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ORIGINAL PAPER

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Psychosurgery and deep brain stimulation as *ultima ratio* treatment for refractory depression

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Abstract For decades, the most severe, protracted and therapy-resistant forms of major depression have compelled clinicians and researchers to look for last resort treatment. Early psychosurgical procedures were hazardous and often associated with severe and persistent side effects including avolition, apathy and change of personality. With the introduction of psychopharmacological treatments in the 1950s, the frequency of ablative procedures declined rapidly. The past decade, however, has witnessed the resurgence of surgical strategies as a result of refined techniques and advances such as high frequency stimulation of deep brain nuclei. Recent data suggest that the overall effect of high frequency stimulation lies in the functional inhibition of neural activity in the region stimulated. Contrary to other psychosurgical procedures, high frequency stimulation reversibly modulates targeted brain areas and allows a postsurgical adaption of the stimulation parameters according to clinical outcome. With increased understanding of the brain regions and functional circuits involved in the pathogenesis of psychiatric disorders, major depression has emerged as a target for new psychosurgical approaches to selectively and precisely modulate neural areas involved in the disease process. Recent studies of minimally intervening procedures report good clinical outcome in the treatment of therapy-resistant forms of major depression. High frequency stimulation was successfully applied in several small samples of patients with treatment-resistant depression when the stimulation focused on different areas, e.g., nucleus accumbens, the lateral habenula or cortical areas. Nevertheless, the reticence toward psychosurgery, even for those patients suffering from the most debilitating forms of depression, still prevails, even though recent studies have shown significant improvement in terms of quality of life with the limitation that the number of treated cases has been small. In any event, valid and unambiguous criteria for patient eligibility have yet to be refined and standardized. In this review, we suggest possible standard criteria for the application of deep brain stimulation on patients suffering from otherwise treatment-resistant depression.

Key words depression · psychosurgery · deep brain stimulation · DBS

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Depression and neural circuits

Chronic depression is one of the most debilitating psychiatric disorders ranking number one among the causes of disability worldwide as measured by years lived with disability (YLD) (WHO [55]). Although pharmacological treatment of depression has advanced substantially in recent years there are still patients resistant to pharmacotherapy. In order to find sufficient means of treatment for those patients, as well, there have constantly been attempts to improve the non-pharmacological methods of psychiatric treatment. Somatic, non-pharmacological biological treatment methods for therapy-resistant depression

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comprise electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), psychosurgery, and, prospectively, deep brain stimulation (DBS). All these methods are based on the theory that damaged brain circuits thought to be causally implicated in the pathophysiology of endogenous or major depression can be selectively targeted [26]. For example, the activity of brain regions such as the prefrontal cortex and the limbic system which are interconnected by regulatory circuits or feedback loops, is modulated by the methods mentioned above in order to improve their intercommunication.

However, ECT, TMS and VNS can only indirectly access areas implicated in depression, in particular subcortical areas, by exerting non-specific effects at the neural level [33]. In the treatment of depression, ECT applied to the non-dominant hemisphere produces global changes of transmitter concentrations, among which elevation of dopamine, GABA, norepinephrine and serotonin are believed to generate the therapeutic effect in depression. Treatment of depression using high-frequency repetitive TMS of the left dorsolateral prefrontal cortex has the advantage of focused application with little side effects. Repetitive TMS has some secondary distant effects on deeper structures and the contralateral hemisphere, but has proven less effective in treatment-resistant depression compared to ECT [14, 20]. VNS has the disadvantage of permitting only nonspecific and relatively unselective modification of the activity of brain structures. The signals caused by stimulation of the cervical vagus nerve are redirected in the medulla oblongata. They then reach and influence the serotonergic raphe nuclei and locus coeruleus which is the main origin of norepinephrine pathways in the human brain. As serotonin and norepinephrine are involved in the pathogenesis of depression, the improvement of depressive patients with VNS is more comprehensible. Despite these effects of VNS, blood flow in different parts of the brain, e.g., orbitofrontal cortex, anterior cingulate cortex, right superior and medial frontal cortex, is affected, as well [11].

In contrast to the indirect access to relevant structures supplied by these methods, recently refined psychosurgical procedures and DBS offer the important advantage of targeting subcortical regions and projection routes with high precision and selectivity. Brain activity—usually via inhibitory control—can be modulated either irreversibly by placing lesions or reversibly with the ON/OFF function of the DBS electrode, providing the possibility of postoperative adjustment of stimulation parameters.

This neuroanatomic accuracy is of high therapeutic relevance. For decades, concepts of the pathophysiology of depression were dominated by a neurochemical model assuming ubiquitous rather than specific changes in neuroanatomic locations. Only in recent years distinct brain circuits have been identified in the pathogenesis of depression.

The central structures in these circuits comprise the prefrontal cortex, the anterior cingulate cortex, the hippocampus, amygdala, ventral striatum (nucleus accumbens), globus pallidus, hypothalamus and thalamus [15, 40, 45]. A distinction is usually made in the circuits of the prefrontal cortex between three subdivisions in which neurons project from the thalamic to the dorsolateral prefrontal cortex, the orbitofrontal cortex and the medial prefrontal cortex and back along fiber tracts to the ventral and dorsal striatum and globus pallidus/subthalamic nucleus (STN)/substantia nigra (SNr), hippocampus and amygdala [24, 48]. It is not clear which specific brain region in these circuits is affected in depression. Nor is it entirely understood how the excitatory and/or inhibitory activity in these circuits is mediated, how the circuits are functionally impaired in depression and which neuron populations are primarily responsible.

Psychosurgical interventions into these circuits improving clinical symptoms in depression and behavioral changes in corresponding animal models suggest therapeutic effectiveness of surgical means on the one hand. On the other hand, such methods have led to a deeper knowledge of the pathomechanisms of depression. Here we review the literature on psychosurgical techniques in severe depression using "psychosurgery", "cingulotomy", "prefrontal leucotomy" and "DBS" as key words in a Medline-based research.

Past and present aspects of psychosurgery

In the 1930s through 1950s, before psychoactive medication became available, psychosurgical procedures were carried out in patients suffering from the most extreme forms of psychiatric disorders. In 1935, the psychiatrist Egas Moniz and the neurosurgeon Almeida Lima initiated psychosurgery in psychiatric patients. Their methods were further developed by Walter Freeman and James Watts in the USA. About 40,000 patients in the USA and 12,000 in Britain underwent so-called "prefrontal leucotomy". Two-thirds of these patients suffered from schizophrenia and approximately 20% from affective disorders [35]. The results of this cutting of connections to and from the prefrontal cortex were irreversible and sometimes disastrous. A frontal lobe syndrome leading to severe personality changes is known as the "postlobotomy syndrome". Operating with the "free hand" method caused unnecessarily large lesions. The extreme invasiveness of these operations and their political and stigmatizing dimensions, as well as increasing success of psychopharmacological treatment of psychiatric disorders, led to an almost complete abandonment of psychosurgery. Due to this negative attribution, nowadays there is a tendency to avoid the historical term "psychosurgery". The more elaborate modern methods can be referred to as psychiatric neurosurgery or by the names of the exact procedure which is performed, e.g., cingulotomy, limbic leucotomy or subcaudate tractotomy. Here, for reasons of conciseness we keep the original term to subsume the divergent surgical methods.

In recent years psychosurgery has undergone a renaissance for two reasons: firstly, despite improved psychopharmacological treatment of psychiatric disorders, psychiatrists are still confronted with patients burdened with the most debilitating forms of depression or obsessive–compulsive disorder, the main fields of application for psychosurgery today [3, 39, 44]. Secondly, advances in neurosurgical techniques, in particular the development of stereotactic operation, have dramatically improved accuracy. Tiny lesions can be placed with utmost precision and minimal side effects in individual brain regions, their substructures or fiber tracts of the projection pathways [36]. About 35–70% of patients resistant to conventional treatment improve if stereotactic neurosurgery is used [28, 44].

Worldwide, the most common applications of lesion surgery being carried out are cingulotomy, limbic leucotomy, anterior capsulotomy and subcaudate tractotomy. All of these procedures concentrate on modulating the structures and/or projection paths of the limbic system [35, 38]. The occasional posteromedial hypothalamotomy is also performed [44]. The cingulotomy involves a bilateral lesion of the cingulum by means of thermocoagulation. The lesions are about 1 cm wide and extend dorsally 2 cm into the callosum. They are administered to interrupt the thalamo-fronto-cortical pathways and thus relieve anxiety [13]. The limbic leucotomy combines the cingulotomy with the subcaudate tractotomy (see below). Both, limbic leucotomy and cingulotomy have been used in depression. The anterior capsulotomy introduced by Lars Leksell entails the selective lesion of the anterior part of the internal capsule and yields maximum effects in patients with severe anxiety and obsessive–compulsive disorder by interrupting fibers between the thalamus and the orbitofrontal cortex. The stereotactic subcaudate tractotomy originated from operations separating the fiber connections in the orbitofrontal white matter and ablating the rostral portions of the cingulate gyrus in order to isolate segments of the ventro-medial prefrontal cortex from deeper structures. Geoffrey Knight extended these methods in London in the late 1960s, achieving maximum effects by severing the fiber connections just frontally to the caudate nucleus. Lesions were initially placed by means of beta radiation, to be replaced by radio-frequent electrocoagulation from 1995 on [35]. The subcaudal tractotomy comprises a lesion of the white substance measuring $2 \times 2 \times 0.5$ cm anterior to the head of the caudate nucleus. It destroys fiber strands between the prefrontal cortex and the limbic system (connections between the prefrontal cortex and the hippocampus, amygdala, thalamus and hypothalamus) and leads to a secondary degeneration of the dorsomedial thalamic nucleus.

The method of subcaudal tractotomy initially showed a very high success rate, with a clinically significant improvement of 56–68% in previously therapy-resistant patients [27, 50]. Due to progressive optimization of pharmacotherapeutic treatment strategies, the number of absolutely therapy-resistant patients has decreased, so methods like subcaudal tractotomy were only employed in most severe cases of depression. That seems to be the reason why the success rate of subcaudal tractotomy declined to 34% in later years. Nonetheless, this figure still represents a definite symptom reduction in 63 out of 183 severely afflicted depressive patients [31].

The therapeutic success of psychosurgical procedures is not immediately evident, and usually cannot be evaluated until 1 year after surgery. Seizures are the most common side effects, occurring in 1–2% of patients. The study group of Marino and coworkers [38] reported optimizing success rates of subcaudate tractotomy by combining it with anterior cingulotomy (a method for which the name "limbic leucotomy" (see above) has been suggested). They operated 19 seriously depressive patients using this method and achieved good clinical improvement in 87.5% of the patients. Kim et al. [34] performed the operation on seven depressive patients, five of whom showed very good improvement after a postoperative observation period of up to 4 years.

Little is known about the actually effective mechanisms of psychosurgery. It has been argued that ablating fibrous connections interrupts dysfunctional circuits, particularly with regard to the prefrontal cortex and anterior cingulate gyrus [35], producing alterations at the neurochemical level by reducing the availability of neurotransmitters or neurotrophic factors [38]. Changes of the overall cerebral metabolism might contribute to efficiency of psychosurgery [1]. Moreover, a relationship between postlobectomy degeneration of thalamus and putamen and affective disorders is discussed [43].

Advances made by psychosurgery have certainly been significant. Indications for surgery are more restricted and patient screening is more thorough. Stereotactic methods promote more selectivity, accurate targeting and minimal lesions with fewer side effects. Specific operative procedures are available for each psychiatric disorder. Thus, psychosurgery seems to be justifiable as an *ultima ratio* treatment for patients with the most severe pharmacotherapy-resistant forms of depression. Particularly regarding the fact that these patients are threatened by an extremely high rate of suicide the further acknowledgement of psychosurgery should become more and more important.

It should be emphasized, however, that more extensive and better-controlled studies with longer observation periods are necessary to evaluate the effectiveness of these invasive and irreversible procedures properly [9, 36, 39]. Standard criteria for patient screening and patient safety, as well as for effectiveness and for postoperative management have to be developed [28]. Only in this way a sound judgment of therapeutic success can be ensured.

Acute and long-term side effects of these new psychosurgical methods will also have to be taken into consideration when calculating the advantages and disadvantages of psychosurgery. So far, corresponding studies show fairly inconsistent results. While some groups did not report any long-term side effects of DBS concerning drive and energy level, positive or negative change of personality after neurosurgery was observed by a minority of patients suffering from obsessive–compulsive disorder [46]. DBS of patients with Parkinson's disease could cause cognitive problems, apathy, depression as well as mania, but also personality changes and psychotic symptoms [18, 30, 51].

Exact patient profiles (symptoms, personality, comorbidity, functional losses) could advance efforts to identify predictors for response to psychosurgical intervention. The left thalamus and the left subgenual prefrontal cortex are relevant in the pathophysiology of depression [19]. Depressive patients, who showed a high glucose turnover in FDG-PET in these regions responded in a particularly positive manner to anterior cingulotomy marked by significant improvements in the BDI scores about 12 months after the operation was performed [16]. This relationship will be an important area for future psychosurgical research.

New perspective for depression: deep brain stimulation

Electric currents have been used in psychiatry ever since the mid nineteenth century [8, 32], and DBS has recently been developed as a new tool to access lower brain centers. While the newer psychosurgical procedures have become more selective and focused thanks to increasingly refined technology, they are still fraught with irreversible lesions measuring an average of 2 cm in diameter. Thus, DBS constitutes a significant step forward because it allows an even more focused intervention into neural circuits. With the use of thin electrodes (1.7 mm in diameter) the smallest brain areas and fiber tracts can be targeted with high accuracy, such that the subsequent rate of side effects is presumably much lower. The intervention can be reversed by turning off the electrodes and modulated postoperatively according to a patient's clinical symptoms. DBS certainly is the most promising new technique in psychosurgery. Using DBS controlled studies with higher case numbers might be conducted while individual control could be granted with the help of electrode ON/OFF and sham operations [3, 28, 44].

DBS was first used in neurology, where it has been applied in patients with movement disorders including Parkinson's disease, tremor and dystonia. Stimulation electrodes are placed in the STN and pallidum. A three-dimensional stereotactic ring system is secured to the head. This method enables the surgeons to access deep brain areas with millimeter precision without opening larger parts of the calvaria in each patient. The stereotactic head frame is applied under local anesthesia. A test electrode is inserted painlessly through a burr hole in the coronal region into the targeted structure using image guidance techniques while the patient is awake. The desired effect can be monitored by switching on and off the electrode such that side effects can be minimized. Final electrode placement is then carried out, and in a second operation in general anesthesia the electrode is connected to an impulse generator which is usually situated subcutaneously below the collar bone. The electrode emits electrical impulses to the targeted brain area. The delicate stimulation electrodes have several contacts at different levels, so that the stimulated location and the stimulation intensity can be adjusted postoperatively. Stimulation is kept constant at a frequency over 100 Hz, which in the case of movement disorders significantly reduces the clinical symptoms in many patients who were previously treatment-refractory [5]. Nevertheless, DBS is an invasive procedure which might have side effects and complications. When the electrodes are implanted, intracerebral bleeding or infections can be caused. There are other reversible side effects like paresthesia, dyskinesia or amentia which can be arrested by adapting the stimulus intensity [21]. Furthermore, depression, anxiety, hypomania, euphoria and hypersexuality have occurred when DBS was applied [10]. Finally, possible irreversible lesions of white matter fiber tracts should not be ruled out.

Electric stimulation functionally intervenes with neuronal circuits by modulating electrophysiological and neurochemical processes in the targeted core areas undergoing stimulation. To date, varied effects of stimulation depending on the area being stimulated and the stimulation frequency have been observed. Stimulation at high frequency (50–333 Hz) has led to inhibition in globus pallidus internus (Gpi) and SNr. In STN, an inhibition followed by a rebound excitation could be found, whereas an excitation preceded the inhibition if the thalamus was observed. Low frequency stimulation induced inhibition in Gpi and SNr, but a short excitation in the thalamus [17]. Functional inhibition is attributed to a hyperpolarization of the neurons surrounding the electrode while the fundamental processes vary depending on the area stimulated. Neurochemical tests in animal models and patients have also shown that DBS causes a marked increase in dopaminergic neurotransmission [22, 42, 56].

In terms of neuropsychiatric disorders, DBS has been applied so far only in isolated cases of obsessive disorders, Tourette syndrome and in refractory major depression [25, 37, 41, 54] suggesting that electric stimulation is therapeutically beneficial in therapy resistant depression. Correa et al. [12] and Heath et al. [29] performed stimulation of the cerebellum in patients with severe depression in relation to earlier animal studies, while Andy and Jurko [4] stimulated the thalamus for reactive depression. First reports about distinct mood changes and depression and on the other hand about improvements in depression and anxiety in stimulated Parkinson patients suggest that DBS can be used to treat affective disorders. While a number of studies found a clinical increase of depression and deteriorating mood after DBS of the STN [6, 7, 52], DBS led to a decrease of depression and anxiety in other cases [49, 53]. Thus, the relationship of DBS and the STN and emotional behavior, appears to be more complex than imagined. Patients suffering from Parkinson's disease reported successfully induced, i.e., happier, mood more often, if they were undergoing DBS of the STN [47]. Recent research suggests, however, that STN-DBS initially leads to an improvement of Parkinson-associated depression, while over a longer period of time significant changes of mood or neuropsychological functions could not be observed [22, 23]. Nevertheless, it could be necessary not just to examine the influence of DBS on certain brain areas and the correlation to changing of clinical symptoms, but also to consider interaction and neural circuits between several cerebral areas.

These empirical findings fit in with the fact that both the STN and the pallidum are involved in depression-relevant brain circuits (see above). Anatomical studies show that the medial STN has connections both with the limbic pallidum and striatum and with the prefrontal cortex and the cingulate gyrus. In total, five limbic circuit connections are known to involve the STN [2]. The STN must consequently be involved in regulating not only motor and oculo-motor developments but also cognitive and affective aspects. However, it still is debatable as to whether stimulation of the STN or the globus pallidus can achieve a sufficient antidepressive effect in therapy-resistant depressive patients, particularly given the fact that major depression and Parkinson-associated depression do not have the same etio-pathogenesis. Although the STN has a limbic subarea, the function of which not fully understood, the majority of its neurons are integrated in motor circuits. The STN or the globus pallidus would therefore not be main stimulation points in refractory major depression [3]. Recently, Mayberg et al. [41] revealed promising results in alleviating the severity of depression in six patients with therapy resistant depression by stimulating the subgenual cingulate (Cg25). They correlated their clinical findings to changes in the activity in depression-relevant brain regions [40]. Our basic knowledge of the neuroanatomy of depression is still too inadequate to answer the question of which other brain regions—for example the medial prefrontal cortex or the hippocampus—could be influenced by stimulation, and what functional parameters—inhibitory or excitatory—are more promising. Furthermore, a myriad technical and neurosurgical problems of DBS implantation in yet unprobed brain regions will appear.

Perspectives

Psychosurgical procedures may play an important, though limited role in basic and therapy research of depression for several reasons. At first, ethical aspects have to be considered. As described above, the history of psychosurgery is quite a dark one and thus, despite the mostly noble intentions, psychosurgery causes negative attributions until today. Psychiatric diagnostics and treatment decisions are far more dependent on the interviewer and personal experience than, e.g., neurological diagnostics which could lead to psychosurgery, as well. Because of the debilitating side effects psychosurgery might exhibit, we suggest that psychosurgery should only be performed after careful examination and calculation of risks by at least two independent psychiatrists and after minute patient information and written consent.

The second reason is the turn to a differential conception of the brain and its constituent parts, in which the cause of depression is being sought in brain circuits and disorders in their patterns of activity. The third reason is the discovery of DBS as a method of selectively modulating these circuits. If the effectivity of DBS in the treatment of depression could finally be proven after future studies, DBS might present an important option and a new dimension of treatment and probably even an ultimate therapy alternative for many patients with chronic and severe depression. Intensive efforts to further advance DBS methods ("demand-controlled DBS") and to find the optimal locations for its application in depression, impulsive and anxiety disorders (e.g., in the nucleus accumbens) are the main focus of current psychiatric research [12]. Much effort is needed to develop a standardized catalogue of criteria for determining which psychiatric patients would benefit from DBS, taking into account the justified political and psychiatry-critical dimensions of psycho-neurosurgical interventions. We suggest as potential criteria treatment resistance of at least three state-of-the-art pharmacological antidepressive treatments, perhaps in combination with psychotherapy, ECT and rTMS before psychosurgery may be discussed as an option. Psychosurgical procedures, including DBS, must be embedded in a treatment plan including pharmacological, psychological, sociotherapeutic and rehabilitative procedures [13]. Only then a patient can accept surgical intervention and only in this framework an improved condition, if not recovery, for these often debilitated and long-suffering patients will be achieved.

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