revisão

A review of the new minimally invasive brain stimulation techniques in psychiatry

Revisão de novas técnicas minimamente invasivas de estimulação cerebral em psiquiatria

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Abstract New knowledge about the specific brain regions involved in neuropsychiatric disorders is rapidly evolving due to recent advances in functional neuroimaging techniques. The ability to stimulate the brain in awake alert adults without neurosurgery is a real advance that neuroscientists have long dreamed for. Several novel and minimally invasive techniques to stimulate the brain have recently developed. Among these newer somatic interventions, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) show promise as therapeutic tools in the treatment of neuropsychiatric disorders. This article reviews the history, methodology, and the future of these minimally invasive brain stimulation (MIBS) techniques and their emerging research and therapeutic applications in psychiatry

Keywords Minimally invasive brain stimulation (MIBS). Transcranial magnetic stimulation (TMS). Vagus nerve stimulation (VNS). Deep brain stimulation (DBS)

Resumo O conhecimento acerca de regiões específicas do cérebro envolvidas em transtornos psiquiátricos está em franca expansão como resultado dos avanços recentes em técnicas de neuroimagem funcional. A capacidade de estimular o cérebro em adultos despertos em estado de alerta, sem necessidade de neurocirurgia, é um avanço real sonhado havia muito pelos neurocientistas. Recentemente, desenvolveram-se várias novas técnicas minimamente invasivas para estimular o cérebro. Entre essas novas intervenções somáticas, a estimulação transcraniana magnética (ETM), a estimulação do nervo vago (ENV) e a estimulação cerebral profunda (ECP) revelam-se promissoras ferramentas terapêuticas no tratamento de transtornos neuropsiquiátricos. Neste artigo se faz uma revisão da história, da metodologia e das perspectivas futuras das técnicas minimamente invasivas de estimulação cerebral (ECMI) e das pesquisas e aplicações terapêuticas em psiquiatria

Descritores Estimulação cerebral minimamente invasiva (ECMI). Estimulação transcraniana magnética (ETM). Estimulação do nervo vago (ENV). Estimulação cerebral profunda (ECP).

Introduction

The rapid development of psychopharmacology during the last half century has revolutionized standard methods for treating clinical psychiatric disorders. Now, most psychiatric disorders are treated with medications or some form of psychotherapy, or both. Although these methods are useful for many psychiatric patients, they are not effective in all cases, and are associated with various side effects. Thus there is a clear need for new and safe therapies to treat psychiatric illnesses. Additionally, if psychiatric illnesses derive from faulty chemical transmission in certain brain regions or circuits, then taking a medication by mouth is a highly inefficient method for delivering needed compounds to these regions. Although some somatic treatments such as insulin coma therapy, electroconvul-

Received on 2/2/2001. Approved on 14/2/2001.

sive therapy (ECT) and prefrontal leucotomy have been used in treating some psychiatric conditions, their high risks, limited therapeutic efficacy and side effects have limited their clinical utility in most areas.[1]

It is believed that successful treatment in some psychiatric disorders is achieved by modifying neuronal activity at a systems or circuit level. Thus clinical and research neuroscientists long have been interested in the development of methods for stimulating the brain directly without great risk. The ability to excite or inhibit local areas of the brain has raised the possibility of whether these techniques might be novel therapeutic tools in the field of psychiatry.[2] With this background, several novel and minimally invasive techniques to stimulate the brain have recently emerged. These new somatic interventions are transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Additionally, as functional imaging methods reveal the relevant circuitry involved in several psychiatric diseases, these techniques offer hope for translating these research findings into novel treatments and for better understanding the pathophysiology of psychiatric disorders.

Here we briefly review of the methodology of these minimally invasive brain stimulation (MIBS) techniques (TMS, VNS, and DBS) and their emerging research and therapeutic applications in psychiatry.

Transcranial magnetic stimulation (TMS)

History and procedure

TMS uses a powerful hand-held magnet to create a time-varying magnetic field where a localized pulsed magnetic field over the surface of the head depolarizes underlying superficial neurons.[3] High-intensity current is rapidly turned on and off in the electromagnetic coil through the discharge of capacitors. TMS, producing powerful but brief magnetic fields that induce electrical currents in the brain, radically differs from the currently popular use of low-level static magnetic fields as alternative therapies. If TMS pulses are delivered repetitively and rhythmically, it is called repetitive TMS (rTMS) (Figure 1).

As early as the late 19th century, D'Arsonval might have been the first to apply something that resembles the modern TMS to the brain.[4] Pollacsek and Beer in 1902 filed a patent for applying electromagnetic fields to the head to treat depression and neurosis.[5] However, the first modern TMS device was developed by Anthony Barker in 1985.[6] The field has developed rapidly since then with many researchers using TMS in a variety of research and clinical applications.

Mechanisms

Although TMS is able to influence many brain functions, including movement, visual perception, memory, attention, speech, and mood, full knowledge of the neurobiological cascade of events triggered by TMS at different settings remains unclear. Several animal studies have been important in guiding and stimulating the understanding of the modes of action of TMS. TMS enhances apomorphine-induced stereotypy and reduces immobility in the Porsolt swim test.[7] Some researchers have found significant alteration of monoamines and their receptors in the brain cortex after TMS similar to those following electroconvulsive therapy (ECT).[8] Some data suggest that TMS may be able to alter brain function through synaptic changes that are potentially long-lasting.[9] Additionally, several studies have shown that TMS produces region-specific changes in TSH and cortisol.[10,11] Thus TMS produces neuroendocrinological changes that may explain some of its behavioral effects. Brain imaging studies have repeatedly documented widespread changes in brain metabolism during TMS. Although conventional TMS can directly activate only cortical neurons, it clearly affects cells at some distance from the stimulation site. Studies combining TMS with other neurophysiological and neuroimaging techniques such as electroencephalography (EEG), positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional MRI (fMRI),[12] are helping to elucidate how TMS achieves its effects. The National Institute of Mental Health intramural group has performed a series of TMS studies using PET. Initial studies over motor or prefrontal cortex demonstrated both local and secondary effects of TMS. Their findings suggested that TMS over motor cortex at 1 Hz showed increased local blood flow, whereas TMS over prefrontal cortex at 1 Hz reduced local blood flow.[13] The authors' group at Medical University of South Carolina (MUSC) has demonstrated that TMS has both local and remote effects in a study using SPECT.[14] This group also pioneered and perfected the technique of interleaving TMS with blood oxygen level dependent (BOLD) fMRI, allowing for direct imaging of TMS effects with high spatial (1-2 mm) and temporal (2-3 secs) resolution.[15] Very recently, the group found that prefrontal TMS at 80% motor threshold (MT) produces much less local and remote blood flow changes than does 120% MT TMS.[12] This combinational technique offers great promise as a neuroscience tool, both to understand the effects of TMS on the brain and to test theories about the relationship between brain activity and behavior.

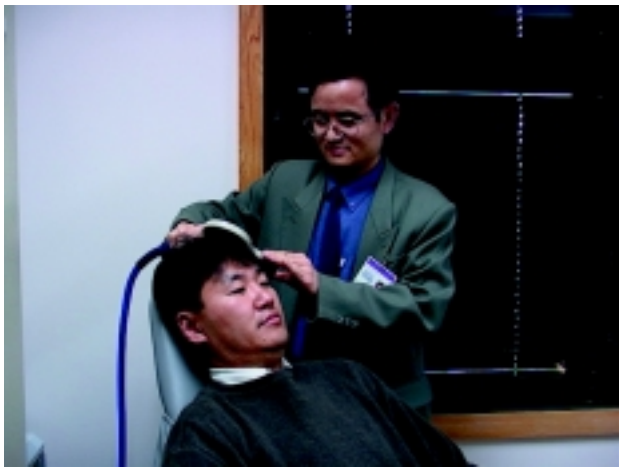

Figure 1 - Application of transcranial magnetic stimulation (TMS): Xingbao Li, M.D. applies the figure-eight electromagnetic coil over Jeong-Ho Chae, M.D.'s left prefrontal cortex.

Basic applications

One of the popular initial uses of TMS was to map the motor cortex, because the effects of the stimulation could easily be measured by electromyography (EMG) of the motor-evoked potential (MEP) in peripheral muscles.[16] TMS has also been widely utilized to measure connectivity and excitability of the cerebral cortex with various measures, such as the motor threshold, MEP input-output curve, MEP map, silent period, and paired-pulse.[17] Since even earlier researchers were aware that TMS could cause suppression of visual perception, speech arrest, and paresthesias, TMS has been used to map specific brain functions in areas other than motor cortex. Several groups have applied TMS to the study of visual information processing, language production, memory, attention, reaction time, and even more subtle brain functions, such as mood and emotion.[18] This ability to stimulate non-invasively and safely the brain of an awake alert individual is an important new neuroscience advance.

Clinical applications

Although the potential utility of TMS as a treatment tool in various neuropsychiatric disorders is rapidly increasing, its use in depression is the most extensively studied clinical application to date. Three initial uncontrolled studies using single pulse TMS applied over the vertex suggested potential antidepressant effects.[19-21] Armed with the preliminary data of TMS' ability in healthy adults to influence mood and stimulate peripheral TSH, which was specific to prefrontal regions, in 1994, George and Wassermann hypothesized that intermittent stimulation of important prefrontal cortical brain regions might also cause downstream changes in neuronal function that would result in an antidepressant response.[22] In an initial open study it was reported that left prefrontal rTMS might be effective in the treatment of depression.[23] In the following years, there have been many open trials of prefrontal rTMS to treat depression suggesting significant antidepressant effect of TMS.[24] In another form of work, add-on TMS therapy to standard antidepressants was more effective than the pharmacotherapy alone.[25] Similarities between the effect and mechanism of ECT and TMS have provoked studies directly comparing the effects of these two modalities in depression. Although ECT was a more potent treatment in patients with psychotic depression, the effects of rTMS were similar to those of ECT in non-psychotic patients.[26] Pridmore and colleagues have recently reported a more interesting study where they compared the antidepressant effects of standard ECT (3 times/week), and one ECT/week followed by TMS on the other four weekdays.[27] At three weeks they found that both regimens produced similar antidepressant effects. Unfortunately, detailed neuropsychological testing was not performed but one would assume that the TMS and ECT group had less cognitive side effects than the pure ECT group.[28]

For any new technology that is proposed as therapeutic tool, double blind studies are crucial. Pascual-Leone et al.[29] performed a double-blind, placebo-controlled multiple cross-over study and reported that rTMS (10 Hz) over the left dorsolateral prefrontal cortex resulted in a significant decrease in depressive symptoms in medication-resistant psychotically depressed patients. They used stimulation at other sites (right prefrontal, occipital, etc.) as their control conditions, which had no antidepressant effects. This study was influential in that it showed large antidepressant effects at one week in a difficult-to-treat group, and the effects were only seen with left prefrontal stimulation. Unfortunately none of the key findings from this study have been replicated, despite good attempts (efficacy at one week, efficacy in psychotic depression, specificity of left prefrontal cortex). In the first US placebo-controlled study, George et al.[30] found that left prefrontal rTMS (20 Hz) had an antidepressant effect that was statistically superior to sham (placebo) stimulation, but the total effect was not clinically significant (only a few point reduction in the overall scores of Hamilton Rating Scale for Depression). This George et al.'s 1997 cross-over study[30] (stimulating at only 80% of motor threshold due to limitations at that time imposed by the US Food and Drug Administration) had a markedly smaller clinical effect at 2 weeks than the Pascual-Leone study[29] found at just one week. Following these forerunning studies, over twelve controlled clinical trials have suggested that daily r TMS over the prefrontal cortex for at least two weeks has significant antidepressant effects.[31] However it is uncertain and even unlikely that the parameters used in these and current studies are maximally optimal. These include frequency, intensity, pulse duration, and stimulation site of TMS. In the largest published double-blind study to date, Klein et al.[32] found evidence for the efficacy of slow (1 Hz) rTMS on the right prefrontal area in patients with recurrent major depression.

The most recent published study from the MUSC group confirms that daily slower (5Hz) or faster (20 Hz) left prefrontal TMS for 2 weeks significantly reduced depressive symptoms greater than did sham.[33] There was no significant difference in response rates between the two groups who received active treatment.

A small study[34] by Loo and colleagues is one of the very few negative TMS trials to date, where they found no difference in antidepressant efficacy between active left prefrontal TMS and sham. In this study there was a high placebo response rate, perhaps due, as the authors speculate, to the type of sham coil used. They suggested that their coil position did not meet the criteria for an ideal sham, which would produce negligible cortical stimulation in conjunction with a scalp sensation akin to real treatment.[35] It is also interesting that some of the highest TMS placebo response rates are in outpatient studies,[34] with lower placebo response rates in inpatient studies.[30,31] Although this may be due to differences in treatment resistance with outpatients being less resistant than inpatients, it may also have to do with the way TMS trials are conducted. For example, in current TMS studies even those receiving sham treatment are seen daily by a researcher. For some depressed patients this may represent a substantial change from pre-study baseline in their daily activity level and degree of interaction with people. In TMS inpatient studies, the additional 20 minutes of treatment per day does not add much to the daily routine.

In summary, TMS is a promising tool in the treatment of depression. Much work remains in order to understand the optimum dosing strategy for the antidepressant effect of TMS. It

is unlikely that the initial combinations of intensity, frequency, coil shape, scalp location, number of stimuli or dosing strategy (daily, twice daily), are optimum or even close to maximum efficacy. Improved knowledge both of the brain circuitry involved in depression, and of the neurobiological effects of TMS will help to guide more effective forms of TMS. For example, it appears that more stimuli, of higher intensity, carry a more powerful antidepressant effect.[36] Further investigations using clinical trials, brain imaging and animal models are needed to find the best antidepressant stimulation parameters. Importantly as well, it will be necessary to examine ways to sustain the therapeutic benefits of TMS and to identify the optimum techniques and indications for its application.

Several psychiatric antidepressant medications or treatments are also effective antimanic agents – e.g. anticonvulsants, and ECT. One recent clinical trial found that right prefrontal TMS is antimanic compared to left prefrontal TMS.[37] However this result is too preliminary to draw any definite conclusions.

A pilot report that compulsive urges decreased after right lateral prefrontal rTMS has shown the potential usefulness of TMS as a probe of cortico-striato-pallido-thalamic circuits and pathophysiological processes potentially involved in the symptoms of obsessive compulsive disorder.[38] In addition, many researchers worldwide are currently conducting studies on TMS in subjects with schizophrenia, Parkinson's disease, Tourette's syndrome, epilepsy, and some anxiety disorders. The observations of reducing negative symptoms[39] and auditory hallucination[40] in schizophrenia are particularly intriguing.

Safety issues

Although there is minimal risk of a seizure when TMS is performed within the published safety guidelines, the most critical safety concern with TMS may be inadvertently causing a seizure.[41] In contrast to single pulse TMS, where seizures have not been reported in healthy persons, to date at least eight seizures have been triggered by rTMS (none in the past four years). A muscle tension type headache and discomfort at the site of stimulation are less serious but relatively common side effects of TMS. In contrast to ECT, no deleterious cognitive effects of 2 weeks of slow or fast rTMS were found.[28] Like magnetic resonance imaging (MRI), TMS could cause the movement of paramagnetic objects. For this reason, subjects with paramagnetic metal objects in the head or eye are generally excluded from TMS studies. TMS can cause heating of metallic implants, and the inactivation of pacemaker, medication pumps, or cochlear devices.[41] Although in the U.S. rTMS is an experimental procedure that requires an investigational device exemption (IDE) from the FDA, substantial experience to date suggests that at least in the short term TMS at moderate intensity has no clear lasting adverse effects in adults.[42] This is supported by a recent report where MRI scans were qualitatively and quantitatively assessed for structural change after two weeks of daily TMS.[43] This small study suggests that TMS at usual intensities and frequencies does not cause observable structural changes over these short time intervals. A recent study using EEG also did not find any enduring EEG changes during TMS session.[44] However, in the clinical setting where potentially therapeutic effects may involve neural reorganization and chronic exposure is required, there is a small theoretical possibility of lasting side effects at subconvulsive dose.[42]

Future of TMS

Although it is too early at this point to tell whether TMS has long lasting therapeutic effects, this tool has clearly opened up new possibilities for clinical exploration and treatment of various psychiatric conditions. Many parameters, such as intensity, location, frequency, pulse width, intertrain interval, coil type, duration, numbers of sessions, interval between sessions, and time of day remain to be systematically explored. It will perhaps always be easier to see a clinician occasionally and take medication rather than daily traveling to a treatment facility for TMS. Thus the ultimate clinical role in treating psychiatric disorders may be in medication refractory cases, or in patients who are unable to tolerate systemic therapy due to pregnancy or a medical condition. Further work understanding normal mental phenomena, and how TMS affects these areas, appears to be crucial for advancement. A critically important area that will ultimately guide clinical parameters is to combine TMS with functional imaging to directly monitor TMS effects on the brain. Since it appears that TMS at different frequencies has divergent effects on brain activity, TMS with functional brain imaging will be helpful to better delineate not only the behavioral neuropsychology of various psychiatric syndromes, but also some of the pathophysiologic circuits in the brain. Regardless of its clinical role as a new therapeutic technique, the capacity of TMS as a research tool to focally alter brain activity should lead to important advances in the understanding of brain-behavior relationships.

Vagus nerve stimulation (VNS)

History

For many years scientists have been interested in whether and how stimulation of cranial nerves might produce changes in higher cortex. In the late 1930s, Bailey and Bremer reported that stimulation of the vagus nerve in cats elicited synchronized activity in the cortex of the orbital gyrus.[45] In 1949, MacLean and Pribram found that inconsistent slow waves were generated from the lateral frontal cortex in monkeys by vagus stimulation.[46] Dell and Olson[47] stimulated the vagus nerve in cats and recorded a slow wave response in the anterior rhinal sulcus and amygdala. Dr. Zabara at Temple University found that VNS in the neck could quiet the muscle contraction in the abdomen that produces vomiting, that is, convulsive contraction. Later this idea progressed into the question of whether recurrent vagus stimulation might also ameliorate epilepsy. In 1985, Zabara demonstrated the anticonvulsant action of VNS on experimental seizures in dogs.[48] From these important observations and ideas have come patents, a procedure (NeuroCybernetic Prosthesis: NCP® system), a company (Cyberonics, Inc.), and, judging by the 2000 meeting of American Epilepsy Society (more than 50 VNS-related abstracts), an expanding amount of research.

Procedure and mode of action

Although the general term of VNS refers to several different techniques used to stimulate the vagus nerve, for practically all studies in humans, VNS™ refers to stimulation of the left cervical vagus nerve using a commercially available device manufactured by Cyberonics, called the NCP® System. This technique has been available for treatment of refractory partial onset seizures in Europe since June 1994 and in the U.S. since July 1997. Now VNS is FDA approved for the treatment of epilepsy and more than 11,000 people worldwide have these generators implanted. VNS is delivered through an implantable, multiprogrammable, bipolar pulse generator called the NCP Pulse Generator (the size of a pocket watch) that is implanted in the left chest wall to deliver electrical signals to the left vagus nerve through a bipolar lead (Figure 2). This bipolar lead is wrapped around the left vagus nerve near the carotid artery through a separate incision at surgery and is connected to the generator. The NCP® Programming Wand and Software — along with a portable computer — provides telemetric communication with the pulse generator, which enables noninvasive programming, functional assessments, and data retrieval (Figure 3). The vagus nerve (cranial nerve X) has been generally considered as a parasympathetic efferent nerve. However, actually the vagus is a mixed nerve composed of about 80% afferent sensory fibers carrying information to the brain from the head, neck, thorax and abdomen.[49] These sensory afferent vagus fibers relay information to the nucleus tractus solitarius (NTS) and then to many areas of the brain.[45-47] The NTS relays incoming sensory information to higher brain regions through at least three main pathways: 1) an autonomic feedback loop, 2) direct projections to the reticular formation in the medulla, and 3) ascending projections to the forebrain including the hypothalamus, and several thalamic regions which control the insula, orbitofrontal and prefrontal cortex largely through the parabrachial nucleus (PB) and the locus ceruleus (LC). The PB/LC has direct connections to the amygdala and the bed nucleus of the stria terminalis, very important structures in the regulation of mood.[50]

Although the exact mechanisms by which VNS exerts its antiepileptic effect is not fully understood, these important brain stem and limbic neuroanatomic connections are considered the sites of therapeutic effects of this procedure. For example, lesioning the LC in rat models of epilepsy totally blocks the anticonvulsant effects of VNS[51] – implying that the anticonvulsant VNS information must be going through the LC. The oncogene c-fos studies in rats during VNS revealed increased activity in the amygdala, cingulate gyrus, locus ceruleus, and hypothalamus.[52]

A recent study showed that increased γ-aminobutyric acid (GABA) or decreased glutamate in the NTS blocked seizures,[53] suggesting VNS causes direct changes to GABA and glutamate in NTS, with secondary changes in the function of specific limbic structures.

Studies using functional brain imaging are also important in elucidating the mode of action of VNS. Several SPECT studies in patients with epilepsy showed that VNS was associated with relatively decreased activity in thalamic regions.[54]

Figure 2 - Demonstration of NeuroCybernetic Prothesis System: comparison with the size of an adult hand.

Figure 3 - Application of Vagus Nerve Stimulation: The NCP® Programming Wand and a portable computer provide telemetric communication with the pulse generator, which enables noninvasive programming, functional assessments, and data retrieval.

These results support the hypothesis that VNS may exert an antiepileptic action by modulating thalamic activity, which then modulates cortex through thalamocortical connections. An earlier study using PET showed VNS causes activation of several brain areas including contralateral thalamus.[55] Thalamus involvement has also been found in PET studies of VNS effects in epilepsy patients performed by Henry and colleagues at Emory University. They suggested that VNS acutely increases synaptic activity in structures directly innervated by central vagus structures and areas that process left-sided somatosensory information, but VNS also acutely alters synaptic activity in multiple limbic system structures bilaterally.[56] They also reported that increased thalamic cerebral blood flow (CBF) during acute VNS correlated with decreases in seizures over time.[57] In a recent study using PET to compare acute and chronic VNS, this group demonstrated that acute VNS caused increased synaptic activity in several sites, including autonomic regions (dorsal-central-rostral medulla, hypothalamus), reticular activating system (thalamus), and limbic cortex (inferior frontal cortex, anterior insu-

lar).[58] Over time there was also observed a progressive decreased VNS induced activity in several limbic sites (amygdala, hippocampus, cingulate gyrus). Many cortical activations and deactivations were less prominent than during the acute VNS PET study, suggesting that the brain undergoes substantial changes over the course of treatment with VNS. The neuroimaging studies of VNS effects in epilepsy patients have differed in many important ways, including differences in subjects, the time from VNS implantation, co-morbid medications, and differences in the time and spatial resolution between SPECT, PET and fMRI.

Recently the MUSC group has succeeded in performing BOLD fMRI studies in depressed patients implanted with VNS generators, and these results show that VNS activates many anterior paralimbic regions.[59] Combining VNS with functional imaging offers the promise of better understanding the neurobiology of VNS as a function of the device settings. It may also be used to individually dose VNS patients.

Uses in epilepsy

Initially, VNS has been used as an alternative treatment for patients with refractory epilepsy who are unsuitable for epilepsy surgery. However, it is increasingly being used in less severely ill patients. In the past decade, several studies have reported its efficacy and safety in both the short term and longer term follow-up.[60-63]

In clinical studies in epilepsy, the efferent peripheral effects of VNS to the left vagus nerve have been minimal, without significant gastrointestinal or cardiac side effects. The NCP® System includes mechanical and electrical safety features that minimize the possibility of high-frequency stimulation, which could lead to tissue damage. In addition, each patient is given a magnet that, when held over the pulse generator, turns off stimulation. When the magnet is removed, normal programmed stimulation resumes.

Uses in psychiatric fields

It is not surprising that direct stimulation of the cranial nerves, which might have observable central effects, would draw the interest of biological psychiatrists.

The idea of afferent vagus connections to many of the brain regions implicated in neuropsychiatric disorders has invited theoretical considerations for potential research and clinical applications of VNS in psychiatry. In addition to the neuroanatomic reasoning above, data from several other domains provided the background and rationale for the first VNS implant for treating depression performed in July 1998 at MUSC in Charleston. These hints were: 1) mood effects of VNS observed in epilepsy patients; 2) the role of anticonvulsants (carbamazepine, valproic acid, and lamotrigine) and/or ECT (also an anticonvulsant) in treating mood disorders; 3) evidence by brain imaging studies that VNS affects the metabolism of limbic structures relevant to mood regulation; and 4) neurochemical studies indicating VNS effects on brain monoamines.[64]

An initial pilot open study of VNS in 30 adult outpatients with severe, nonpsychotic, treatment-resistant major depressive episode reported a 40% response rate after 8 weeks of VNS therapy, using ≥ 50% reduction in baseline Hamilton Depression Rating Scale (HDRS) 28-point total score to define response (12/30 responders).[65] In this medication resistant group, there was a 17% complete remission rate (exit HDRS28 ≤ 10), suggesting efficacy of this technique in depression. This study has been extended for longer-term follow-up, and after 6 months of treatment, 17/30 (57%) of the treatment-resistant patients met criteria for response.[66] Although some adverse events, such as infection, leg pain, agitation, panic, irritability, and dysphoria have occurred, all but one subject has elected to keep the device implanted, suggesting good tolerability. A recent additional open study extending this cohort to 60 subjects (30 new added to the initial 30) found similar but slightly less efficacy.[67] In the 60 subject sample, the response rates were 30.5% for the primary HDRS-28 measure, 34.0% for the Montgomery-Äsberg Depression Rating Scale, and 37.3% for the Clinical Global Impression-Improvement score (CGI-I of 1 or 2). An additional analysis found that VNS appeared to be most effective in patients with low-to-moderate, but not extreme, antidepressant treatment resistance. To overcome the limits of these studies such as the open design, a multi-site randomized, sham control study is underway.

This potential success of VNS in treating depression has encouraged the possibility of other therapeutic uses. Several theories of the anxiety disorders speculate either a faulty interpretation of, or erratic availability of, peripheral information into the CNS. One might suggest that altering the flow of this information using VNS could have therapeutic potential in the treatment of anxiety disorders.

Similarly, the vagus contains information about hunger and satiety, as well as pain fibers, and potential studies are also theoretically justified in the areas of treatment resistant obesity, addictions or pain syndromes. Moreover, the NTS sends fibers into the dorsal raphe and areas that are known to control levels of alertness. Thus, VNS might be considered as a potential treatment for some sleep or alertness disorders, such as coma or narcolepsy. In this arena, a study in 10 epilepsy patients found that high intensity, high frequency stimulation reduced total time in REM sleep, and REM sleep was less fragmented.[68] Anecdotal reports have suggested a "brightening" effect (i.e., improved alertness) in persons with epilepsy after receiving VNS. This observation raises the question of whether VNS may affect alertness. Malow and colleagues[69] reported the effects of VNS on wakefulness, as measured by the mean sleep latency test, in 6 adults with epilepsy. They found that patients who received VNS with lower levels of current (0.75-1.0 mA) had longer sleep latencies after 3 months of therapy than at baseline, but those who had received higher currents had even longer sleep latencies. This small study suggests that VNS may modulate wakefulness in a dose dependent manner.

A recent study[70] by Clark and colleagues hints at the potential for VNS to be used to investigate brain circuits involved in memory, learning and alertness. These researchers examined word-recognition memory in 10 patients enrolled in a clinical study of VNS for epilepsy. Vagus stimulation administered after learning, during memory consolidation, caused intensity-

dependent enhancement of word-recognition relative to sham stimulation. Other work by these authors and others has shown that vagotomy attenuates the memory enhancing properties of amphetamine, suggesting that these substances modulate emotional memory through messages about autonomic states to the brain through the vagus nerve.

Therefore, due to the known neuroanatomy of vagus connections into the brain, there is reason to hope that VNS might have other therapeutic applications, as well as advance understanding about the pathophysiology of these disorders.

Future of VNS

Better understanding of the brain effects of VNS might make it a more powerful intervention, especially if it will be found ways of VNS 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 in different neuropsychiatric conditions.

Deep brain stimulation (DBS)

Technique

The most anatomically discrete, and most invasive method of stimulating deep brain structures is called Deep Brain Stimulation (DBS). In this procedure, a thin electrode about the width of a human hair is inserted directly into the brain. Then different currents are applied at varying depths until the desired effects are found. Recently, DBS at different targets within the basal ganglia has become an appealing therapeutic alternative in late stage Parkinson's disease. High frequency (> 80Hz) electrical stimulation of the middle thalamus or subthalamic nucleus has been found effective in this chronic neurological disorder.[71] In contrast to stereotaxic surgery, i.e. pallidotomy or thalamotomy, the advantages of DBS are its reversibility, the individual adjustment of the stimulation parameters and the reduction of side effects and morbidity. Stimulation can be performed at high frequencies(> 50 Hz), which are thought to create a transient functional lesion and inhibit a brain region from normal participation in brain activity. Alternatively, low frequency stimulation may intermittently activate a region. Thus, high frequency DBS effects on emotions and tremor are likely the result of a "functional ablation", or the switching off and inhibition of on-going neuronal activity, although this is not well understood.[72-74]

Possible uses in psychiatry

Although DBS has not been used to treat depression, mood effects of DBS have been reported. In one patient with Parkinson disease (PD) who had never suffered from depression in her life, the testing of the stimulation caused the acute onset of tearfulness, sadness and despair. These symptoms remitted immediately when the surgeon moved the stimulator away from the substantia nigra, directly below the subthalamic nucleus (STN).[73] Transient acute depression was evoked 5 s after 130 Hz DBS of the left substantia nigra, and ceased 90 s after DBS was stopped.[73] In another report, Kumar and colleagues[74] found that uni- or bilateral DBS of STN in 2 subjects resulted in involuntary laughter, and triggered imaginative associations, and feelings of well-being, which lasted for several minutes until the stimulation intensity was lowered, or it was discontinued. This emotional reaction was accompanied with improvement of parkinsonian symptoms and led the authors to conclude that "the STN is part of a neuronal network that may influence the emotional state and cause laughter – or depression." A study in patients receiving STN-DBS, showed movement-related increased rCBF in the supplementary motor area, the cingulate cortex and the dorsolateral prefrontal cortex.[75] Early studies during diagnostic DBS prior to neurosurgical ablations have also demonstrated emotional reactions. Much of this work involved stimulation of the thalamus. For example, microstimulation of the nucleus ventrocaudalis (somatosensory) was accompanied with a strong affective component of visceral pain similar to that which was previously observed in a patient during a panic attack.[76] Weeping, anxiety and depression were reported to be elicited during neurosurgery in unanesthetized PD patients with 32 Hz stimulation for several seconds of ventral anterior, ventrooralis anterior and other thalamic nuclei as well as from pallidum, septum and hypothalamus.[77] Different emotional reactions have occurred while stimulating the nucleus ventrolateralis with a floating electrode.[78] Summarizing the effects of diagnostic and therapeutic DBS via long term implanted electrodes in a large sample of PD patients, Smirnov[79] indicated that positive emotional states occurred after stimulation of the centrum medianum area of the thalamus. Interestingly, high frequency (ablative) DBS as well as stereotaxic destruction of the anterior thalamic nuclei resulted in relief from intractable agitated depression.[80] And finally, the thalamus was one of the brain structures where Heath and colleagues recorded EEG correlates of pleasure during orgasm. The MUSC group has an ongoing project funded by the National Institutes of Health that builds on these observations by using interleaved DBS/fMRI to define the neuronal network associated with the STN and mood effects, and then to determine if stimulation of this network has therapeutic potential in treating depression in PD.

Future of DBS

Pioneering work studying mood effects in PD or obsessive-compulsive disease patients implanted with DBS devices is needed before one could have the neuroanatomical knowledge needed to use DBS in primary mood disorders. Because of its invasiveness, DBS would likely only be used for those patients who have failed less invasive techniques, including other minimally invasive brain stimulation techniques such as TMS and/or VNS.

Conclusion

The ability to non-invasively stimulate the brain in an awake alert individual is a real advance that neuroscientists have long dreamed for. The new techniques described in this overview that allow for the direct stimulation of brain regions with mini-

mal invasiveness are promising tools to investigate regional brain activity and to treat various psychiatric diseases.

Further research is necessary to firmly establish the efficacy and safety of these tools. As functional imaging tools reveal the relevant circuitry involved in several psychiatric diseases, TMS, VNS and DBS offer hope for translating these research findings into novel treatments.

Regardless of their clinical roles as new therapeutic techniques, the capacity of these novel procedures as research tools to focally alter brain activity should lead to important advances in the understanding of brain-behavior relationships.

Acknowledgements

Some of the studies discussed in this review were partially funded by grants from, or research collaborations with Dupont Pharma, Cyberonics, Medtronic, The National Alliance for Research on Schizophrenia and Depression (NARSAD), the Stanley Foundation, and NINDS RO1 NS40956-01.

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