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Depression and neurosurgery: past, present, and future

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Abstract

Neurosurgery has been used to treat depression since 1935, when open surgery was first used to isolate relatively large areas of the limbic system from the rest of the brain. Soon thereafter, more selective leucotomies were performed based on a growing knowledge of the role played by brain limbic circuitry in processing the emotions. Subsequent discovery of the effectiveness in depression of both electroconvulsive therapy and various pharmacotherapies raised serious doubts about "psychosurgical" treatments, but the introduction of stereotactic techniques revived interest in the selective-lesion, neurobiology-based approach. However, neurosurgery has only come to be regarded as an appropriate treatment of severe depression since Benabid introduced the frequency-dependent chronic electric stimulation technique. Because of its nondestructive nature, this procedure will undoubtedly be favored in the future. One can anticipate that, eventually, frequency-dependent chronic electric stimulation will be complemented by newer techniques such as microdialysis and reverse dialysis, with concomitant functional magnetic resonance imaging and/or positron emission tomography scanning, and the use of chemodes for microinfusion or for in situ insertion of reactivated-stem cells. To optimize success, these modern methods will require a new taxonomy of "depressions" based on up-to-date neurobiological criteria.

1. The beginning

Flirtation of neurosurgery with the array of pathologies known as "depressions" began while both fields were still in their adolescence. Neurosurgeons, encouraged by their conquest of space-occupying lesions, were emboldened to open that "black box"—the brain—and seek the anatomic sites of origin of various attributes of mind, mood, or behavior—normal and abnormal. "Psychosurgery" and "functional neurosurgery" were thus born. Neurosurgery of psychiatric diseases has known successes and failures, fervent praise, and vehement criticism. While helping many patients, neurosurgery has also created much damage at the hands of unscrupulous practitioners.

As for the illness to be treated, "depression," it covered, and still covers, a large domain in psychiatry, not only because of depression's multiple manifestations, but also because of its many degrees of intensity, ranging from the simplest form—often experienced in everyday life—to states of suicidal despair. Because "depression" is also a frequent and often severe illness, therapists have employed a wide array of approaches to address its various manifestations. These approaches have extended from psychoanalysis and other psychotherapeutic techniques to various physical stimuli (light/dark, magnetic, electrical), to the various pharmacotherapies that prevail today. Naturally, such an eminently brain-related disturbance, particularly when it was so resistant to therapy, did not escape the attention of the pioneers of neurosurgery.

Whatever the historical adventures of psychosurgery, today, with enhanced knowledge in the field of neurobiology, stereotaxy, and the introduction of new technologies and strict rules regarding their application, neurosurgery promises to open new horizons in the struggle against various psychiatric illnesses, particularly depression. Moreover, I believe modern neurosurgery will be high on the agenda of future practitioners and will generate new insights and discoveries relevant to the broader areas of behavior, mood, affect, and human thought itself.

2. The era of lesions

2.1. From post-Moniz lobotomies to more circumscribed lesions, and from open to stereotactic surgery

In the early 1930s, the science and practice of neurosurgery were spreading throughout the world, and, as a

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consequence, management of an increasing number of brain pathologies was made possible. In parallel, it was observed that surgical manipulations were capable of altering behavior and thinking in an area-dependent way. During that same period, knowledge of neurophysiology was also rapidly expanding and a variety of brain functions were found to be localized within large circuits (not just in "centers"), the pathways and projections of which were identified with increasing precision. Thus, it became foreseeable that interruption of such pathways could modify the underlying functions themselves when they were abnormal. Hence the idea of using leucotomy in human pathology.

Late in 1935, the Portuguese neurologist Egas Moniz introduced the prefrontal leucotomy [1]. The operation (later called *lobotomy*) and its descendants (which minimized the area of cortical exclusion) involved making incisions along the junction between white and gray matter (*prefrontal* leucotomy or "standard prefrontal lobotomy," and *trans-orbital* leucotomy) that destroyed connections between the prefrontal region(s) and its connections with the limbic system. The open operation made use of a superior approach to each frontal lobe and, by means of a specially lit speculum, attempted to interrupt the white fibers under direct vision. (For the record, it should be noted that open neurosurgery for the management of dramatic psychiatric illnesses had been attempted before Moniz; see review by Diering and Bell [2].)

Starting in the 1950s, the most damaging techniques were abandoned in favor of much more circumscribed surgical procedures, although they were still destructive. At first, operations were performed on a majority of patients with affective disorders (ie, various types of depression, such as involutional depression, agitated depression, etc). Note that, at that time, pharmacotherapy had little to offer and effective treatments of any kind were unavailable. Leucotomies managed, at least, to make life more endurable for many of the patients and those around them. Yet, personality changes brought about by the early destructive techniques were frequent and often very negative, with the appearance of a significant "frontal lobe" syndrome (characterized by permanent apathy or euphoria, inconsistent and/or puerile behavior, boorishness, impaired judgment, and chaotic behavior). In addition to effects directly related to the mutilation of cerebral tissue, potentially harmful side effects occurred such as epileptic seizures or aggressiveness, making patients more difficult to manage. At the same time, other therapists introduced alternative techniques such as seizure therapy (by intravenous injection of cardiazol) and, in 1938, electroconvulsive therapy—which is still in use.

2.1.1. Circumscribed leucotomies: introduction of stereotactic neurosurgery

In the 1950s, because of strong feelings against psychosurgery that emerged in the developed countries, and the discovery, first of chlorpromazine and, subsequently, other neuroleptics and several antidepressants, the use of neurosurgery to treat serious mental illnesses declined, although it never entirely disappeared, being reserved for certain cases that were refractory to all other kinds of treatment.

Because of the critical need to produce exquisitely circumscribed therapeutic brain lesions, psychosurgery adopted the newly invented Horsley and Clark stereotactic approach, first employed to access, with enhanced reliability, deep brain structures in laboratory animals. The stereotactic approach permitted neurosurgeons to reach deep structures of the human brain for either electric- or freezing-based lesioning.

The latter procedure had the advantage—in a first attempt—of allowing the surgeon to abolish the function of the targeted area by cooling it to a point slightly above freezing. In a second attempt, with the target area now properly identified, it could be frozen and irreversibly damaged. Also, thanks to advances in neurophysiological technology, present-day neurosurgeons use microelectrodes to record neuronal activity to identify the brain structures encountered in the way to the targeted area before destroying it by means of electrocoagulation.

The more recent γ-knife technique for lesioning deep structures offers some advantages such as the avoidance of infection and the possibility to repeat the procedure in case of failure. The downside is that the only landmark for positioning the target is now morphological.

Initially, circumscribed brain lesions were mainly aimed at interrupting the "reverberating circuit" (first described by Papez) at various nodes of its circular chain. The discovery of this physioanatomical network exerted a powerful influence on neurosurgery in the 1930s, 1940s and 1950s, at a time when the "psychencephalon" (which became the "limbic system") was already considered to be the structure where the emotions, normal or abnormal, are processed. The idea was "since we can not repair the defective circuit, let's interrupt it". How? "By damaging it." Where? Depending on the year, the school, the country, or merely the neurophysiological convictions of the leader of the intervention team, various targets have been and still are chosen. The clinical type of depression and its comorbidities were, of course, taken into account, but the correspondence between this clinical variety and the proper anatomical target was decided by criteria that do not stand up under critical examination. Some 17 brain locations that were regarded as targets for the treatment of depression or other disorders with a depressive component can be readily identified. Several excellent reviews on this subject are available [2-4].

3. Present and future

3.1. End of the destructive techniques. New approaches and future developments from Benabid on

3.1.1. Electric excitatory or inhibitory neurostimulation or auto-neurostimulation

The main drawback of the "conventional" neurosurgical treatment of depression has been and still is its irreversible

character—which raises more ethical issues than does any other treatment. The neurosurgical approach to functional and psychiatric abnormalities becomes increasingly problematic as new pharmacotherapies continue to be developed. Whatever the disadvantages of the latter may be, drug treatment—in contrast to the placement of brain lesions—can always be discontinued. The issue of reversibility or nonreversibility of neurosurgical treatments has been addressed today by the method introduced by Benabid [5] in Grenoble. This technique was originally introduced as a neurosurgical treatment for Parkinson disease. It consists of implanting bilateral or unilateral probes equipped with 4 linear but independent electrodes 2 mm apart. Each electrode can be used to transmit a low- or high-frequency bipolar electric current. In this way, the neurosurgeon can choose the electrode most appropriate for the treatment. The merit of Benabid's [5] approach was his observation that frequencies close to double those used for brain stimulation (110 to 130 Hz instead of 50 or 60 Hz) have an inhibitory rather than an excitatory effect.

Many acute or chronic stimulations had been used in the past, either as a test of brain localization or as a treatment of pathologies such as epilepsy. But nobody had previously observed the inhibitory properties on neuronal function of relatively higher frequencies. Consequently, nobody had previously observed the considerable advantages inherent in the practice of this novel, permanent, stimulation-based form of functional neurosurgery. The currently applied procedure consists of high-frequency cerebral stimulation via the "best" of the 4 electrodes chosen during the intervention and subsequently connected to an indwelling stimulator. If for some reason such indwelling electrodes have to be removed, the procedure is simple and no scar tissue is left behind. Thus, the "functional neurosurgeon" avoids the destruction of a more-or-less large volume of cerebral tissue. As a result, neurostimulation (guided by modern techniques of functional brain imaging), used initially in the treatment of Parkinson disease, has created a novel therapeutic modality—one that provides an entirely new approach to the treatment of hitherto incurable and therapy-resistant psychiatric diseases.

3.1.2. A circuit that conveys depressive and (perhaps) euphoric feelings. Opening a therapeutic opportunity?

In 1999, a perspicacious medical observation by a group working in the Salpêtrière hospital in Paris with the neurosurgeon P Cornu and the neurologist Y Agid [6] may, if properly exploited, lead to a new use of neurostimulation-bound treatment for certain kinds of depression. The case in point is that of a patient who received an implant of chronic electrodes for Parkinson disease, aimed at the classic subthalamic area. This patient, a 65-year-old woman, showed a transient acute depression when unilateral, left, high-frequency stimulation was delivered to the substantia nigra, 2 mm below the site where a similar stimulation had alleviated the signs of her extrapyramidal syndrome. The investigators were able to make a detailed study of the picture induced by stimulation—it was a typical, major, and reversible depression. The expression of this temporary depression fulfilled most of the classic criteria for a "depressive syndrome." This depressive picture was reproducible when a subsequent session of stimulation took place. It appeared within 5 seconds and disappeared within 60 to 90 seconds. Neuroimaging showed the location of the effective electrode to be "in the central substantia nigra, including part of the pars compacta and pars reticulata." In a subsequent positron emission tomography study, performed at the time of the same depression-producing stimulation, an increase in blood flow was found "in the right parietal lobe, in the left orbitofrontal cortex and globus pallidus, and also in the left amygdala and anterior thalamus."

It would have been extremely interesting if this patient had received low- instead of high-frequency stimuli. Conceivably, the low-frequency stimulation could have induced the reverse phenomenon (ie, euphoria). The existing data and Benabid's principle [5] (the effect produced by low-frequency impulses, inducing excitation, can be reversed by high-frequency impulses, inducing inhibition) suggest that a reverse stimulation could have had an "antidepressive" effect in the patient described above. It is also based on the observation, in this patient, of a euphoria-like state that occurred after the end of the depression-inducing stimulation. In effect, this sequence of manifestations has the characteristics of a true rebound effect, which generally reverses the action of a stimulation.

3.1.3. "Volume transmission" and its use in future treatments?

Another observation of the Salpêtrière group is important. Contrary to the action of high-frequency stimulations on motor, extrapyramidal manifestations, their effect on the onset of depression took approximately 5 seconds, whereas the period needed for this response to terminate was more than 60 seconds the first time, and almost 90 seconds the second time, after the stimulation ceased. Contrary to the well-documented explanations in the article, one can hypothesize that, unlike the immediate action upon the motor syndrome, the effect on mood involved a mechanism other than the postulated classic "action-potential followed by synaptic neurotransmision" mechanism. A humoral spreading mechanism of onset, compatible with a 5-second latency (longer than the time of release of a mediator) and an even longer latency (90 seconds) for the disappearance of the depression, seems to have taken place. Such a delay may be due to the deactivation or to the clearance of some signalling factor. Thus, it can be hypothesized that the phenomenon was attributable to a purely humoral (and particularly a "volume transmission" mechanism) rather than a polysynaptic mechanism.

The mechanism of action that underlies this observation is of great interest because it suggests a possible treatment

of depression by means of a neuroactive substance (not necessarily dopamine [6]) to be delivered via "reverse dialysis," followed by a slow infusion from a chemode (see below).

3.1.4. A circuit conveying euphoria?

Other published data seem to suggest a location that should be considered for the chronic-stimulation treatment of depression. Investigators in Belgium have reported an incidental observation made in the course of applying high-frequency stimulation in a patient suffering from obsessive-compulsive syndrome. They noted that stimulation of the magnocellular part of the dorsomedial nucleus of the thalamus induced an unexpected and striking episode of uncontrollable laughter and euphoria [7]. The authors also reported that the patient experienced a "cheerful and happy feeling" and occasionally displayed a unilateral smile.

While this manuscript was in preparation, interesting data were reported by the group of Francisco Velasco in Mexico City, which tend to suggest that high-frequency stimulation of the inferior thalamic peduncle may have both acute and more prolonged effects on depression [8].

One could combine all the anatomical localizations arising from the observations of stimulus-bound depression and stimulus-bound euphoria to assemble a putative circuitry that embodies both depression-generation and euphoria-producing components.

Clearly, the vision of electric stimulation–bound management of psychiatric diseases is still at a very early phase. But the above fortuitous observations are suggestive of anatomical sites from which euphoria/depression can be induced. These sites may or may not have been those the therapists were seeking. In any case, these preliminary findings indicate that the notion of antidepression neurostimulation is viable and deserving of further study.

3.1.5. Auto-neurostimulation

It is foreseeable that stimulation-based treatment of mood-related disorders might be enhanced if the patient had the ability to switch the stimulus "on" and "off" in a manner previously used (and misused) for other purposes [9]. This technique requires chronic implantation of a receiver that can be activated by an external source. Regulating his/her own mood, switching on the "up" electrode or frequency when depressed, and switching on the "down" electrode or frequency when hypomaniac could be an effective way of treating patients with bipolar disorder (assuming that they possess the insight necessary to make such decisions).

Related to the above is the long experience of physiologists and experimental psychologists with self-stimulation in animal studies when the tip of the electrode is located in the "reward" area. Similarly, when the electrode is located in the "aversion" area, one observes a self-stimulated interruption of hetero-stimulations given randomly by the experimenter. Because we have no way of knowing what a rat reward or rat aversion really feels like, we may learn a lot from a happy patient who benefits from such an intervention, after all the other available "therapies" have failed.

3.1.6. Neurotrophic effect

A number of observations by Benabid et al [5] have shown the appearance of a trophic effect, both upstream and downstream from the site of a chronic stimulation (personal communication). These observations, combined with other experimental data, suggested to the authors that prolonged stimulation may result in a relative recovery of the neurosecretory function of the cells connected to the circuitry under treatment.

3.1.7. Microdialysis, reverse dialysis, and indwelling chemodes

Now that acute, semichronic, and chronic probe implants have begun to be used in human, one can begin to think about placement of microdialysis (and reverse dialysis) devices in deep brain structures. By this means, it should be possible to detect pathological alterations of the neurochemical traffic within a given structure and to relate such alterations to the proximate clinical picture. Moreover, although microdialysis may serve the diagnostic purpose of disclosing which neurochemical changes have occurred, the corresponding reverse dialysis may be used as a method of neurochemical treatment, either by providing the missing factor or by blocking the factor that is present in excess.

Once reverse dialysis has shown which neurochemical agent was altered, it will be possible, with today's technology derived from animal studies [10], to implant a chemode for miniperfusion of a corrective agent.

3.1.8. Graft of postdifferentiated and "activated" stem cells

The time is near when therapists will have at their disposal a virtual "library" of postdifferentiated and "activated" stem cells. The current technology of probe placement is sufficient to permit the neurosurgeon to implant a suitable colony of stem cells at the appropriate target site. It is foreseeable that the selected, activated stem cells will then replace the deficient neurochemical factor.

3.1.9. Localized telestimulations by means of magnets or transcranial magnetic stimulation

This nonsurgical approach is developing slowly. Many of its possibilities remain to be explored. The nondamaging aspect of this technique makes it especially attractive. Also, today, organic chemists are capable of adding a paramagnetic atom to a given molecule. If one chooses a molecule that is present in specific areas of the brain or just introduces the desired molecule via a probe, it should be possible to activate or neutralize this area by applying alternating magnetic fields.

4. Need for an updated taxonomy

The new nondestructive neurosurgical approach to the treatment of psychiatric illness in general, and to depression in particular, cannot be truly efficient unless a modern, neuroanatomy-, and neurochemistry-bound taxonomy is established. One would not propose today to treat an infection of unknown etiology by just any antibiotic. The agent responsible for the illness needs to be (taxonomically) identified and its specific sensitivity to an array of antibiotics determined.

For the neuroanatomical criteria, we could use depression-bound changes in regional cerebral metabolic rate (like the anterior cingulum, the anterior left temporal lobe, and inferior frontal lobe) revealed by interventional- and functional magnetic resonance imaging, or by single-photon emission computed tomography or positron emission tomography scan. Further improvement in the accuracy of these techniques can be expected to provide a better localization of CNS areas associated with a given depressive entity.

Metabolic changes may of course reflect neurochemical changes that may underlie vulnerability to depression. If this proves to be the case, the foreseeable development of human brain microdialysis will allow us to verify the neurochemical changes of the candidate location and, subsequently, to use these changes as a criterion for the proper taxonomy of the syndrome and, hence, proper placement of a "therapeutic" electrode or chemode.

5. Conclusion

We are currently witnessing a new era in psychiatric (and functional) neurosurgery—one that treats without destroying brain tissue. Novel chronic stimulation-based neurosurgical techniques will make it possible to extend surgical intervention to an ever-wider array of indications. Such an expansion will also give rise to advances in our knowledge of both physiological and pathological processes.

The number of successful outcomes of these operations should increase because of a better taxonomy of depressions—a taxonomy based largely on objective criteria that will help unravel the tangle of today's conceptions of "depression" and will allow the creation of a taxonomic *lingua franca* and, with it, enhanced communication between different schools of psychiatry and between psychiatry, neurobiology, and neurosurgery.

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