New Methods of Minimally Invasive Brain Modulation as Therapies in Psychiatry: TMS, MST, VNS and DBS

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Over the past 20 years, new methods have been developed that have allowed scientists to visualize the human brain in action. Initially positron emission tomosynthesis (PET) and now functional magnetic resonance imaging (fMRI) are causing a paradigm shift in psychiatry and the neurosciences. Psychiatry is abandoning the pharmacological model of ‘brain as soup’, used for much of the past 20 years. In stead, there is a new realization that both normal and abnormal behavior arise from chemical processes that occur within parallel distributed networks in specific brain regions. Many of these pathological circuits are coming well characterized, in disorders ranging from Parkinson’s disease, to obsessive-compulsive disorder, to depression.

Most recently, there has been an explosion of new techniques that allow for direct stimulation of these brain circuits, without the need for open craniotomy and neurosurgical ablation. The techniques include transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). This review will describe these new tools, and overview their current and future potential for research and clinical neuropsychiatric practice. [Chin Med J (Taipei) 2002;65:349-360]
For most of the 1900’s many in the medical community thought that clinical depression was a disease of the mind and not the brain, and that even if the brain was involved, it was likely involved in a general rather than a regionally specific way. These notions were also held about a similar neuropsychiatric disorder—epilepsy.\(^1,2\) Over the century, the electroencephalogram (EEG) and neuroimaging\(^3\) have transformed understanding of the regional neuropathogenesis of ‘the epilepsies’ (as they are now called). There are now multiple different epilepsy syndromes, all with detailed knowledge about the regions that are dysfunctional, their pathogenesis and their pharmacological or surgical management. On the other hand, most psychiatrists who treat patients with mood disorders talk of ‘depression’ in a very general sense, perhaps making a distinction based on the historical knowledge of whether there are associated manias (bipolar or unipolar depression). There is still little understanding of disease pathogenesis or even regional neuroanatomic involvement.

It is likely that ‘the depressions’ will undergo a profound and rapid change in understanding and management in the next century, much as ‘the epilepsies’ did in the last. Advances in functional and structural neuroimaging, and work with treatment-resistant or refractory patients, will push for more refined diagnoses, which will then lead to ever more sophisticated treatments in ‘the depressions’.

Functional brain imaging - the key role of the anterior paralimbic system and the prefrontal cortex

With the advent of positron emission tomography (PET) scanning 20 years ago, many thought that psychiatry would be transformed. However, research advances with functional imaging have impacted only minimally on clinical practice. Psychiatrists still do...
not or der brain im aging tests for di ag no sis, ex cept for the oc ca sional scan to ex clude a brain tu mor or stroke as the caus ative dis ease.5,5 Why? To date, there has not been a large con sensus on which brain regions change during an episode of depression.6-9 While many stud ies have found de creased rest ing ac tiv ity in the prefrontal cortex with as soci ated limbic hy po ac tiv ity (Fig. 1), these find ings are nei ther spe cific to de pression,10 nor pres ent in all cases11 in a mag ni tude that al lows one to use im aging as a clin i cal tool. Fur ther, the di ag no sis of the de pres sions as cur rently clas si fied is straight for ward with a com pe tent clin i cal exam and his tory. On top of this, most of the phar maco log i cal treat ments for the de pres sions work regard less of whether the depression is ‘pri mary’ or sec ond ary to some other ill ness like a brain tu mor or stroke. Thus, in the ab sence of the need to re fine di ag no sis in or der to max i mize treat ment, there has not been a push to de vel op im aging par a digms for better un der stand ing of different disease pathogenesis. Nev er the less, there have been re mark able im aging stud ies show ing clear dif fer ences in re gional brain ac tiv ity in dif fer ent sub sets of ‘the de pres sions’. For ex am ple, late on set de pres sion is as soci ated with more white mat ter dis ease than de pres sion that oc curs early in life.12 Resting brain scans have been shown to dis tin gui sh pa tients with bi po lar de pression,13 and to show who among a group of de pressed pa tients will re spond to sleep de priva tion,14-16 fluox etine,17 ECT,18,19 or TMS.20 More over, im aging stud ies in pa tients with long re mit ted de pres sion can even dis tin gui sh those that will suf fer a tem porary re lapse with a phar maco log i cal de ple tion par a digm.21

With this ev er ad vanc ing body of stud ies, it is pu zzling why brain im aging has not had more of an impact in clin i cal set tings. It is ironic that the de but of many of these new im aging tools co in cided with the emer gence of strin gent cost-con tainment mea sures in the US in all ar eas of med i cine and par tic u larly men tal health. Thus, these tools were never placed in large clin i cal set tings where their clin i cal use might slowly emer ge. Fur ther, the rev o lu tion in phar macol ogy has pro ce eded at a breath taking pace and these de vel op ments have been in de pend ent of a need for more de-
tailed regional neurobiology. Thus, if most people with the de pres sion re spond to med i ca tions with few side ef fects, then the mo men tum is not gen er ated for more de vel op ments un der stand ing of dis ease pathogenesis and re gional neurobiology.

On the other hand, theo ret i cally giving an oral med i ca tion is one of the least ef ficient ways to change activity in specific brain regions. The med i ca tion must be ab sorbed by the gut, and travel through out the body, where a small por tion of it is trans ported across the blood-brain bar rier. There, within the brain the medication travels through out, with only some of it reach ing its in tended target. Thus, there are po ten tials for side-effects in the periphery and in the brain through un in tended ex po sure. The more dis crete the place ment of a drug or in ter ven tion, the more ef fective and fewer the side-effects. For ex am ple, some ef fective an ti de pres sants, like thy roti n re leas ing hor mone (TRH), are mar gin ally ef fective when given pe ripher ally, but are pro found ly ef fective when in jected intrathecally di rectly into the CNS.22 Better un der stand ing of the brain re gions in volved in de pres sion pro ves to im prove all as pects of de pres sion treat ment. How ever, cur rently avail able med i ca tions have not worked for all per sons with the de pres sions, and in these in di vid u als there has been a push for more ag gressive so matic in ter ven tions. In the last cen tury, these in volved brain sur gery and elec tro con vulsive ther apy (ECT). ECT has been re fined and im proved and is the most ef fective treat ment for re frac tory de pression. Brain sur gery has been largely aban doned for treat ment of the de pres sions, al though it is in creas ingly used for OCD.

Sev eral of the other new so matic in ter ven tions dis cussed be low can be com bined with func tional im aging and pro vides a way to trans for m un der stand ing and treat ment of the de pres sions in this cen tury (Ta ble 1).

**Transcranial electrical stimulation (TES)**

In the late 1800’s, many phy si cans ex per i mented with pass ing low lev els of the newly avail able ‘elec tric ity’ through nerves and mus cles in an at tempt at ther apy.23,24 None of the early uses for electricity
caught on.\textsuperscript{25} However, to ward the end of this century, interest has flourished in whether passing low level electrical energy over the skull [cranial electro-stimulation (CES) or transcranial electrical stimulation (TES)] might affect brain function. Commonly one electrode is placed over the forehead and the other behind the ear. In some ways, electroconvulsive therapy is a form of TES, with the difference being that current thinking holds that the therapeutic effects of ECT come not from the electricity delivered, but rather the generalized seizure that the electrical currents induce. TES can cause changes in endogenous opiates.\textsuperscript{26,27} Clinical studies, mostly but not entirely from Russia, Canada and France, have found efficacy in treating Parkinson’s Disease and alcoholism.\textsuperscript{28-30} Although not thoroughly studied, different effects are found with reversal of the current flow, as well as with stimulation over different hemispheres.\textsuperscript{31} TES appears to pass current through large areas of the brain although the exact action of the ictal changes may be due to these currents acting in specific regions. TES has also been known as ‘electrosleep’ which is a misnomer in that it induces EEG changes in awake subjects that do not resemble physiological sleep. Because the skull acts as a large resistor and directs electrical currents to the scalp, it is unclear how TES can be made regionally selective. Further research into this area is needed, particularly with regard to understanding where the current is acting in the brain to modify EEG activity and limbic neurotransmitter function (Fig. 2).

**Table 1. Current and potential somatic interventions for the treatment of severe depression**

<table>
<thead>
<tr>
<th>Somatic intervention</th>
<th>Regionally specific</th>
<th>Clinically applicable</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroconvulsive therapy (ECT)</td>
<td>+</td>
<td>+++</td>
<td>++ (Anesthesia, generalized seizure)</td>
</tr>
<tr>
<td>Magnetic seizure therapy (MST)</td>
<td>+++</td>
<td>(No efficacy work done)</td>
<td>++ (Anesthesia, generalized seizure)</td>
</tr>
<tr>
<td>Transcranial electrical stimulation (TES)</td>
<td>+</td>
<td>++</td>
<td>+ (Scalp irritation)</td>
</tr>
<tr>
<td>Transcranial magnetic stimulation (TMS)</td>
<td>+++</td>
<td>+++ (Clinical trials underway)</td>
<td>+ (Painful at high intensities)</td>
</tr>
<tr>
<td>Vagus nerve stimulation (VNS)</td>
<td>++ (Discrete brainstem nuclei initially, different parameters likely involve other brain regions)</td>
<td>+++ (On the market for epilepsy, clinical trials in depression underway)</td>
<td>++ (Surgery for generator implant)</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>+++</td>
<td>+++ (Approved in US for treatment of movement disorders, pain syndromes, no work in depression yet)</td>
<td>+++ (Brain surgery)</td>
</tr>
</tbody>
</table>

+ Minimal – ++++ Marked.

**Fig. 2.** This is a drawing of the various new ways of stimulating the brain. On the left side of the image are techniques that cause seizures (ECT, MST). On the right are the techniques that modify mood without causing a seizure (TMS, VNS, DBS). Initially it was widely thought that the only way a somatic treatment could improve mood was by causing a seizure, like in ECT. How ever, data from all of the non-convulsive techniques now clearly show that this was a mistaken belief and that mood can be changed through stimulation of specific brain regions short of a seizure.
The first widely adopted somatic intervention - ECT

Early in this century, electroconvulsive therapy (ECT) was first considered as a potential treat ment following the likely faulty observation that patients with schizophrenia had no seizures, or that epileptic patients were not psychotic (subsequent work has shown that both of these statements are likely false). Thus generalized seizures were given to patients with psychosis, some of whom improved (likely those with psychotic depression). Years of ECT use then allowed the clinical winnowing of applications to its current use profile of mood disorders, and occasionally catatonia or Parkinson's Disease. In fact the history of ECT can be seen as an initial broad application of a powerful brain intervention to many conditions, with clinical use narrowing both the clinical applications where it is effective, and the ways of application that affect efficacy (e.g., dose titration). Thus, psychiatrists used ECT for 30 years before it was determined that prefrontal application of the electric shock, and not parietal, was necessary for a therapeutic effect, regardless of whether a generalized seizure occurred. How ever, things will likely change rapidly within the next few years. No bler and colleagues have found that those patients who go on to respond to ECT have a greater degree of efficacy (e.g., dose titration). Thus, psychiatrists used ECT for 30 years before it was determined that prefrontal application of the electric shock, and not parietal, was necessary for a therapeutic effect, regardless of whether a generalized seizure occurred. How ever, things will likely change rapidly within the next few years. No bler and colleagues have found that those patients who go on to respond to ECT have a greater degree of efficacy (e.g., dose titration).

Transcranial magnetic stimulation (TMS)

An other method for non-invasively modifying regional brain activity uses a powerful hand-held magnetic device to create a time-varying magnetic field. When held on the scalp, this strong magnetic field creates electrical currents in superficial cortex - a form of 'electrodeless electrical stimulation'. Transcranial magnetic stimulation (TMS) thus able to depolarize cortical neurons and cause downstream changes in connected brain regions. Recently there has been much enthusiasm revolving around whether TMS can modify mood in health or disease. To date, three studies have found that left prefrontal TMS results in slight increases in subjective sadness whereas right prefrontal rTMS causes increased happiness. These initial studies found small effects. One study has confirmed these effects while two attempts at replication have failed to find effects. These studies however are important in an historical context for they raised the possibility that TMS could affect circuital mood. They thus set the stage for using TMS as an antidepressant.

The notion of using powerful magnetic fields to treat depression was around at the beginning of the century (Patent, 1903, Vienna, Austria, A. Pollacsek and B. Beer). How ever, it was not until 1985 that battery technology developed to the point where TMS could create a magnetic field powerful enough to move the thumb when applied to motor cortex. Initially psychiatrists began using TMS applied over the vertex to treat depression, with mixed results. George and Wasmann in 1994 hypothesized, based on the functional imaging and ECT response data discussed above, that TMS over the prefrontal cortex...
might have antidepressant effects. Initial open, cross-over, and parallel double-blind studies all suggest that left prefrontal rTMS has antidepressant effects. Although these studies have small samples, and the effect sizes vary widely, it is now reasonable to conclude that the 1994 hypothesis is correct that prefrontal TMS applied over several weeks can reverse depression. Prefrontal TMS has been approved as a treatment for depression in Canada and Israel, and the US Food and Drug Administration (FDA) is currently reviewing TMS antidepressant treatment trials.

There is how ever a great deal of work needed before TMS can be used to its full capacity. There is little understanding of the brain effects of TMS as a function of the use parameters (in intensity, frequency, train length, location, dosing schedule), in either health or disease. Combining TMS with functional brain imaging can help understanding of some of these effects. A current limitation of the field involves using TMS in small animals. Unfortunately small TMS coils, that are the same relative size to a mouse brain as those used in humans are to our brains, explode with the electricity needed to stimulate mouse brain. Much work is needed here in producing small TMS coils that will not explode.

The real potential of TMS will come when critical studies are performed to determine if TMS at a given region or circuit might be able to effect long-term changes in the circuit. If this were to be the case, and this is a huge if with no hard data at the moment, then TMS at specific regions, in tens of frequencies might serve as a new treatment option for a host of conditions and might have applications as well for enhancing or modifying normal functions such as memory or skill acquisition (Fig. 3).
Newer therapies - vagal nerve stimulation and deep brain stimulation

An other new somatic intervention involves stimulating the vagus nerve with electrical current. In 1985 Zabara first demonstrated the anticonvulsant action of vagus nerve stimulation (VNS) on experimental mental seizures in dogs. Although the vagus is an autonomic nerve, he hypothesized that VNS could prevent or control the motor and autonomic components of epilepsy. This hypothesis is built on previous research identifying extensive projections of the vagus nerve via its connection in the nucleus tractus solitarius to many areas of the brain. Thus, stimulation of theafferent aspects of the vagus nerve in the neck could reach areas of brain epileptic activity. Now vagus nerve stimulation (VNS) is FDA approved for the treatment of epilepsy and about 10,000 people worldwide have these generators implanted. Most epilepsy patients using VNS have failed many medical treatments and have considered using VNS prior to resective brain surgery. In these clinical studies, the efferent peripheral effects of VNS have been minimal with or without significant GI or cardiac side effects.

Within the last century, many anticonvulsants have been found to have mood stabilizing effects (carbamazepine, valproic acid, lamotrigine). In the VNS clinical trials, many clinicians noted that their patients had improved mood during a PET study of VNS effects in patients with epilepsy revealed that VNS could change blood flow in brain regions implicated in mood regulation. These observations provided the rationale for a multisite open pilot study of VNS in 30 adults with treatment-resistant depression. A double-blind, randomized trial showed that VNS was successful in treating depression with low-to-moderate, but not extreme, antidepressant resistance. Evidence concerning long-term therapeutic benefits with VNS and tolerability relative to alternative treatments will be critical in determining the role of VNS in treatment-resistant depression.

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Like with TMS, there is little understanding of the brain effects of different VNS parameters (frequency, intensity, pulse width, train length, dosing schedule), with many clinicians being largely ignorant of the specific effects of VNS parameters on learning and memory in a classic inverted u-shape, mimicking the actions of peripheral stress (which at low doses improves performance but at higher doses interferes with learning and memory tasks). This implies that one of the mechanisms by which stress changes memory function is vagally mediated, and that VNS can modify this signal. Obviously, better understanding of the brain effects of VNS could make VNS a powerful intervention, especially if ways were found of vagus nerve stimulation that were less invasive than the current method. It is also possible, and even likely, that different VNS settings (intensity, frequency, duty cycle) have different regional effects. This would imply that finding the VNS settings that maximally affect specific brain regions would be an effective way to dose and guide clinical trials of VNS within a functional MRI scanner. This combination technique may allow for efficient exploration of VNS use parameters on brain function.

Deep brain stimulation

The most anatomically discrete, and also the most invasive, method of stimulating deep brain structures is called deep brain stimulation. In this technique, a thin electrode is inserted directly into the brain and then different currents are applied at varying depth levels until the proper effects are found. This technique was used by some researchers in the US, as well as extensively by Russians. High frequency (> 80 Hz) electric stimulation has been shown to be effective in treating Parkinson’s Disease. DBS has the clear advantage over brain surgery (pallidotomy) of being reversible. Although this technique has not been used for treating depression, mood effects of the stimulation have been reported. For example, in one Parkinson’s patient who had never suffered from depression in her life, during the testing of stimulation, she noted the acute onset of tearfulness, sadness, and despair, which immediately remitted when the surgeons moved the stimulator out away from the substantia nigra, directly below the subthalamic nucleus. Parkinson’s Disease leads the neuro-psychiatric field in terms of understanding the pathologic circuitry and it is thus natural that deep brain stimulation be used first in PD. However, as the neuroanatomy of normal and pathologic mood regulation becomes better understood, DBS may be used in primary mood disorders as well.

Conclusions

One can envision a day when a depressed patient may have a resting and activated brain scan for diagnosis. There would then be a host of anatomically discrete options available for correcting the dysfunctional circuits both to treat the immediate disease state, but also to strengthen the circuitry so that relapse might be prevented. Lagging behind the pharmacological expertise of modern psychiatry, knowledge of the regional neuroanatomy of depression is rapidly catching up. This knowledge will serve as the background for the development of several new somatic interventions that will surely change the way clinicians think about and treat ‘the depressions in the next century.

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