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Review Article

Neurosurgery for mental conditions and pain: An historical perspective on the limits of biological determinism

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ABSTRACT

Neurosurgical operations treat involuntary movement disorders (MvDs), spasticity, cranial neuralgias, cancer pain, and other selected disorders, and implantable neurostimulation or drug delivery devices relieve MvDs, epilepsy, cancer pain, and spasticity. In contrast, studies of surgery or device implantations to treat chronic noncancer pain or mental conditions have not shown consistent evidence of efficacy and safety in formal, randomized, controlled trials. The success of particular operations in a finite set of disorders remains at odds with disconfirming results in others. Despite expectations that surgery or device implants would benefit particular patients, the normalization of unproven procedures could jeopardize the perceived legitimacy of functional neurosurgery in general. An unacknowledged challenge in functional neurosurgery is the limitation of biological determinism, wherein network activity is presumed to exclusively or predominantly mediate nociception, affect, and behavior. That notion regards certain pain states and mental conditions as disorders or dysregulation of networks, which, by implication, make them amenable to surgery. Moreover, implantable devices can now detect and analyze neural activity for observation outside the body, described as the extrinsic or micro perspective. This fosters a belief that automated analyses of physiological and imaging data can unburden the treatment of selected mental conditions and pain states from psychological subjectivity and complexity and the inherent sematic ambiguity of self-reporting. That idea is appealing; however, it discounts all other influences. Attempts to sway public opinion and regulators to approve deep brain stimulation for unproven indications could, if successful, harm the public interest, making demands for regulatory approval beside the point.

Keywords: Deep brain stimulation, Depression, Neurostimulation, Obsessive compulsive disorder, Pain, Psychiatric surgery

INTRODUCTION

Advances in the science and technology of diagnostic imaging, molecular genetics, surgery, pharmacology, and immunotherapy have accelerated at a pace unimaginable just a few decades ago. Accordingly, one sees investigative efforts to extend procedures that are effective in one condition to others. This is especially true for certain mental conditions and chronic noncancer pain. We and others previously have analyzed the neurostimulation, cerebrospinal fluid drug delivery, and surgical pain literature over the past 30 years; we cite that work here without repeating the analyses.[52,54,55,58,59,195,196,248,343-345] On the other hand, historical overviews of psychiatric

surgery in the functional and general neurosurgery literature predominantly reproduce case reports, series, and claims without critical analysis, often omitting material from outside the specialty.[3-5,15,36,34,35,37,38,41,47,46,50,51,60,53,76,95,106,127,146,193,212,237,240,333,349,369] Herein, the authors examine influential contributions from the pain and psychiatric surgery literature in the context of archival sources from outside those specialties as a framework to critique broadening surgical indications to treat noncancer pain and mental conditions.[4,5,81,109,183,202,237,244,245,255,259,283-293,308,309,338,340,350,354]

CHALLENGES IN THE STUDY OF TREATMENT EFFICACY FOR PAIN AND MENTAL DISORDERS

Effectiveness of functional neurosurgery in selected disorders

The success of neurosurgical lesions, neurostimulation devices, and cerebrospinal fluid drug administration in movement disorders (MvDs), epilepsy, spasticity, and cancer pain are well-established and will be alluded to but not explored in depth here.[24,30,71,99,128,129,147,176,177,232-234,315,320,367] Surgical candidates with those disorders have neurological disabilities for which the benefits of intervention justify the associated risks. Although some physicians and specialty societies recommend similar operations for chronic noncancer pain (pain) and psychiatric conditions, efficacy in those indications remains unproven, while adverse events (AEs) remain troublesome.[45,46,52,53,56,57,58,59,60,77,165,166,195,196,208-210,237,248,270,279-281,343-345,363,364,375] In contrast to treatments for pain and mental conditions, ineffective investigational therapies for other medical and neurological disorders were abandoned on the basis of clinical trial evidence. Principled disagreements lingered, but adrenal autografts, fetal transplants, viral transfection, and intracerebral growth factors, all of which were based upon bonafide effects at the cellular and neural network level in experimental models, are no longer performed.[104,108,114,180,188,239,318,326] Spinal cord stimulation (SCS) for angina pectoris was abandoned in the US but not in the Europe Union (EU) after a controlled, multi-center trial revealed no benefits.[375] Support groups and physicians who advocated bone marrow transplantation for advanced breast cancer stopped doing so once clinical trials showed that it was ineffective and higher risk than they had believed.[28,118]

Advances in the treatment of Parkinson's disease (PD) also followed a postenlightenment scientific trajectory that began two centuries ago with the identification of paralysis agitans as a distinct disorder, followed by correlation with structural pathology.[251,252] After observations that a stroke or other brain injury diminished adventitious movements on the opposite side of the body, a century of research and debate ensued before surgeons commenced to section the pyramidal motor pathways to relieve parkinsonian tremor. Many felt certain that only operations that caused partial paralysis could reduce involuntary movements. Once evidence revealed that the idea was mistaken, surgeons stopped operating on the pyramidal tracts and directed their attention to the extrapyramidal system.[1,39,67,68,265,356] After unpredictable results and serious complications from open operations, surgeons conceived safer and more effective stereotactic techniques.[1,24,67] Decades passed before incremental discoveries suggested levodopa therapy and better surgical targets.[43,132,139,164]

Biological determinism confounds neurosurgery for subjective conditions

Operations for pain and psychiatric surgery are the focus of this article and have benefited from the same technical advances as surgery for PD, other MvDs, and epilepsy. However, the reasoning behind surgery for pain and mental conditions did not benefit as much from empirical methods, serial hypothesis testing, and impartial analyses. In addition, the limitations of patient insight, subjectivity, self-reporting, and language that leave pain and mental symptoms open to unintentionally incomplete representations by patients or misinterpretation by doctors are surmountable only using methods of inquiry developed by generations of physicians.[70,203,235,278,322,324,325] But now, much neuroscience research has moved away from investigating symptom origins toward a focus on quantifiable phenomena – namely, a biologically deterministic micro or extrinsic perspective.[181] These refer to detection, recording, and analysis of neural signals from outside the organism.[9,15,135,136,168,314,348,349,366] In this view, activity within and among interconnected neuronal clusters or nodes determines what a person perceives, thinks, feels, and does – including moods, attractions, and intimate attachments. Consequently, unproven operations for mental conditions and chronic pain are compared to effective stereotactic surgery and deep brain stimulation (DBS) for objectively defined MvDs. In contrast to their effectiveness in MvDs, lesion surgery or neurostimulation predicated on extrinsic, quantifiable network dysregulation theories of pain and mental processes has performed poorly, or at best, inconsistently in practice.[53-55,58,59,60,83,84,269,271,310,349,350]

One embodiment of the extrinsic model is the human connectome project: a computer-optimized representation of merged physiological and imaging data in living humans.[66,83,84,189,269] Granting that connectomic models are anatomically and physiologically accurate, it does not necessarily follow that model-inspired surgical operations must be effective. While the surgical risks of operations for pain and mental conditions have been underreported, the efficacy of such operations remains to be proven.[15,50,53,62-65,76,183,202,237,259,281,283-291,340] That makes the contemporary literature on surgery for psychiatric conditions an echo of the neurostimulation pain literature

wherein electrophysiological, imaging, pharmacological, or psychological factors believed to predict efficacy were not supported because efficacy could not be proven in the first place [Table 1].[73,107,142,143,312,313,316]

The importance of a broad biological, psychological, and social approach to diagnosis

Clinical research in pain and mental conditions relies primarily on subjective complaints or statements that suggest but do not by themselves establish a particular diagnosis. Words with affective connotations versus those that describe intrusive thoughts suggest a depressive disorder versus obsessive-compulsive disorder (OCD), respectively. Moreover, pain descriptors such as aching versus burning suggest nociceptive versus deafferentation pain. However, absent deeper critical analysis, diagnostic codes, guidelines, rating scales and language-based algorithms that depend upon patient self-reporting are susceptible to error.[9,70,150,203,235,238,278,322,324,325,332]

Vigilant psychological assessment and insightful back-checking of medical histories and records to clarify and verify the plausibility and accuracy of self-reports are time-consuming but necessary to assess subjective complaints. Accepting imprecise or ambiguous narratives and complaints at face value risks erroneous diagnostic conclusions that compromise individual patient treatment and muddle the results of clinical research.[97,179,203,329,331]

The design and conduct of clinical trials to gather high-level evidence of efficacy for surgery in mental conditions are especially fraught, given the likelihood that at least some operated conditions wherein diagnoses are based on self-reports have an as-yet undefined biological basis.[44,46,47] We use conditions as a neutral term to describe thoughts, feelings, and behaviors that are susceptible to or mediated by socio-cultural or psychological influences.[70,250,322,357,374] Contributors to the first Diagnostic and Statistical Manual [of] Mental Disorders (DSM) used similar reasoning when they settled on the word "disorders" instead of disease or illness. Use of conditions now, as disorders did then, leaves room for future advances while avoiding terms that imply greater certainty than may be justified at present.[9,10,197,198] In that context, we believe that it is useful to draw parallels between portrayals of psychiatric surgery and the history of surgery for chronic noncancer pain.

Multiple factors have abbreviated the medical history and examination to the point that physicians, at times, elicit insufficient information to notice contradictions or complexities in patient stories.[130] Chief among the distractions are time-constrained patient contact and administrative pressures. Tasks mandated by third party payers and computerized data collection often are relegated to nonphysicians in place of the listening, questioning, and concentration that ideally should characterize doctor-patient interactions. Anxieties, inner distress, and psychological turmoil can outstrip some patients' abilities to cope and elicit physiological reactions that exacerbate their troubled feelings or simulate genuine medical or biological conditions – especially when omnipresent media augment anxieties and fears with medical misinformation and biased or sensationalized messages.[70,133,140,149,250,319,357,372]

Because speech and behavior entail self-awareness and insight to a variable degree, at least some cases of subjective, self-reported somatic or mental symptoms arise from preoccupation with minor physical sensations. In other cases, symptoms represent a patient's efforts to provide rational somatic explanations for their inner distress. Attempts to resolve internal psychological conflicts often align with media exposure and other socio-cultural influences.[70,321] Sometimes symptoms are encouraged and solidified by social media that provide group affirmation of popular, although unproven, theories of disease, including mental conditions.

Doctors and patients naturally default to their concepts of disease, each according to their training, lay knowledge, and cultural background. Thus, one sees unflattering portrayals of doctors in times gone by who performed unnecessary surgery or committed other errors when faced with nonorganic complaints.[81,96,126,214,282,308,309] Then and now, worried, fearful, and troubled patients who believe that they have a certain illness may adopt, identify with, or overinterpret behaviors they think or have learned that people with their suspected disorder ought to exhibit. For example, patients with nonorganic low back and leg pain wince during the straight leg raise maneuver when supine but do not react when seated.[236] In patients worried or convinced they have dementia, depression, anxiety states, MvDs, tics, or other conditions, they may assume, adopt, or overinterpret symptoms they have read about, seen, or imagined.[70,140,149,322] Whether conscious or unconscious, deliberate or unintentional, some patients find resolution or comfort by expressing psychological distress in somatic terms. These are powerful defense mechanisms that provide socially acceptable explanations without having to confront their inner or interpersonal conflicts. Somatic defenses also have positive reinforcement value in terms of secondary gain. Thus, the uncritical acceptance of subjective complaints operates to the detriment of all individuals.

Several studies of DBS for mental conditions employed single- or double-blinding that was limited to treatment parameters: stimulation on or off, voltage setting, or stimulation site when multiple targets were implanted.[79,80,138,201,206,231,346,362] Only one group in Montreal used deliberate misdirection to quantify the nontreatment-related effects of neurostimulation for pain.[208-210] In their DBS pain study, subjects were shown fake oscilloscope

Table 1: Summary of efficacy, safety, and level of evidence for operations to treat chronic noncancer pain and mental conditions.[12,40,42,49,297,361]

Disorder or condition	Surgical site/target	Surgical approach	Treatment modality	Efficacy	Adverse events	Evidence level/strength
Noncancer pain: Lesion procedures[59,195,248,363,364]						
Trigeminal Neuralgia, Classic (Tic douloureux)	Trigeminal root, ganglion, division, branch	Open surgery, percutaneous, stereotactic, freehand, radiosurgery	Surgical, RFL, alcohol, radiosurgery	Effective	Corneal numbness, paresis, anesthesia dolorosa	Level II/ Strong
Atypical, nonclassic, deafferentation, postherpetic	Trigeminal root, ganglion, division, branch	Open surgery, percutaneous, stereotactic, freehand	Surgical, RFL, alcohol, radiosurgery	Not effective	Corneal numbness, paresis, anesthesia dolorosa	Level IV-V/ Weak
Glossopharyngeal Neuralgia	Glossopharyngeal roots, extracranial nerve	Open surgery, percutaneous	Surgical, RFL	Effective	Dysphagia	Level II/ Strong
Sphenopalatine (Sluder's) neuralgia	Sphenopalatine ganglion	Open surgery, percutaneous	Surgical, RFL, alcohol	Not effective	Mucosal atrophy	Level IV-V/ Weak
Occipital neuralgia, chronic or nonclassic migraine	Occipital nerves	Open surgery, percutaneous, freehand	Surgical, RFL	Not effective	Anesthesia dolorosa	Level IV-V/ Weak
Classic migraine	Trigeminal nerve, ophthalmic division	Open surgery, percutaneous	Surgical, RFL	Effective	Corneal numbness, anesthesia dolorosa	Level IV/ Moderate
Brachial or lumbosacral plexus avulsion	Dorsal root entry zone	Open surgery	Surgical, RFL	Effective	Ataxia, paresis	Level IV/ Moderate
Somatic etiology: spinal, trunk, limb	Cordotomy, midline myelotomy, roots, ganglia, nerves, cingulum, frontal lobes	Open surgery, percutaneous, stereotactic	Surgical, RFL	Not effective	Anesthesia dolorosa, paresis, numbness, frontal lobe deficits	Level IV-V/ Weak
Central, deafferentation, phantom	Spinal cord, roots, ganglia; peripheral nerves thalamus, internal capsule, cingulum	Open surgery, percutaneous, stereotactic, radiosurgery	Surgical, RFL, radiosurgery	Not effective	Paresis, numbness, frontal lobe deficit	Level IV-V/ Weak
Noncancer pain: Neurostimulation and intrathecal drug delivery[45,58,55,59,119,187,344,345]						
Somatic-etiology: face, head, neck, trunk or limbs	Thalamus, periaqueductal/ periventricular gray matter, internal capsule, cortex, spinal cord, peripheral nerves	Open, percutaneous, stereotactic, freehand	DBS, SCS, DRG, PNS, intrathecal drugs	Not effective	Spinal cord injury, infection, overdose, death	Level IV-V/ Weak
Central, deafferentation, phantom	Thalamus, periaqueductal/ periventricular gray matter, internal capsule, cortex, spinal cord	Open, percutaneous, stereotactic, freehand	DBS, SCS, DRG, PNS, intrathecal drugs	Not effective	Spinal cord injury, infection, overdose, death	Level IV-V/ Weak
Mental conditions: Stereotactic and historical open lesion procedures[237,281,283]						
Depression	Internal capsule, cingulum, frontal lobes, subcaudate	Stereotactic, freehand, open surgery	RFL, surgical	Not effective	Frontal lobe deficit, seizure disorder, hemorrhage, death	Level IV-V/ Weak

(Contd...)

Table 1: *(Continued)*

Mental conditions: Stereotactic and historical open lesion procedures[237,281,283]						
	tract, limbic leukotomy					
OCD, other tics, Tourette syndrome	Internal capsule, cingulum, frontal lobes, subcaudate tract, limbic leukotomy	Stereotactic, freehand, open surgery, radiosurgery	RFL, surgical	Not effective	Frontal lobe deficit, seizure disorder, hemorrhage, death	Level IV-V/ Weak
Drug, alcohol, nicotine abuse/ addiction	Internal capsule, cingulum, frontal lobes, subcaudate tract, limbic leukotomy	Stereotactic, freehand, open surgery	RFL, surgical	Not effective	Frontal lobe deficit, seizure disorder, hemorrhage, death	Level IV-V/ Weak
Anorexia, obesity	Hypothalamus, frontal lobes,	Stereotactic, freehand, open surgery	RFL, surgical	Not effective	Frontal lobe deficit, seizure disorder, hemorrhage, death	Level IV-V/ Weak
Violence, aggression	Amygdala, hypothalamus	Stereotactic, freehand, open surgery	RFL, surgical	Not effective	Frontal lobe deficit, seizure disorder, amnesia, hemorrhage, death	Level IV-V/ Weak
Mental conditions: Neurostimulation[53,62-65,80,138,237]						
Depression	Thalamus, internal capsule, Cg25, cortex	Stereotactic, image-guided open surgery	DBS, cortical stimulation	Not effective	Mania/hypomania, infection	Level I/Strong
Depression	Vagus nerve, extracranial	Open surgery	‡Vagus nerve stimulation	Effective (FDA-approved)	Mania/hypomania, infection	Level I/Strong
OCD, Tourette's, other tics	Thalamus, internal capsule, Cg25, cortex	Stereotactic	DBS	†Not effective, HDE approved for OCD	Mania/hypomania, infection	Level II-V/ Weak
Addiction, substance abuse	Thalamus, internal capsule, Cg25, cortex	Stereotactic	DBS, cortical stimulation	Not effective	Mania/hypomania, infection	Level IV-V/ Weak
Anorexia, obesity	Hypothalamus	Stereotactic	DBS	Not effective	Mania/hypomania, infection	Level IV-V/ Weak
Violence, aggression	Amygdala, temporal lobes, hypothalamus	Stereotactic	DBS	Not effective	Mania/hypomania, infection	Level IV-V/ Weak

Evidence Level/Strength refers to evidentiary quality (e.g., randomized trial, case series) and has no bearing on assessments of efficacy. Efficacy assessments are based on reviews and meta-analyses cited in the table, and on other references in the text. †HDE approval for DBS to treat OCD was based upon weak evidence without a robust efficacy signal, as discussed in the text. ‡PMA approval of Vagus nerve stimulation for depression indicates therapeutic efficacy based on Level I evidence in a formal sense; longer-term experience has raised efficacy questions.[80,138] Abbreviations: Cg25: Subgenual cingulate, Brodmann area 25, DRG: Dorsal root ganglia, DBS: Deep brain stimulation, HDE: Humanitarian device exemption, OCD: Obsessive-compulsive disorder, RFL: Radiofrequency-thermal lesion, FDA: Food and Drug Administration, SCS: Spinal cord stimulation, DRG: Dorsal root ganglion, PNS: Peripheral nerve stimulator

tracings and told that their stimulators were on when, in fact, their devices were turned off. To our knowledge, misdirection similar to the Montreal group's was not employed to verify diagnoses or the veracity of subject responses in any other pain or psychiatric surgery trials. Given the multiplicity of factors that influence nontreatment-related effects, deceptive methods would have revealed subject emulations of mental disorders or expectation bias during subject selection and also would have strengthened end-of-study surveys on the effectiveness of blinding.[80,138,350,352]

A TIMELINE OF NEUROSURGICAL TREATMENTS AND TRIALS FOR PAIN AND MENTAL CONDITIONS

Operations to relieve pain transmitted over anatomic pathways came of age in the late 19th and early 20th centuries. Painful industrial injuries were common when a predominantly male workforce engaged in manual labor.[243] Workers became worried when discomfort at rest worsened during exertion, especially if previous injuries had required surgery or unpaid

leave.[172,246,247,272] What most pain surgery histories overlook is that surgical pioneers found their operations ineffective against pain that did not conform to anatomic distributions: so-called neuropathic, central, postamputation, or pains from other unclear etiologies [Table 1].[144,195,227,234,248,363,364] Although pejorative caricatures influenced physician trainee impressions of patients with low back pain, better informed contemporaneous literature provided more nuanced and insightful explanations for the expression of subjective symptoms in the absence of detectable pathology.[7,31,82,236] Even after the exclusion of malingering, delusions, anxiety, depression, and other disorders listed in the then-current DSM-III, a majority of nonphysiological pain complaints turned out to be heavily influenced, not by monetary gain, but by psychological factors that made such complaints unlikely to benefit from any kind of somatic intervention, including surgery.[7,96,144,227]

Today, the practice of pain medicine dovetails with insurance coverage that incentivizes reimbursable procedures supported by no clear evidence of efficacy: injections, radiofrequency nerve lesions, implantations of SCS or peripheral nerve stimulators (PNS), or intraspinal drug delivery devices. Insurance guidelines pose few barriers, and patients express global satisfaction even when their pain scores remain little changed.[59,77,78] In turn, patients acquiesce to reimbursable treatments or implantation procedures of questionable efficacy but that carry risks [Table 1].[20,45,52,56,57,96,151,172,187,279-281,302,306]

In retrospect, after mechanical failures of prosthetic heart valves led the Food and Drug Administration (FDA) to assert authority over implantable medical devices, the grandfathered-in approval of already marketed analgesic devices (SCS, PNS, intraspinal drug delivery) unintentionally created conditions for adverse public health consequences.[32] Those approvals in the 1970s and 1980s were supported by expert physician testimony in the absence of clinical trial evidence or FDA analyses, similar to recent demands for FDA approval and insurance coverage of DBS to treat psychiatric conditions.[351] Another similarity is the phenomenon of diagnostic inflation whereby face-value acceptance of nonfalsifiable, subjective, self-reported complaints inflates the number of psychiatric treatment candidates, as occurred for chronic noncancer pain.[59,72,122,150,238,302,306] In a third similarity between interventional pain medicine and psychiatric indications, US registries and trials of neurostimulation or intraspinal drug delivery revealed no efficacy, while separate studies revealed higher than anticipated risks of death or paralysis [Table 1].[45,52,56,57,100,101,151,172,187] Regardless, "The Neurostimulation Devices Market stood at US $11.1 billion in 2022 and the global market is projected to reach US $36.5 billion by 2032," and "North America is expected to witness the largest market share during the forecast period with a value of USD 4,858 million [$4.8 billion] in 2021 and will grow [to] an estimated value of USD 10,027 million [$10 billion] in 2030."[112,113] The largest market share comes from grandfathered-in SCS implants for pain, plus a minor share from US and global markets for DBS devices approved for MvDs, including Humanitarian Device Exemptions (HDEs) for dystonia in 2009 and for DBS in one psychiatric condition, OCD, also in 2009.[93] Notably, several critical analyses of neurostimulation for pain have had no adverse market impact on the number of devices implanted annually.[119,196,343-345]

Historical portrayals of psychiatric surgery are incomplete

The tenor of psychiatric surgery histories from within the specialty[3,84,95,127,193,212,369] differs from reports by patients, families, and independent historians.[4,5,34-36,41,50,69,76,87-89,109,135,186,219,237,255,292,298,308,309,340,350] Inside histories relate a timeline of progress, improving ethical safeguards, and conservative surgical practices that other research reveals to be inaccurate. Most inside specialty accounts assure readers that psychiatric surgery was aligned with the state of medical knowledge and social mores at the time.[95,106,127,193,212,311,369] Another theme is that interdisciplinary teams obviated the perils of surgeons operating on their own. Surgeons always were active participants, but tens of thousands of psychiatric operations took place only after psychiatric referrals. James Watts, the neurosurgeon who worked with Walter Freeman for approximately 10 years, ended their collaboration when Freeman commenced an office-based transorbital leukotomy practice in 1946. Freeman, a neurologist by training, is best known among the thousands of practitioners who recommended or performed lobotomies and leukotomies.[19,26,33-36,50,85,148,204,244,277,281,330,338,340-342]

Approximately 40,000–50,000 lobotomy or leukotomy operations were performed in the US between 1936 and 1959, including 3500–4000 by Freeman alone. Lobotomy, leukotomy, topectomy, orbital undercutting, and related operations were so well-integrated into general neurosurgery that many prominent surgeons made contributions.[35,75,102,103,110,120,124,137,169-171,178,200,216,217,256,260,261,296,301,307,330,333,341,347,355,371] Reporting at the time read much like today's, except that major complication rates for postoperative hemorrhage and infection are lower now using stereotactic techniques. Approximately 20% of lobotomy or leukotomy patients improved sufficiently for discharge from asylums, whereas 15% in some series experienced an intracranial hemorrhage or death. The medical community and lay public accepted the complications and low threshold for success because patients appeared resistant to less invasive somatic therapies, such as insulin coma or electroconvulsive therapy (ECT), in the prepharmacological era. Recent authors have tried to rehabilitate Freeman on the grounds that "psychiatric care

in the mid-twentieth-century USA must be considered. [L]obotomy was considered revolutionary and quickly gained widespread acceptance. No other alternative treatment at the time demonstrated comparable efficacy. [P]sychosurgery was sometimes applied inappropriately, but records across the USA demonstrate that these were exceptional cases, whereas, as a rule, selection of surgical candidates was based on very strict criteria."[106] That glosses over the criteria in actual practice during the lobotomy-leukotomy era. What most would call arbitrary, capricious, or social convention-driven criteria were strict only in the sense that physicians adhered to them. But from the 1930s to 1970s, pregnancy out of wedlock, homosexual desires, or defiance of authority within the asylum system were common surgical criteria, with defiance among the indications considered to have been treated most effectively. As none of those are medical diagnoses or indications, "very strict criteria" cover a lot of socially determined surgical decisions that had no medical or scientific basis. Other researchers have mined institutional archives physician records and interviewed surviving patients to reach conclusions indicative of abuse, e.g., surgery performed for reasons other than a patient's benefit.

An estimated 10,000 lobotomies or leukotomies were performed in Europe, predominantly in Scandinavia, where hospital psychiatrists prescribed surgery at a per-capita rate approximately three times higher than in the US. Between 1944 and 1966, Swedish surgeons performed approximately 4500 operations, the majority on women (61.2% at Umea), similar to other Nordic and European countries (84% women in France, Switzerland, and Belgium).[18,175,240,244,245,338] Sweden accounted for almost half of the operations in Europe, with a surgery rate slightly >$6/10^5$ population. In the peak surgical years of 1936–1960 in the US, an estimated 40,000–50,000 lobotomy or leukotomy operations amounted to a per-capita rate of only 2.0–$2.5/10^5$ population.[244,245]

Serial retrospectives on psychiatric surgery in Sweden highlight the differences between inside-specialty and independent assessments. Lars Leksell, the neurosurgical polymath and inventor, performed the first anterior capsulotomy operations in Sweden shortly after Talairach's 1949 report from France.[224,335] Leksell *et al.* published results over three epochs, first with Herner (1952–1957), then with Bingley (1970–1976), and then with Rylander (1979).[29,134,224,294] Stereotactic surgery at the Karolinska Institute relied on ventriculography until approximately 1976, computed tomography (CT) until 1988, and magnetic resonance imaging (MRI) thereafter. The goal by all methods was to create bilateral, oblong vertical lesions within the anterior limb of the internal capsule (ALIC) having their inferior margin at the level of the Foramen of Monro. As with lobotomy and leukotomy series at the time, a majority of capsulotomy patients in the first (Herner *et al.*) series were schizophrenic, with 9/64 (14%) reportedly having a satisfactory outcome where "satisfactory" was not defined further.[134] No additional psychotic patients were operated on after 1957. Nine of the 18 (50%) Herner *et al.*[134] patients with what was then called obsessional neurosis had satisfactory results (also not defined), while 3/15 (20%) with anxiety neurosis had a satisfactory outcome. In the next (Bingley *et al.*) series of 35 OCD patients operated between 1970 and 1976, 70% had a satisfactory result (not described in detail), and four of 35 (11%) were incapacitated by surgery.[29] In Leksell's final series, treated using the ^{60}CO Gamma Unit with Rylander, 10/14 patients (71%) with expanded indications of OCD plus other anxiety disorders had satisfactory results (also not described in detail).[294]

During the 1970s–1990s, Per Mindus *et al.* described the long-term results of the Karolinska OCD and anxiety surgical series in a limited, qualitative fashion.[192,218,220-226] They acknowledged that it was impossible to compare results among patients diagnosed, treated, and followed-up differently in retrospective series where uniform data were not recorded. Consequently, their graphical depictions of aggregate results communicated general impressions, few hard data, and sample numbers that did not correspond to the original publications.[29,134,224,294] Mindus' reports focused on 22 available patients among 24 who underwent radiofrequency-thermal lesion capsulotomy for OCD (n = 10) or other anxiety disorders (n = 14) between 1979 and 1990, spanning portions of the CT and MRI eras.[224] In their assessment, six of 10 (60%) with OCD had satisfactory long-term results, with 5/10 (50%) reportedly in complete remission; thirteen of 14 (93%) with other anxiety disorders had satisfactory outcomes, with 7/14 (50%) in complete remission. They further acknowledged that their data and analyses provided inconclusive evidence on the long-term safety and efficacy of capsulotomy. Like others before and after, they suggested that an international registry or formal clinical trials should be undertaken.[13,277,286]

Years later, Ruck re-interviewed Mindus' cohort of surviving Karolinska capsulotomy patients and their families reported the results after Mindus passed away and reached opposite conclusions, especially regarding safety.[283-291] They included Mindus as a posthumous author in one report on the results of capsulotomy for non-OCD anxiety disorders wherein they noted: "To some extent, our data contradict other reports indicating that the risk of adverse symptoms is small. One possible explanation might be that few of the earlier studies used systematic examinations of symptoms attributable to frontal lobe dysfunction, and some studies of neurosurgery for mental disorders might, therefore have underestimated the risks."[283] Ruck's work revealed frontal lobe dysfunction on a Karolinska in-house Execution, Apathy, Disinhibition (EAD) Scale in which the highest possible (best) single component score = 3; the best aggregate score = 9; the worst single component or aggregate score = 0; and a significant

frontal lobe deficit was a three-component aggregate <3.[283] Nineteen of 26 patients tested (73%) exhibited significant frontal lobe deficits (aggregate score <3) that were severe in 18 of them (aggregate score = 0 or 1), meaning that 18 patients scored 0 in at least two of the three domains tested.[283] Viewed in the most positive light, seven of the 19 patients with detectable deficits had frontal lobe EAD scores ≥3 out of a possible 9 points. One patient scored 9, which indicated no detectable frontal lobe dysfunction. Among the cohort with OCD restudied by Ruck, "About every third patient experienced apathy, executive problems, or disinhibition at long-term follow-up. Therefore, we conclude that capsulotomy is not a safe procedure."[285,290] To our knowledge, the Ruck studies were the first at Karolinska (or anywhere) conducted "by psychiatrists not involved in patient selection or postoperative treatment."[283] Reappraisal of inside-specialty histories in light of later independent work suggests that Mindus' nonascertainment bias of not finding what he was not looking for continues to shape selectively-referenced reports, reviews, and histories.[127,192,230,276,369,373]

Major tranquilizers were introduced, and older drugs were repurposed for psychiatric use in the 1950s and 1960s. Most historical accounts convey the impression that effective medications spelled the end of lobotomy, leukotomy, orbital undercutting, and other open operations. However, contemporaneous publications and historical records reveal that the impression was mistaken, especially in the UK and former Commonwealth countries.[17,163,211,263,307,330,334,336] During that transitional era, medications were administered as an alternative to surgery, as supplements to surgery, in multi-drug combinations, or combination with ECT or psychotherapy. Hepatic toxicity and epileptogenicity associated with phenothiazines, the most effective drugs, were cited by surgical proponents as reasons not to rely on medication and not to abandon surgery.[22,23,25,61,74,111,167,190,191,199,317,323,328,353] However, concerns over epileptogenicity conflated association with causality because seizure disorder was the most frequent AE after lobotomy or leukotomy, regardless of whether or not a patient was administered phenothiazines.

Successful results for lobotomy, leukotomy, and later, stereotactic lesion surgery were also the subject of case reports and small series on miscellaneous mental conditions. Most described surgical goals in terms of managerial expedience, not patient benefit. Operations were successful when difficult or unruly inmates were rendered more docile within the asylum system or less commonly when families could manage them at home. Collective institutional and societal considerations outweighed individual concerns.[41,106,358]

Lobotomy and leukotomy for psychiatric indications and intractable pain did not so much go away as become displaced by stereotactic surgery.[14] Targets included thalamic nuclei, the cingulum bundle (replacing open cingulectomy), the ALIC (capsulotomy), the amygdala (for pathological aggression), hypothalamic nuclei (for aggression, sexual offenses, or eating disorders), the subcaudate region, and limbic leukotomy. Like today, different countries or regions have preferred targets and operations. For psychiatric indications and mostly cancer pain, cingulotomy – first open, then stereotactic – was popular in New England, Seattle, and the Great Lakes region.[21,62-65,102,103,131,257,370] In the 1990s, a debate ensued regarding whether or not stereotactic cingulotomy was psychosurgery when performed on pain patients.[131,183,202,259,368,370] In the UK, Ireland, British Commonwealth, and New England, subcaudate tractotomy was a popular operation either alone, combined with capsulotomy, cingulotomy (limbic leukotomy), or *ad hoc* after a failed cingulotomy.[23,48,146,160-163,228,230,274,276,295,311,373] Anterior capsulotomy was popular in Scandinavia before its adoption elsewhere, and similar preferences continue today. Limbic leukotomy, a bilateral two-target operation (subcaudate tractotomy plus anterior cingulotomy), was introduced in the UK in the early 1970s, well into the era of effective psychopharmacology, and is practiced there and elsewhere to this day.[37,230] Moreover, for noncancer pain as well as for better established cancer pain indications, a few surgeons still perform open, percutaneous, or image-guided cordotomies and lower brainstem lesions.[152-156,174,233,234,339]

NEUROSURGICAL TREATMENT OF MENTAL CONDITIONS AS THE NEW CHRONIC PAIN

Major depression versus melancholia

The diagnosis of mental conditions using the most recent edition of the DSM became easier as DSM entries expanded, analogous to International Classification of Disease (ICD) codes for noncancer pain.[8,9,11,16,238,306] Diagnostic validation provides patients with rational and socially conventional explanations for their perceived discomfort and ill-health. In addition to general medical and neurologic examinations, psychiatric diagnosis relies on mental status examinations to ascertain an individual's objective syndromal signs and subjective psychological formulations. However, owing to the lack of validated, confirmatory imaging or laboratory biomarkers, contemporary psychiatric diagnosis in clinical practice and research settings is often limited to listing subjective symptoms and/or completing standardized rating scales that are self-rated by patients or para-professionals with little medical or psychiatric training.[11,354] With the benefit of hindsight, studies, and trials of DBS in treatment-resistant depression (TRD) appear to have implanted individuals with complex mental conditions other than endogenous melancholia or a primary depressive disorder.[53,80,138]

While case reports and testimonials uncritically affirm the efficacy of DBS in behavioral disorders,[27,37,253,332] other plausible explanations for perceived efficacy include features of the clinical trial setting: intensive emotional support, concurrent psychotherapy and medications, expectation bias, and unintentional or surreptitious coaching, conditioning, and positive reinforcement by the investigative team.[53,275,322,332] When customarily effective medications, ECT, or transcranial magnetic stimulation fail to relieve depression, prudence dictates revisiting the diagnosis before escalating treatment to surgery, especially in patients with long-term emotional and diagnostic instability. To our knowledge, the entry criteria in case series and trials for TRD did not probe the possibility (and neither did chronic pain publications) that some subjects, while apparently depressed and hopeless, expressed psychologically complex or ambiguous complaints and behaviors that contributed to their past treatment failures.

The semantics of treatment resistance to justify the escalation of therapy in psychiatric conditions is as circular as the historical semantics of intractability in chronic pain. Patients are treatment resistant or intractable because they do not respond to noninvasive treatments, and patients do not respond to conventional treatments because they are resistant or intractable. While some DBS trial subjects with depression truly may have been treatment resistant, it is worth considering that some other patients failed to respond because treatments were being administered for a disorder they did not have. Moreover, in retrospect again, trial subjects turned out to have more complicated psychiatric and/or medical co-morbidities than anticipated. In small studies and trials of fewer than 150–200 subjects, a few aberrant cases can skew analyses one way or another. In one example, two high-responding outliers drove the mean outcome measure to statistical significance in a 14-subject trial of DBS for Tourette syndrome wherein greater than half of the evaluable cohort had their Yale Global Tic Severity Scale scores drop substantially before DBS was administered.[159]

A separate matter is that candidates for DBS or lesion surgery are diagnosed using DSM criteria, with trial or cohort enrollment based on quantitative severity thresholds on rating scales. Dysfunctional responses to stress used to be called "nonpsychotic depressive reaction[s]" in the first DSM when the subconscious or unconscious mind was said to defend itself by expressing a depressed mood.[10] Mild, often psychologically-determined dysthymic reactions were distinguished from "depressive, psychotic reactions" by the "absence of malignant symptoms (hypochondriacal preoccupation, agitation, delusions [particularly somatic], hallucinations, severe guilt feelings, intractable insomnia, anorexia and weight changes, anhedonia, suicidal ruminations, severe psychomotor retardation, profound retardation of thought, stupor)" and other features that historically defined genuine melancholia. In that era, depression was primarily diagnosed in older adults under the now discarded (we believe, mistakenly) category of involutional melancholia.[10] Many patients diagnosed with major depressive disorder or TRD today do not have malignant symptoms and, in earlier days, would not have been administered antidepressant medication ECT or have been hospitalized. Moreover, clinicians and researchers sometimes devote insufficient attention to the differential specificity between and among multiple underlying causes for a patient's depressed mood. That created a conundrum in the DBS depression trials, which only appeared obvious afterward. To qualify, candidates had to be treated with (and failed) medications and ECT and had to have been hospitalized as if they suffered from the malignant melancholic symptoms of a bygone era. However, candidates did not need to have a history of malignant melancholic symptoms to qualify for trial entry.[80,138] Recruiting an adequate number of patients who were sufficiently depressed to justify surgery but not so depressed that their mood dial could never budge turned out to be impossible.[267] Both industry sponsors shut down their programs for lack of efficacy, although the companies continued to support small investigator-sponsored studies.[53]

Depression was the indication from which manufacturers anticipated recovering program costs and making a profit. The large estimated TRD demographic required them to pursue a premarket approval route (PMA) that entailed FDA-approved safety and efficacy trials in approximately 200 subjects.[91,254] By contrast, because the estimated number of patients with medically refractory OCD anticipated to qualify for DBS was fewer than 2000 per year in the US population, Medtronic, Inc. (Dublin, Ireland, formerly Minneapolis, MN) applied for and obtained HDE approval of DBS in 2009.[93]

OCD and the US-HDE

The sponsor's HDE submission contained data on 26 DBS subjects: 15 subjects (five each) from three US academic centers implanted under separate FDA-approved Investigational Device Exemption research protocols and 11 subjects from Leuven, Belgium.[90,92] Implantations in the US began with the ALIC target reported by Nuttin *et al.* in 1999, after which investigators revised their targets on a case-by-case basis until they settled on the ventral capsule/ventral striatum location (VC/VS).[115,121,241] Parenthetically, VC/VS was also the target in the reclaim DBS depression trial.[80] The 11 Belgian subjects were implanted with EU commercial leads that had the same configuration as the investigational HDE lead used in the US: 4 × 3.0 mm contacts spaced 4.0 mm apart; total spread = 24.0 mm. It can stimulate greater than twice the brain volume as the leads approved for MvDs like tremor, PD, and dystonia.

DBS leads marketed under the OCD-HDE include a "Summary of Safety and Probable Benefit."[123] Some US

centers were not included in the FDA submission because they used the smaller commercial leads marketed for MvDs, enrolled no subjects, or had only a single subject who was referred elsewhere for lesion surgery after DBS failed.[2,194] Other centers in the US and abroad also received industry support for OCD projects outside the HDE program. Those data were not audited, monitored, or adjudicated independently for AEs. The same applies to lesion surgery (which is not investigational in a US regulatory sense) and to DBS-OCD cases implanted after the HDE approval in 2009. From an evidentiary standpoint, this makes the OCD lesion and DBS surgical literature equivalent to case series wherein the same physicians diagnosed, selected, operated, and evaluated the patients and reported the results – weak Level II evidence, at best.[42,361] In short, every publication said to support the efficacy and safety of DBS or stereotactic lesions in OCD is subject to limitations that, in the case of DBS, disqualify the data from consideration by the US FDA.

Outside of industry trials and published reports, AEs that occurred after the US HDE and EU (CE-mark) approvals were reported through relatively inaccessible regulatory databases. CE-mark grants marketing approval based on a manufacturer's declaration that products comply with EU directives. Unlike PMA or HDE submissions in the US, the CE-mark does not require EU regulatory agency analyses of safety, efficacy, or probable benefit. In the US, patients with depression have been implanted off-label using OCD-HDE devices, which constitute diversion to an unapproved indication. Moreover, OCD patients implanted under HDE (US) or CE-Mark (EU) who experience therapeutic failure need not be reported to the manufacturer or regulatory agencies because lack of efficacy is not, technically speaking, a device-related AE.

Regulatory and reimbursement response to inconclusive surgical trials

The current consensus on surgery for pain and mental conditions goes only so far as agreement that surgery is a good option. Reference citations in consensus guidelines indicate that no agreement exists on where to operate (anatomic targets) or what to do there (stimulation or lesions). As in the past 60 years of publications on neurostimulation for chronic pain, the positive appraisal and degree of certainty expressed in consensus and guideline statements for psychiatric surgery, especially DBS for OCD, escalated from urging cautious research at first to later calls for carte blanche regulatory and insurance approval.[241,351]

In brief, a US-FDA PMA approval establishes the marketability of drugs and medical devices in the US. FDA does not regulate or control the practice of medicine and has no authority over what physicians can prescribe or what operations they may perform.[53,254] Neither do medical boards or any government entity, with abortion being an exception beyond the scope of the present discussion. Although FDA-approved drugs and devices are labeled for indications listed in package inserts, a majority of drug prescriptions and many device implants are for off-label indications not evaluated or approved by FDA. Again, no laws or regulations prevent US surgeons from implanting any device to treat any diagnosis in a patient who consents to surgery. Moreover, surgery that does not involve implantable devices is unregulated in the US. In the case of psychiatric surgery, compliance with the 1977 National Commission Report is voluntary and subject to no preoperative restraint and no postoperative regulation.[293]

Another question is the supposed crisis of access for DBS in psychiatric indications.[38,98,351] Notably, all of the case series cited to justify bypassing FDA and insurance processes originated outside the US, while at the same time, no regulatory barriers exist in the US or EU that limit the use of DBS for any indication, including psychiatric conditions.[53,79,201,206,231,346,351,362] A principal concern for US physicians is payment because insurance carriers are obligated to make sure, certain, or safe that they are paying for things that work. As a consequence, insurance generally does not cover off-label device usage. Thus, the FDA and insurers have not failed to acknowledge convincing evidence, nor have they singled out DBS or psychiatric indications for adverse decisions. Agency and insurance reviewers observe the same scatter-plot of materials, methods, and results as other readers who have no bias in favor of psychiatric surgery, including DBS. A recent publication stated, "Action is needed by psychologists, psychiatrists, and insurers so that patients with otherwise intractable cases can receive this therapy to improve their mental health."[351] The real issues are not therapy availability and patient access but public and private insurance nonpayment for unproven indications and mental health professionals' perceived lack of need for psychiatric DBS.

FDA regulations do impose financial constraints on manufacturers. HDE devices must sell at a discount that permits recuperation of costs but without profit. Because humanitarian approvals only apply to low-incidence conditions, an Annual Distribution Number limits the number of devices allowed to be sold in the US to approximately 8000.

Recent functional surgery society policy suggestions also reverse earlier recommendations [italics added]: "… The US FDA granted a so-called HDE to allow patients to access this intervention, thereby removing the requirement for a clinical trial of the appropriate size and statistical power. *Bypassing the rigors of such trials puts patients at risk, limits opportunities for scientific discovery, and gives device manufacturers unique marketing opportunities.* We argue that Congress and federal regulators should revisit the HDE to ensure that it is not used to sidestep careful research that can offer valuable data with appropriate patient safeguards."[98]

Regional target preferences for DBS and lesion surgery make it impossible to compare the results from one center to another – much less to analyze aggregate results in support of regulatory or insurance decisions. Investigators in France targeted the subthalamic nucleus (STN) after they observed mood elevation in PD patients at Grenoble, where STN DBS was introduced. Investigators in Belgium and the Netherlands initially targeted the ALIC, Leksell's early capsulotomy target.[29,182,241] They and their US counterparts modified the target over time to VC/VS.[80] Moreover, German investigators targeted the nucleus accumbens.[145,337] Efforts to sort things out led a few centers to implant four DBS leads per subject to test single- and multiple target combinations.[346,362] The variety of DBS targets for mental conditions corresponds to past and present regional preferences in stereotactic lesion surgery and the earlier history of lobotomy or leukotomy methods. A further irony is that the OCD HDE approval was based exclusively on data provided by the same investigators who have objected to it ever since.[93,115,121,242]

In short, to state that "Deep brain stimulation is an effective treatment for obsessive–compulsive disorder" on the basis of a few publications from outside the US is unwarranted.[351] The list of features that disqualify those data from FDA consideration include nonuniform methods and subject selection; different devices, targets, and stimulation parameters; small or unbalanced N numbers between centers; variable outcome measures and durations of treatment; absence of independent AE review; and noncompliant database integrity and personnel oversight.[94,254] Regardless of whether or not a new indication receives FDA approval, recent trials of DBS in epilepsy and depression required comparisons between parallel cohorts of active- and sham-treatment control groups in approximately 200 subjects. Non-US data are rarely considered in Class-III "significant risk device" submissions.[91,94,254] A more realistic appraisal is that small and medium-sized investigator-sponsored studies still generate hypotheses that remain to be tested. In this regard, the announcement of an "FDA Breakthrough Device Designation" for DBS in depression misled conference attendees to believe that FDA approval was imminent, whereas FDA Breakthrough refers only to manufacturer-paid access for expedited administrative communications.[38]

The nonequivalence of lesion surgery and DBS

Rhetorically, one might ask, if one target or method, such as DBS versus lesion surgery, carries lower risks or is more effective than another, why do practice guidelines and consensus publications treat both categories of operations as if they were equivalent? More to the point, why do some surgeons exclusively perform lesion surgery instead of DBS? The consensus within the functional neurosurgery community appears unanimous only insofar as practitioners are in favor of it – meaning psychiatric and pain surgery – although what it differs from one surgeon or institution to another. Publications shy away from addressing how factors such as payment, administrative effort, operating room tasks, and postoperative care affect surgical decisions.

Once a US patient consents to surgery, leaving aside those who self-pay, reimbursement dominates preoperative concerns. DBS for depression and pain are off-label, and the HDE for OCD makes payment unlikely. Prior approval by insurance carriers often fails, and hospitals discourage or prohibit elective surgery without a payment guarantee. Moreover, expenses for neurostimulation or targeted drug infusion therapies do not end with hospitalization, surgical fees, and implant costs. Patient control units, battery chargers or replacements, and other items carry downstream costs. Insurance, regulatory, and administrative difficulties added to uncertain payment are strikes against DBS that do not apply to lesion surgery, which is covered by longstanding Current Procedural Terminology insurance and billing codes.

DBS also requires more work in the operating room: two sterile fields, different anesthesia for cranial and neurostimulator stages, plus device-related instruments, accessories, and supplies. Stimulation leads are fragile, and any device can malfunction or become a nidus for infection. Those are additional strikes against DBS compared to lesion surgery.

Follow-up after a device implant requires labor-intensive device interrogation and recordkeeping. Moreover, requests for unscheduled programming visits are inevitable because the capability to fine-tune stimulation or drug delivery parameters elevates patient expectations. Surgical versus nonsurgical aftercare responsibilities also must be managed so that patients know whom to call for what kinds of care or troubleshooting. In the best case, lesion surgery is a one-and-done proposition, marking another strike against DBS.

Device heating during MRI and therapy interruption from interference by metal detectors, electric motors, or generators has been reduced, but not to zero.[57] That is another strike against DBS that does not apply to lesion surgery. On the other hand, although lesion surgery customarily has immediate results, initial efficacy can decay after weeks or months. Repeat surgery to enlarge or extend a therapeutic lesion requires a second operation. Delayed loss of efficacy in device-based therapies can sometimes be recaptured by noninvasive programming – a plus for stimulation.[247,271]

Most important, and regardless of the workload and administrative strikes against DBS, neurostimulation is safer than lesion surgery for every indication. The common, permanent neuropsychological sequelae of lesion surgery for psychiatric indications have not been observed in DBS series, clinical trials, or FDA audits. Nothing that compares to the "apathy, executive problems or disinhibition at long-term

follow up" described by Ruck, and by Cohen *et al.,* others has occurred outside of lesion operations – nor have the painful numbness, ataxia, incoordination, and other potential sequelae of aberrant lesion surgery for pain.[62-65,264,290,285] Whether or not they are effective, device-based therapies are safer than lesions. The lack of clarity and absence of pertinent comparative data have frustrated independent systematic reviewers' efforts to address the issue.[281,321] The most plausible reasons we can find for why lesion procedures of questionable value in mental conditions and noncancer pain have not been abandoned boil down to administrative expedience, insurance payment, and because some surgeons prefer it to DBS.

The connectome versus a biological, psychological, and social model: Are we there yet?

Whether they speak about nociceptive sensations or unwanted thoughts, patients use language to communicate. Physicians then must interpret what they hear to grasp what the patient is trying to convey. Language occupies the space between what a person feels or thinks, what they express to others, and what others understand. Vocabulary, grammar, dialect, and perceptions evoke inferences about education, temperament, and credibility on both sides of the conversation. Persistent or pointed questioning is required to clarify ambiguities, even when the patient and physician share common backgrounds. However, time consuming interviews are anathema to the extrinsic perspective of current clinical neuroscience research – not to mention the accelerated pace of medical practice.[130]

Given those limitations, and in spite of how large the DSM and ICD have grown, some investigators view them as antiquated, subjective, language-burdened catalogues subject to psychological, social, political, and commercial considerations.[6-10,16,238] A solution under study by researchers who share the extrinsic perspective is to implant devices that record, stimulate, and map neural networks in projects funded by government, military, and venture-capital sources.[45,334] Although details differ between institutions and whether pain or mental conditions are under study, the projects use implantable devices to record neural activity for weeks at a time between data downloads from device memory. The goal is to replace language-based patient reports with multi-source data profiles that theoretically should correspond to pathological states.[46,300,338]

An implantable closed loop epilepsy device approved in 2014 was among the first neurological applications to have sensing, stimulation, and recording capabilities (Neuropace, Inc., Mountain View, CA). It records seizure-associated intracranial electroencephalographic (EEG) events during a postoperative trial period, and when seizure-associated waveforms recur, the system administers stimulation to override and extinguish the impending seizure. After success in cardiac pacing and defibrillation, epilepsy was the most practical episodic neurological disorder to introduce closed-loop technology. Electrical or convulsive episodes (or their absence) are objective evidence that a seizure did or did not occur after a previously defined trigger event. While recognizing that modeling mental conditions and pain is more complicated than epilepsy, investigators believe that they already possess implantable systems that, in different research programs, can sense pain, mood- and other symptom-associated network activity. Presumably, pathological waveforms are identified through correlation with patient diaries during a postimplant test-period. Detection of those signals triggers a stimulation output intended to extinguish the incipient symptoms – analogous to closed-loop epilepsy therapy.[46,300,338]

Claims to have created autonomous digital psychiatry and pain medicine detached from subjectivity and language deserve closer examination. The absence of unambiguous, involuntary convulsions (as in epilepsy) poses a dilemma in pain and mental conditions wherein subjectivity, psychology, and language are inescapable. For example, when an implanted patient experiences symptoms, feelings, or emotions, they must decide to act to record the onset and termination of those symptoms or sensations.[46,153] Unlike the 1:1 correlation between an EEG signal and seizures, no physician or investigator, much less an electronic device, can know for certain whether or not a diary entry corresponds to something the subject felt or why they felt it. Moreover, when diary data do not correlate with divergent neural activity (compared to background), neither the device nor the investigator can know for certain whether the patient was mistaken, flustered, or confused. Many people under psychiatric care lack sufficient insight and awareness of the motives that underlie their feelings and behaviors, especially unconscious motives. However, if the network dysregulation hypothesis is correct and the patient really experienced symptoms, pathological neural activity must have occurred. Hence, in a scenario of genuine symptoms without a corresponding recorded signal, disordered network activity must have gone undetected by the implant. Such interpretive dilemmas appear inevitable. Deep brain and cortical surface electrode recordings are more sophisticated and in tune with an extrinsic, micro perspective of neuroscience than the scalp EEG. However, given these and other limitations, to use of intracranial electrodes as the sensing limb of a closed-loop therapy for subjective disorders harks back to the mid-20th Century when the EEG was believed to have relevance in psychiatry. That became subject to "Considerable difference of opinion" before being discarded by the mid-1970s.[105,158] At present, the hypothesis that electrical waveforms in a few brain regions reveal or predict emotions, memories, mood states, or nociceptive experiences, respectively, remains to be

tested before adoption as the sensing limb of an implantable, closed-loop psychiatric or pain therapy device.

Neuroscientists who are not involved in closed-loop projects note that for subjective conditions like pain and mental conditions, the technology struggles to answer the kind of multiple-choice question where the correct answer is "true, true, and unrelated." They observe that the extrinsic or micro perspective can provide accurate and detailed insights into the activities of neural networks; period. Signal recordings do not appear to explain or predict much else.[135,136,356] Related impediments arise during candidate selection when initial diagnoses rely upon subjective, language-based self-reports and the ICD for pain or DSM for mental conditions. The present studies also employ language-based follow-up measures such as the Yale-Brown Obsessive Compulsive Scale, Montgomery-Asberg Depression Rating Scale, Hamilton-D scale, and various pain scales to determine whether signals correlate with symptoms.[116,117,125,229] after that, diagnoses and assessments remain entangled with subjectivity, language, and self-reporting. Even if a patient reports feeling depressed and a replicable neural signal pattern could be identified, that reveals practically nothing about whether the cause of the feeling or emotional state was biological, psychological, or situational. That determination is essential to select among a host of very different treatment modalities. However, a closed loop system administers only one electrical stimulation, for which efficacy in TRD arguably has been disproven and remains to be proven in OCD and other conditions even when used continuously as an open-loop therapy. The complexities and pitfalls in correlating extrinsic data with subjective self-reported feeling states are captured in one observer's description of a closed-loop pilot research subject's experience.[46]

In other work, closed-loop pain therapy investigators addressed the limitations of subjectivity by administering nociceptive thermal stimuli to elicit pain-related signals recorded by intracranial electrodes.[312] However, the correlation between the stimuli and recordings still required subjective language and voluntary action for the implanted person to sense, report, and record the onset and termination of their nociceptive experience. Researchers believe those are unavoidable but surmountable limitations in the early stages of a long-term project. To check the validity of subject responses, closed-loop pain researchers should consider a similar approach to the Montreal group's use of misdirection to trick patients into believing their stimulators were on when the devices were turned off.[210] If closed-loop hypotheses are correct, and network activity is determinative, what an implanted subject believes should not affect neural recordings or therapeutic effects. For the time being, and unless proven otherwise, ordinary human traits constrain both arms of closed-loop systems with the same ambiguities they aim to eliminate: interpretation of afferent inputs and a requirement for complete, accurate, and voluntary reporting. Finally, it has been straightforward to collect normative scalp EEG recordings, CT or MR images, and other relatively noninvasive diagnostic data from large population samples. That is not the case for intracranial recordings where normative population data are scarce to nonexistent. Moreover, the implant data are collected from a few brain deep brain and cortical surface regions selected on the basis of unproven functional imaging-based extrinsic hypotheses in patients who, arguably, might be diagnosed with DSM or ICD codes that do not represent genuine biological disorders.

COMMERCIAL INTEREST

Curiosity drives scientists to increase their knowledge, and post enlightenment Western methods of inquiry provide confidence in their discoveries.[249] Neutral methods are essential to acquire verifiable, reproducible, and factual data as input for unbiased analyses.[81,214,282,319,372] Equipoise requires that initial hypotheses remain open to revision or rejection based on new information. Replication by independent teams provides but does not guarantee, validation if they find the same results. One difference between technology and science is that real or perceived necessity, not natural curiosity, drives technology when manufacturers seek to identify and fill an unmet medical need with a new product or with a new application for an existing product – for example, DBS. Pertinent scientific knowledge increases the likelihood of technical success; however, new scientific discoveries are not required to achieve technical goals. We perceive the unmet needs driving investment in closed-loop neurostimulation for pain and mental conditions as predominantly commercial and medical practice-related. Apart from the disappointing results of the DBS depression trials, industry executives realized that there was no feasible business model there and no rewarding or manageable medical practice model there either. Before the trials commenced, investigators and consulting groups were certain that subjects would benefit and, consequently, consume fewer healthcare resources than beforehand. Scheduling study visits at three-month intervals reflected that belief. However, as investigators struggled to achieve efficacy and as device programming and lead implant revisions proved futile, psychiatric AEs and device complications required substantially more unscheduled visits and hospitalizations than anticipated. Elusive efficacy and numerous AEs consumed so much time and effort that some investigators requested additional payments, and one center abandoned the trial.[53,80] The combination of physician dissatisfaction with a heavier than expected workload, no efficacy signal, and escalating trial expenses forced difficult decisions. In light of results from FDA-mandated interim analyses, program closure was the only sensible, regulatory-

compliant, and ethical decision available – notwithstanding the criticism that ensued.[349]

Those experiences make commercial and practice-related considerations the main drivers of closed-loop technology investment. The goal is to unburden physicians and office staff – and, if successful, to make closed-loop analgesic and psychiatric devices as valuable as comparable products for epilepsy, cardiac rhythm disorders, and diabetes. The nonquantifiable nature of subjective conditions has not deterred investors, investigators, or manufacturers. Neither has the lack of demonstrable efficacy for continuous, open-loop stimulation as the treatment limb for closed-loop therapy. Just as the market for arguably ineffective pain devices continues to grow, logical barriers and evidence gaps will not deter investment in closed-loop therapies or their eventual market acceptance in mental conditions.

ETHICS AND INEVITABILITY

Some may find it disturbing to contemplate a future where neuropsychiatric diagnosis and treatment devolve into a machine-reading task similar to automated electrocardiogram reports. After emotional language is excised from diagnosis, and if experts agree that machines do a better job than doctors, one can imagine that doctors would no longer be involved. Some have expressed concerns over the specter of mind control or brainwashing.[173,215] Such predictions are scary only if one believes the technology actually works, that extrinsic model-derived data are useful in patient care, and that terabytes of data not only correlate with one's interior life and behavior but also that the data determine one's inner life and actions. On the other hand, substantial evidence points toward the therapeutic value of closed-loop network modulation being an illusion. Even so, the ideas that underlie the extrinsic micro perspective are so internally consistent, coherent, and attractive to researchers and investors that regulatory approval outside the US (as a first step), successful marketing, and profits eventually will ensue.

As human research continues toward such goals, the medical ethics principles of beneficence, nonmaleficence, autonomy, and justice remain sufficiently malleable to bend in one direction or another from case to case.[157,262] Consider the repercussions of human experimentation for its own sake – meaning, for the sake of the experiment itself, to increase the sum of human knowledge, or potentially to benefit future patients. Those appear to be sound rationales for clinical research. However, none hold up under the means versus ends test of conventional Western ethics. That places ethicists' endorsement of- and participation in advocacy for social policies that encourage the practice of psychiatric surgery in conflict with the categorical imperatives of Kant and Popper.[98,157,262,351]

Ethical conflicts arise because impartial analyses of recent and historical trials and case series indicate that no realistic expectation of clinically meaningful benefit exists for individual research subjects, especially when weighed against risks in closed-loop programs or other experimental uses of neurostimulation for pain and psychiatric indications. That also makes our recent observation "that study participation is largely an altruistic endeavor for research purposes" fall short of Kant's and Popper's standards and violates the means versus ends principle.[53] With no realistic expectation or prospect of benefit, repeated investigations to implant devices (or create lesions that carry risks of cognitive or neurological harm) reduce a person to laboratory substrate – the very definition of a means to an end.[46,332,333]

Scientifically curious investigators naturally foresee benefits from research into somatic (connectomic) causes and cures for subjective conditions. However, it is past time for those who recognize logical flaws in the theories and who observe contradictory evidence in the reported results to find space in the indexed medical literature apart from independent websites.[34,36,329,350] Other examples of flawed and misleading theories include DBS or SCS for coma;[141,213,303,304] DBS for obesity,[86,365] drug addiction[27,205,268,273] or cluster headache;[184,185,207,258,305,327] and occipital nerve stimulation for chronic migraine – migraine being a prototypical episodic disorder.[299,359,360] All revealed no efficacy during trials designed to replicate initial positive reports, yet the original false-positive reports remain uncorrected.

DISCUSSION

Functional neurosurgery was an integral part of general neurosurgery before it became a distinct subspecialty. Neurologists, surgeons, pathologists, and their collaborators introduced effective operations for cranial neuralgias, epilepsy, spasticity, involuntary MvDs, and selected painful conditions.[24,30,71,99,128,129,147,176,177,233,234,315,347,367] Numerous studies have sought Level I evidence of reproducible, clinically meaningful, or statistically significant efficacy for conventional open, or microsurgical, stereotactic or image-guided lesions, neurostimulation, or targeted drug delivery to treat chronic noncancer pain and mental conditions. However, whenever controlled conditions and unbiased analyses were undertaken, efficacy was limited in the best case and nonexistent in others.[81,133,214,282,372] Yet most published reviews still tabulate anecdotal, uncontrolled, or inadequately controlled series as evidence of efficacy.[55,59,310] However, even White and Sweet's seminal pain surgery texts revealed that operations for noncancer pain provided few long-term benefits.[363,364] Unbiased assessments of neurostimulation or drug delivery techniques by independent reviewers arrive at similar conclusions.[77,144,195,196,266,343-345] As discussed earlier, the same applies to open, stereotactic, or neurostimulation surgery for psychiatric conditions. Independent reviewers found insufficient evidence to support efficacy claims, while

others reported unacceptable risks, including for stereotactic lesion surgery.[76,146,148,204,281,338,340]

On a positive note, other applications of functional neurosurgery experienced a boost between the late 1970s and mid 2000s when CT and MR imaging expanded anatomic stereotaxis to diagnose, treat, and remove deep-seated lesions safely. Then, as a new generation of neurologists and surgeons took up MvD surgery, modern imaging did away with imprecise targeting dependent on ventriculography. Regulatory approvals were required only after investigators substituted DBS devices for lesions. Straightforward clinical trials led to approvals in objectively-defined disorders such as essential tremor, PD, dystonia (under HDE), and epilepsy. Anatomic and physiological knowledge and experience guided the selection of objective biological disorders, suitable patients, safe and effective targets, and low voltage – high frequency stimulation parameters.

However, investigators have been unable to extrapolate success from objectively defined neurological disorders to more complex subjective conditions. Accurate psychiatric diagnosis remains clinically based while the search continues for reproducible, validated biomarkers and underlying biological mechanisms. To-date, those have remained elusive. Meanwhile, recent practice trends have lowered the bar for diagnosis and treatment such that many individuals are diagnosed and treated as if they have a biological disorder. That makes apparent treatment-resistance or treatment failure inevitable, leading to escalation of therapy to ECT, repetitive transcranial magnetic stimulation, DBS, or lesion surgery. Moreover, symptoms that were used to suggest a biological disorder and justify treatment were not required for DBS trials or lesion surgery. Consequently, at least some treatment-resistant surgical patients, including subjects in formal trials, likely were assigned incomplete or erroneous diagnoses, and others probably had no biological disorder at all.

OCD, originally classified as a psychoneurotic disorder or reaction of psychogenic origin, is now suggested to arise from "[d]ysfunction in the orbitofrontal cortex, anterior cingulate cortex, and striatum" in the DSM – which is cited to justify drug treatment or escalation of therapy to DBS or lesion surgery.[9,269] However, the positive conclusions of influential and frequently cited surgical series subsequently were contradicted by later investigations, especially with respect to safety, but only after the original surgical proponents had passed away.[29,182,192,218,220-226,283-291,294] As with older series, the level of evidence attached to the past 25 years of publications on DBS and lesion surgery for OCD remains weak to very weak, below Level II, and with no consistent or reliable efficacy signal.[21,42,44,60,53,83,268,269,281,329,361]

CONCLUSION

Historical coincidence, overlapping surgical methods, and reasoning by analogy foster confidence in re-expanding functional neurosurgery into long-practiced pain and psychiatric indications where, historically, surgery has not proven safe or effective. However, the extrinsic micro perspective of neuroscience research embodied in the human connectome project now provides an attractive theoretical foundation. Because the phenotype of psychologically or situationally determined mental conditions is indistinguishable on the surface from intrinsic biological disorders in many individuals, detailed inquiry beyond disorder-specific questionnaires and functional imaging is required to uncover what underlies self-reported feelings or behavior. To-date, clinical trials based on DSM criteria and disorder-specific rating scales for subject recruitment, including closed-loop studies, have not done so successfully.

Moreover, connectomic images within which are embedded the nodes and circuits targeted by DBS and lesion surgery can distract attention from the underlying sameness of psychiatric surgery's theoretical underpinnings over the past century. However, surgical methods evolved from blind leukotomy to open lobotomy and thence to stereotactic surgery and DBS – all intended to disrupt or alter the function of thalamo-cortical and/or limbic circuits.[3,35,50,84,95,127,193,212,230,269,369] The difference now is that MRI provides images and coordinates of the surgical targets in each patient in place of the atlas photographs of preserved specimens in the preimaging era. However, the imputation of causality from connectomic data differs little from inferential notions of causality derived from preserved specimens or animal experiments.[3,21,76,87-89,95,148,163] John Fulton performed ablative cingulate gyrus surgery as well as frontal lobe surgery in chimpanzees. Those experiments influenced his former pupil, Watts, as well as Moniz, Freeman, Ballantine, and others to undertake frontal lobe surgery followed (on the part of Ballantine) by cingulate gyrus operations in humans. However, despite his endorsement of psychosurgery, Fulton subsequently expressed doubts about the scientific validity of extrapolating findings in a few caged chimpanzees to human psychiatric patients.[50,76] We view the connectomic psychiatric surgical treatment hypothesis as analogous to a now disfavored Type-K examination question of causality wherein the model is internally valid, as is an individual's inner life. However, no law of nature dictates that extrinsically observable network activity determines a person's perceptions, emotions, or behavior.

Therapeutic hypotheses based on coherent, internally consistent, and accurate physiological models are unlikely to change direction. Capital investment enables human experiments to continue toward regulatory approval of open- and closed-loop surgical technology in mental conditions and pain – most likely outside the US at first. Moreover, for the foreseeable future, psychiatric surgery that includes lesion surgery will continue. Accordingly, physicians must exercise critical judgment and counsel their patients with noncancer pain or selected mental conditions

to withhold their consent if other physicians propose futile and risky surgery.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Abel TJ, Walch T, Howard MA 3rd. Russell Meyers (1905-1999): Pioneer of functional and ultrasonic neurosurgery. J Neurosurg 2016;125:1589-95.
2. Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, *et al*. Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry 2005;57:510-6.
3. Abosch A, Cosgrove GR. Biological basis for the surgical treatment of depression. Neurosurg Focus 2008;25:E2.
4. Afkhami AA, Fatollahi JJ, Peace MA, Yadgar RJ. Spinning lobotomy: A conventional content analysis of articles by the pioneers of the procedure in the United States. SSM-Mental Health 2022;2:100123.
5. Alexander F. The nature and consequences of prefrontal lobotomy. Honors Paper, Department of Psychology, The Woman's College of the University of North Carolina, Greensboro, North Carolina; 1955. Available from: https://libres.uncg.edu/ir/uncg/f/alexander_frances_1955.pdf [Last accessed on 2024 Sep 24].
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 2nd ed. Washington, DC: American Psychiatric Association; 1968.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed (DSM-III). Washington, DC: American Psychiatric Publishing; 1980.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, Text Revision (DSM-IV TR). Washington, DC: American Psychiatric Association; 2000.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed (DSM-5TM). Washington, DC: American Psychiatric Publishing; 2013.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 1952.
11. American Psychological Association. Multicultural guidelines: An ecological approach to context, identity, and intersectionality; 2017. Available from: https://www.apa.org/about/policy/multicultural-guidelines.pdf [Last accessed on 2024 Sep 24].
12. American Society of Plastic Surgeons. ASPS evidence-based clinical practice guideline methodology. Available from: https://www.plasticsurgery.org/documents/medical-professionals/quality-resources/asps-evidence%e2%80%90based-clinical-practice-guideline-methodology.pdf [Last accessed on 2024 Sep 24].
13. Andréewitch S, Edman G, Meyerson B, Rück C. Controlled trials of surgical treatment of mental diseases?. Lakartidningen 1999;96:1164.
14. Anonymous (editorial). Standard lobotomy: The end of an era. Can Med Assoc J 1964;91:1228-9.
15. Anonymous. A future for neuromodulation in psychiatric disease. Stereotact Funct Neurosurg 2015;93:69.
16. Anonymous. Book review. J Nerv Ment Dis 1933;78:679.
17. Anonymous. Modified prefrontal leucotomy. Br Med J 1971;3:595-6.
18. Anonymous. Norway compensates lobotomy victims. BMJ 1996;313:708.
19. Baker AA, Minski L. Social adjustment of neurotic patients after prefrontal leucotomy. Br Med J 1951;2:1239-43.
20. Baker DW. History of the joint commission's pain standards: Lessons for today's prescription opioid epidemic. JAMA 2017;317:1117-8.
21. Ballantine HT Jr., Cassidy WL, Flanagan NB, Marino R Jr. Stereotaxic anterior cingulotomy for neuropsychiatric illness and intractable pain. J Neurosurg 1967;26:488-95.
22. Barnes GJ, Cameron ME. Skin and eye changes associated with chlorpromazine therapy. Med J Aust 1966;1:478-81.
23. Barraclough BM, Mitchell-Heggs NA. Use of neurosurgery for psychological disorder in British Isles during 1974--6. Br Med J 1978;2:1591-3.
24. Benabid AL, Chabardes S, Mitrofanis L, Polack P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8:67-81.
25. Benaim S. The effect of chlorpromazine on the incidence of epileptic phenomena during insulin coma therapy. A statistical investigation. J Ment Sci 1960;106:317-21.
26. Bennett AE, Cesarman FC. Transorbital lobotomy; its use in relapsing psychotic states. Calif Med 1953;78:453-5.
27. Bernstein L. Addiction treatment had failed. Could brain surgery save him? Washington Post; 2021. Available from: https://www.washingtonpost.com/health/2021/06/18/deep-brain-stimulation-addiction [Last accessed on 2024 Sep 24].
28. Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Smith DA, *et al*. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: Overview of six randomized trials. J Clin Oncol 2011;29:3224-31.
29. Bingley T, Leksell L, Meyerson BA, Rylander G. Long term results

of stereotactic capsulotomy in chronic obsessive-compulsive neurosis. In: Sweet WH, Obrador S, Martin-Rodriguez JG, editors. Neurosurgical treatment in psychiatry, pain and epilepsy. Baltimore: University Park Press; 1977. p. 287-99.
30. Bischof W. Die longitudinale Myelotomie, erstmalig zervikal durchgeführt [Cervical longituidinal myelotomy performed for the first time]. Zentralbl Neurochir 1952;12:205-10.
31. Black RG. The chronic pain syndrome. Surg Clin North Am 1975;55:999-1011.
32. Bonnabeau RC Jr., Lillehei CW. Mechanical "ball failure" in Starr-Edwards prosthetic valves. A report of three cases. J Thorac Cardiovasc Surg 1968;56:258-64.
33. Braslow J. Therapeutic effectiveness and social context: The case of lobotomy in a California state hospital, 1947-1954. West J Med 1999;170:293-6.
34. Breggin PR. Psychosurgery for political purposes. Duquesne Law Rev 1975;13:841-62.
35. Breggin PR. The return of lobotomy and psychosurgery. In: Edwards RB, editor. Psychiatry and Ethics. Buffalo, NY: Prometheus Books, 1982; p. 350-88.
36. Breggin PR. The second wave. MH 1973;57:11-3.
37. Brune A. Changing Minds. Undaunted by mistakes of the past, a new generation of brain surgeons is ready to step in when pills and therapy fail. Chicago Tribune; 2005. Available from: https://adrianbrune.com/the-chicago-tribune-magazine [Last accessed on 2024 Sep 24].
38. Bublitz C, Gilbert F, Soekadar SR. Concerns with the promotion of deep brain stimulation for obsessive-compulsive disorder. Nat Med 2023;29:18.
39. Bucy PC. Cortical extirpation in the treatment of involuntary movements. Am J Surg 1948;75:257-63.
40. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305-10.
41. Cabrera LY, Bittlinger M, Lou H, Müller S, Illes J. The re-emergence of psychiatric neurosurgery: Insights from a cross-national study of newspaper and magazine coverage. Acta Neurochir (Wien) 2018;160:625-35.
42. Canadian task force on the periodic health examination. The periodic health examination. Can Med Assoc J 1979;121:1193-254.
43. Carlsson A. Treatment of Parkinson's with L-DOPA. The early discovery phase, and a comment on current problems. J Neural Transm (Vienna) 2002;109:777-87.
44. Caroff S. Depression, other behavioral disorders, and DBS: Furor therapeuticus redux. Clin Psych News; 2017. p. 12. Available from: https://www.mdedge.com/psychiatry/article/132967/depression/depression-and-deep-brain-stimulation-furortherapeuticus-redux [Last accessed on 2024 Sep 24].
45. Carome MA. Implanted spinal cord stimulators for pain relief. Illustrating the FDA's dangerously lax regulatory oversight of high-risk implantable medical devices. Public Citizen, Health Research Group; 2020. Available from: https://www.citizen.org/wp-content/uploads/2526_200610_Spinal-Cord-Stimulator-Report_FINAL.pdf [Last accessed on 2024 Sep 24].
46. Carr D. Excess in the avant-garde of the data subject. Language and quantification in digital psychiatry. Terrain 2022;76:44-63.
47. Carr D. Is America really in a mental health crisis? Mental health is political. New York Times; 2022. Available from: https://www.nytimes.com/2022/09/20/opinion/us-mental-health-politics.html [Last accessed on 2024 Sep 24].
48. Cauley KA, Waheed W, Salmela M, Filippi CG. MR imaging of psychosurgery: Rostral atrophy following stereotacic subcaudate tractotomy. Br J Radiol 2010;83:e239-42.
49. Centre for evidence based medicine. Levels of evidence for therapeutic studies. Available from: https://www.cebm.net [Last accessed on 2024 Sep 24].
50. Christmas DM. Functional neurosurgery for intractable mental disorder: long term effects on mental health, neuropsychological performance, social function, and quality of life. Thesis submitted for the degree of Doctor of Medicine, University of Dundee (Scotland); 2006. Available from: https://www.advancedinterventions.org.uk/wp-content/uploads/2023/10/md_thesis_dmbchristmas_dec_2006.pdf [Last accessed on 2024 Sep 24].
51. Clair AH, Haynes W, Mallet L. Recent advances in deep brain stimulation in psychiatric disorders. F1000Res 2018;7:F1000 Faculty Rev-699.
52. Coffey RJ, Burchiel K. Inflammatory mass lesions associated with intrathecal drug infusion catheters: Report and observations on 41 patients. Neurosurgery 2002;50:78-86.
53. Coffey RJ, Caroff SN. Commentary on the continued investigational status of DBS for psychiatric indications. Stereotact Funct Neurosurg 2022;100:156-67.
54. Coffey RJ, Hamani C, Lozano AM. Evidence base: Neurostimulation for pain. In: Winn HR, editor. Youmans neurological surgery. 6th ed. Philadelphia, PA: Elsevier; 2011.
55. Coffey RJ, Lozano AM. Neurostimulation for chronic non-cancer Pain: An evaluation of clinical evidence, and recommendations for future trial designs. J Neurosurgery 2006;105:175-89.
56. Coffey RJ, Owens ML, Broste SK, Dubois MY, Ferrante FM, Schultz DM, *et al*. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. Anesthesiology 2009;111:881-91.
57. Coffey RJ, Pearce J, Kalin R, Olsen J. MRI conditionally safe neurostimulation leads: Experimental results and thermal dose calculations of the maximum safe lead tip temperature. Neurosurgery 2014;74:215-25.
58. Coffey RJ. Deep brain stimulation for chronic pain: The results of two multi-center trials and a structured review. Pain Med 2001;2:183-92.
59. Coffey RJ. Evidence, the practice of pain surgery, and the Institute of Medicine Report In: Burchiel K, editor. Surgical management of pain. 2nd ed. New York: Thieme; 2015.
60. Coffey RJ. The enduring vitality of implausible claims for neurostimulation and psychosurgical therapies. Stereotact Funct Neurosurg 2015;93:366-9.
61. Cohen IM, Archer JD. Liver function and hepatic complications in patients receiving chlorpromazine. J Am Med Assoc 1955;159:99-101.
62. Cohen RA, Kaplan RF, Meadows ME, Wilkinson H. Habituation and sensitization of the orienting response following bilateral anterior cingulotomy. Neuropsychologia 1994;32:609-17.
63. Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H. Impairments of attention after cingulotomy. Neurology 1999;53:819-24.
64. Cohen RA, Kaplan RF, Zuffante P, Moser DJ, Jenkins MA,

Salloway S, *et al*. Alteration of intention and self-initiated action associated with bilateral anterior cingulotomy. J Neuropsychiatry Clin Neurosci 1999;11:444-53.
65. Cohen RA, Zawacki PR, Moser TM, Sweet DJ, Wilkinson H. Emotional and personality changes following cingulotomy. Emotion 2001;1:38-50.
66. Connectome coordination facility. Available from: https://www.humanconnectome.org [Last accessed on 2024 Sep 24].
67. Cooper IS, Poloukhine N, Hoen TI. St. Barnabas symposium on surgical therapy of extrapyramidal disorders. J Am Geriatr Soc 1956;4:1167.
68. Cooper IS. Surgical alleviation of Parkinsonism; effects of occlusion of the anterior choroidal artery. J Am Geriatr Soc 1954;2:691-718.
69. Cooper R. On deciding to have a lobotomy: Either lobotomies were justified or decisions under risk should not always seek to maximise expected utility. Med Health Care Philos 2014;17:143-54.
70. Coriat IH. Abnormal psychology. London, William Rider & Son; 1911.
71. Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, *et al*. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: Long-term results. J Neurosurg 2004;101:189-94.
72. Dahlhamer J, Lucas J, Zelaya C, Nahin CR, Mackey S, DeBar L, *et al*. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001-6.
73. Daniel MS, Long C, Hutcherson WL, Hunter S. Psychological factors and outcome of electrode implantation for chronic pain. Neurosurgery 1985;17:773-7.
74. Daugherty C, Devore JK, Schneider EM. The effect of chlorpromazine on hepatic function and morphology. Gastroenterology 1956;31:391-8.
75. Davidoff LM, Brenner C. A new instrument for the performance of bifrontal lobotomy. Res Publ Assoc Res Nerv Ment Dis 1948;27:638-41.
76. de Mille R. Intellect after lobotomy in schizophrenia: A factor-analytic study. Ph.D. Thesis, Faculty of the Graduate School, University of Southern California, Los Angeles, California; 1961. Available from: https://digitallibrary.usc.edu/archive/intellect-after-lobotomy-in-schizophrenia---a-factor-analytic-study-2a3bf17kdlju.html [Last accessed on 2024 Sep 24].
77. Deer T, Chapple I, Classen A, Javery K, Stoker V, Tonder L, *et al*. Intrathecal drug delivery for treatment of chronic low back pain: Report from the National Outcomes Registry for Low Back Pain. Pain Med 2004;5:6-13.
78. Deer TR, Leong MS, Buvanendran A, Kim PS, Panchal SJ, editors. Treatment of chronic pain by interventional approaches. The American academy of pain medicine textbook on patient management. New York: Springer; 2015.
79. Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, *et al*. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2010;67:1061-8.
80. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, *et al*. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry 2015;78:240-8.
81. Dror IE. Cognitive and human factors in expert decision making: Six fallacies and the eight sources of bias. Anal Chem 2020;92:7998-8004.
82. Drossman DA. The problem patient. Evaluation and care of medical patients with psychosocial disturbances. Ann Intern Med 1978;88:366-72.
83. Elias GJB, Germann J, Boutet A, Pancholi A, Beyn ME, Bhatia K, *et al*. Structuro-functional surrogates of response to subcallosal cingulate deep brain stimulation for depression. Brain 2022;145:362-77.
84. Elias WJ, Ray DK, Jane JA Sr. Lennart Heimer: Concepts of the ventral striatum and extended amygdala. Neurosurg Focus 2008;25:E8.
85. Eljamel MS. Ablative neurosurgery for mental disorders: Is there still a role in the 21st century? A personal perspective. Neurosurg Focus 2008;25:E4. Erratum in: Neurosurg Focus 2018;44:E16.
86. Eskandar E. Deep brain stimulation and obesity. J Neurosurg 2013;119:54.
87. Faria MA. Violence, mental illness, and the brain - A brief history of psychosurgery: Part 1 - From trephination to lobotomy. Surg Neurol Int 2013;4:49.
88. Faria MA. Violence, mental illness, and the brain - A brief history of psychosurgery: Part 2 from the limbic system and cingulotomy to deep brain stimulation. Surg Neurol Int 2013;4:75.
89. Faria MA. Violence, mental illness, and the brain - A brief history of psychosurgery: Part 3 from deep brain stimulation to amygdalotomy for violent behavior, seizures, and pathological aggression in humans. Surg Neurol Int 2013;4:91.
90. FDA, U.S. Food and Drug Administration. CFR - code of federal regulations title 21. 21 CFR 812.3(m). Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.3 [Last accessed on 2024 Sep 24].
91. FDA, U.S. Food and Drug Administration. CFR - code of federal regulations title 21. 21 CFR 860.3(c). Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=860.3 [Last accessed on 2024 Sep 24].
92. FDA, U.S. Food and Drug Administration. Humanitarian device exemption (HDE) program guidance for industry and food and drug administration staff. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program [Last accessed on 2024 Sep 24].
93. FDA, U.S. Food and Drug Administration. Humanitarian device exemption (HDE). H050003D. Medtronic (Activa) deep brain stimulation for OCD therapy. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=375533 [Last accessed on 2024 Sep 24].
94. FDA, U.S. Food and Drug Administration. PMA clinical studies. Available from: https://www.fda.gov/medical-devices/premarket-approval-pma/pma-clinical-studies#investigations [Last accessed on 2024 Sep 24].
95. Feldman RP, Alterman RL, Goodrich JT. Contemporary psychosurgery and a look to the future. J Neurosurg 2001;95:944-56.
96. Ferrante FM, Rana MV, Ferrante MA. Conversion disorder

mimicking Dejerine-Roussy syndrome (thalamic stroke) after spinal cord stimulation. Reg Anesth Pain Med 2004;29:164-7.
97. Feynman R. California institute of technology commencement speech transcript; 1974. Available from: https://speakola.com/grad/richard-feynman-caltech-1974 [Last accessed on 2024 Sep 24].
98. Fins JJ, Mayberg HS, Nuttin B, Kubu CS, Galert T, Sturm V, *et al*. Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder. Health Aff (Millwood) 2011;30:302-11.
99. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, *et al*. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory partial epilepsy. Epilepsia 2010;51:899-908.
100. Follett KA, Boortz-Marx RL, Drake JM, DuPen S, Schneider SJ, Turner MS, *et al*. Prevention and management of intrathecal drug delivery and spinal cord stimulation system infections. Anesthesiology 2004;100:1582-94.
101. Follett KA, Burchiel K, Deer T, Dupen S, Prager J, Turner MS, *et al*. Prevention of intrathecal drug delivery catheter-related complications. Neuromodulation 2003;6:32-41.
102. Foltz EL, White LE Jr. Experimental cingulumotomy and modification of morphine withdrawal. J Neurosurg 1957;14:655-70.
103. Foltz EL, White LE Jr. Pain "relief" by frontal cingulumotomy. J Neurosurg 1962;19:89-100.
104. Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, *et al*. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344:710-9.
105. Freedman AM, Kaplan HI, Sadock BJ. Science of human behavior: Neurology. Comprehensive textbook of psychiatry-II. Baltimore: Williams & Wilkins; 1975. p. 188-265.
106. Galante J, Schulder M. The proud history of psychosurgery in the USA. Acta Neurochir Suppl 2021;128:161-7.
107. García-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, *et al*. Electrical stimulation of motor cortex for pain control: A combined PET-scan and electrophysiological study. Pain 1999;83:259-73.
108. Gash DM, Zhang Z, Ai Y, Grondin R, Coffey R, Gerhardt GA. GDNF distribution predicts dopaminergic restoration in Parkinsonian monkeys. Ann Neurol 2005;58:224-33.
109. Getz MJ. The ice pick of oblivion: Moniz, Freeman and the development of psychosurgery. Trames 2009;13:129-52.
110. Gillies H, Hickson B, Mayer-Gross W. A follow-up study of 238 leucotomized patients. Br Med J 1952;1:527-9.
111. GINSBURG M, SHULMAN L. A preliminary review of the uses of chlorpromazine in psychiatric diseases. S Afr Med J 1956;30:815-8.
112. Globe Newswire; 2022. Available from: https://www.globenewswire.com/en/news-release/2022/07/11/2477549/0/en/neurostimulation-devices-market-size-is-projected-to-reach-usd-14-billion-by-2030-growing-at-a-cagr-of-13-straits-research.html [Last accessed on 2024 Sep 24].
113. Globe Newswire; 2023. Available from: https://www.globenewswire.com/en/newsrelease/2023/05/24/2675061/0/en/neurostimulation-devices-market-revenue-is-predicted-to-surpass-a-valuation-of-us-36-5-billion-by-2032-states-by-market-us.html [Last accessed on 2024 Sep 24].
114. Goetz CG, Olanow CW, Koller WC, Penn RD, Cahill D, Morantz R, *et al*. Multicenter study of autologous adrenal medullary transplantation to the corpus striatum in patients with advance Parkinson's disease. N Engl J Med 1989;320:337-41.
115. Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, *et al*. Deep brain stimulation for intractable obsessive compulsive disorder: Pilot study using a blinded, staggered-onset design. Biol Psychiatry 2010;67:535-42.
116. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, *et al*. The Yale-brown obsessive compulsive scale. II. Validity. Arch Gen Psychiatry 1989;46:1012-6.
117. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, *et al*. The yale-brown obsessive compulsive scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46:1006-11.
118. Gottlieb bS. Bone marrow transplants do not help in breast cancer. BMJ 1999;318:1093.
119. Grabow TS, Tella PK, Raja SN. Spinal cord stimulation for complex regional pain syndrome: An evidence-based medicine review of the literature. Clin J Pain 2003;19:371-83.
120. Grantham EG, Spurling RG. Selective lobotomy in the treatment of intractable pain. Ann Surg 1953;137:602-8.
121. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, *et al*. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology 2006;31:2384-93.
122. Groenewald CB, Murray CB, Battaglia M, Scaini S, Quinn PD. Prevalence of pain management techniques among adults with chronic pain in the United States, 2019. JAMA Netw Open 2022;5:e2146697.
123. H050003b. Summary of safety and probable benefit. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf5/H050003b.pdf [Last accessed on 2024 Sep 24].
124. Halstead WC, Carmichael HT, Bucy PC. Prefrontal lobotomy; a preliminary appraisal of the behavioral results. Am J Psychiatry 1946;103:217-28.
125. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
126. Hansotia P. A neurologist looks at mind and brain: The enchanted loom. Clin Med Res 2003;1:327-32.
127. Hariz M, Cif L, Blomstedt P. Thirty years of global deep brain stimulation: Plus ça change, plus c'est la même chose? Stereotact Funct Neurosurg 2023;101:395-406.
128. Hartley F. I. Intracranial neurectomy of the fifth nerve. Ann Surg 1893;17:511-526.1.
129. Hartley F. Intracranial neurectomy of the second and third divisions of the fifth nerve. A new method. N Y Med J 1892;55:317-9.
130. Hartzband P, Groopman J. Medical taylorism. N Engl J Med 2016;374:106-8.
131. Hassenbusch SJ, Pillay PK, Barnett GH. Radiofrequency cingulotomy for intractable cancer pain using stereotaxis guided by magnetic resonance imaging. Neurosurgery 1990;27:220-3.
132. Hayne R, Meyers R. An improved model of a human stereotaxic instrument. J Neurosurg 1950;7:463-6.
133. Healy D, Howe G, Mangin D, Le Nourya J. Sudden cardiac death & the reverse dodo verdict. Int J Risk Saf Med 2014;26:71-9.
134. Herner T. Treatment of mental disorders with frontal

stereotactic thermo-lesions. A follow-up of 116 cases. Acta Psychiatr Scand 1961;158:36.
135. Hoel E. The overfitted brain: Dreams evolved to assist generalization. Patterns (N Y) 2021;2:100244.
136. Hoel EP, Albantakis L, Marshall W, Tononi G. Can the macro beat the micro? Integrated information across spatiotemporal scales. Neurosci Conscious 2016;2016:niw012.
137. Holland R, Kopel D, Carmel PW, Prestigiacomo CJ. Topectomy versus leukotomy: J. Lawrence Pool's contribution to psychosurgery. Neurosurg Focus 2017;43:E7.
138. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, *et al*. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: A multisite, randomised, sham-controlled trial. Lancet Psychiatry 2017;4:839-49.
139. Hornykiewicz O. Basic research on dopamine in Parkinson's disease and the discovery of the nigrostriatal dopamine pathway: The view of an eyewitness. Neurodegener Dis 2008;5:114-7.
140. Horowitz E. Studies show many studies are false. Boston Globe; 2014. Available from: https://www.bostonglobe.com/lifestyle/2014/07/01/studies-show-many-studies-are-false/PP2NO6lKd7HMyTZa1iCHGP/story.html [Last accessed on 2024 Sep 24].
141. Hosobuchi Y, Yingling C. The treatment of prolonged coma with neurostimulation. Adv Neurol 1993;63:247-51.
142. Hosobuchi Y. Periaqueductal gray stimulation in humans produces analgesia accompanied by elevation of beta-endorphin and ACTH in ventricular CSF. Mod Probl Pharmacopsychiatry 1981;17:109-22.
143. Hosobuchi Y. Tryptophan reversal of tolerance to analgesia induced by central grey stimulation. Lancet 1978;2:47.
144. Hsu E, Cohen SP. Postamputation pain: Epidemiology, mechanisms, and treatment. J Pain Res 2013;6:121-36.
145. Huff W, Lenartz D, Schormann M, Lee SH, Kuhn J, Koulousakis A, *et al*. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. Clin Neurol Neurosurg 2010;112:137-43.
146. Hussain ES, Freeman H, Jones RA. A cohort study of psychosurgery cases from a defined population. J Neurol Neurosurg Psychiatry 1988;51:345-52.
147. Hyndman OR. Lissauer's tract section. A contribution to chordotomy for the relief of pain (Preliminary report). J Int Coll Surgeons 1942;5:394-400.
148. Indiana Medical History Museum. Lobotomy: Intentions, procedures, effects. Available from: https://www.imhm.org/page-1854827 [Last accessed on 2024 Sep 24].
149. Ioannidis JP. Why most published research findings are false. PLoS Med 2005;2:e124.
150. IOM (Institute of Medicine). Relieving pain in America: A blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press; 2011. Available from: https://nap.nationalacademies.org/catalog/13172/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care [Last accessed on 2024 Sep 24].
151. Kainer MA, Reagan DR, Nguyen DB, Wiese AD, Wise ME, Ward J, *et al*. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med 2012;367:2194-203.
152. Kanpolat Y, Deda H, Akyar S, Caglar S. C.T.-guided pain procedures. Neurochirurgie 1990;36:394-8.
153. Kanpolat Y, Ozdemir M, Al-Beyati E. CT-guided percutaneous cordotomy for intractable pain in what is more than a disease: Lung malignancies. Turk Neurosurg 2013;23:81-7.
154. Kanpolat Y, Savas A, Caglar S, Temiz C, Akyar S. Computerized tomography-guided percutaneous bilateral selective cordotomy. Neurosurg Focus 1997;2:e4.
155. Kanpolat Y. Percutaneous destructive pain procedures on the upper spinal cord and brain stem in cancer pain: CT-guided techniques, indications and results. Adv Tech Stand Neurosurg 2007;32:147-73.
156. Kanpolat Y. The surgical treatment of chronic pain: Destructive therapies in the spinal cord. Neurosurg Clin N Am 2004;15:307-17.
157. Kant I. Groundwork of the metaphysics of morals. UK: Cambridge University Press; 1998.
158. Kaplan HI, Sadock BJ, Freedman AM. The brain and psychiatry. Chapter 2.5 in Freedman AM, Kaplan HI, Sadock BJ, editors. Comprehensive textbook of psychiatry. Vol. 1., 2nd ed. Baltimore: Williams & Wilkins; 1975. p. 143-66.
159. Kefalopoulou Z, Zrinzo L, Jahanshahi M, Candelario J, Milabo C, Beigi M, *et al*. Bilateral globus pallidus stimulation for severe Tourette's syndrome: A double-blind, randomised crossover trial. Lancet Neurol 2015;14:595-605.
160. Kelly D, Mitchell-Heggs N. Stereotactic limbic leucotomy--a follow-up study of thirty patients. Postgrad Med J 1973;49:865-82.
161. Kelly D, Richardson A, Mitchell-Heggs N, Greenup J, Chen C, Hafner RJ. Stereotactic limbic leucotomy: A preliminary report on forty patients. Br J Psychiatry 1973;123:141-8.
162. Kelly D, Richardson A, Mitchell-Heggs N. Stereotactic limbic leucotomy: Neurophysiological aspects and operative technique. Br J Psychiatry 1973;123:133-40.
163. Kelly D. Psychosurgery and the limbic system. Postgrad Med J 1973;49:825-33.
164. Kelly PJ, Gillingham FJ. The long-term results of stereotaxic surgery and L-dopa therapy in patients with Parkinson's disease. A 10-year follow-up study. J Neurosurg 1980;53:332-7.
165. Kemler MA, de Vet HC, Barendse G, van der Wildenberg F, Van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy - five-year follow-up (letter to the editor). N Engl J Med 2006;354:2394-6.
166. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: Two years' follow-up of the randomized controlled trial. Ann Neurol 2004;55:13-8.
167. Kinross-Wright V, Moyer JH. Chlorpromazine and hepatic function. AMA Arch Neurol Psychiatry 1956;76:675-80.
168. Kleiner J, Hoel E. Falsification and consciousness. Neurosci Conscious 2021;2021:niab001.
169. Knight G. The orbital cortex as an objective in the surgical treatment of mental illness. The results of 450 cases of open operation and the development of the stereotactic approach. Br J Surg 1964;51:114-24.

170. Knight GC. Bi-frontal stereotactic tractotomy: An atraumatic operation of value in the treatment of intractable psychoneurosis. Br J Psychiatry 1969;115:257-66.
171. Knight GC. Discussion on psychosurgery. Proc R Soc Med 1959;52:209-10.
172. Knox S, Atkinson RP, Stephens R, Zusman E, Coffey RJ. Thoracic myelopathy in association with continuous intrathecal drug infusion for chronic intractable pain Arch Neurol 2007;64:286-7.
173. Koivuniemi A, Otto K. When "altering brain function" becomes "mind control". Front Syst Neurosci 2014;8:202.
174. Konrad P. Dorsal root entry zone lesion, midline myelotomy and anterolateral cordotomy. Neurosurg Clin N Am 2014;25:699-722.
175. Kragh JV. Last resort? Some incidents in the history of psychosurgery in Denmark. Dan Medicinhist Arbog 2007;35:9-36.
176. Krause F. The question of priority in devising a method for the performance of intra-cranial neurectomy of the fifth nerve. Ann Surg 1893;18:362-4.
177. Krause F. Concerning trigeminal resection within the cranial cavity with case report. Berl Klin Wschr 1892;29:734.
178. Krayenbuhl H. Die Technik der präfrontalen leukotomie [The technique of prefrontal leukotomy]. Schweiz Med Wochenschr 1948;78:841.
179. Kruger J, Dunning D. Unskilled and unaware of it: How difficulties in recognizing one's own incompetence lead to inflated self-assessments. J Pers Soc Psychol 1999;77:1121-34.
180. Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R, *et al*. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann Neurol 2006;59:459-66.
181. Laplace PS (Marquis). A philosphical essay on probabilities. 6th French edition. New York: John Wiley & Sons; 1902. p. 4.
182. Leksell L, Backlund EO. Stereotactic gammacapsulotomy. In: Hitchcock ER, Ballantine HT, Meyerson BA, editors. Modern concepts in psychiatric surgery. Elsevier/North Holland; 1979. p. 213-5.
183. Lempka SF, Malone DA Jr., Hu B, Baker KB, Wyant A, Ozinga JG 4th, *et al*. Randomized clinical trial of deep brain stimulation for poststroke pain. Ann Neurol 2017;81:653-63.
184. Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 2001;345:1428-9.
185. Leone M, Franzini A, Felisati G, Mea E, Curone M, Tullo V, *et al*. Deep brain stimulation and cluster headache. Neurol Sci 2005;26 Suppl 2:S138-9.
186. Lerner BH. Last-ditch medical therapy - revisiting lobotomy. N Engl J Med 2005;353:119-21.
187. Levy R, Henderson J, Slavin K, Simpson BA, Barolat G, Shipley J, *et al*. Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. Neuromodulation 2011;14:412-22.
188. Lewin R. Disappointing brain graft results. Science 1988;240:1407.
189. Li N, Baldermann JC, Kibleur A, Treu S, Akram H, Elias GJB, *et al*. A unified connectomic target for deep brain stimulation in obsessive-compulsive disorder. Nat Commun 2020;11:3364.
190. Liddell DW, Rettertstol N. The occurrence of epileptic fits in leucotomized patients receiving chlorpromazine therapy. J Neurol Neurosurg Psychiat 1957;20:105-7.
191. Lindsay S, Skahen R. Jaundice during chlorpromazine (thorazine) therapy; a histologic study of the hepatic lesions in five patients. AMA Arch Pathol 1956;61:84-90.
192. Lippitz BE, Mindus P, Meyerson BA, Kihlström L, Lindquist C. Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: Relevance of the right hemisphere. Neurosurgery 1999;44:452-8.
193. Lipsman N, Meyerson BA, Lozano AM. A narrative history of the International Society for Psychiatric Surgery: 1970-1983. Stereotact Funct Neurosurg 2012;90:347-55.
194. Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 1999;96:15222-7.
195. Loeser JD. Dorsal rhizotomy for the relief of chronic pain. J Neurosurg 1972;36:745-50.
196. Loeser JD. What's to be done? Comments on Grabow *et al*. Clin J Pain 2003;19:384.
197. Logie HB, editor. Standard classified nomenclature of disease. Compiled by the national conference on nomenclature of disease. New York: The Commonwealth Fund; 1933.
198. Logie HB. Suggestions for a national nomenclature of diseases. Bull N Y Acad Med 1930;6:668-81.
199. Logothetis J. Spontaneous epileptic seizures and electroencephalographic changes in the course of phenothiazine therapy. Neurology 1967;17:869-77.
200. Love JG. Proceedings of the staff meetings of the mayo clinic, Rochester; 1943. p. 72-3.
201. Luyten L, Hendrickx S, Raymaekers S, Gabriëls L, Nuttin B. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry 2016;21:1272-80.
202. Machado AG, Baker KB, Plow E, Malone DA. Cerebral stimulation for the affective component of neuropathic pain. Neuromodulation 2013;16:514-8.
203. Mack JE. Abduction. Human encounters with aliens. New York: Ballantine; 1994.
204. Maclay WS. Death due to treatment. Proc R Soc Med 1953;46:13-20.
205. Madhusoodanan J. When addiction treatment fails, can a brain implant succeed? Available from: https://undark.org/2024/01/29/brain-implant-addiction [Last accessed on 2024 Sep 24].
206. Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, *et al*. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 2008;13359:2121-34.
207. Maniyar FH, Starr P, Goadsby PJ. Paroxysmal sneezing after hypothalamic deep brain stimulation for cluster headache. Cephalalgia 2012;32:641-4.
208. Marchand S, Bushnell MC, Molina-Negro P, Martinez SN, Duncan GH. The effects of dorsal column stimulation on measures of clinical and experimental pain in man. Pain 1991;45:249-57.
209. Marchand S, Charest J, Li J, Chenard JR, Lavignolle B,

Laurencelle L. Is TENS purely a placebo effect? A controlled study on chronic low back pain. Pain 1993;54:99-106.
210. Marchand S, Kupers RC, Bushnell MC, Duncan GH. Analgesic and placebo effects of thalamic stimulation. Pain 2003;105:481-8.
211. Marks IM, Birley JL, Gelder MG. Modified leucotomy in severe agoraphobia: A controlled serial inquiry. Br J Psychiatry 1966;112:757-69.
212. Mashour GA, Walker EE, Martuza RL. Psychosurgery: Past, present, and future. Brain Res Brain Res Rev 2005;48:409-19.
213. Matsui T, Asano T, Takakura K, Yamada R, Hosobuchi Y. Beneficial effects of cervical spinal cord stimulation (cSCS) on patients with impaired consciousness: A preliminary report. Pacing Clin Electrophysiol 1989;12:718-25.
214. Matute H, Blanco F, Yarritu I, Díaz-Lago M, Vadillo MA, Barberia I. Illusions of causality: How they bias our everyday thinking and how they could be reduced. Front Psychol 2015;6:888.
215. McCarthy-Jones S. Corrigendum: The autonomous mind: The right to freedom of thought in the twenty-first century. Front Artif Intell 2021;4:672279.
216. Mckenzie KG, Kaczanowski G. Prefrontal leukotomy: A five-year controlled study. Can Med Assoc J 1964;91:1193-6.
217. Mettler FA. editor. Selective partial ablation of the frontal cortex. A correlative study of its effects on human psychotic subjects. By the Columbia-Greystone Associates. New York: Paul B Hoeber, Inc.; 1949.
218. Meyerson BA, Mindus P. Capsulotomy as treatment of anxiety disorders. In: Lunsford LD, editor. Modern stereotactic neurosurgery. Boston: Martinus Nijhoff; 1988. p. 353-64.
219. Miller A. The lobotomy patient--a decade later: A follow-up study of a research project started in 1948. Can Med Assoc J 1967;96:1095-103.
220. Mindus, Jenike MA. Neurosurgical treatment of malignant obsessive compulsive disorder. Psychiatr Clin North Am 1992;15:921-38.
221. Mindus P, Bergstrom K, Levander SE, Noren G, Hindmarsh T, Thoumas KA. Magnetic resonance images related to clinical outcome after psychosurgical intervention in severe anxiety disorder. J Neurol Neurosurg Psychiatry 1987;50:1288-93.
222. Mindus P, Nyman H, Rosenquist A, Rydin E, Meyerson BA. Aspects of personality in patients with anxiety disorders undergoing capsulotomy. Acta Neurochir Suppl (Wien) 1988;44:138-44.
223. Mindus P, Nyman H. Normalization of personality characteristics in patients with incapacitating anxiety disorders after capsulotomy. Acta Psychiatr Scand 1991;83:283-91.
224. Mindus P. Capsulotomy in anxiety disorders - a multidisciplinary study. Doctoral Thesis, departments of psychiatry, psychology and neurosurgery, Stockholm, Karolinska Institute; 1991.
225. Mindus P. Present-day indications for capsulotomy. Acta Neurochir Suppl (Wien) 1993;58:29-33.
226. Mindus P. Some thoughts on the anti-psychosurgery attitude in Sweden. In: Hitchcock ER, Ballantine HT Jr., Meyerson BA, editors. Modern concepts in psychiatric surgery. Amsterdam: Elsevier; 1979. p. 359-65.
227. Mitchell SW, Morehouse GR, Keen WW. Gunshot wounds and other injuries of nerves. Philadelphia, PA: J. B. Lippincott & Co.; 1864. Available from: https://wellcomecollection.org/works/d7cphccr [Last accessed on 2024 Sep 24].
228. Mitchell-Heggs N, Kelly D, Richardson A. Stereotactic limbic leucotomy--a follow-up at 16 months. Br J Psychiatry 1976;128:226-40.
229. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
230. Montoya A, Weiss AP, Price BH, Cassem EH, Dougherty DD, Nierenberg AA, *et al*. Magnetic resonance imaging-guided stereotactic limbic leukotomy for treatment of intractable psychiatric disease. Neurosurgery 2002;50:1043-9.
231. Mosley PE, Windels F, Morris J, Coyne T, Marsh R, Giorni A, *et al*. A randomised, double-blind, sham-controlled trial of deep brain stimulation of the bed nucleus of the stria terminalis for treatment-resistant obsessive-compulsive disorder. Transl Psychiatry 2021;11:190.
232. Moyes PD. Longitudinal myelotomy for spasticity. J Neurosurg 1969;31:615-9.
233. Nashold BS Jr, Ostdahl RH. Dorsal root entry zone lesions for pain relief. J Neurosurg 1979;51:59-69.
234. Nathan PW. Cordotomy and neurosurgical history. J Neurosurg 1995;83:764-5.
235. Navidad AE. Rosenhan experiment – "On being sane in insane places". Available from: https://www.simplypsychology.org/rosenhan_experiment.html [Last accessed on 2024 Sep 24].
236. Netter FH. The CIBA collection. Vol. 1. Nervous System, Part II, Section X Plate 16. West Caldwell, NJ: CIBA Medical Education Division; 1986. p. 168.
237. Neumaier F, Paterno M, Alpdogan S, Tevoufouet EE, Schneider T, Hescheler J, *et al*. Surgical approaches in psychiatry: A survey of the world literature on psychosurgery. World Neurosurg 2017;97:603-34.e8.
238. Nicholas M, Vlaeyen JW, Rief W, Barke A, Aziz Q, Benoliel R, *et al*. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain 2019;160:28-37.
239. Niethammer M, Tang CC, LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, *et al*. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight 2017;2:e90133.
240. Nilsson U. Emotional archives and body politics: Towards an analysis of early lobotomy praxis in Sweden (1944-45). Available from: https://www.academia.edu/1810028/emotional_archives_and_body_politics_towards_an_analysis_of_early_lobotomy_praxis_in_sweden_1944_1945_ [Last accessed on 2024 Sep 24].
241. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 1999;354:1526.
242. Nuttin BJ, Gabriëls LA, Cosyns PR, Meyerson BA, Andréewitch S, Sunaert SG, *et al*. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 2003;52:1263-72.
243. O'Neill A. Distribution of the workforce across economic sectors in the United States from 2011 to 2021; 2023. Available from: https://www.statista.com/statistics/270072/distribution-of-the-workforce-across-economic-sectors-in-the-united-states [Last accessed on 2024 Sep 24].
244. Ogren K, Sjöström S, Bengtsson NO. The unknown history of lobotomy: Women, children and idiots were lobotomized.

Lakartidningen 2000;97:3395-8.
245. Ogren K. Psychosurgery in Sweden 1944-1958. The practice, the professional and the media discourse. Thesis, department of clinical sciences, division of psychiatry and department of culture and media, Umeå, Sweden Umeå University; 2007. Available from: https://umu.diva-portal.org/smash/record.jsf?pid=diva2%3A140147&dswid=7349 [Last accessed on 2024 Sep 24].
246. Okoro CA, Hollis ND, Cyrus AC, Griffin-Blake S. Prevalence of disabilities and health care access by disability status and type among adults - United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:882-7.
247. Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, *et al*. Management of referred deep brain stimulation failures: A retrospective analysis from 2 movement disorders centers. Arch Neurol 2005;62:1250-5.
248. Onofrio BM, Campa HK. Evaluation of rhizotomy. Review of 12 years' experience. J Neurosurg 1972;36:751-5.
249. Oppenheimer JR. In the Matter of J. Robert oppenheimer, USAEC transcript of hearing before personnel security Board; 1954. Available from: https://www.oxfordreference.com/display/10.1093/acref/9780191826719.001.0001/q-oro-ed4-00007996 [Last accessed on 2024 Sep 24].
250. Ozdemir O, Kolfal B, Messinger PR, Rizvi S. Human or virtual: How influencer type shapes brand attitudes. Comput Hum Behav 2023;145:107771.
251. Parent M, Parent A. Substantia nigra and Parkinson's disease: A brief history of their long and intimate relationship. Can J Neurol Sci 2010;37:313-9.
252. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2022;14:223-36.
253. PBS. Your fantastic mind season 2 episode 5. Available from: https://www.emoryhealthcare.org/your-fantastic-mind/season-two/Episode%205.html [Last accessed on 2024 Sep 24].
254. Peña C, Bowsher K, Costello A, De Luca R, Doll S, Li K, *et al*. An overview of FDA medical device regulation as it relates to deep brain stimulation devices. IEEE Trans Neural Syst Rehabil Eng 2007;15:421-4.
255. Persaud R. The lobotomist: A maverick medical genius and his tragic quest to rid the world of mental illness. BMJ 2005;330:1275.
256. Petersen MC, Love JG. Graded lobotomy. Am J Psychiatry 1949;106:65-8.
257. Pillay PK, Hassenbusch SJ. Bilateral MRI-guided stereotactic cingulotomy for intractable pain. Stereotact Funct Neurosurg 1992;59:33-8.
258. Pinsker MO, Bartsch T, Falk D, Volkmann J, Herzog J, Steigerwald F, *et al*. Failure of deep brain stimulation of the posterior inferior hypothalamus in chronic cluster headache - report of two cases and review of the literature. Zentralbl Neurochir 2008;69:76-9.
259. Plow EB, Malone DA Jr., Machado A. Deep brain stimulation of the ventral striatum/anterior limb of the internal capsule in thalamic pain syndrome: Study protocol for a pilot randomized controlled trial. Trials 2013;14:241.
260. Pool JL, Heath RG, Weber JJ. Topectomy; surgical indications and results. Bull N Y Acad Med 1949;25:335-44.
261. Poppen JL. Technic of prefrontal lobotomy. J Neurosurg 1948;5:514-20.
262. Popper K. Utopia and violence. In: Conjectures and refutations. The growth of scientific knowledge. Ch. 18. New York: Basic Books; 1963. p. 362.
263. Post F, Rees WL, Schurr PH. An evaluation of bimedial leucotomy. Br J Psychiatry 1968;114:1223-46.
264. Pugh J. No going back? Reversibility and why it matters for deep brain stimulation. J Med Ethics 2019;45:225-30.
265. Putnam TJ. Relief from unilateral paralysis agitans by section of the pyramidal tract. Arch Neurol Psychiatry 1938;40:1049-50.
266. Raja SN, Grabow TS. Complex regional pain syndrome I (reflex sympathetic dystrophy). Anesthesiology 2002;96:1254-60.
267. Ramasubbu R, Golding S, Williams K, Mackie A, MacQueen G, Kiss ZH. Recruitment challenges for studies of deep brain stimulation for treatment-resistant depression. Neuropsychiatr Dis Treat 2021;17:765-75.
268. Ranjan M, Ranjan N, Deogaonkar M, Rezai A. Deep brain stimulation for refractory depression, obsessive-compulsive disorder and addiction. Neurol India 2020;68:S282-7.
269. Rauch SL, Dougherty DD, Malone D, Rezai A, Friehs G, Fischman AJ, *et al*. A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. J Neurosurg 2006;104:558-65.
270. Rauck R, Coffey RJ, Schultz DM, Wallace MS, Webster LR, McCarville SE, *et al*. Intrathecal gabapentin to treat chronic intractable non-cancer pain. Anesthesiology 2013;119:675-86.
271. Real E, Plans G, Alonso P, Aparicio MA, Segalàs C, Cardoner N, *et al*. Removing and reimplanting deep brain stimulation therapy devices in resistant OCD (when the patient does not respond): Case report. BMC Psychiatry 2016;16:26.
272. Reno VP, Price DN. Relationship between the retirement, disability, and unemployment insurance programs: the U.S. Experience. Soc Secur Bull 1985;48:24-37.
273. Rezai AR, Mahoney JJ, Ranjan M, Haut MW, Zheng W, Lander LR, *et al*. Safety and feasibility clinical trial of nucleus accumbens deep brain stimulation for treatment-refractory opioid use disorder. J Neurosurg 2023;140:231-9.
274. Richardson A. Stereotactic limbic leucotomy: Surgical technique. Postgrad Med J 1973;49:860-4.
275. Riva-Posse P, Crowell AL, Wright K, Waters AC, Choi K, Garlow SJ, *et al*. Rapid antidepressant effects of deep brain stimulation and their relation to surgical protocol. Biol Psychiatry 2020;88:e37-9.
276. Robertson MM, Doran M, Trimble M, Lees AJ. The treatment of Gilles de la Tourette syndrome by limbic leucotomy J Neurol Neurosurg Psychiatry 1990;53:691-4.
277. Robin AA. A controlled study of the effects of leucotomy. J Neurol Neurosurg Psychiatry 1958;21:262-9.
278. Rosenhan DL. On being sane in insane places. Science 1973;179:250-8.
279. Royal College of Anaesthetists (Australia). Risks associated with your anaesthetic. Section 12: Nerve damage associated with peripheral nerve block. Information for Patients: South Infirmary Victoria University Hospital. Available from: https://www.sivuh.ie/download.aspx?f=Risk+of+nerve+injury+after+peripheral+nerve+block.pdf [Last accessed on 2024 Sep 24].
280. Royal College of Anesthetists (UK). Risks associated with

your anaesthetic. Section 12: Nerve damage associated with a spinal or epidural injection. East Sussex Healthcare NHS Trust. Available from: https://www.esht.nhs.uk [Last accessed on 2024 Sep 24].
281. Royal College of Psychiarists. Neurosurgery for mental disorder. Report from the neurosurgery working group of the royal college of psychiatrists; 2005. Available from: https://www.google.com/search?client=firefox-b-1-d&q=Neurosurgery+for+mental+disorder+Report+from+the+Neurosurgery+Working+Group+of+the+Royal+College+of+Psychiatrists [Last accessed on 2024 Sep 24].
282. Rozenblit L, Keil F. The misunderstood limits of folk science: An illusion of explanatory depth. Cogn Sci 2002;26:521-62.
283. Rück C, Andréewitch S, Flyckt K, Edman G, Nyman H, Meyerson BA, *et al*. Capsulotomy for refractory anxiety disorders: long-term follow-up of 26 patients. Am J Psychiatry 2003;160:513-21.
284. Rück C, Edman G, Asberg M, Svanborg P. Long-term changes in self-reported personality following capsulotomy in anxiety patients. Nord J Psychiatry 2006;60:486-91.
285. Rück C, Karlsson A, Steele JD, Edman G, Meyerson BA, Ericson K, *et al*. Capsulotomy for obsessive-compulsive disorder: long-term follow-up of 25 patients. Arch Gen Psychiatry 2008;65:914-21.
286. Rück C, Larsson JK, Mataix-Cols D, Ljung R. Register-based 13-year to 43-year follow-up of 70 patients with obsessive-compulsive disorder treated with capsulotomy. BMJ Open 2017;7:e013133.
287. Rück C, Svanborg P, Meyerson BA. Lesion topography in capsulotomy for refractory anxiety--is the right side the right side? Stereotact Funct Neurosurg 2005;83:172-9.
288. Rück C. Adverse events following neurosurgery. Br J Psychiatry 2003;183:366-7. author reply 367.
289. Rück C. Antidepressive agents and cost-efficiency. Lakartidningen 2000;97:2898-9.
290. Ruck C. Capsulotomy in anxiety disorders. Doctoral Thesis, department of clinical neuroscience, Karolinska Institute, Stockholm, Sweden; 2006. Available from: https://www.dissertations.se/about/Christian+Ruck [Last accessed on 2024 Sep 24].
291. Rück C. Psychosurgery. J Neurosurg 2003;99:1113-4; author reply 1114.
292. Rucker E. Rapid response: Re: Re: Re: Family of lobotomy victims speak. BMJ. 2003;327:1449.
293. Ryan KJ. The National commission for the protection of human subjects of biomedical and behavioral research. Report and recommendations. Psychosurgery; 1977 DHEW Publication No. (OS) 77-0001 Available from: https://videocast.nih.gov/pdf/ohrp_psychosurgery.pdf [Last accessed on 2024 Sep 24].
294. Rylander G. Stereotactic radiosurgery in anxiety and obsessive-compulsive states: Psychiatric aspects. In: Hitchcock ER, Ballantine HT Jr., Meyerson BA, editors. Modern concepts in psychiatric surgery. Amsterdam: Elsevier; 1979. p. 235-40.
295. Sachdev PS, Sachdev J. Long-term outcome of neurosurgery for the treatment of resistant depression. J Neuropsychiatry Clin Neurosci 2005;17:478-85.
296. Sachs E Jr. A simple, gentle, self-retaining brain retractor. J Neurosurg 1953;10:555.
297. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95:2S-4S.
298. Saleh C, Hasler G. Deep brain stimulation for psychiatric disorders: Is there an impact on social functioning? Surg Neurol Int 2017;8:134.
299. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ, *et al*. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 2011;31:271-85.
300. Scangos KW, Khambhati AN, Daly PM, Makhoul GS, Sugrue LP, Zamanian H, *et al*. Closed-loop neuromodulation in an individual with treatment-resistant depression. Nat Med 2021;27:1696-700.
301. Scarff JE, Kalinowsky LB. Prefrontal lobotomy under direct vision; survey of psychiatric aspects. N Y State J Med 1947;47:2669-75.
302. Scher C, Meador L, Van Cleave JH, Reid MC. Moving beyond pain as the fifth vital sign and patient satisfaction scores to improve pain care in the 21st century. Pain Manag Nurs 2018;19:125-9.
303. Schiff ND, Giacino JT, Fins JJ. Deep brain stimulation, neuroethics, and the minimally conscious state: Moving beyond proof of principle. Arch Neurol 2009;66:697-702.
304. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, *et al*. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007;448:600-3.
305. Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, *et al*. Hypothalamic stimulation in chronic cluster headache: A pilot study of efficacy and mode of action. Brain 2005;128:940-7.
306. Scholz J. Finally, a systematic classification of pain (the ICD-11). Pract Pain Manag. 2019;19.
307. Scoville WB. Late results of orbital undercutting. Report of 76 patients undergoing quantitative selective lobotomies. In: Strom-Olsen R, editor. President, Symposium on Orbital Undercting. Vol. 53. Proceedings of the Royal Society of Medicine; 1960. p. 721-40.
308. Scull A. Desperate remedies. Cambridge, MA: Belknap Press; 2022.
309. Scull A. Psychiatry and its discontents. Oakland, CA. University of California Press; 2019. Available from: https://lithub.com/a-brief-and-awful-history-of-the-lobotomy [Last accessed on 2024 Sep 24].
310. Serghiou S, Goodman SN. Random-effects meta-analysis: Summarizing evidence with caveats. JAMA 2019;321:301-2.
311. Shields DC, Asaad W, Eskandar EN, Jain FA, Cosgrove GR, Flaherty AW, *et al*. Prospective assessment of stereotactic ablative surgery for intractable major depression. Biol Psychiatry 2008;64:449-54.
312. Shirvalkar P, Prosky J, Chin G, Ahmadipour P, Sani OG, Desai M, *et al*. First-in-human prediction of chronic pain state using intracranial neural biomarkers. Nat Neurosci 2023;26:1090-9.
313. Shulman R, Turnbull IM, Diewold P. Psychiatric aspects of thalamic stimulation for neuropathic pain. Pain 1982;13:127-35.
314. Siddiqi SH, Kording KP, Parvizi J, Fox MD. Causal mapping of human brain function. Nat Rev Neurosci 2022;23:361-75.
315. Sindou M, Fischer G, Mansuy L. Posterior spinal rhizotomy and selective posterior rhizidotomy. Prog Neurol Surg

1976;7:201-50.
316. Sindou MP, Mertens P, Bendavid U, García-Larrea L, Mauguière F. Predictive value of somatosensory evoked potentials for long-lasting pain relief after spinal cord stimulation: Practical use for patient selection. Neurosurgery 2003;52:1374-83.
317. Sjöqvist F. Psychotropic drugs (2). Interaction between monoamine oxidase (MAO) inhibitors and other substances. Proc R Soc Med 1965;58:967-78.
318. Sladek JR Jr, Shoulson I. Neural transplantation: A call for patience rather than patients. Science 1988;240:1386-8.
319. Smaldino PE, McElreath R. The natural selection of bad science. R Soc Open Sci 2016;3:160384.
320. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, *et al*. Implantable drug delivery systems study group. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002;20:4040-9.
321. Soomro GM. Obsessive compulsive disorder. BMJ Clin Evid 2012;2012:1004.
322. Spanos NP. Multiple identities & false memories: A sociocognitive perspective. Washington, DC: American Psychological Association; 1996.
323. Spaulding WB. Dangers in the use of some potent drugs. Can Med Assoc J 1962;87:1275-81.
324. Spitzer RL. More on pseudoscience in science and the case for psychiatric diagnosis. A critique of D.L. Rosenhan's "On Being Sane in Insane Places" and "The Contestual Nature of Psychiatric Diagnosis". Arch Gen Psychiatry 1976;33:459-70.
325. Spitzer RL. On pseudoscience in science, logic in remission, and psychiatric diagnosis: A critique of Rosenhan's "On being sane in insane places". J Abnorm Psychol 1975;84:442-52.
326. Stacy M, Turner D, Wooten GF, Elias WJ, Laws ER, Dhawan D, *et al*. A multicenter, randomized, double-blind, placebo-controlled trial of liatermin (r-metHuGDNF) administered by bilateral intraputamenal infusion to patients with idiopathic Parkinson's disease. Ann Neurol 2006;59:459-66.
327. Starr PA, Barbaro NM, Raskin NH, Ostrem JL. Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. J Neurosurg 2007;106:999-1005.
328. Stein AA, Wright AW. Hepatic pathology in jaundice due to chlorpromazine. J Am Med Assoc 1956;161:508-11.
329. Sterling P. Causality in mental disturbance: A review of the neuroscience. Available from: https://www.madinamerica.com/2023/07/causality-mental-disturbance [Last accessed on 2024 Sep 24].
330. Strom-Olsen R, Carlisle S. Bi-frontal stereotactic tractotomy. A follow-up study of its effects on 210 patients. Br J Psychiatry 1971;118:141-54.
331. Sunstein CR, Kuran T. Availability cascades and risk regulation. Stanford Law Rev 1999;51:683-768.
332. Sweet J, Viswanathan J (moderators). AANS/CNS section on stereotactic & functional neurosurgery section session. Sunday, May 1, 2022, 2:25-2:45 pm. Patient perspective: DBS for depression. p. 74. Available from: https://www.aans.org/-/media/files/meetings/an22/aans-qp22-final.pdf [Last accessed on 2024 Sep 24].
333. Sweet WH. Treatment of medically intractable mental disease by limited frontal leucotomy--justifiable? N Engl J Med 1973;289:1117-25.
334. Sykes MK, Tredgold RF. Restricted orbital undercutting; a study of its effects on 350 patients over the ten years 1951-1960. Br J Psychiatry 1964;110:609-40.
335. Talairach J, Hecaen H, David M. Lobotomie préfrontal limitée par éléctrocoagulation des fibres thalamo-frontales a leur émergence du bras antérieur de la capsule interne. In Congress neurologique international, Paris, Masson; 1949.
336. Tan E, Marks IM, Marset P. Bimedial leucotomy in obsessive-compulsive neurosis: A controlled serial enquiry. Br J Psychiatry 1971;118:155-64.
337. Tass PA, Klosterkötter J, Schneider F, Lenartz D, Koulousakis A, Sturm V. Obsessive-compulsive disorder: Development of demand-controlled deep brain stimulation with methods from stochastic phase resetting. Neuropsychopharmacology 2003;28 Suppl 1:S27-34.
338. Terrier LM, Levêque M, Amelot A. Brain surgery: Most lobotomies were done on women. Nature 2017;548:523.
339. Tomycz L, Forbes J, Ladner T, Kahn E, Maris A, Neimat J, *et al*. Open thoracic cordotomy as a treatment option for severe, debilitating pain. J Neurol Surg A Cent Eur Neurosurg 2014;75:126-32.
340. Torkildsen Ø. Lessons to be learnt from the history of lobotomy. Tidsskr Nor Laegeforen 2022;142. doi: 10.4045/tidsskr.22.0505
341. Turnbull F, Davidson A. Experience with leucotomy at the provincial mental hospital, British Columbia. Can Med Assoc J 1949;60:130-3.
342. Turner E. Custom psychosurgery. Postgrad Med J 1973;49:834-44.
343. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. JAMA 1994;271:1609-14.
344. Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: A systematic literature synthesis. Neurosurgery 1995;37:1088-95.
345. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: A systematic review of effectiveness and complications. Pain 2004;108:137-47.
346. Tyagi H, Apergis-Schoute AM, Akram H, Foltynie T, Limousin P, Drummond LM, *et al*. A randomized trial directly comparing ventral capsule and anteromedial subthalamic nucleus stimulation in obsessive-compulsive disorder: Clinical and imaging evidence for dissociable effects. Biol Psychiatry 2019;85:726-34.
347. Uihlein A, Love JG. A new mechanical aid to prefrontal lobotomy; the cranial localizer. Proc Staff Meet Mayo Clin 1948;23:470-2.
348. Varley TF, Hoel E. Emergence as the conversion of information: A unifying theory. Phil Trans R Soc A 2022;380:20210150. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9131462/pdf/rsta.2021.0150.pdf [Last accessed: 2024 Dec 17].
349. Vedam-Mai V, Deisseroth K, Giordano J, Lazaro-Munoz G,

Chiong W, Suthana N, *et al*. Proceedings of the eighth annual deep brain stimulation think tank: Advances in optogenetics, ethical issues affecting DBS research, neuromodulatory approaches for depression, adaptive neurostimulation, and emerging DBS technologies. Front Hum Neurosci 2021;15:644593.
350. Vertosick FT Jr. Lobotomy's Back; 1997. Available from: https://www.discovermagazine.com/mind/lobotomys-back [Last accessed on 2024 Sep 24].
351. Visser-Vandewalle V, Andrade P, Mosley PE, Greenberg BD, Schuurman R, McLaughlin NC, *et al*. Deep brain stimulation for obsessive-compulsive disorder: A crisis of access. Nat Med 2022;28:1529-32.
352. Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic efficacy. JAMA 2008;299:1016-7.
353. Waitzkin L. Hepatic dysfunction during promazine therapy. N Engl J Med 1957;257:276-7.
354. Waldrep EE. Unsafe Science. The anti-American Psychological Association. Psychology and the declining public trust; 2023. Available from: https://unsafescience.substack.com/p/the-anti-american-psychological-association [Last accessed on 2024 Sep 24].
355. Walker AE, Von Bonin G, Pool JL, Heath RG. Psychosurgery: Indications and sequelae. Clin Neurosurg 1953;1:143-65.
356. Walker AE. Cerebral pedunculotomy for the relief of involuntary movements. II. Parkinsonian tremor. J Nerv Ment Dis 1952;116:766-75.
357. Ward L. Social-media influencers don't always have to be human to be believable. Wall Street Journal; 2023. Available from: https://www.wsj.com/articles/virtual-influencers-social-media-advertising-9cabecd2?page=1 [Last accessed on 2024 Sep 24].
358. Wayne GJ. Impressions of Soviet psychiatry. Calif Med 1960;93:351-4.
359. Weiner RL, Alo K. Occipital nerve stimulation for treatment of intractable headache syndromes. In: Krames ES, Peckham PH, Rezai AR, editors. Neuromodulation (Second Edition) comprehensive textbook of principles, technologies, and therapies. Cambridge, MA: Elsevier; 1975. p. 2018.
360. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation 1999;2:217-21.
361. Weintraub M. How to evaluate reports of clinical trials. Pharm Ther 1990;14:1463-76.
362. Welter ML, Alves Dos Santos JF, Clair AH, Lau B, Diallo HM, Fernandez-Vidal S, *et al*. Deep brain stimulation of the subthalamic, accumbens, or caudate nuclei for patients with severe obsessive-compulsive disorder: A randomized crossover controlled study. Biol Psychiatry 2021;90:e45-7.
363. White JC, Sweet WH. Pain and the neurosurgeon. 2nd ed. Springfield, IL: Charles C Thomas; 1969.
364. White JC, Sweet WH. Pain: Its mechanisms and neurosurgical control. Springfield, IL: Charles C. Thomas; 1955.
365. Whiting DM, Tomycz ND, Bailes J, de Jonge L, Lecoultre V, Wilent B, *et al*. Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism. J Neurosurg 2013;119:56-63.
366. Widge AS, Deckersbach T, Eskandar EN, Dougherty DD. Deep brain stimulation for treatment-resistant psychiatric illnesses: What has gone wrong and what should we do next? Biol Psychiatry 2016;79:e9-10.
367. Wilkins RH, editor. Neurosurgical classics. New York: Johnson Reprint Corporation; 1965.p. 404-27.
368. Wilkinson HA, Davidson KM, Davidson RI. Bilateral anterior cingulotomy for chronic noncancer pain. Neurosurgery 1999;45:1129-34. [discussion/comment in: [Myerson B. [Letter] Meyerson B: Bilateral anterior cingulotomy for chronic noncancer pain. Neurosurgery 1999;45:1135-6. (comment). [Wilkinson HA. Bilateral anterior cingulotomy for chronic noncancer pain. Neurosurgery 2000;46:1535-6.
369. Wind JJ, Anderson DE. From prefrontal leukotomy to deep brain stimulation: The historical transformation of psychosurgery and the emergence of neuroethics. Neurosurg Focus 2008;25:E10.
370. Wong ET, Gunes S, Gaughan E, Patt RB, Ginsberg LE, Hassenbusch SJ, *et al*. Palliation of intractable cancer pain by MRI-guided cingulotomy. Clin J Pain 1997;13:260-3.
371. Yacorzynski GK, Boshes B, Davis L. Psychological changes produced by frontal lobotomy. Res Publ Assoc Res Nerv Ment Dis 1948;27 (1 vol.):642-57.
372. Yadav K, Lewis RJ. Immortal time bias in observational studies. JAMA 2021;325:686-7.
373. Yang JC, Ginat DT, Dougherty DD, Makris N, Eskandar EN. Lesion analysis for cingulotomy and limbic leucotomy: Comparison and correlation with clinical outcomes. J Neurosurg 2014;120:152-63.
374. Zimmer B. On language. Wellness; 2010. Available from: https://www.nytimes.com/2010/04/18/magazine/18FOB-onlanguage-t.html [Last accessed on 2024 Sep 24].
375. Zipes DP, Svorkdal N, Berman D, Boortz-Marx R, Henry T, Lerman A, Ross E, *et al*. Spinal cord stimulation therapy for patients with refractory angina who are not candidates for revascularization. Neuromodulation 2012;15:550-8.

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