



Reviews

Psychosurgery: past, present, and future

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Abstract

Psychosurgery, the neurosurgical treatment of psychiatric disease, has a history dating back to antiquity, and involves all of the clinical neurosciences. This review discusses the history of psychosurgery, its development in the 19th century, and the conditions of its use and abuse in the 20th century, with a particular focus on the frontal lobotomy. The transition to the modern era of psychosurgery is discussed, as well as the neurobiology underlying current psychosurgical procedures. The techniques of stereotactic cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leukotomy are described, as well their indications and side effects. Due to the past abuse of psychosurgery, procedures are currently under strict control, and the example of the Cingulotomy Committee at the Massachusetts General Hospital is discussed. Finally, future directions of psychosurgery and somatic therapies are explored, including transcranial magnetic stimulation, vagal nerve stimulation, deep brain stimulation, gene therapy, and stem cell therapy. In summary, this review provides a concise yet comprehensive introduction to the history, current practice, and future trends of neurosurgery for psychiatric disorders.

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1. Introduction

The neurosurgical treatment of psychiatric disease has a rich, complex, and controversial history, involving all of the clinical neurosciences. The origins of psychosurgery will be traced from antiquity, with a more recent historical perspective developed from the mid-19th century and the genesis of brain–behavior correlation. From this groundwork, the innovations of psychosurgical pioneers such as Gottlieb Burckhardt, Egas Moniz, and Walter Freeman will be discussed. The rise and fall of the frontal lobotomy will be emphasized, as well as the transition to the modern era of psychosurgical procedures. The discussion of the current state of psychosurgery will involve the description of four major procedures: anterior cingulotomy, subcaudate tractomy, limbic leukotomy, and capsulotomy. The indications, safety, and efficacy of these procedures will be discussed, as well as the cognitive neuroscience underlying their approach. The future trends of psychosurgical procedures will be described: vagal nerve stimulation, deep brain stimulation, gene therapy, and cellular therapy, as well as the alternative therapy of transcranial magnetic stimulation.

2. The origins of psychosurgery

The origins of psychosurgery can be traced to antiquity through the practice of trephination, the procedure of craniotomy with the cylindrical saw termed the “trephine.” At the Ensisheim burial site in France, a trephined skull has been identified that carbon dates to the neolithic period of the stone age, or approximately 5100 BC [1]. The evidence of proper healing and the estimation of a relatively long lifespan of the individual suggest a surgical rather than a traumatic origin of the wound. Irrespective of the validity of this interpretation, literature on trephination for the relief of neuropsychiatric symptoms including affective and psychotic disorders can be dated to 1500 BC [4]. Thus, the history of psychosurgery is as ancient as the recorded history of psychiatric disease itself.

The groundwork for the modern era of psychosurgery, however, was established in the 19th century during an era of neuroscientific inquiry characterized by brain–behavior correlation. Clinicopathologic correlation of neurologic insults provided critical insight into the neuroanatomical substrates of higher cognitive functions such as language, most notably the aphasias described by Broca and Wernicke [13,94]. There is little doubt, however, that the most famous “experiment of nature” in the cognitive

neurosciences occurred on September 13, 1848 to a Vermont railroad worker named Phineas Gage. The strange explosion on that day resulted in a 109 cm-long, 3 cm-thick, fine-pointed rod being shot into his orbit, through his brain, through his skull and onward into the air. The consequences were remarkable: much to the surprise of all he quickly recovered consciousness and survived the blast. More importantly, however, he was transformed from an intelligent, upstanding citizen to an uninhibited vagabond. His physician Dr. John Harlow [34] noted the disruption of “the equilibrium...between his intellectual faculty and animal propensities,” but his friends were perhaps more eloquent when they said that “Gage was no longer Gage.” Almost 150 years later, Damasio et al. [21] published a study of Gage’s skull, proposing a trajectory of injury through the ventromedial portion of the prefrontal cortex, and correlated symptomatology with a cohort of patients with similar neuropathology.

The birth of modern psychosurgery is attributed to the Swiss psychiatrist Gottlieb Burckhardt. Influenced by the climate of brain–behavior correlation in the latter half of the 19th century, and in particular the demonstration by Mairet of hypertrophic temporal gyri in schizophrenic patients [54], he performed the first psychosurgical procedures of the modern era in 1888. The process involved the excision of cerebrum (the so-called “topectomy”) at multiple foci in frontal, parietal, and temporal cortices. The outcomes of the six cases ranged from success (in three patients) to failure (in one fatal case). Needless to say, the criteria of post-operative success were ambiguous, a difficulty of evaluation that has historically plagued psychosurgery. Burckhardt’s psychosurgical innovation was not received favorably in Switzerland, and he abandoned this project after the publication of his results in 1891 [14,39]. Despite the fame of Egas Moniz and the infamy of Walter Freeman, Gottlieb Burckhardt enjoys the distinction of being the founder of psychosurgery.

The early decades of the 20th century saw a continued interest in brain–behavior and clinicopathologic correlation, and a variety of somatic and neurosurgical therapies for psychiatric disorders were being explored. It is of significance to note, however, that these early decades deepened a schism between the fields of neurology and psychiatry that was to reach its apex with the era of Freudian psychoanalysis [74]. Neurology and psychiatry—which were historically unified—became conceptually, academically, clinically, and physically isolated from one another. By the time of World War II, psychiatry had minimized the importance of biological theories and approaches to mental illness. Thus, it comes as no surprise that many of the so-

called somatic therapies developed in the early 20th century originated from neurologists and neurosurgeons, rather than psychiatrists. Such somatic therapies included psychosurgery, convulsive therapy, hydrotherapy, and insulin shock therapy.

After the time of Burckhardt, neurosurgeons continued the investigation of frontal lobe ablation. The Estonian neurosurgeon Puusepp [76] performed frontal lobotomies with little success, while other neurosurgical luminaries such as Penfield [73] described the relief of psychiatric symptomatology after the resection of tumors, abscesses, and other brain lesions. The work of Fulton and Jacobsen [32] provided a key foundation on which the practice of psychosurgery grew. At the Second World Congress of Neurology in 1935, they presented data on calming behavioral changes associated with the resection of anterior frontal association cortex. It was at this meeting that the famous Portuguese neurologist Egas Moniz—much to the surprise of those in attendance—suggested the ablation of the frontal cortex in humans with psychiatric disease.

3. The rise and fall of the frontal lobotomy

It was the influence of Moniz, a charismatic neurologist who was also the Dean of Medicine at the University of Lisbon, that galvanized the field of psychosurgery. It was, in fact, Moniz who first coined the term “psychosurgery,” a term that is now often replaced by “functional neurosurgery for psychiatric disease.” Following the work of Fulton and Jacobsen, Moniz hypothesized that it would be necessary to interrupt the afferent and efferent fibers of the frontal lobe in order for the procedure to be efficacious. His neurosurgical colleague Almeida Lima performed the first series of experimental surgeries with the injection of ethanol [63,64]. The procedure evolved with the use of a rod that had a retractable wire loop that could be inserted and rotated to cavitate neural tissue. Over 100 such operations were performed, with post-operative evaluation consisting of the subjective evaluations of psychiatric examination. The operations were deemed a success, and Moniz began to popularize the procedure. In reality, Moniz kept sparse records of the follow-up, and several patients were returned to asylums and never seen again [89]. Thus, a thoroughly critical audience would not be satisfied with the quality of these studies. Nonetheless, his multiple articles and books on the subject, in addition to his keen political savvy, resulted in the award of the Nobel Prize in Medicine or Physiology in 1949. It is of interest to note that Moniz received independent nominations for his development of cerebral angiography.

While the Europeans Moniz and Lima brought fame to psychosurgery, it was the Americans Freeman and Watts that brought infamy. The neurologist Walter Freeman and his neurosurgical colleague James Watts were physicians from the George Washington Medical School in Washing-

ton, DC and were also present at the Second World Congress. They modified the procedure with the hope that it would produce more consistent results than those seen by Moniz and Lima [30]. The modifications resulted in a closed procedure whereby frontal white matter tracts were severed by a leukotome inserted in 1-cm burr-hole along the coronal suture superior to the zygomatic arch. Their initial series of several hundred cases was deemed successful—but not without consequences. The adverse effects of psychosurgical procedures were becoming evident, ranging from post-operative seizure disorders to infections to death [78,89].

The crucial transformation in the evolution of psychosurgery was the development of the transorbital frontal lobotomy [29]. This procedure was relatively easy to perform and was often done by Freeman without the presence of a neurosurgeon. This led to an estrangement between Freeman and his neurosurgical colleague Watts, as the surgery fell to the hands of non-surgeons as well as non-physicians. Electroconvulsive treatment (another controversial somatic therapy in psychiatry) was used for anesthesia, and then an instrument resembling an ice pick was inserted into the orbital roof and swept across the prefrontal cortex. Freeman was an enthusiastic promoter of this procedure, and it soon came to be used with indiscretion by physicians without surgical training [78,89]. Its use became widespread, and was not only enthusiastically promoted, but also enthusiastically received. The interesting point, therefore, is not simply *that* psychosurgery was abused, but also *why*.

It is important to consider the plight of psychiatric patients at the time. In 1937, over 400,000 patients lived in approximately 477 American psychiatric institutions [24]. Over half of the hospital beds in the United States were used by psychiatric patients, and by the 1940s, US\$1.5 billion was required to treat mental illness. From 15 million men, 1.8 million were rejected from the armed forces because of mental illness, and over 500,000 men were later dismissed for the same reason [89]. Thus, mental illness was regarded as a great burden to society, and the lobotomy provided a way of relieving the heavy costs of the asylums. Fulton [31] predicted that the use of the lobotomy would save Americans US\$1 million per day in taxes to fund psychiatric institutions. It is also crucial to note that prior to the 1950s there were few effective psychoactive medications for the treatment of mental illness, and the use of the lobotomy often allowed patients to leave asylums and re-enter society. Successful cases of lobotomy were praised in publications such as *Life*, *Time*, *Newsweek*, *Reader's Digest*, and the *New York Times*, and the Nobel Prize of 1949 brought the psychosurgical procedure a high degree of attention and validation. Thus, the lack of effective psychopharmacologic agents, the overcrowded and often sub-par conditions of the asylums, and the large social and financial burden of psychiatric illness all contributed to an environment in which the frontal lobotomy was warmly welcomed [90].

The lobotomy started to fall out of favor as the follow-up neurologic sequelae became more evident. Reports in the

scientific and medical literature suggested that the efficacy of the lobotomy was dubious. Moreover, the clinical indications were rather poorly defined and its side-effects could be severe. Inertia, unresponsiveness, decreased attention span, blunted or inappropriate affect, and disinhibition led to the conclusion that the treatment was worse than the disease. It became clear that many unqualified practitioners were performing lobotomies in unsterile conditions, further increasing the risk of serious and sometimes fatal sequelae. Thereafter, lobotomy became less and less popular, and, in many countries and states, illegal. Many criticized the practice of merely quieting, rather than curing the patient. Nonetheless, the procedure was still in use. The decline of the lobotomy was primarily achieved by the introduction of chlorpromazine in the 1950s, the first effective pharmacologic therapy for psychosis. After its approval in 1954, it was administered to approximately 2 million patients in that year alone [27]. The use of psychiatric medications, the rejection of Freeman's procedure by neurosurgeons, and the increasing appeal of psychoanalysis led to the ultimate decline of the frontal lobotomy.

4. Psychosurgery in transition

Despite the widespread abuse of psychosurgery, the field of functional neurosurgery for psychiatric disease was nonetheless maturing. Probably the single most important technical contribution to the field was the development of stereotactic neurosurgical devices in the late 1940s [85]. Stereotactic surgery enabled a much more circumscribed lesion, resulting in fewer side-effects and less mortality. Furthermore, developments in the neurobiology of emotion provided more refined targets for neurosurgical intervention. The pioneering work of Papez [71] and its further evaluation by MacLean [53] led to the elucidation of important structures in the limbic system regulating the function and dysfunction of emotions. After decades of psychopharmacologic therapy, it was becoming clear that a subpopulation of patients were afflicted with medically refractory disease, and the use of surgical procedures continued to be evaluated.

The role of psychosurgery in psychiatry and society became scrutinized in the 1960s and 1970s [28]. The social unrest during this era led some sociobiologists to consider psychosurgery as a potential tool for addressing violence. The physician and physiologist Jose Delgado promoted the idea of "psychocivilizing society," through the use of implantable brain electrodes that could be modulated via remote control [22]. In a famous publicity stunt in 1965 he stopped a charging bull in the Cordoba bullring with the use of such an electrode. In the 1970s, the psychosurgery controversy was again ignited with the publication of *Violence and the Brain*, by Mark and Ervin in 1970 [57]. The book suggested that much of the violent behavior

observed in society could be attributed to aberrant limbic system function, and that neurosurgical procedures might be a viable approach to its elimination. This issue came to prominence in the landmark case of *Kaimowitz vs. Department of Mental Health*, a case in which a prison inmate was offered a psychosurgical procedure that might temper his aggressive behavior [67]. It was argued that voluntary consent was virtually impossible in this setting, an argument for which the Nuremberg Code was cited.

These publications and events culminated in a fury of ethical debate about the use of neurosurgery as a tool for government control and suppression. The emerging cadre of bioethicists, outspoken psychiatrists such as Peter Breggin, as well as other activists led to the ethical evaluation of psychosurgical procedures by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [66]. Contrary to expectations, the Commission issued a favorable report and guidelines for the ethical use and regulation of neurosurgical procedures for psychiatric disease was established [18,88]. A 1974 study by the Hastings Institute surveyed the Commissioners of Corrections from all 50 states to assess the use of psychosurgery as a means of behavioral control [12]. Based on these reports, the claim that psychosurgery was being used as a tool of establishment control was discredited, the restricted use of procedures such as cingulotomy was endorsed, and the foundation for the modern era of these procedures was created.

5. Neuropsychiatry of the frontal lobes and related systems

No description of the current procedures nor discussion of future trends of psychosurgery can be fully appreciated without a basic understanding of the functional neuroanatomy involved. We will thus describe the basic circuitry of the frontal lobes, and their connections with subcortical systems such as limbic structures and the basal ganglia.

Although a simplified model, frontal lobe circuits can be divided into several groups [15,20,86].

Dorsolateral Circuit—originates in the dorsolateral aspect of the frontal lobe and projects to the head of the caudate and medial putamen.

Orbitofrontal Circuit—originates in inferolateral prefrontal cortex and projects to the medial caudate and nucleus accumbens.

Anterior Cingulate Circuit—originates in the anterior cingulate gyrus and projects to the ventromedial striatum.

The motor circuit and oculomotor circuit are two other pathways that are involved in the mediation of somatic and ocular movement, and also converge on the basal ganglia.

A clinicopathologic association of neuropsychiatric phenomena can now be linked to specific frontal lobe

circuits, rather than the gross brain–behavior correlation of the 19th and early 20th centuries. Three syndromes emerge that help elucidate the functions of the frontal lobe, and how these functions may be manipulated by surgical intervention. The *dorsolateral prefrontal syndrome* is characterized by impairment of executive functions, clinically evidenced by executive dysfunction such as perseveration. Perseveration is often gauged by difficulties with the Wisconsin Card Sort Test, an exam that probes the subject's ability to shift strategies when appropriate [9,61]. The *orbitofrontal syndrome* results in features that seem to have afflicted Phineas Gage as well as a countless number of lobotomy patients: disinhibition, irritability, lability [21]. The *anterior cingulate syndrome* in its most dramatic manifestation results in akinetic mutism and profound apathy [6,68]. The anterior cingulate circuit projects to the ventral striatum, a target for many limbic structures. It becomes clear via these syndromes that higher functions such as executive activity and social control are regulated by the frontal circuits. It has also been well-documented that orbitofrontal and dorsolateral regions play a role in mood control [59,60].

It should be emphasized that the basal ganglia is the initial target for all of the frontal lobe circuits, and that an understanding of basal ganglia structure and function is essential. The basal ganglia comprise a complex processing system that, in essence, interprets diffuse cortical signals in the striatum, and returns information to the cortex through the globus pallidus, substantia nigra, and thalamus. It is important to note that lesions of basal ganglia structures within the frontal circuitry can give rise to disorders that resemble frontal lobe lesions themselves. Although not as prevalent or extensively studied, such “striatal syndromes” also exist in which disinhibition and executive dysfunction have been documented [20].

There are well-documented neuropsychiatric sequelae in classic basal ganglia diseases. In Huntington's, and less so in Parkinson's, psychiatric compromise is present in addition to the classic motor symptoms [19,59,60]. Features of Huntington's disease include dementia, affective disorders, and even psychosis. Parkinson's patients exhibit depression, dementia, and confusional states. Other neuropsychiatric diseases such as obsessive-compulsive disorder (OCD) and Tourette's have also been associated with frontal lobe and basal ganglia dysfunction [77,83]. Positron emission tomography studies of patients with OCD and Tourette's have shown increased metabolism and blood flow in the frontal lobes, the cingulum, and the basal ganglia (especially the caudate nucleus). Executive dysfunction, impairment of procedural memory, and visuospatial deficits have been found consistently in Huntington's, Parkinson's, OCD, and Tourette's syndrome.

No discussion of the neurobiology of emotion and cognition is complete without mention of the limbic system. The *limbic lobe* (a term by Broca originating from the Latin *limbus*, meaning “border”) comprises the arcuate convolution of the cingulate and parahippocampal gyri of the medial

aspect of the cerebral hemispheres. Structures of the limbic system [53,71] further include the amygdaloid complex, septal nuclei, hippocampus, nucleus basalis of Meynert, mamillary bodies, hypothalamus, epithalamus, and various thalamic nuclei. The limbic system does indeed form a “border” or connection point between the neocortex (mediating external stimuli) and hypothalamic and brain-stem structures (mediating internal stimuli) [81,82]. Thus can it regulate the complex processes of subjective, visceral, somatic, and behavioral processes associated with emotion. These reciprocal connections converge in the amygdala, which has been shown to be crucial to emotional processing, particularly aversive stimuli [97]. Lesioning of the amygdala in monkeys results in the Kluver–Bucy syndrome [42], also characterized by decreased emotional arousal (even in the presence of threat), as well as hypersexuality, hyperorality, hyperphagia, amnesia and agnosia.

6. Current procedures in psychosurgery

There are currently four commonly employed neurosurgical procedures for psychiatric disease that target various components of the neural systems described above. At present, such psychosurgical procedures are typically used for affective or anxiety disorders, rather than cognitive disorders. The present state of psychosurgery is destructive rather than constructive, i.e., relies on lesioning of neural structures rather than their stimulation. The procedures discussed in this section are anterior cingulotomy, subcaudate tractotomy, limbic leukotomy, and anterior capsulotomy.

6.1. Anterior cingulotomy

Fulton introduced the idea of modulating the anterior cingulum in order to attenuate psychiatric disease, and the procedure was first performed in the early 1950s [10,95]. The procedure was subsequently made popular in America by Ballantine, who has since conducted extensive research on the procedure [5]. As mentioned above, the cingulate cortex is an important structure in the circuit of Papez, and increased metabolism in the anterior cingulate has been associated with OCD. Non-surgical lesions of the anterior cingulate result in a profound inattention and akinetic mutism. After a rigorous multidisciplinary screening process discussed below, bilateral stereotactic thermocoagulation lesions are produced in the cingulum of the patient [58].

There have been a series of retrospective and prospective studies of cingulotomy published by physicians at the Massachusetts General Hospital. In a retrospective study of 33 patients receiving cingulotomy from 1965 to 1986, 25–30% of medically refractory OCD patients were found to be improved post-operatively, where treatment success was defined as an improvement of 35% or more on the Yale–Brown Obsessive Compulsive Scale [38]. The first prospective study of cingulotomy patients found a similar success

rate of 25–30% in 18 medically refractory OCD patients [4]. A recent prospective study of 44 patients (which included follow-up of the 18 patients in the 1995 study) demonstrated that at a mean follow-up of 32 months, 14 patients (32%) met criteria for treatment response, and 6 others (14%) were found to be partial responders [4]. Of the 44 patients, 1 patient reported exacerbated urinary incontinence, 1 developed medically responsive seizures, and 1 subsequently committed suicide. The risk of post-operative epilepsy has been previously reported to be approximately 1% [26].

6.2. Subcaudate tractotomy

The subcaudate tractotomy was designed in England by Knight in 1964 as a method of minimizing frontal lobe lesioning by interrupting fibers from the frontal lobes to subcortical structures such as the amygdala [44]. The procedure tends to be more popular in England, while anterior cingulotomy is preferred in the United States. Like the cingulotomy, the procedure is indicated for affective and anxiety disorders such as refractory depression and OCD rather than cognitive disorders such as schizophrenia. This was originally performed with radioactive seeds implanted in the frontal lobes. The site of the lesion is the substantia innominata, just below the head of the caudate nucleus. In a study of 208 patients in the 1970s, approximately 2/3 patients with depression or anxiety demonstrated improvement, and approximately 50% of obsessive patients demonstrated improvement. Both immediate and longer-term side effects, however, appear to have occurred at a higher rate than with cingulotomy. Approximately 2% demonstrated post-operative seizures, and almost 7% demonstrated negative personality traits after surgery [33]. A more recent retrospective study investigating 249 patients treated from 1979 to 1991 estimated treatment response at 34% [37].

6.3. Limbic leukotomy

The limbic leukotomy is essentially the combination of stereotactic lesions created in the anterior cingulotomy and subcaudate tractotomy. A recent study from the Massachusetts General Hospital including patients with a variety of symptoms indicates a treatment response of 36–50% of patients with major depressive disorder and OCD, with only transient adverse effects reported [65]. A series of 5 patients with medically refractory OCD or schizoaffective disorder who were engaged in self-mutilation were treated with limbic leukotomy, with 4/5 showing sustained reduction in self-injurious behavior at a mean post-operative follow-up of 31.5 months, and 2/3 showing a reduction in assaultive behavior [75].

6.4. Anterior capsulotomy

This procedure was designed by the French neurosurgeon Talairach in the late 1940s, and popularized in

Europe [10]. Due to the innovation of the Swedish neurosurgeon Leksell, it currently employs thermocoagulation or gamma-knife stereotaxis to lesion the fronto-limbic fibers that pass in the anterior limb of the internal capsule as it courses between the caudate and putamen nuclei of the basal ganglia [48,49]. Success rates of 70% have been demonstrated in patients with OCD [11], and a direct comparison indicates higher efficacy than anterior cingulotomy [46]. While it is generally agreed that capsulotomy is superior to cingulotomy in terms of efficacy, the potential for adverse effects with capsulotomy are of concern. Common side-effects of the procedure are confusion, weight-gain, depression, and nocturnal incontinence. Some patients have been reported to exhibit cognitive and affective dysfunction, as well as decreased initiative and drive. Studies by Mindus, a Swedish psychiatrist from the Karolinska Institute, indicate that these adverse effects appear to normalize in the long-term [62].

Since its development, evaluating the efficacy of psychosurgical procedures has been notoriously difficult. In the series of Moniz to Freeman, the long-term follow-up results were negligible. Problems have plagued virtually every aspect of the evaluation process. For many years, diagnostic inaccuracy and non-standardized nosology created difficulty in assessing what precise disease was being treated. Surgical center bias as well as non-standardized outcome measurements are also problematic. Comparing or collecting studies over different time periods (metastudies) is also a difficult task, as improvements in psychopharmacology result in more profoundly refractory cases presenting for surgery. Finally, due to the infrequency and highly invasive nature of the surgeries, no prospective placebo-controlled (sham surgery) studies have been performed.

Standardized nosology through the DSM-IV, as well as objective and subjective rating scales for psychiatric symptoms (such as the Yale–Brown Obsessive Compulsive Scale), has greatly improved the capacity for evaluation. The studies discussed above demonstrate clear efficacy of psychosurgery, most notably for affective and anxiety disorders. Furthermore, it is clear that safety and ethical standards have markedly improved. Psychosurgical procedures are always performed by qualified neurosurgeons using sophisticated instrumentation, with patients under adequate anesthesia in sterile environments. This, in addition to the advance of stereotactic techniques for lesioning and more precise ablative techniques such as the radiosurgical “gamma knife” [52], has dramatically decreased the morbidity and mortality associated with functional neurosurgery for psychiatric disorders.

7. Guidelines for the clinical use of psychosurgery

Neurosurgical procedures for psychiatric disease are reserved for patients who are refractory to pharmacologic, psychotherapeutic, or electroconvulsive therapies. The

patient's psychiatrist is the only individual who may recommend a surgical procedure, and must provide detailed documentation regarding the course of therapy, and the reasons for discontinuation of therapy. It is the responsibility of the psychiatrist to follow the recovery of the patient post-operatively. The family of the patient must also express interest in the surgery, as well as support for the recovery process. It is important to determine that the interests of the family are directed to the best outcome for the patient.

The severity of the psychiatric disease takes precedence over the chronicity of the disorder, although refractory cases have usually failed treatment for five years. Quantitative data is usually obtained, including the Yale–Brown Obsessive Compulsive Scale, the Beck Depression Inventory, and the global assessment of function. Each institution typically has its own criteria for psychosurgical procedures. The Cingulotomy Committee at the Massachusetts General Hospital, for example, is a multidisciplinary board of neurosurgeons, psychiatrists, and neurologists, who all must clinically evaluate the patient. Electroencephalogram, magnetic resonance imaging, electrocardiogram, neuropsychological testing, and laboratory testing are all required in addition to an extensive review of the medical record. All involved family members and committee members must give consent for the surgery [25].

8. Future directions: functional neurosurgery, somatic therapies, and beyond

The future of psychosurgery, like its past, is linked to the developments of neurosurgery, neurology, psychiatry, and cognitive neuroscience. As pharmacologic treatments become more efficacious, there will be less need for neurosurgical intervention, but refractory cases will be more challenging. Greater understanding of the neurobiology of emotion through basic research or cognitive neurology will result in more rational and more precise techniques. Advanced neuroimaging techniques will also contribute to the translation of investigative findings to human intervention [93]. Furthermore, other interventions in the clinical neurosciences for conditions such as epilepsy, Parkinson's, or chronic pain will find greater application in the neuropsychiatric arena.

Again, it is important to recognize psychosurgery as one of many interventions historically referred to as somatic therapies. Somatic, or physical treatment for psychiatric disease is best exemplified by psychosurgery and electroconvulsive therapy, formerly known as “shock therapy.” Another method of non-surgically modulating electrical activity in the brain is transcranial magnetic stimulation (TMS). A coil is placed against the scalp, and a pulse of radiofrequency electric current is passed through it, creating a magnetic field that results in depolarization of the superficial cortex [55]. The neural response is dependent on the site, number, and intensity of the applications [17].

TMS has been employed as a neurophysiologic tool for the investigation of cortical excitability, but has also been shown to induce changes in neurochemistry that are similar to those found with anti-depressants or electroconvulsive therapy [8,50]. Reports and metastudies have been ambiguous, but repeated TMS applications to the area adjacent to the left prefrontal cortex are being explored for anti-depressant activity [72]. The most prominent adverse effect of repeated TMS is the precipitation of seizures, thought to result from increased cortical excitability [55].

One of the promising future directions of psychosurgery is the combination of surgical and electrical approaches. While electroconvulsive therapy delivers a non-specific electrical surge to the brain, and TMS causes disruption or excitation of more focal areas, there are more circumscribed uses of electrical manipulation that are currently employed. The use of implantable electrodes for focal modulation of the vagus nerve and the basal ganglia are promising treatments for epilepsy and Parkinson's disease and may have relevance for neuropsychiatric disorders.

The vagus nerve relays information that can function in an autonomic feedback loop, and also delivers signals to the forebrain via the parabrachial nucleus and locus ceruleus, both of which have important connections to crucial limbic system structures such as the amygdala [91]. Vagal nerve stimulation acts via an electrode attached to the nerve in the neck, coupled to a pulse generator implanted in the chest wall. It is currently being used for treatment-refractory epilepsy patients, with encouraging and sustainable results [87]. It has also been explored as a treatment for refractory depression, and in a multicenter trial of 30 patients has led to a sustainable reduction in depressive symptoms in 12 patients [80]. Vagal nerve stimulation has been shown to increase serotonergic and noradrenergic transmission in the brain, and has also been posited to improve limbic system blood flow [35,40]. Adverse effects in the post-operative period include pain, cough, vocal cord paralysis, hoarseness, and nausea [84]. Asystole has been reported to occur transiently in a small amount of patients, but there were no persistent effects. Dyspnea and voice alteration have also been associated with stimulation [16]. In general, though, the procedure has been tolerated well in epilepsy patients, and may hold promise in the neuropsychiatric population.

Deep brain stimulation (DBS) is a technique used to modulate basal ganglia and thalamic function in order to attenuate the symptoms of Parkinson's disease. Chronic electrical stimulation of basal ganglia structures such as the globus pallidus internus and subthalamic nucleus are achieved by an implantable electrode coupled to a pulse generator, and has been found to ameliorate bradykinesia, tremor, rigidity, as well as postural and gait abnormalities [23,51]. Stimulation of the ventral intermediate nucleus of the thalamus has been shown to attenuate tremor. DBS has been shown to be highly efficacious, especially in younger Parkinson's patients. Adverse effects of DBS result from the surgical procedure itself, most notably intracerebral hemor-

rhage. More common effects are perioperative or stimulation-related confusion [55].

The technique of chronically stimulating focal brain structures may hold promise as an alternative to ablative neurosurgery for psychiatric disorders [45]. In patients with co-existing Parkinson's and OCD, the subthalamic electrodes and the use of DBS was found to ameliorate compulsive symptoms in addition to the motor abnormalities [56]. It has also been widely recognized that stimulation of the subthalamic nucleus can also result in an improvement of mood [3,96]. Interestingly, bilateral stimulation of the subthalamic nucleus in patients with Parkinson's has been reported to induce laughter [43,47] as well as acute depression [7]. Stimulation of other brain sites have also been shown to affect psychiatric symptoms. DBS of the internal globus pallidus has been shown to decrease symptoms of anxiety in Parkinson's patients independently of motor symptoms [36]. Thalamic stimulation has been suggested to attenuate the tics associated with Tourette's [92]. Bilateral stimulation of the anterior limbs of the internal capsule has been shown to be beneficial in attenuating the effects of OCD, and suggests DBS as an alternative to ablative capsulotomy [2,69].

As the functional neuroanatomy underlying OCD, depression, and other psychiatric disease continues to be elucidated, DBS may become more frequently employed. Again, it is important to note that the "stimulation" ultimately results in an *inhibition* of neural activity, and thus is the functional equivalent of lesioning. The prominent difference, of course, is that the functional lesion is controllable and reversible. Furthermore, whereas it has not proven possible in the past to do controlled studies with destructive lesions, it may prove feasible with these "inhibitory" stimulators. The stimulator can be implanted and activated at various time points in certain patients. In this manner, an ethically appropriate study could finally answer whether such surgery is efficacious. Furthermore, such stimulators could be implanted at more than one target site and relative efficacy of various targets could be tested. Such studies would be a major advance in the field.

Most of the psychosurgical procedures described in this review have been destructive rather than constructive, and, indeed, lesioning in one form or another has been the mainstay of neurosurgical treatment of psychiatric disease. The advances in neurobiology over the last decade have created the future possibility for *constructive* psychosurgery—an intervention that augments or stimulates neural function for therapeutic benefit rather than ablating it. The stereotactic delivery of genetic or cellular material with specific functions to specific brain areas holds the promise of augmenting rather than inhibiting neural function. As the complex genetic factors of psychiatric disorders are elucidated, specific gene replacement strategies in focal areas may become viable therapeutic modalities. The expression of gene products in the brain by modified herpes, adeno- or adeno-associated viruses is already being explored for brain

tumors and other neurologic dysfunctions such as epilepsy, and can conceivably play a role in psychiatric disease [41]. Another future direction of neurosurgical intervention will be the delivery of cellular products such as stem cells to degenerated or malfunctioning brain regions. Stem cell research is currently in an explosive phase, and is beset with its own complex ethical questions. The introduction of modified neural stem cells as a therapeutic modality has already had experimental success in other neurologic disorders [79], and may hold potential for psychiatric disease.

9. Discussion

Psychosurgery has a complex and controversial history dating back to antiquity, and continues to evolve in the present era of neurosurgery. Its modern origins are linked to the era of brain–behavior correlation in the 19th century, and its abuse was due in part to the early 20th century schism of psychoanalysis and biological psychiatry, and in part to the lack of effective pharmacologic treatment for psychiatric disease. The field of psychosurgery survived this turbulent era, and currently employs four main procedures focused on the lesioning of limbic system structures. Due to its invasive nature and the refractory nature of the disease, psychosurgery has not thus far been readily amenable to double-blind placebo-controlled trials. Despite this lack of scientific precision, it can be said that currently used neurosurgical procedures for refractory affective and anxiety disorders are safe and effective. The use of such procedures is now tightly regulated by multidisciplinary committees that stringently examine potential cases by ethical and clinical standards. Current directions of the field include electrical modulation of neural structures to cause neural inhibition. Such techniques may, for the first time, allow ethically designed controlled studies to be performed as discussed above. Future directions may include direct implantation of genetic and cellular products. It is important to recognize that the new frontiers of psychosurgery, such as deep brain stimulation, are subject to the same potential for abuse as procedures in the past. It is critical that clinicians and ethicists alike maintain a clear perspective on surgical intervention for psychiatric disorders so that the dark history of psychosurgery does not repeat itself. Indeed, there are already ethical guidelines emerging in the current era of psychosurgical intervention [70].

There is little question that surgery for psychiatric disorders can affect psychological function, tragically in ways that have sometimes harmed the patient. In experienced hands, however, such procedures are often beneficial. Even when successful, our understanding of this therapeutic process is, at best, rudimentary. In the example of OCD, one cannot conclude that cingulotomy is curative simply because post-operative benefits are observed. Cingulotomy may allow the patient with OCD to be more effectively

treated with other psychiatric techniques. Indeed, it is not clear that a permanent lesion is even necessary. With reversible stimulators it can be tested whether transient stimulation, appropriately timed with psychiatric intervention, could benefit outcome. Were this possible, stimulators might be viewed as important adjuncts to standard psychiatric care in patients with serious mental disorders refractory to current standard therapies.

The development of psychosurgery is linked to the development of all of the clinical neurosciences, as well as the underlying cognitive and basic neurosciences. A multi-disciplinary approach with careful regulation will be essential to the advancement and ethical administration of such therapies for medically refractory psychiatric disease.

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