Since prehistory, humans have been fascinated with the possibility of physically manipulating the brain to target conditions of the mind. Consequently, the first recorded neurosurgical procedure, trephination, was born out of a daring pursuit to try to alleviate disorders of magical or supernatural possession. Later, procedures to reverse pathological behavior entered a period of unethical treatment known as psychosurgery, during which they were applied with inadequate selection criteria and lack of oversight. In contrast, today’s psychiatric neurosurgical techniques have evolved substantially and are practiced in the context of both a modernized ethical framework and scientifically rigorous testing. Moreover, the prevalence of psychiatric disorders continues to grow, affecting 1 in 10 people worldwide, and a preponderance of new data suggest that surgery is increasingly considered a viable option.

Trephination

The earliest indications of cranial manipulation by humans with the intent to heal can be traced to historical artifacts of trephination. Trephination (or trepanation), a procedure that involves incising the scalp and cutting or drilling a hole in the skull, is now believed to be the oldest documented surgical procedure ever performed by humans. One of the oldest trephined skulls dates back to the Neolithic period of the Stone Age, or approximately 5100 BC. In the days of prehistoric man, opening the skull was seen as a way for evil spirits or confined demons to be released from a person’s head, although in the New World, the concept of behavior was not formally linked to the brain until after the time of Descartes in the 1600s. More practically, trephination was also used to alleviate symptoms of head trauma sustained during animal attacks, falls, or violent conflict. Interestingly, anthropologists believe that...
a large percentage of subjects survived the procedure (approximately 50%), as evidenced by the appearance of cortical bone growth on the edges of many trephined skulls. This fact astounded modern anatomists and clinicians in the 1800s, leading to a dramatic rebirth of interest in this area (Fig. 1).\textsuperscript{,5} Even after the establishment of the Greek and Roman civilizations, the practice of trephination continued to be used. Artifacts recovered from these areas suggest that Hippocrates, Celsus, Galen, and many others conducted the procedure and developed specialized tools, including the terebra serrata, which was specifically made for perforating the cranium.\textsuperscript{4,5} However, it was not until the Middle Ages and Renaissance that trephination was routinely prescribed for the treatment of mental disorders, particularly madness, and epilepsy.\textsuperscript{6} Illustrations of trephination practice are also reflected in the art of the Middle Ages and Renaissance. Hieronymus Bosch’s work The Cure of Folly (also known as The Operation for the Stone or The Extraction of the Stone of Madness) depicts a man undergoing a form of cranial surgery for removal of a “stone of madness,” illustrating the possible use of the procedure as a treatment option for neuropsychiatric disorders.\textsuperscript{7}

\section*{Cerebral Localization and the Prepsychosurgery Period}

By the 18th and 19th centuries, use of trephination for the treatment of neurological and psychiatric disorders greatly declined and was being used to a much more limited extent.\textsuperscript{4,8} Beginning around that same time, however, the concept of functional localization, or the idea that particular regions of the brain served specific functions, was advanced by Franz Gall through his work associated with the pseudoscientific field of phrenology.\textsuperscript{4,9} Although the field itself was ultimately discredited, its works concerning the compartmentalization of the brain (i.e., associating different areas to specific neurological functions) persisted. The idea of cerebral localization was further supported after the publication of the fascinating case of a 25-year-old railway foreman who survived a tamping rod being driven through his frontal lobe after an explosion.\textsuperscript{10,11} Sometimes referred to as the “American Crowbar Case,” this accident permanently altered his behavior and personality, driving him to become disinhibited and belligerent.\textsuperscript{12} It was this case and disagreement regarding other cerebral localization theories at the time that prompted prominent physicians such as Flourens, Broca, and Wernicke to begin systematically investigating regions of cerebral cortex in order to better understand their associated functions (Table 1).\textsuperscript{3,14} Their groundbreaking findings would later go on to serve as the basis of the field of psychiatric neurosurgery.\textsuperscript{15}

\section*{Moniz and the Introduction of the Leukotomy}

In 1935, the second International Neurological Congress took place in England at Dorman’s Park Hotel.\textsuperscript{9} At this meeting, physiologists John Fulton and Carlyle Jacobsen presented their work on behavioral changes in non-human primates following frontal lobe dissection. They showed that, after partial lobotomy, the animals became aggressive and hurled their own feces at the research staff. After complete frontal lobectomy, however, the animals displayed blunted emotional responses but exhibited no change in overall cognition.\textsuperscript{9,16} The results were so striking to one audience member in particular, Egas Moniz, a neurologist from Portugal, that he exclaimed, “Those are just like my patients, I think that might be done in man!” (personal communication to Dr. Walter Freeman, also in the audience at the time).\textsuperscript{17} Moniz returned to Portugal and began collaborating with neurosurgeon Almeida Lima, who carried out prefrontal leukotomies on 20 patients with pathologies including anxiety, depression, and schizophrenia (Table 2).\textsuperscript{10,18} The first 10 patients underwent frontal lobe ablations using absolute alcohol (i.e., containing at least 99% pure alcohol) injections, although this version of the procedure was later revised because of the unpredictable nature of alcohol dispersion.\textsuperscript{10,19} As a result, the last 10 patients were treated with a device known as a leukotome, an 11-cm-long device with a wired loop at the end, which, when inserted into the brain through burr holes and rotated, could sever white matter tracts in the frontal lobe of afflicted patients.\textsuperscript{18,20} Moniz and Lima published the results of the trial less than 4 months after its start, showing that 7 patients were “healed,” 7 patients improved, and 6 patients were unchanged with no worsening symptoms or

\begin{table}[h]
\centering
\caption{Landmark studies in cerebral localization}
\begin{tabular}{|l|l|l|l|}
\hline
Authors & Year & Description & Brief Study \\
\hline
Flourens, 1824\textsuperscript{42} & & Destruction of various neural regions was used for studying the function of various parts of the brain; study looked at the properties of various cerebral regions, the role & functions of the cerebral lobes, & the role & functions of the cerebellum & \\
\hline
Broca, 1864\textsuperscript{51} & & Observation of a pt w/ widespread cerebral damage, which led to evidence of the cerebral regions responsible for receptive & expressive components of speech as well as the motor component of speech, w/ the latter region receiving the eponym “Broca’s area” & \\
\hline
Wernicke, 1884\textsuperscript{54} & & Study demonstrated that circumscribed lesions in the temporal region around the sylvian fissure can produce aphasia that is different from aphasia caused by damage to Broca’s area & \\
\hline
Burckhardt, 1895\textsuperscript{55} & & Cortical excision was explored as a possible surgical treatment for psychosis in 6 pts, w/ results of the procedure provided & \\
\hline
Fulton, 1935\textsuperscript{56} & & 2 chimpanzees that underwent bilateral lobectomy of their frontal lobes displayed significant changes in emotional response as a result of the procedure, while their cognitive abilities were spared & \\
\hline
\end{tabular}
\end{table}

Pt = patient.
It was from this study and others like it exhibiting “good results” that the popularity of the leukotome procedure eventually began to escalate. Moniz went on to be awarded the Nobel Prize for Medicine or Physiology in 1949 for his contributions to the popularization of this technique. Although actually a neurologist who had never received any form of surgical training, Moniz remains to this day the only person ever to have received the Nobel Prize for Medicine or Physiology while listed as a “neurosurgeon.”

**Freeman, Watts, and Lobotomies**

American neurologist Walter Freeman, also in the audience when Fulton and Jacobsen presented their results, followed Moniz’s and Lima’s work closely and felt the technique could be modified further. He recruited neurosurgeon James Watts, and the pair conducted the first frontal lobotomy in the US at George Washington University in 1936 on a woman diagnosed with agitated depression. Through two burr holes in the patient’s cranium, a modified version of Moniz’s leukotome was used bilaterally to remove cores of white matter tracts between the prefrontal cortex and thalamus. The entire procedure was completed in approximately 1 hour. After it was deemed a success, Freeman and Watts would go on to perform approximately 200 frontal lobotomies by 1942. The published report of these 200 cases reported that 63% of patients showed improvement following the procedure, 23% demonstrated no change, and 14% had severe post-operative neurological deficits or death as a result of the procedure. No formal psychiatric scales were presented, as the first edition of *Diagnostic and Statistical Manual: Mental Disorders* was not published until 1952.

Convinced that the procedure could be modified further for nonsurgically trained personnel, Freeman and Watts developed a variation of the transorbital lobotomy, an operation originally created by psychiatrist Amarro Fiamberti. This variant of the procedure did not require an operating room and could be conducted in an outpatient office. An icepick-like device known as an orbitoclast was inserted above the eyelid of a patient and driven through the orbital roof with a mallet. In sweeping the orbitoclast in the desired planes, the white matter tracts of the frontal lobe would be severed. After repeating the process on the opposite side, the procedure was complete. Because of the ease and speed of this variant of the technique, it was performed in psychiatric hospitals and clinics across the world, with an estimated 60,000 transorbital lobotomies performed in the US alone between 1936 and 1956. Several major factors were responsible for the rapid use of the lobotomy as a means of neuropsychiatric treatment. First and foremost was the enormous scale of psychiatric burden within the US healthcare system during this era of American history. In 1937 alone, an estimated 400,000 patients lived in psychiatric institutions in the US, occupying more than half of the available hospital beds in the country. In addition, alternative therapies for mental disorders in the early 20th century were dangerously lacking. Insulin coma therapy, metrazol convulsive therapy, and Freudian psychoanalysis were available to patients in psychiatric hospitals; however, these therapies often resulted in severe side effects and/or unpredictable benefits. Even in the context of these factors, the frontal lobotomy began to be used indiscriminately, sometimes without proper patient informed consent or documented patient selection criteria, for the treatment of a variety of intractable psychiatric illnesses including schizophrenia, depression, anxiety, and obsessive-compulsive disorder (OCD).

Despite the perceived benefit of the procedure and its reported results, skepticism regarding the transorbital lobotomy’s safety and efficacy began to surface as early as 1949. The procedure was condemned not only for the occurrence of frontal lobe syndrome, consisting of apathy, impulsivity, and blunted affect, but also for the not infrequent occurrence of intracerebral hemorrhage, epilepsy, and death. Public backlash to lobotomies also led to the formation of a US congressional commission in the late 1970s tasked with investigating the selection and treatment of patients with psychiatric disorders using surgical techniques. Some notable recommendations from the report include psychosurgical procedures requiring approval by an institutional review board and meeting criteria for appropriateness, safety, and postoperative follow-up; that procedures should not be performed on prisoners; that a national database regarding outcomes be established; and that stringent guidelines for informed consent are met, especially in cases where patients are involuntarily committed or lack decision-making capacity. The report created by the commission would go on to serve as the forerunner of the ethical guidelines by which the field of psychiatric neurosurgery is currently governed.

**Introduction of Stereotactic Procedures**

In the 1960s, James Papez and Paul D. MacLean, two scientists at Cornell University, began studying the hypothalamus and arrived at a startling conclusion: this structure and its connections to the thalamus, cingulate gyrus, and hippocampus represented a fundamental circuit for emotion. Although by this time the use of lobotomies had greatly tarnished the image of psychiatric neurosurgery,
the importance of Papez’s circuit was slowly realized and allowed the field to experience a revival aimed at focal lesioning of this circuit and related structures with greater precision.\textsuperscript{1, 13, 17} Moreover, stereotactic procedures referencing the brain to a 3D atlas were also being developed and allowed for ablation of specific limbic structures (Table 3). The result of these two critical developments was improved outcomes and reduced complications in comparison with lobotomies.\textsuperscript{13, 17} Four neurosurgical procedures were developed using the stereotactic technique: cingulotomy, subcaudate tractotomy, limbic leukotomy, and capsulotomy.\textsuperscript{29} At limited centers across the world, these same stereotactic procedures, including radiofrequency ablation and stereotactic radiosurgery, are still performed today for patients with severe psychiatric conditions refractory to conventional pharmacological and behavioral therapies, particularly for OCD, major depressive disorder, and bipolar disorder.\textsuperscript{6, 19} Numerous studies have shown that these procedures result in few long-term side effects and have relatively high response rates ranging from 30% to 70% depending on the pathology and technique.\textsuperscript{9, 16, 23}

### Deep Brain Stimulation and Modern Uses

Roughly around the same time that stereotactic procedures were being developed and refined, the concept of neuromodulation and use of long-term high-frequency electrical stimulation of the brain for treatment of psychiatric conditions were introduced.\textsuperscript{30} To our knowledge, the first recorded use of deep brain stimulation (DBS) for the treatment of a neuropsychiatric illness occurred in 1954, in which Heath and colleagues implanted multiple targets in 25 patients diagnosed with schizophrenia, again drawing broad criticism due to inconclusive results.\textsuperscript{3} In the 1980s and 1990s, however, DBS became widely used as a treatment modality for Parkinson’s disease and other movement disorders, primarily because of advancements in the understanding of dopaminergic and corticobasal ganglia-thalamic circuits important in the pathophysiology of those disorders (Table 4).\textsuperscript{32, 33} As use of DBS for the treatment of Parkinson’s disease increased, investigations into its use for the treatment of psychiatric diseases followed closely behind in incremental but meaningful steps.
Currently, DBS is being investigated for the treatment of numerous neuropsychiatric conditions, although the only neuropsychiatric condition to date to receive FDA humanitarian exemption status is severe, refractory OCD. To disrupt the cortico-striato-thalamo-cortical circuit, which is thought to be overactive in OCD, several anatomical sites have been targeted with high-frequency stimulation with favorable results, including the ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAc), and inferior thalamic peduncle. Some authors have suggested that these and other targets are likely different regions in a common network. Moreover, in a recent meta-analysis, DBS of these and other regions resulted in a 47% reduction in Yale-Brown Obsessive-Compulsive Scale scores, similar to ablative procedures for OCD. It is worth emphasizing that until more prospective, blinded placebo-controlled trials for people with severe, refractory OCD are conducted, the procedure may continue to be underutilized and inaccessible to those most in need. A recent work addressing the need for improved access was discussed by Davis et al., who suggested that restriction of DBS for OCD by insurers on the basis of being investigational is both unethical and illegal.

Given that major depression is one of the leading causes of disability worldwide, DBS has also been investigated as a treatment option for severe and treatment-resistant depression (TRD), defined as depression refractory to standard therapeutic approaches such as medication management and psychotherapy. Several cortical and subcortical structures, particularly the subcallosal cingulate gyrus (SCG), NAc, VC/VS, medial forebrain bundle, and inferior thalamic peduncle, have been tested in recent years. In one of the largest randomized controlled trials of DBS for TRD in which the SCG was targeted, no clinically significant change in depressive symptoms was observed after 6 months with DBS activation, which was the study’s primary endpoint. It should be cautioned that this study was not complete but rather stopped at an interim analysis and should not be interpreted as full trial results. Notwithstanding, in a follow-up, longitudinal open-label trial, remission rates rose dramatically over the next 2–8 years in subjects from the original pivotal trial, suggesting that longer post-DBS periods may be incorporated into future trial designs. Furthermore, using probabilistic tractography data from subjects in the original trial, Riva-Posse et al. showed that responders to SCG DBS all had electrode placement in one of three white matter tracts: the medial forceps, uncinate fasciculus, or cingulum bundle (along with related subcortical nuclei). Results such as these encourage further work with DBS for TRD and perhaps closer attention to stimulation in these precise tracts. Finally, some authors have noted that clearer delineation of major depressive disorder as a heterogeneous disease entity might allow DBS for TRD to take the next leap forward in its evolution by targeting more specific disease subtypes.

Similar to OCD, severe, refractory Tourette syndrome is also thought to be associated with dysfunction in the cortico-striato-thalamo-cortical circuit. High-frequency stimulation of the dorsomedial thalamus, centromedian-parafascicular complex, anteromedial or posteroventral globus pallidus pars interna, or the anterior limb of the internal capsule/NAc has demonstrated a greater than 50% reduction in severity in published case series. Although there have been approximately 150 cases performed to date, many experts believe that further refinement of anatomical targeting is needed in larger studies.

The use of DBS has been extended to the possible treatment of severe obesity and other eating disorders, although the underlying biology and pathoanatomy of these disorders is still highly debated. For obesity, both the lateral hypothalamus and the NAc have been studied as potential targets for DBS with varying degrees of success. For example, in one report, 3 obese patients in whom gastric bypass surgery failed underwent chronic DBS in the lateral hypothalamus, which resulted in an increase in resting metabolism and weight loss. In a more recent study, 2 patients with binge eating disorder underwent electrode implantation in the NAc. Using a novel stimulation paradigm time locked to periods of food craving rather than continuous stimulation, both patients lost weight even without significant caloric reduction or changes in physical activity. Although the numbers of these patients are still small, DBS has also been trialed for the possible treatment of anorexia nervosa, substance abuse, posttraumatic stress disorder, and anxiety.

Revisiting Minimally Invasive Techniques

Aside from DBS, another potential modality is high-intensity focused ultrasound (HIFU). This procedure was first studied as a potential surgical technique for treating intracerebral pathologies as early as 1942. Using intraoperative MRI as guidance, an ultrasonic transducer targets and heats a deep anatomical structure using adjustable, high-frequency ultrasound rays in a process known as sonication. Aside from its utilization in treating essential tremor and more recently Parkinson’s disease, HIFU has also been used in treating medically refractory OCD with favorable results. Despite this, overall research in the field remains limited, and further work on the use of HIFU for the treatment of OCD and other psychiatric diseases is needed.

Laser interstitial thermal therapy (LITT) is a technique in which an optical wire is inserted through a burr hole into a desired structure and laser illumination is activated at the tip, which heats and ablates the targeted tissue. LITT has been extensively researched for use in the treatment of epileptic foci and brain tumors. Satzer et al. used LITT to perform bilateral anterior capsulotomy and observed a mean 46% ± 32% decrease in Yale-Brown Obsessive-Compulsive Scale scores. Interestingly, tractography of the dorsoventral pathways revealed disconnections positively associated with symptom relief.

Future Directions

Neurosurgery for psychiatric disorders (NPD) remains an active area of current research with a number of promising applications. A significant impediment to progress has been the lack of reliable neural biomarkers for psychiatric disease, although several groups have recently identified potential electrochemical and electrophysiological markers. Local field potential data collection (e.g., using
sculpt electroencephalography [EEG], stereo-EEG, magnetoencephalography, and electrocorticography) is one of the most active areas of research, in particular, investigations assessing changes related to internal emotional states. Artifcial intelligence algorithms are increasingly being used to process these vast amounts of information. Moreover, most research on invasive neuromodulation for psychiatric disorders has involved open-loop neurostimulation, such as conventional DBS, which provides constant stimulation without feedback to guide treatment. Closed-loop stimulation is guided by biomarker-based data and stimulates only when necessary to achieve the desired output. In the recent obesity trial discussed previously, patients received NAc stimulation only during craving periods, which was triggered by detection of low-frequency, delta-band signals from the implanted electrode. They performed continuous intracranial stereo-EEG monitoring for a 10-day period to identify neural patterns associated with depressive symptoms in a patient with comorbid epilepsy. This was followed by implantation of a responsive neurostimulation system that targeted both the VC/VS and amygdala—identifed in this individual by machine learning analyses—when these neural patterns were detected, thereby leading to successful depressive symptom reduction. The private sector is also heavily involved in this research; one high-prole example is Neuralink, which has made claims of potentially being used to treat other forms of mental illness.

Conclusions

Over the centuries, psychosurgery has not been free of missteps and is rightfully regarded warily. Yet despite the mistakes of the past, alleviation of debilitating psychiatric symptoms in those without other treatment options has continued to serve as a catalyst for progress in NPD. From trephination in the prehistoric era to stereotactically guided electrical stimulation of deep brain structures today, the field of psychiatric neurosurgery has progressed immensely. Regulatory oversight and ethical considerations are now standard in all cases of NPD and have led to safer, more precise, and more accepted research and clinical practice. As more randomized controlled trials are conducted and the resulting data delineate the appropriate populations, targets, and modalities, psychiatric neurosurgical procedures are poised to become one of the treatment pillars in patients recalcitrant to psychotherapeutic, medical, and less invasive procedural management strategies.

References

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Author Contributions

Conception and design: Larrew, Short, Rowland. Acquisition of data: Bauerle, Rowland. Analysis and interpretation of data: Bauerle, Palmer, Larrew, Short, Rowland. Drafting the article: Salazar. Bauerle, Palmer, Larrew, Short, Rowland. Critically revising the article: Salazar, Palmer, Larrew, Kerns, Short, George, Rowland. Reviewed submitted version of manuscript: Salazar, Palmer, Larrew, Short, George, Rowland. Approved the final version of the manuscript on behalf of all authors: Salazar. Administrative/technical/material support: Salazar. Study supervision: Salazar, Rowland.

Correspondence

Claudia A. Salazar: College of Medicine, Medical University of South Carolina, Charleston, SC. salazarc@musc.edu.