Neuronal anatomy, circuitry and physiology targeted in the treatment of psychiatric disease via surgical intervention

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Abstract
Mental health awareness is a central focus of our society. It is essential that we begin to analyze the various forms and methods of treatment with which we provide patients with neuropsychiatric disorders. The introduction of innovative biomedical technologies, as well as enhanced neuropharmacologic therapies, has provided the mental health community with the ability to treat these patients with quality care. The long medical history of the integration of neuropsychiatric treatment into formal medical practice becomes imperative if we are to improve the treatment plans this field offers. Understanding the neurobiological basis of psychiatric disease may afford us with the ability to further our comprehension of the underlying mechanisms in these diseases, and thereby develop improved methodologies of treatment. Under limited conditions, mental health patients may seek neurosurgical intervention to better treat their disease. This practice, though ancient, illustrates how the biomedical community identifies neuro-substrate regions of the brain which may account for specific psychiatric disorders. Understanding the development and history of the psychosurgery procedure provides glaring information as to how the treatment of mental health patients needs to continuously evolve and adapt, catering to the medical needs of the mental health community. Advances in neurobiology, psychiatry, functional imaging, and stereotaxy, converge in support of further investigation of modern functional neurosurgical procedures to treat psychiatric disorders in patients with conditions refractory to all other therapies.

Keywords: Neurosurgery; Neuropsychiatry; Psychosurgery; Mental health; Neuroethics

An Introduction to Psychosurgery
Psychosurgery, which was defined in 1976 by the World Health Organization as "the selective surgical removal or destruction of nerve pathways for the purposes of influencing behavior" [1], has a long and controversial history. Beginning, ideally perhaps, in the Neolithic Period of the Stone Age, psychosurgery rose to the heights of the Nobel Prize when Egas Moniz won the award in 1949. Modern understanding of functional neuroanatomy and neurobiology, combined with advances in stereotactic technology and functional imaging, is creating a setting in which neurosurgery may represent a minimal invasive and highly selective treatment for a variety of psychiatric illnesses, which include depression, severe anxiety, and obsessive-compulsive disorders [2]. What is most interesting about our present understanding of psychiatric diseases and how they may be treated by neurosurgical intervention is its rich, controversial and dynamic evolution. Since its introduction as a treatment for severe mental illness in 1936, psychosurgery has at times been enthusiastically embraced and flatly rejected by both the medical profession and society at large. Currently, the accepted therapeutic approach to most psychiatric disease involves a combination of well-supervised psychotherapy, pharmacological intervention and even in some instances, electroconvulsive therapy [3]. However, despite these modern treatment methods, many patients fail to respond to treatments sufficiently, and unfortunately remain severely disabled by their disease. When certain very specific selection criteria are met, these patients who have been proven to be treatment refractive can be given a surgical intervention option to alleviate their symptoms. Although its mechanisms can be ethically debated, the introduction of psychosurgery into our medical regimen of treatment has helped the lives of many dire patients. Furthermore, the 4th edition of Comprehensive Textbook of Psychiatry defines psychosurgery as "the surgical intervention to sever fibers connecting one part of the brain with another or to remove, destroy, or stimulate brain tissue with the intent of modifying or altering disturbances of behavior, thought content, or mood for which no organic pathological cause can be demonstrated [4]. Many facets of medicine are inherently linked to psychosurgery, such as psychiatry, bioengineering, psychology, nuclear medicine, and obviously neurosurgery. Therefore, a comprehensive analysis of how this methodology has evolved in each arena is imperative for its full comprehension. Thus, I will set out to thoroughly explain these domains, how they have contributed to the current state of psychosurgery, and how our medical community is progressing towards a more successful future for the surgical intervention of severe psychiatric illnesses.

The Inception and History of Psychosurgery: What We Thought and How it Evolved
Before modern psychosurgery
Although the groundwork for the modern era of psychosurgery was established in the 19th century, the origins of this procedure, and this ideology, can be traced to antiquity through the practice of trephination, the procedure of craniotomy with the cylindrical saw termed the "trephine [5]". According to an article published in Nature, scientists have confirmed that trephined skulls have been identified at the Ensisheim burial site in France, which carbon dates back to the Neolithic period of the stone age, or approximately 5100 BC [6] (Figure 1). The indications for trephination in historical times included...
was approximately a 25% increase in psychiatric illness, and the development of pharmacological interventions were not available. As the Asylums were overflowing with patients, psychiatrists were forced to develop new methods to treat these patients. Thus, it is quite logical to state that these forces also influenced Burckhardt in his psychosurgical procedures. However, it is simultaneously evident that he clearly did base his procedures on the published scientific data of his time.

On the basis of his belief in the anatomical and brain-behavior theories of the time, Burckhardt decided that he could help patients with behavioral disturbances by eliminating or decreasing the mass of a particular pathologically functioning brain area. Therefore, on December 29, 1888, Gottlieb Burckhardt, who is considered by some to be the father of modern psychosurgery, performed the first experimental topectomy. In 1891, Burckhardt published his report on six patients with severe psychiatric illnesses whom he described as demented and aggressive; his patients received bilateral localized topectomies, based on anatomical models that Burckhardt deduced as the origins of their pathological behaviors [13]. Most of the cortical excisions performed by Burckhardt were localized in and around the areas now known as Broca's and Wernicke's areas, as well as in various regions in the parietal and temporal cortices [13]. Initially, several patients experienced unsatisfactory results and returned to surgery for subsequent topectomies; one patient actually underwent four operations. Burckhardt classified three of his surgical patients as successes, two as partial successes, and one as failure due to death. It has been documented that throughout several conferences in which Burckhardt presented his data he was met by disapproval and much speculation; the medical field of his time was anything but receptive [13]. After his 1891 publication Dr. Burckhardt ceased his experimental topectomies and returned to his daily duties at the Prefargier Asylum for an additional 5 years before his retirement.

The neuroanatomy of neuropsychology

The work of Dr. J.F. Fulton and Dr. C.F. Jacobsen provided a key foundation on which the practice of psychosurgery grew. At the Second World Congress of Neurology in 1935, they presented data on calming behavioral changes associated with the resection of anterior frontal association cortex. The significance of this early finding was clear: not only did we discover a neuroanatomical substrate for emotional behavior, but we successfully targeted it. More importantly, this meeting had historical significance: it was at this meeting that the famous Portuguese neurologist Egas Moniz, much to the surprise of those in attendance, suggested the ablation of the frontal cortex in humans with psychiatric disease [14]. This inspired Moniz to perform prefrontal leucotomies on 20 psychiatric patients. Moniz reported that 14 of 20 severely ill, institutionalized patients showed “worthwhile” improvement after operation and coined the phrase ‘psychosurgery’ to describe his interventions [14]. As science progressed, in 1937, James W. Papez, published his paper entitled “A Proposed Mechanism of Emotion” in which he postulated that a reverberating circuit in the brain might be responsible for emotion and anxiety. The neurostructural components of this circuit consisted of the hypothalamus, septal area, hippocampus, mamillary bodies, anterior thalamic nuclei, cingulate gyrus and their interconnections [15] (Figure 2). These structures comprise the rudimentary limbic system of the human brain, illustrated by Broca in 1878, and subsequently expanded by McLean in 1952 to incorporate the orbital frontal, insular and anterior temporal cortices, the amygdala and dorso-medial thalamic nuclei. In analyzing the rich evolution of this highly controversial neurosurgical procedure, it is important to emphasize the great impact

A Father of psychosurgery: Gottlieb Burckhardt in a historical context

Advances in the scientific community began to illustrate that functional centers and neuronal interconnections responsible for emotions and cognition could be found within the brain, and mapped on the gross brain as well. Various key figures advanced this neurocortical substrate theory of cognition, which played a key role in the progression from theoretical diagram-making models of the anatomy of cognition, to animal studies and then to the first human neurosurgical procedure to treat mental disease. In 1870, Fritsch and Hitzig [9] described the effects of systematic electrical stimulation over the entire cortex of the dog brain. A relationship between emotion and brain structure was also illustrated by Goltz et al. who described the calming effect of temporal cortex removal in dogs [10]. Autopsy studies of the brains of demented patients by Luys and those of patients with language disorders by Broca and Wernicke provided more evidence for the brain-behavior theories of the latter 19th century [11,12]. These scientific advancements, as well as the general thought process of the scientific environment of the late 19th century, had a profound effect on a young Swiss psychiatrist, Gottlieb Burckhardt. After being appointed director of the contemporary Prefargier Asylum in Switzerland, Burckhardt thoroughly studied the publications of the current neuroscientists who were illustrating the relationship between gross brain structures and cognition. Burckhardt deduced that there was a direct relationship between localized cortical brain mass and the degree to which certain functions (or malfunctions) were present in a given individual. It is also documented that Burckhardt was ultimately influenced by the observations of Mairét, who published an article in 1883, which documented hypertrophic temporal lobes in patients with severe auditory hallucinations. In addition to break-through views developing in the scientific community, it is imperative to also take into account the great economic burden these patients were having on society at the time. In the late 1800’s there

secular phenomena such as fractures or other traumatic injuries, as well as symptoms interpreted as spiritual, such as headaches, seizures, or psychiatric disturbances. Although evidence of trephination has been documented in skulls predating the late Neolithic Period, Alt et al. [6] question their validity and point out that there are many other causes of holes in ancient skulls, such as infection, tumors, fractures, and postmortem animal activity. The use of trephination continued throughout the ages, and sporadic documentation of its use can be observed in the writings of authors such as Frugardi in the 12th century [7] and Burton in the 17th century [8].

Figure 1: 1655 illustration of trephination.
developed a technique, called leucotomy, which consisted of severing the prefrontal cortex to the rest of the brain. He then observed that the symptoms of neurotic patients in chimpanzees could be decreased by cutting the nerve fibers connecting the thalamus to the frontal lobes, which illustrated that certain neurotic symptoms induced by psychological stress could be alleviated by surgical intervention. Moniz based his innovative operation on a discovery he made a few years earlier, which illustrated that certain neurotic symptoms induced in chimpanzees could be decreased by cutting the nerve fibers connecting the prefrontal cortex to the rest of the brain. He then developed a technique, called leucotomy, which consisted of severing fiber tracts between the thalamus and the frontal lobes, using a special knife, which he called a leucotome.

Walter Freeman, an American psychiatrist and member of the American Psychiatric Association, and his colleague James Watts, adopted the procedure Moniz invented, yet improved it on their own patients. Together they developed the trans-orbital leucotomy, which could be conducted within a few minutes under local anesthesia. This procedure consisted of the insertion of an ice pick instrument, with the blow of a hammer, through the roof of the orbits, and subsequently a rapid sideways movement to sever the white matter tracts of the frontal lobes. Dr. Freeman popularized leucotomy as a tool to control undesirable behavior across the nation’s insane asylums, hospitals, and psychiatric clinics. Freeman and Watts were both impressed by the results they obtained from their first 200 patients in 1942; however, they did admit to a significant complication rate including frontal lobe syndrome, seizures, apathy, decreased attention and inappropriate behavior. Nevertheless, prefrontal lobotomy became widely performed throughout the United States largely because of the lack of satisfactory therapeutic alternatives. Consequently, in the 1940s and 1950s, more than 50,000 patients had a lobotomy performed on them, even without strong scientific data backing it up. However, with time it became clear to the medical community, and the general community, that prefrontal lobotomy produced “zombies”, or people without emotions who were completely apathetic to everything they did. It is also reported that during this time it became evident that the lobotomy had impaired important higher mental functions, such as socially adequate behavior and the capability to plan actions. In a study assessing the efficacy of this procedure on over 10,000 patients from 1943-1954, Tooth and Newton confirmed that 70% of patients showed improvement with the operation, yet there was also a 6% mortality rate.

The next noteworthy advancement in the neurosurgical treatment of psychiatric illness occurred with the introduction of stereotactic techniques to create localized lesions in specific target sites within brain matter. Stereotactic anterior cingulotomy was first reported by Foltz and White in 1962 and subcaudate tractotomy carried out in England by Knight in 1964. Lars Leksell described his experience with anterior capsulotomy in 1972 and Kelley reported limbic leucotomy in 1973. The anatomical details of these procedures, along with their precise methodologies, risk factors, and signicant published data are described in a further section of this paper (Figure 4).

Historical prominent figures in psychosurgery: neurosurgical intervention innovation

The first consistent technique for psychosurgery was developed by Portuguese neurologist Dr. Antonio Moniz, and performed for the first time in 1935, with his colleague, Almeida Lima. Moniz based his innovative operation on a discovery he made a few years earlier, which illustrated that certain neurotic symptoms induced in chimpanzees could be decreased by cutting the nerve fibers connecting the prefrontal cortex to the rest of the brain. He then developed a technique, called leucotomy, which consisted of severing
The Current State of Neurosurgical Techniques Treating Psychiatric Disorders

Although the history of this discipline may lead some to conclude that its reputation is somewhat justified, the current era of functional neurosurgery is providing new opportunities for scientific advances in the surgical treatment of psychiatric disorders, as well as a set of new challenges. In order for the field of neuroscience to affectively treat psychiatric disorders, we must probe the depths of the following imperative questions: Which brain systems underlie emotions? Do different regions underlie different emotions, or are all emotions rooted in the same neural circuitry? How does emotion processing in the brain interact with cognition, motor behavior, language and motivation?

Psychiatric genetics and psychosurgery: What does The future hold?

The connection between the field of genetics and psychosurgery is scarcely discussed in the scientific literature, if at all. The direct relationship between psychiatric genetics and what goes on in the operating room for a mentally ill patient may be weak, and perhaps in its most basic sense these two realms of medicine seem not to be related at all. Genome-Wide Association Studies have discovered SNPs in many illnesses, including depression, OCD, anxiety and schizophrenia. These genetic abnormalities show us exactly what is being altered on the most microscopic level within the cell. In a 2001 *Nature* article, Kay et al. explains that the stereotactic delivery of genetic or cellular material with specific functions to specific brain areas holds the promise of augmenting rather than inhibiting neural function, in comparison to ablative surgeries or even deep brain stimulation [20]. As the complex genetic factors of psychiatric disorders are elucidated, specific gene replacement strategies in focal areas may become viable therapeutic strategies, as opposed to our conventional approaches nowadays. The expression of gene products in the brain by modified herpes, adeno- or adeno-associated viruses is already being explored for brain tumors and other neurologic dysfunctions such as epilepsy, and can conceivably play a role in psychiatric disease within future [20].

The 4 internationally accepted neurosurgical procedures

The rich history and evolution of psychosurgery has finally lead to the acceptance of 4 commonly employed neurosurgical procedures used to treat psychiatric disease. Although they each differ in their technique and methodology, each procedure is performed bilaterally and under stereotactic conditions, which allows for precise lesioning of the targeted structures. However, each procedure contains its specific risk factors and distinct efficacy data.

Subcaudate tractotomy

This procedure was designed in England by Geoffrey Knight in 1964 as a method of minimizing frontal lobe lesioning by interrupting fibers from the frontal lobes to subcortical structures such as the amygdala [21] (Figure 3). The site of the lesion is the substantia innominata, just below the head of the caudate nucleus [21]. Surgical indications included major depressive illness, obsessive compulsive disorder and anxiety. In a study of 208 patients in the 1970s, approximately 2/3 of patients with depression or anxiety had post-operative improvement, while 50% of obsessive patients also demonstrated improvement (22). 20 to 30 psychosurgical procedures have been performed in Britain in the past decade at the Geoffrey Knight National Unit for Affective Disorders [22]. Since 1961 approximately 1300 subcaudate
tractotomy procedures have been performed. Subcaudate tractotomy has been largely free of major complications. The most troublesome short-term complication is transient postoperative disorientation, which is observed for approximately 10% of patients. The most common long-term complications are seizures, which are observed for 1.6% of patients. Follow-up data on specific subsets of patients who have undergone this procedure has been completed. Nine female patients with bipolar disorder were studied 4 years post operation, and 5 demonstrated marked improvement, while 4 showed mild improvement. In 1991 Poynton et al. [23] reported a psychological assessment of 23 patients who underwent subcaudate tractotomy. An array of psychometric tests was performed 9 days prior to the operation, as well as 2 weeks and 6 months after surgery. These exams illustrated that no significant long-term cognitive deficits were incurred by this procedure. Again in 1995 Poynton et al. reported psychiatric outcome data for the same group of 23 patients. A variety of mental state assessment tests were performed. By the 6 month follow-up assessment, the group demonstrated significant decreases on Hamilton and Beck depression – rating scales [23].

Anterior cingulotomy

The anterior cingulum was first suggested as a surgical target for psychiatric disease by Fulton in 1947. This was based on evidence that stimulation of the anterior cingulum in monkeys produced autonomic responses associated with emotion. Lesions in this region significantly resulted in less fearful and more aggressive animals [24]. This procedure is currently used to treat refractory major affective disorder, severe chronic pain, chronic anxiety states or OCD. The cingulate cortex is an important structure in the circuit which Papez outlined, and increased metabolism in the anterior cingulate has been associated with OCD [25]. MRI guided stereotactic techniques are used to properly isolate target coordinates, and lesions are created via thermocoagulation. The day after surgery, a post-operative MRI scan is obtained to visualize the placement and extent of the lesions. Jenike et al. published a retrospective study in 1987 which demonstrated the results of bilateral cingulotomy in 198 patients suffering from a variety of psychiatric disorders. With a mean follow-up of 8.6 years, 62% of patients with severe affective disorder and 56% of patients with OCD were found to have had worthwhile improvement. Additionally, in 14 patients suffering from anxiety disorders, 50% were found to be functionally well and 29% were found to have shown improvement [26]. Using a 35% improvement rate on the Yale-Brown Obsessive Compulsive Scale, Jenike et al. reported that 30% of their 33 patients showed improvement post-operatively. An important outcome of this study was its illustration of the safety of the procedure. No surgery-related deaths were reported, and postoperative complications were limited to medication responsive seizures.

Limbic leucotomy

Introduced in 1973 by Mitchell-Heggs et al. this procedure is essentially the combination of stereotactic lesions created in the subcaudate tractotomy and anterior cingulotomy in order to disconnect orbital-frontal-thalamic pathways; lesions are created using a either cryoprobe or thermocoagulation [27]. Price et al., has demonstrated 36-50% of patients with major depressive disorder and OCD showed improvements with little adverse side effects from the procedure, while 4/5 patients who were engaged in self mutilation showed sustained reduction in self-injurious behavior post operative follow up at 32 months [28]. In 1976 Kelly’s group assessed 66 patients approximately 16 months post-operatively utilizing a 5-point global rating scale. According to their data, patients with OCD exhibited an 89% improvement of symptoms, while there was a 66% improvement for patients with chronic anxiety and a 78% improvement in patients with depression [27]. Prospective studies are necessary to establish the efficacy of any form of psychiatric neurosurgery, and longer detailed follow-up studies are needed.

Anterior capsulotomy

This procedure was designed by the French neurosurgeon Talairach in the late 1940s. Due to the innovation of the Swedish neurosurgeon Leksell, it currently uses thermocoagulation or gamma-knife stereotaxis to lesion the fronto-limbic fibers that pass in the internal capsule as it courses between the caudate and putamen nuclei of the basal ganglia [29]. Clinical indications for capsulotomy initially included schizophrenia, depression, chronic anxiety states and obsessive neurosis. Leksell initially operated on 116 patients with a variety of psychiatric disorders; 50% of patients with obsessional neurosis and 48% of depressed patients had a satisfactory response, while 20% of patients with anxiety neurosis and 14% of patients with schizophrenia also showed improvement. Success rates as high as 70% have been reported in the literature [30], and a direct comparison with anterior cingulotomy indicates higher efficacy. However, it should be noted that out of the 4 procedures, anterior capsulotomy is known to have the most difficult side effects, such as weight gain, confusion and some forms of cognitive dysfunction [30].

Radiosurgery to treat neurobiological disease

Beyond the capacity of radiosurgery to treat brain tumors and arteriovenous malformations is illustrated in its promising effectiveness in the treatment of other neurological disorders. These include epilepsy, movement disorders and trigeminal neuralgia. There is significant potential to utilize stereotactic radiosurgery to treat pharmacologically resistant trigeminal neuralgia. In 1971, Leksell analysed the results from two patients who had undergone radiosurgery for trigeminal neuralgia in 1953 [31]. The patient initial was treated with a total dose of 16.5 Gy and had residual pain after 2 weeks. After 5 months this patient became pain free. After 18 years this patient experienced no trigeminal neuralgia. The second patient was treated with a total dose of 22 Gy and demonstrated marked improvement 1 day postradiosurgery. For the following 17 years of follow up, this patient experienced no pain due to trigeminal neuralgia [31]. Kondziolka et al. hypothesize that with the aid of stereotactic high-resolution magnetic resonance imaging to define the trigeminal nerve, we could relieve the pain and preserve facial sensation using radiosurgery [32]. In a multi institutional study conducted to evaluate the technique, dose- selection parameter and results of gamma knife stereotactic radiosurgery in the management of trigeminal neuralgia, 50 patients at 5 centers underwent radiosurgery performed with a single 4-mm isocenter targeted at the nerve root entry zone. 29 patients (58%) responded with pain free results, 18 (36%) obtained manageable results (50%-90% relief) and three (6%) experienced treatment failure. The median time to pain relief was 1 month and responses remained consistent for up to 3 years postradiosurgery [32]. At a 2 year follow up, 54% of patients were pain free, while an inclusive 88% had between 50% and 100% pain relief.

In 1973, Kelly et al. reported the results of 30 patients with various psychiatric impairments post stereotactic limbic leucotomy [33]. Prior to psychosurgical intervention psychological measurements were made. Anxiety was assessed by the Taylor Scale of Manifest Anxiety, the Hamilton Anxiety Scale and Somatic Anxiety scales of the Middlesex Hospital Questionnaire. Depression was assessed by...
the Beck and Hamilton Depression Scales. Obsessions were measured by the Leyton Obsessional Inventory. Neuroticism and extraversion were assessed by the Maudsley Personality Inventory. Intelligence had been assessed by the Wechsler Adult Intelligence Scale, which was administered by clinical psychologists [33].

The patients’ response before surgery as well as 6 weeks and 17 months after the procedure was documented [34]. 17 months post operation, patients were significantly less neurotic, as illustrated by the fall of 8.6 points on the Neuroticism Score. The mean values on the Beck and Hamilton depression scales were all significantly less 17 months after surgery. A great decease in anxiety was shown on the Taylor and Hamilton scales. Importantly, there was no decrease in intelligence post operatively as demonstrated by an increase in the mean full-scale verbal and performance scores on the Wechsler Adult Intelligence Scale 6 weeks post operatively [34].

Severity of illness and inclusion criteria

Only patients with severe, chronic, disabling and treatment refractory psychiatric illness are considered for surgical intervention. In terms of chronicity, patients are required to have been treatment refractive for at least 5 years before entertaining the thought of surgical intervention. The severity of the patient’s illness is also taken into account; patients must manifest both in terms of subjective distress and a decreased in psychosocial functioning ability. The illness must prove to be refractory to systematic trials of pharmacologic, psychological and even electroconvulsive therapy before considering psychosurgery [35]. The severity of the illness is measured using acceptable clinical research instruments corresponding to specific indicators which are known throughout the medical community, such as a Yale-Brown Obsessive Compulsive Scale (YBOCS) score of >20 for OCD or a Beck Depression Inventory (BDI) score >30. Disability may be reflected, for instance, by a Global Assessment of Function (GAF) score of <50. In order to determine that their psychiatric illness is refractory to treatment despite appropriate care, all patients must be referred for surgical intervention by their treating psychiatrist [35]. Adequate trials of electroconvulsive therapy or behavioral therapy when clinically appropriate must also be demonstrated [35]. An accurate diagnosis is paramount in the eligibility process for a neurosurgical procedure. The majority of the concerns regarding the historical efficacy of psychosurgery are that it does not specify a particular diagnosis that is reproducible today. We are unaware whether the patients whom initially underwent these interventional operations had schizophrenia, bipolar disorder, unipolar depression, anxiety of severe personality disorder.

Rationalizing anatomical targets

Neurosurgeons must know which neuroanatomical region within the brain to lesion or ablate when attempting to alleviate symptoms of a severe mood disorder. Mayberg et al. published functional neuroimaging studies which confirm a consistent involvement of the subgenual cingulate (Cg 25) in the modulation of negative mood states, such as depression [36]. This study further reported a decrease in Cg 25 activity in patients who respond positively to various antidepressant treatments such as SSRIs, ECT and ablative surgery. Further evidence for the labeling of Cg 25 as a culprit in the depression pathway is the fact that it is connected to the brainstem, hypothalamus and insula, which have all been implicated to be disturbed during a depressed episode. Additionally, studies link Cg 25 to orbitofrontal, medial prefrontal, and part of the anterior and posterior cingulate cortices, which are all involved in the regulation of homeostatic and autonomic functioning of learning, memory and mood—all core behaviors altered in a depressed state [36]. Long term electrical stimulation of basal ganglia structures, such as the globus pallidus internus and subthalamic nucleus, are achieved by an implantable electrode that is connected to a pulse generator within the chest of the patient. This technique, before being used on psychiatric patients, has been found to ameliorate bradykinesia, tremor, and muscle rigidity. The patients are kept awake throughout the procedure in order for them to describe any changes in the language or speech capabilities; the only drug administered is a local anesthetic. Mayberg et al. [36] tested the hypothesis that the use of deep brain stimulation can modulate its pathological metabolic activity in the known neural circuitry being altered in the brains of treatment-resistant depressed patients. The neurosurgeons used MR-imaging to place the DBS electrodes within the subgenual cingulate and used a frequency parameter of 10-130 Hz, and the voltage of the electrodes was changes every 30 seconds with a 1.0V increase. After 5 months of the DBS electrode therapy, 4/6 (66%) of the patients met the antidepressant response positive threshold. Mayberg et al. used PET imaging to characterize the activity in the brain networks involved in treatment-resistant depression. These results provided a quantitative measure of brain changes which are associated with DBS stimulation and their correlating positive psychological effects on depressed patients. In comparing PET images from 6 patients to control data of the same gender and age group, Mayberg et al. demonstrate that depressed patients show a unique pattern of elevated Cg25 blood flow at pretreatment baseline. Furthermore, a hyperactive Cg25 and hypoactive prefrontal cortex was seen in DBS responders and nonresponders.

Neuroimaging, Depression and Psychosurgery: Is It Feasible?

Neuroimaging in psychiatry and psychosurgery

The majority of patients suffering from major depression can be successfully treated with some combination of psychotherapy, pharmacotherapy, and even electroconvulsive therapy. A subset of patients with severe forms of depression fail to respond to conventional forms of therapy, and are thus considered for surgical intervention [37]. Nuclear medicine techniques can be used in the field of psychiatry, and psychosurgery, in a variety of ways. Of initially importance, the utilization of neuroimaging in the field of psychiatry has contributed a great deal to the formation of contemporary neurobiological models of major depression. Functional neuroimaging has produced replicable results which indicate a network of brain regions, such as the dorsal and ventral regions of the prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, striatum and thalamus, in the pathophysiology of major depression [37]. In addition to highlighting the underlying neuropathophysiology of depression, another clinical application of neuroimaging modalities is their ability to examine the efficacy of a certain treatment, whether pharmacological or surgical.

Biophysics of neuroimaging techniques and mr imaging guided stereotactic surgery

The intricate biophysics engineering these various neuroimaging modalities is responsible for the vast spectrum of both the advantages and disadvantages per technique, as well as each modality’s specific repertoire of capabilities. Magnetization transfer imaging (MTI) is a technique that increases the contrast between tissues by detecting the exchange of protons between water and macromolecules. A radio frequency pulse is applied which selectively saturates the protons bound to macromolecules. MTI is an advantageous clinical
technique as it provides information about tissue changes not detected with conventional T1- and T2-weighted MR images. A magnetization transfer ratio (MTR) represents a quantitative measure of the structural integrity of brain tissue. Any reductions in MTR are suggestive of neuropathology [38]. Diffusion-weighted imaging (DWI) measures the random motion of water molecules in brain tissue. The integrity of white matter tracts are clearly elucidated with diffusion tensor imaging. DWI measures a fundamentally different physiologic parameter than conventional MRI. Image contrast is related to differences in the diffusion of water molecules within brain tissue rather than a change in total tissue water. Consequently, DWI can reveal pathology where conventional MRI is negative [38]. Magnetic resonance spectroscopy (MRS) offers a unique non-invasive approach for assessing the metabolic status of the brain in vivo. In contrast to neuroimaging modalities which detect structural abnormalities in injured brain matter, MRS offers in vivo neurochemical information through its detection of magnetic signals from specific nuclei (1H or 31P) in response to a radiofrequency pulse. Positron emission tomography (PET) is an analytical imaging technology developed to use compounds labeled with position emission radioisotopes as molecular probes to image and measure biochemical processes in vivo. Positron emitters contain proton rich nuclei and attempt to stabilize themselves by gaining neutrons and ridding themselves of excess protons. A PET scanner detects annihilation photons in coincidence, which results in a PET image. This image is a map of the distribution of annihilation points within the object (brain tissue) being scanned. The resulting map shows the tissues in which the molecular tracer has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient’s diagnosis and treatment plan [38]. FDG-PET is used to illustrate the efficacy of a psychosurgical intervention, while MR imaging is used in the application of stereotactic neurological intervention, such as stereotactic anterior cingulotomy [39]. After a pair of burr holes ismade bilaterally in the patients skull, electrical insulated thermistor electrodes are positioned stereotactically into the anterior cingulate gyrus with the aid of MR imaging guidance [38], lesions are then created by heating the uninsulated tip of the electrode by using radiofrequency current. Dr. Cogrove has published that optimal created by heating the uninsulated tip of the electrode by using gyrus with the aid of MR imaging guidance [39], lesions are then electrodes are positioned stereotactically into the anterior cingulate made bilaterally in the patients skull, electrical insulated thermistor cortex with the aid of MR imaging guidance [39]. After a pair of burr holes ismade bilaterally in the patients skull, electrical insulated thermistor electrodes are positioned stereotactically into the anterior cingulate gyrus with the aid of MR imaging guidance [38], lesions are then created by heating the uninsulated tip of the electrode by using radiofrequency current. Dr. Cogrove has published that optimal lesions. Courtesy of G. Rees Cosgrove, M.D.

Using FDG-PET in psychosurgery: OCD and major depressive disorder

One of the most difficult challenges facing the future of PET imaging in psychiatric disorders is the controversy revolving around obtaining a baseline metabolic rate in these patients. Mayberg et al. illustrated precise altered metabolic rates in depressed patients using FDG-PET prior to treatment. In this study, pretreatment FDG-PET data was obtained in depressed patients, and investigators were able to find a baseline hypermetabolism in the rostral anterior cingulate cortex in the group of patients which responded to antidepressant treatment. Since 1997 several studies from Pizzagali et al., have all demonstrated a reliable hypothesis [40]: baseline hyperactivity in the anterior cingulate cortex and medial prefrontal cortex correlate with a positive response to an array of psychiatric interventions in major depressive disorder and OCD [13].

Conclusion: Future Tense

This comprehensive review has outlined the involvement of several fields in medicine in the treatment of psychiatric illnesses. Neurosurgeons, psychiatrists, biomedical engineers, and pharmaceutical companies are only a few departments which need to be heavily funded in order to provide care for the mentally-ill community. Neurosurgical treatment for psychiatric disorders has a long and controversial history. From the Stone Age use of trephining to release the demons of the spirit to the millimeter accuracy of stereotactic instruments currently used in the operating room, psychosurgery has had great support and intense scrutiny. Today, psychosurgery is mastered in a minimally invasive and highly selective manner that is performed only for a few patients with severe and treatment-refractory psychiatric disorders. Despite remarkable advances in pharmacotherapy, the side effects of many drugs can be debilitating, and a substantial number of patients treated with drugs and behavioral therapy either do not improve or relapse. It is unfortunate that the prognoses of treatment resistant affective disorders are quite poor, leaving patients and their families left with relatively no options and extreme emotional burden. Advances within the scientific community, such as functional neuroimaging, as well as economic pressure to decrease the costs of caring for ill patients, may provide an opportunity for psychosurgery to become a more attractive option for the treatment of psychiatric diseases in the future [41]. The modern procedures described herein are rather safe, with an extremely low surgical mortality rate. Further, it is clear from retrospective neuropsychological assessments that patients initially exhibiting refractory conditions showed gradual, if not significant, improvement via psychosurgical intervention. In order to develop a stronger future for neurosurgical intervention in the treatment of psychiatric disease, research must undergo an attempt to further delineate anatomic substrates for emotional states. The application of modern functional imaging techniques is surely assisting in this avenue. Although the innovations of Paper were significant, they are insufficient if we are to treat patients on a common basis with surgical intervention. The scientific community must develop concise data as to the anatomical regions in the brain which are specifically responsible for emotional and cognitive states of mind. It is also important that the biomedical community begins to innovate our interventional approaches to attacking and healing the brain via surgical instrumentation. Theoretically, we can begin to hypothesize that psychosurgery need not be limited to destroying dysfunctional brain tissue. It is conceivable that in the future we may begin to incorporate the advances taking place in neuroengineering in order
to not only decrease activity within a defected area of the brain, but to also increase activity. Drug secreting capsules, neuromodulator pumps, and the implantation of genetically engineered vectors for gene delivery may all be methods we begin to implement in the foreseeable future. Overall, our approach to treating patients with refractory neuropsychiatric disease needs improvement which will come with innovative experimentation on the human brain in the next generation.

References