettle some observers. If the past is a prologue, we might expect new charges of mind control and a call for the prohibition of this new technology. If history’s lessons are heard, however, we will appreciate that a more fruitful response is articulating an ethic of responsibility that palliates the suffering of those with intractable psychiatric illness. As Willard Gaylin told us a quarter of a century ago, “To be afraid of our technology is to be afraid of ourselves. It is only essential that we protect ourselves here, as everywhere, from arrogance and insensitivity. The answer is not to prohibit technology but to insist that it always be subservient to the transcending values of human worth and human dignity” [116].

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The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Use of psychosurgery in practice and


Color Plates
Plate 1. Magnetoencephalographic data from three patients in this series. Power spectra (four top panels) and coherence plots (three bottom panels) are displayed. The top left panel shows the power spectra from controls (blue) and thalamocortical dysrhythmia (TCD) patients, including neuropsychiatric as well as parkinsonian, neurogenic pain, and tinnitus patients. A peak shift into the theta domain and power increase in the theta and beta bands are demonstrated for TCD patients in comparison to controls. The top right panel presents the power spectrum of Patient 2, with a postoperative (blue) curve demonstrating the reappearance of the alpha peak and the power decrease in the theta and beta bands. The postoperative power spectra of Patient 7 (middle left) and Patient 1 (middle right) are mainly characterized by a reduction in the theta and beta power, allowing reappearance (Patient 7) or better visualization (Patient 1) of the alpha peak. Coherence was analyzed applying a cross-correlation analysis of the variation along time of the spectral power for frequencies between 0 and 40 Hz. The bottom left panel shows such coherence for controls, the middle panel shows coherence for Patient 2 before surgery, and the right panel shows coherence for the same patient after surgery. (See also Fig. 3 in article by Jeanmonod et al.)
Plate 1.
Plate 2. Magnetoencephalographic source localization for Patient 2. Projection of 4- to 10-Hz activity onto the patient’s MRI examination before (eight top images) surgery. The thalamocortical dysrhythmia of this patient is localized in the right-sided paralimbic domain comprising the temporopolar, anterior parahippocampal, orbitofrontal, and basal medial prefrontal areas. This low-frequency focus disappears after surgery. (See also Fig. 4 in article by Jeanmonod et al.)
Plate 3. Schematic diagram of the thalamocortical circuits that support the thalamocortical dysrhythmia mechanisms. Three thalamocortical modules are shown, each with its specific (yellow) and nonspecific (green) thalamic relay cell projecting to the cortex and reticular nucleus, one (blue) pyramidal cell with its corticothalamic and corticoreticular output, and two reticular cells (red) with their projections back to thalamic relay cells. Three thalamocorticothalamic loops are thus displayed, with their feed-forward thalamocortical activation and their respective recurrent feedback is proposed to generate increased cortical activation through temporal coincidence. Either thalamic cell disfacilitation or overinhibition (central module) hyperpolarizes thalamic cell membranes. This allows the deinactivation of calcium T-channels and the generation of low-threshold calcium spike bursts, thus resulting in low-frequency thalamocortical substrate for low-frequency coherent discharge of an increasing number of thalamocortical modules. At the cortical level, low-frequency activation of corticocortical inhibitory interneurones (red), by reducing lateral inhibitory drive, results in high-frequency coherent activation of the neighboring (right) cortical module (edge effect). (See also Fig. 5 in article by Jeanmonod et al.)
Plate 3.
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