[Frontiers in Bioscience 4638-4648, May 1, 2008]

The evolution of deep brain stimulation for neuropsychiatric disorders

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TABLE OF CONTENTS

1. ABSTRACT

Deep brain stimulation (DBS) is the most focal method for stimulating the human brain. In contrast to lesions, DBS is nonablative, with the advantages of reversibility and adjustability. Thus, therapeutic effectiveness can be enhanced and stimulation-related side effects minimized during long-term patient management. While DBS is an approved adjunct therapy for severe, medication-refractory movement disorders, it remains investigational in neuropsychiatry. However, experience to date, though limited, suggests that DBS may offer a degree of hope to patients with severe and treatment-resistant neuropsychiatric illness. Thus far, work in obsessive-compulsive disorder (OCD), the first psychiatric condition studied using modern DBS devices, has shown consistently positive results across multiple small-scale studies. Work in treatment-resistant Major Depressive Disorder (MDD) also suggests therapeutic potential in preliminary studies, generating cautious optimism for this indication. With the increase in potential applications, a number of clinical and preclinical research efforts have now focused on understanding the mechanisms of action of DBS. Further development of DBS for these and other illnesses with primarily behavioral symptoms will require thoughtful collaboration among multiple disciplines.

2. INTRODUCTION

2.1. The burden of depression

The term depression connotes a group of conditions that impose a serious public health burden (1). For unipolar type Major Depressive Disorder (MDD), conservative estimates find a population prevalence of 2.6%-5.5% in men and 6.0%-11.8% in women (2). Most (50%-85%) patients have recurrent episodes of depressive illness. In addition to marked distress, depression can cause profound disability, with pervasive impairment in marital, parental, social, vocational, and academic functioning. The Global Burden of Disease Study ranked depression as the leading cause of disability in adults in developed countries (3). For comparison, disability due to unipolar major depression is almost three times greater than that due to

chronic obstructive pulmonary disease (4). Death from suicide is a major complication (5). Moreover, depression is associated with increased mortality from co-occuring illnesses, such as cardiovascular disorders or cancer (6-7).

2.2. Phenomenology

MDD is usually treated as a categorical construct in research, albeit one that allows considerable heterogeneity of clinical presentation. However, depressive syndromes can also be described by continuous symptom dimensions. Factor analyses of depression rating instruments have generated a variety of resultant structures, which is not unexpected given the variations among the scales used and the clinical heterogeneity within groups of depressed patients studied. Some of the major symptom dimensions emerging in factor analyses are: depressed mood (a bias toward negative emotion), anhedonia (loss of pleasurable experiences), amotivation (impaired goal-directed behavior), energy, other somatic symptoms (sleep and psychomotor disturbances, food-intake and body-weight dysregulation), depressive cognitions (pessimistic thoughts, feelings of guilt, low self-esteem and suicidal ideation), cognitive impairments, and anxiety. Different symptom dimensions may be differentially associated with activity across brain regions and networks (8-10).

2.3. Pathophysiology

A thorough understanding of the causes and pathological processes underlying neuropsychiatric disorders, and specifically mood disorders, remains elusive. Evidence increasingly suggests that there are many genetic and environmental factors likely to be relevant to depressive syndromes at the population level, and interpretations tend to favor interactive models of genetic and environmental susceptibility, at the individual level (11-16). Translational work focusing on associations between neuroanatomical networks and psychopathology (i.e., phenomenology) has a relatively long history. It was proposed two decades ago that pathological changes in activity within cortical–limbic–thalamic–striatal networks might disrupt normal reinforcement contingencies, and contribute to the affective components of both psychiatric and neurologic disease states (17). Cortico-basal ganglionic circuits implicated in modulation of mood and reward signals have also figured prominently in neuroanatomical models of the pathophysiology of depressive illness which have been developed more recently based largely on functional neuroimaging (18-19). A recent review (2) described how this circuitry may relate to symptom improvement after lesion procedures that, though derived empirically (20-21), target different nodes within these networks.

2.4. Pharmacologic treatments

Conventional antidepressants were largely developed after serendipitous observations that agents such as iproniazid and imipramine (originally developed for tuberculosis and psychosis, respectively) improved depression in patients treated for other illnesses. The insight that agents with effects on monoamine neurotransmitter systems were associated with depression improvement led to successful attempts to "improve on serendipity," resulting in the development of drugs with fewer side effects, such as selective serotonin reuptake inhibitors (SSRIs). Currently, over twenty antidepressants are commonly used. The drugs are usually grouped by their chemical classes or pharmacological actions, such as: 1) tricyclics and tetracyclics; 2) selective serotonin reuptake inhibitors (SSRIs); 3) monoamine oxidase inhibitors (MAOIs); and 4) those affecting other or combinations of biogenic amine systems. Medications from different classes are frequently combined in practice, particularly in refractory cases.

2.5. Treatment resistance

Conventional antidepressant drug treatments, while effective, have limitations. Medications, often used in conjunction with certain psychotherapies, alleviate depression symptoms in many but not all patients. Though antidepressant efficacy has been well demonstrated in clinical trials, antidepressant monotherapy is estimated to effect and maintain remission in only 45-50% of MDD patients. Only 20-30% of patients will experience remission with their first antidepressant trial, and greater than 40% of patients with MDD will remain refractory to all standard medication treatments for depression (22). Severe depression which resists medication and psychotherapies is often treated with Electroconvulsive Therapy (ECT), still a therapeutic gold standard after 70 years. ECT, however, is associated with significant adverse effects, particularly memory loss, which can limit its acceptance. Moreover, ECT's therapeutic effects are transient in a large proportion of patients, and so continuation or "maintenance" treatment may be needed (23). Although different definitions and levels of "treatment resistance" have been developed (24), it is clear that individuals with the most resistant illnesses, those who have an inadequate response to medications, psychotherapies, and ECT, currently have little prospect of recovery.

Several non-ablative techniques directly or indirectly alter the electrical activity of the brain are in clinical use or are in development for depression. In ECT, electrical current is delivered to the brain across the large electrical resistance of the scalp and skull. Transcranial Magnetic Stimulation (TMS) and Magnetic Seizure therapy (MST) magnetically induce electrical currents in brain tissue using an electromagnetic coil placed on the scalp. Vagus Nerve Stimulation (VNS), in contrast, uses electrodes wrapped around the left vagus nerve in the neck to activate its afferent projections to target nuclei and related neural circuits. Neurosurgical intervention has remained a therapeutic option for patients with otherwise untreatable and severe psychiatric illness. Ablative procedures like cingulotomy and capsulotomy have been best known in the U.S. Such procedures, in which focal lesions are produced, are currently in use for a small number of patients with intractable Obsessive-Compulsive Disorder (OCD) and depression. Although irreversible side effects of brain lead implantation are possible, a major advantage of DBS compared to conventional ablative neurosurgery is that the effects of stimulation itself are reversible. The implantation of the lead is not thought to damage brain tissue beyond transient edema and the small

tissue volume displaced by the lead itself. The stimulation can be modified or discontinued in the event of DBS-induced side effects.

3. DEVELOPMENT OF DBS FOR PSYCHIATRY

3.1. History

Development of DBS for psychiatric illness, and specifically for depression, is not a new idea, although the devices are new and the theoretical models of depression neurocircuitry have advanced. For example, in 1948, Pool used implantation of a silver electrode in the caudate nucleus in an attempt to treat a woman with depression and anorexia. But it is the introduction and technical refinement, over the past fifteen years, of DBS for the treatment of movement disorders that resulted in a renaissance in such functional neurosurgery. The treatment has FDA-approved uses for tremor and Parkinson disease and, under a Humanitarian Device Exemption, for dystonia. These developments spurred renewed interest in the use of such procedures for the treatment of other refractory neurologic conditions. Investigational uses of DBS for neurologic illness include epilepsy, pain, cluster headaches, tardive dyskinesia, Gilles de la Tourette syndrome, brain injury and persistent vegetative states.

As noted above, DBS was conceived as a treatment for psychopathology at least as early as 1948, when caudate nucleus stimulation was tried for treatment of depression and anorexia. In work that began soon afterwards, and was contemporary with Sem-Jacobsen's, Heath and colleagues (25) stimulated the "septal region," an area including the ventral anterior capsule (VC) and ventral striatum (VS) that was just posterior to our current target. Heath chose it, in part, because tumors there and nearby in the forebrain had been related to psychiatric symptoms. Heath, et al (25) selected 20 patients with heterogeneous symptoms including delusions, hallucinations, poverty of speech or near mutism, depression, and compulsions, though all had a formal diagnosis of schizophrenia. Stimulation was limited to 1-3 days after electrode implantation, at amplitude of 2-15 mA. Three of the 20 patients had "no objective signs," and 2 more "could not be evaluated," during stimulation. The others had these acute effects: "…patients became more alert [13 of 15];…had increased motor activity and spontaneous [speech] production; …[in] previously almost inaudible or expressionless [subjects], speech became louder and enunciation clearer and inflection more appropriate" [in 5 who had been the least verbal]. One of these, "who had been almost mute, became talkative and later almost hypomanic." Three patients appeared acutely more tense, two less so (4).

Accompanying and subsequent (following discontinuation of stimulation) behavioral changes included improved social interaction and enhanced emotional expression. As observed by Heath, et al (25), DBS subjects demonstrated "…ability to relate to other people, increased responsiveness to pleasure, gradual appearance of a sense of humor, and more overt expression of anxiety and ambivalence," as well as improved functioning, e.g., "Less negativism…everyday problems were approached more realistically and more interest was shown in ward activities." Eleven patients, described as generally "idle, seclusive, and withdrawn before operation, afterward participated actively in some or all of the ward activities." Improved emotional responsiveness in social settings was "even more dramatic." "Twelve patients showed significant improvement in their ability to relate to other people," one of the "outstanding aspects" of which was the "emergence of pleasurable feelings." Nine patients showed the "development of humor." Monroe and Heath believed that "…patients who respond particularly well … [were those] whose main abnormalities seem to consist of flattened affect or disturbed motor behavior" (4). The time course and persistence of therapeutic benefit after stimulation ceased is not entirely clear in this work, although effects apparently could be transient. Some lasting or emerging benefit might have been due to concerted multidisciplinary therapies also used in these patients, described as a "total push" approach - which had, however, also been tried before stimulation without improvement. In our own experience to date, ongoing DBS has been required for persistent behavioral and emotional change.

This work from the 1950s did not use modern research standards with regard to diagnostic or severity measures, limiting interpretation. However, recorded observations of acute and subacute DBS effects by Monroe and Heath (26) have high face validity as manifestations of affective state. These include enhanced production, volume, and prosody of speech; greater affective range, social relatedness, sense of humor, functioning, and increased level of activation or hypomania.

3.2. Affect and mood effects observed during depth electrode stimulation

The recent observations of affective/mood effects of DBS used for movement disorders (discussed below) are also important in pointing to regions and networks that might represent potential therapeutic targets. Recent observations, taken together with results of early attempts to both map focal brain stimulation effects and to use stimulation therapeutically, provide a convergence of data supporting the conclusion that there are *multiple* brain targets that may be clinically useful for depression. Understanding the potential points where brain stimulation effects may converge at the systems level is now a reasonable goal, given more recent technical developments. It remains useful to consider the efforts of an earlier era, with a view towards eventually integrating key findings with our evolving anatomical models of pathophysiology.

DBS for movement disorders is associated with benefits across several dimensions of health-related quality of life. There are numerous published reports demonstrating safety and efficacy of DBS for intractable movement disorders. For example, clinical trials of DBS of the STN and GPi for Parkinson disease have shown overall improvements of 41-67% as measured by standardized ratings of motor symptoms. In current practice, patients with tremor and Parkinson disease who are potential DBS

candidates have either medication intolerance of significant illness that has proven refractory to the best conventional medication therapies. The field's advancing understanding of the anatomical networks underlying pathophysiology of movement disorders has subsequently informed research on DBS as an investigational treatment for other syndromes.

Starting in the early 1950s, Sem-Jacobsen studied and recorded effects of acute and chronic (several days) stimulation in 220 movement-disordered patients over more than two decades (27). Most patients subsequently underwent lesion procedures for Parkinson's disease, but some were studied before ablative surgery. Stimulation of sites throughout the frontal lobes induced affective/mood changes, with apparent selectivity noted for stimulation of ventromedial brain areas. Positive effects, ranging from mild relaxation and feelings of tranquility (most common) to marked euphoria, were observed twice as often as negative mood effects, which ranged from mild tension and/or mild sadness (most common), to more pronounced sadness and overt sobbing necessitating stimulation cessation.

The same responses were elicited by unilateral stimulation on the right (at 327 sites) or left (316 sites), with no significant laterality differences (27), suggesting stimulation of many different brain loci could induce positive and negative mood states. Further, effects of opposite affective valence (e.g., mild tension and sadness vs. mild euphoria) were sometimes seen with stimulation of sites 5-10mm apart in the same individual.

Modern therapeutic uses of DBS for movement-disordered patients have at times entailed dramatic effects on the affective state of patients. In a case report, a patient without a prior history of depression illustrated modulation of a mood-regulating network by DBS in the region of the STN. When the electrodes, implanted slightly below the STN, were activated, the subject experienced severe dysphoria that remitted when stimulation was interrupted. Other marked affective effects of DBS of the STN, or Fields of Forel/zona incerta in Parkinson patients have been described, including hypomania, merriment and involuntary laughter, depressive dysphoria, anhedonia, apathy, and blunted affect. These findings are extremely intriguing, although their relevance for development of therapeutic DBS for neurologically intact patients with primary depressive illness remains to be determined with more precise techniques and more rigorous scientific method.

DBS of the STN in two patients with severe Parkinson Disease who also had moderately severe OCD produced improvement in OCD symptoms by two weeks after the start of therapy. In one of the two patients, OCD improvement was seen despite little change in Parkinson symptoms. Similar effects were seen more recently in an additional case, and a controlled trial of STN stimulation is underway by a collaborative group of investigators in France.

3.3. DBS for obsessive compulsive disorder

As described in more detail elsewhere, the first contemporary report of DBS for psychiatric illness focused on treatment of OCD. The rationale for development of DBS for OCD in large part paralleled that for tremor, Parkinson disease, and dystonia, where DBS was applied to structures where lesions had therapeutic effects. Small-scale case studies of severely ill, treatment-resistant OCD patients treated with DBS of the anterior limb of the internal capsule and/or the adjacent striatum have been published. (28-33) These reports have supported the therapeutic potential of DBS in this population, and have suggested that DBS is generally well-tolerated (34).

For any surgical intervention for psychiatric illness, a key issue is long-term outcome. Therapeutic treatment decisions need to be made based on the probability that therapeutic effects will be durable while taking into account the burdens imposed by potential adverse effects. Based on our own experience and that of others with ablative lesion procedures for OCD (21), it is very likely that beneficial changes in symptom severity, functioning, and quality of life may develop gradually in individuals who have had chronic and severely impairing illnesses which have disrupted not only the patients' functional capacities but also their family and social relationships.

Our research group very recently reported (35) on ten OCD patients meeting stringent criteria for severity and treatment resistance who underwent DBS of a ventral internal capsule/ventral striatum target, following initial work by Nuttin and colleagues beginning in 1998. These patients had quadripolar stimulating leads implanted bilaterally in the VC/VS. DBS was activated openly three weeks later. Mean Yale-Brown Obsessive Compulsive Scale (YBOCS) scores decreased significantly from baseline to 36 months ($p < 0.001$). Four patients had at least 35% threshold decrease in YBOCS severity at 36 months, and scores declined between 25% and 35% for two others, consistent with the categorical response definition commonly used in modern treatment trials for OCD. Mood and non-OCD anxiety symptoms improved in these patients, and there was evidence of improvements in self-care, independent living, and work, school, and social functioning. Surgical adverse effects included asymptomatic hemorrhage (n=1), intraoperative seizure (n=1), and superficial infection (n=1). Psychiatric adverse effects included transient mood elevation, which met diagnostic criteria for a hypomanic episode (n=1).

Long-term effects observed by our research group during open-label VC/VS DBS include worsened depression followed by a more gradual exacerbation of OCD symptoms, at the point when DBS is interrupted by stimulator battery depletion. These observations are in accord with a hypothesis of overlapping neurocircuitry mediating at least some dimensions of depression and OCD. Another interesting observation from this OCD patient series is that two patients had sufficient

improvement with VC/VS DBS to be able to engage in adjunct cognitive behavioral therapy (CBT).

4. TECHNICAL ASPECTS OF DBS

4.1. Implantation surgery

Modern stereotactic surgery combines multiple imaging modalities, computerized surgical navigation, and often physiological mapping and to allow for targeting of intracranial structures with millimeter precision. As opposed to epidural and subdural surface electrodes, DBS involves the placement of multi-contact brain leads in sub-cortical nuclei or in specific white matter tracts. The surgeon drills burr holes in skull bone under local anesthesia and places the electrodes, guided by imaging and precise stereotactic landmarking. The subject is typically sedated but awake during the surgery.

Intraoperative physiological mapping is routine clinical practice for movement disorders, where targets are cell nuclei with characteristic physiological signatures, i.e., the globus pallidus interna (GPi), subthalamic nucleus (STN), or thalamic nuclei. A number of methods of intraoperative physiologic verification of the anatomical target exist: microelectrode recording (MER), semimicroelectrode recording, and macrostimulation. Both microelectrode and semimicroelectrode recording attempt to define the boundaries of a given structure based on the known spontaneous and/or evoked electrical activity of that structure and surrounding structures. In some movement disorders, patients' responses to intraoperative stimulation may help guide the final positioning of the electrodes. In DBS for essential tremor, initial electrode placement is guided via stereotactic coordinates. Changes in neuronal firing patterns are monitored as probes are lowered as a further guide to placement. With this approach, evidence that the electrodes have reached the desired target is generated by concurrent activation of the electrodes and cessation of the patient's tremor.

In contrast, the placement of DBS stimulating leads for dystonia and for psychiatric disorders does not rely on intraoperative effects. Typically in a second surgical phase, the surgeon places the "pacemaker" (also known as an implantable neurostimulator or pulse generator) subdermally in the upper chest wall and connects it, via extension wires tunneled under the skin, to the electrodes in the brain.

4.2. Stimulation technique

The electrode used for DBS is typically referred to as a "lead." Each lead has multiple electrode contacts, which are the sites of stimulation. A commonly-used lead is 1.27 mm in diameter, implanted stereotactically with millimeter accuracy into specific brain targets as described above. There are typically four or more platinum/iridium electrode contacts on each lead. Usually one lead is implanted on each side in a symmetrical fashion, for bilateral stimulation. Available DBS device systems are undergoing rapid technical refinements [Medtronic, Inc. (Minneapolis, MN, USA), Advanced Neuromodulation Systems Inc. (Piano, TX, USA) or (NeuroPace, Inc. Mountain View, CA, USA)]. Currently only the Medtronic devices are approved for therapeutic brain stimulation, and others remain investigational with regard to regulatory status.

Since the leads have independently programmable electrode contact sites, the anatomical extent of stimulation is adjustable. By configuring a positive, negative or no charge at each of the contact sites, the shape and size of the stimulation field can be varied greatly. Chronic stimulation can thus be unipolar, bipolar or multipolar, as each of the electrode contacts can be used as an anode or cathode. The frequency, intensity, and pulse width are also programmable for each lead, within safety limits that restrict the maximum density of the electrical charge induced. These limits are intended to prevent tissue damage due to excessive current. Stimulation parameters include frequency ranges of 2-185 Hz, a voltage range of 0-10.5 volts, and pulse widths ranging from 60 to 450 microseconds. High frequency DBS (HF-DBS) is used most often for neurological conditions, a practice that has been followed for psychiatric indications. The stimulators are programmed via a portable computer system which communicates with the implanted generator via telemetry. The patient holds the programming "wand" up to his/her chest wall area over clothing while the programming clinician enters desired stimulation parameters or interrogates the system for data regarding system integrity and battery status through a handheld or laptop computer. Stimulation can be delivered continuously or intermittently, cycling on and off during fixed time intervals. Patient self-programming devices are also available. These allow patients to activate and deactivate the stimulator via handheld controllers, and to modify a subset of the stimulation parameters within given limits set by the programming clinician. Such devices are not yet available for use in pilot studies with psychiatric patients.

4.3. Customizing therapy

This large potential parameter space provides both an opportunity to optimize the therapy, and a challenge to doing so. In this sense, DBS is similar to rTMS and VNS, in having a large number of potential combinations of stimulation parameters. Despite this challenge of parameter optimization, for any given target, stimulation can be optimized to enhance a therapeutic response or to minimize adverse effects.

5. DBS FOR PRIMARY DEPRESSIVE ILLNESS

The potential application of DBS for the treatment of refractory depression is supported by a number of factors. First, the success of DBS in the treatment of neurologic conditions is dramatic and long-term. Second, the feasibility and success in refractory psychiatric conditions has been demonstrated in severe cases of OCD. Finally, the potential for dramatic effects on mood, affect and other dimensions of affective illness has been observed throughout the evolution of DBS treatment for both neurologic and psychiatric conditions. In fact, in many cases, observed improvements in mood and affective symptoms emerge prior to the resolution of target

symptoms in OCD. The question of whether immediate or very early changes in mood, as demonstrated during intraoperative lead testing or immediately post stimulation, may be reliable predictors of long-term treatment success remains open. However, as has been evidenced through many years of experience with psychotherapeutic, pharmacologic, and electroconvulsive treatments, dramatic or immediate shifts in affect are generally not reasonable therapeutic goals. The most effective treatments will be both safe and sustainable.

The terms primary and secondary illness tend to be used somewhat differently in psychiatry and neurology. Descriptive psychopathology in psychiatry often designates a diagnosis as "primary" when its symptoms are what a patient finds most distressing and for which the patient seeks treatment. In this tradition, which understandably arose in a field where the pathogeneses of illnesses were unknown, disorders which appear later in the clinical course, or those judged to be less pressing clinical issues, can be viewed as "secondary." Secondary psychiatric illnesses are often referred to simply as "comorbid." Advances in clinical neuroscience are gradually moving the field towards a position more familiar to neurologists, in which 'primary' mechanisms implicate, if not pathogenesis, at least central pathophysiologic processes mediating key features of psychiatric disorders.

Results of research investigating DBS for primary depressive syndrome have been described for stimulation at several different neuroanatomical targets, as reviewed below. Randomized controlled trials, the scientific standard for antidepressant efficacy, have not yet been conducted for any DBS target.

5.1. Defining the antidepressant target in modern DBS

As in movement disorders, development of specific structural targets for DBS for psychiatric illness has derived, in part, from clinical outcomes observed following lesion procedures. A group of lesion procedures with overlapping targets within cortico-basal- thalamic circuits (anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy) have appeared effective in severe and resistant depression in multiple open studies, including large series (more than 1000 patients) for subcaudate tractotomy.

5.2. Inferior thalamic peduncle (ITP)

A recent case report (presented at the World Stereotactic and Functional Neurosurgery Society Meeting, Rome, 2005) described effects of bilateral DBS lead placement and stimulation in the ITP in a woman with refractory depression (36). Stimulation at this target, via effects propagated by ITP fibers which continue rostrally in the ventral portion of the anterior limb of the internal capsule, would be expected to modulate projections of the dorsolateral prefrontal cortex (DLPFC), of the orbitofrontal cortex (OFC), and of the ventromedial striatum, as they extend to the dorsomedial and intralaminar thalamus. A substantial period of clinical benefit was observed following lead insertion itself, before initiating stimulation of ITP, perhaps reflecting a "microlesion" effect (mass effect of the peri-electrode edema after implantation), a placebo response, or the natural waxing/waning course of the depressive illness itself. With subsequent, chronic IPT stimulation, however, longer-term improvements were noted, particularly in association with relatively low stimulation intensities. This is of interest given that fibers coursing from rostral structures become more compact as they enter the ITP. Further exploration and follow up will be necessary to establish whether this approach is both safe and beneficial.

5.3. Subgenual cingulate (Brodmann area 25 region)

Recently, researchers armed with a body of functional neuroimaging research have targeted neuronal networks implicated in both the normal experience of sadness, in symptoms of depressive illness, and in responses to treatment (37). Using positron emission tomography (PET), the group observed a link between changes in metabolism in subgenual cingulate cortex (SCC), Brodmann area 25 (BA25), and response to antidepressant medications. They then used DBS to target these networks in refractory depression. Six patients were selected for notable but not extreme levels of treatment resistance, and for a relative lack of psychiatric comorbidity. Unblinded stimulation of white matter tracts adjacent to SCC was associated with rapid improvement, with substantial mean benefit at one week after stimulation initiation. Chronic DBS for up to 6 months was associated with sustained remission of depression in 4 of the 6 patients. Three patients showed decreased metabolism in BA25 compared with preoperative baseline PET scans, consistent with studies of responses to some other therapeutic modalities for depression. It is intriguing that the subgenual white matter tracts targeted appear to overlap with those targeted by clinically beneficial 1970's lesion procedures to treat mixed depressive and anxiety pathology (38).

5.4. Ventral capsule/ventral striatum (VC/VS)

Results from small-scale or case studies of severely ill, treatment-resistant OCD patients treated with DBS of the anterior limb of the internal capsule and/or the adjacent striatum have supported the therapeutic potential of DBS in OCD. Onset of VC/VS stimulation was associated with the rapid onset of mood enhancing and anti-anxiety effects in OCD patients. Rapid worsening in these same clinical domains was noted with cessation of VC/VS stimulation. DBS-induced changes in mood and nonspecific anxiety symptoms seemed to precede observable changes in core OCD symptoms. In line with these observations in our OCD patient population, we undertook long-term studies of DBS at this same target in patients with severe and disabling primary major depression. The depressive syndromes of the patients who volunteered for VC/VS DBS were refractory to multiple adequate trials of antidepressant medications, to medication combinations from multiple classes and with augmenting agents, to standard psychotherapy, and to bilateral ECT. Preliminary results indicate clinically significant antidepressant responses in half of the 15 patients studies thus far (39). Induction of transient, reversible mood elevation, which has occasionally reached the diagnostic

threshold for hypomania, has been the most significant adverse effect of active stimulation. This effect has appeared to be stimulation intensity-dependent, and has become less problematic following refinements to our stimulation titration methodology.

5.5. Antidepressant mechanism of action of DBS

Most likely, brain stimulation exerts its effects via a number of differing but interrelated mechanisms-- across system, neuronal and genetic levels-- each of which may come into play depending on the site of stimulation, the illness being treated, and the stimulation parameters used. A putative mechanism of antidepressant or antianxiety action of DBS is not known, but there is evidence supporting a number of potential mechanisms. HF-DBS, (approximately 100Hz or greater), has been proposed to modify neurotransmission, for example, via synaptic fatigue or "neural jamming" (the functional suppression of spontaneous neuronal signaling within the affected circuits) (40-42). Either of these phenomena would in effect produce a "functional lesion," mimicking the effect of ablative lesion procedures via a nondestructive mechanism. This is not an exact parallel, since the clinical effects of lesions and of DBS in movement disorders do not always correspond. The limited data currently available from DBS therapy for psychiatric disorders suggest a time course for effect onset which is not consistent with that observed for therapeutic lesion procedures. For example, some therapeutic effects of stimulation appear more rapidly than those seen following lesions. Other proposed mechanisms of DBS action include direct inhibition of spike initiation at the level of the neuronal membrane via blockade of voltage-gated ion channels, and activation of GABA-ergic inhibitory terminals. A process known as stochastic resonance, in which stimulation actually enhances information flow within key neural pathways, may work to reduce symptoms by reducing chaotic information processing. It is possible that high-frequency electrical stimulation produces several of these effects simultaneously or sequentially within the brain, with the specific therapeutic effects depending on variables such as the spatial distributions of voltages and currents relative to the relevant group of neural elements (41). It is also possible that the effect of DBS on the functional state of a structure or pathway changes as distance from the electrode increases.

Most likely, the clinical effects seen with DBS reflect the complex combination of inhibition and activation of cell bodies and axons, and depend on the orientation of the electrode, the cytoarchitecture of the structure being stimulated, and the quality (i.e., frequency, pulse width, and duration) of stimulation. Active research in clinical and preclinical laboratories is expected to help identify which of the proposed physiological mechanisms are most relevant to the clinical effects of DBS. Ongoing research efforts by our group and others include investigating the acute and long-term functional effects of DBS for OCD and MDD using PET imaging (6), as well as work examining potential predictors of response to DBS for OCD (7). Recent findings regarding the compatibility of DBS devices with certain MRI systems have opened additional avenues for research on neuroanatomical networks affected by DBS. The MRI-based DBS research remains technically challenging, but will be superior to PET techniques for study designs that require reproducible scan conditions. Such investigations hold considerable promise for elucidating the therapeutic mechanism of action of DBS for psychiatric disorders.

Until a putative DBS mechanism of therapeutic action for psychiatric disorder can be demonstrated, available data from functional neuroimaging studies suggest hypotheses about activity in neural networks that may be associated with clinical OCD symptomatology. A considerable body of published imaging research findings implicate fronto-basal brain networks in mediating OCD symptoms and, possibly, in mediating the response to conventional OCD treatments. The most common findings in untreated obsessive-compulsive patients are increased glucose metabolism or blood flow in the medial and orbitofrontal cortex (OFC) and anterior cingulate gyrus, in the caudate nucleus, and, to a lesser extent, in the thalamus. These imply a pathophysiologic dysregulation in the basal ganglia/limbic striatal circuits that modulate neuronal activity in and between the OFC and the dorsomedial thalamus. The observed localized elevations in brain activity are, to varying degrees, accentuated during symptom provocation, and effective treatment of OCD with medications or behavior therapy tends to normalize activity in these same regions. One might speculate that modulation of these circuits by DBS could exert therapeutic effects by reducing drive to engage in repetitive, stereotyped behaviors and alleviating the negative emotional charge associated with such behaviors.

With regard to the neuroanatomy of MDD, several regions have been indirectly implicated. Sadness and depressive illness are both associated with decreased activity in dorsal neocortical regions, and with relatively increased activity in ventral limbic and paralimbic areas. Relative to that measured in healthy control subjects, MDD patients have shown increased regional cerebral blood flow and metabolism in the amygdala, orbitofrontal cortex and medial thalamus, while relative decreases have been observed for MDD patients in the dorsomedial/dorsal anterolateral PFC, subgenual ACC and dorsal ACC (42-43). Though these primarily cross-sectional findings cannot distinguish primary processes relevant to pathogenesis from more "downstream" pathophysiologic consequences, dysregulation in these regions is thought to be related to the clinical syndrome characteristic of Major Depression (i.e. mood, motor, cognitive, vegetative symptoms), and as such may be involved in the mechanism of DBS antidepressant action. Other important regions implicated in the pathoetiology of depressive syndromes include the hippocampus, insula and midbrain monoamine nuclei, as well as structural abnormalities such as reduction in volume or glia density. Future DBS research examining the impact of therapeutic stimulation on these structures, pathways, and regions in MDD populations will help clarify the biological basis of the disorder and inform our understanding of how the treatment produces relief from MDD symptoms.

6. ADVERSE EFFECTS

The complications of DBS can be separated into those related to the surgical procedure, to active stimulation, and to the device. Some adverse effects such as clinical deterioration observed in clinical trials of DBS therapy may of course also be related to the natural course of the underlying illness. The major risks of device implantation include seizure, intracerebral hemorrhage, and infection. Experience with DBS for movement disorders indicates that these adverse effects range from less than 1% per procedure for seizure, to about 2-3% for hemorrhage (with a mortality rate up to 1.6%), to 4-9% for infection. The device-related complications include fracture of leads, disconnection, lead movement, and malfunction. These are less common with increasing surgical expertise and evolution of device technology. In addition, there have been rare but very serious side effects when patients with implanted DBS systems were exposed to therapeutic ultrasound or diathermy. Not surprisingly, when DBS is effective, subsequent battery depletion may result in symptom re-emergence.

Adverse effects due to the actual stimulation are the most common type observed, but these are fully reversible with changes in stimulation parameters. Many stimulation-related effects have proven transient, even without changes in parameters. Stimulation-induced sensorimotor effects can include parasthesias, muscle contraction, dysarthria, and diplopia. DBS has produced marked mood/affective changes in movement-disordered patients (44-45). Side effects in memory, impulsivity, and cognition have also been reported (46). As in movement disorder populations, patients with primary neuropsychiatric illness may experience untoward effects including changes in mood, suicidality, impulsivity, anxiety (e.g., panic), and other symptoms (e.g., obsessive thoughts or compulsive urges). Distinguishing adverse effects of stimulation from symptomatology of the illness being treated may represent a challenge at times.

7. ETHICAL CONSIDERATIONS

As discussed above, DBS is now a conventional therapeutic option for intractable movement disorders. The efficacy of the procedure is well established, although questions remain about the optimal stimulation targets and "dosing" techniques for movement disorders. While serious adverse events are possible, the overall side effect burden is favorable for individuals who cannot benefit substantially from standard therapies. DBS has therefore become useful therapeutic option in an otherwise untreatable group of patients who experience tremendous suffering and functional impairment.

Recent rapid growth in interest in DBS as a potential treatment for patients with severe neuropsychiatric illness is not surprising. Patients with treatment-resistant depression as well as those with other severe disorders of mood, thought, and emotion regulation experience extreme distress and inability to participate in social and occupational life. Hopelessness and suicide are common outcomes for individuals who feel they have exhausted all available treatment options without relief. While there are strong parallels between the existing application of DBS for intractable neurological illness and its potential use in neuropsychiatry, there are also noteworthy differences. The most salient of these arises from historical experience in treatment for profoundly mentally ill persons. Special concern arising over the use of modern neurosurgical interventions for psychiatric illnesses is mainly the legacy of the widespread use of early destructive procedures, particularly frontal lobotomy, in the mid-20th century. Many patients underwent frontal lobe surgery before adequate long-term safety data were obtained, and without careful characterization of their primary disorder. Tragic consequences were reported and remain a vivid reminder of the need for caution in this area. The current practice of psychiatric neurosurgery in place for DBS research trials is much more refined, restricted and regulated. Candidates must meet stringent criteria for symptom severity and for resistance to conventional, multimodal therapies. DBS is an invasive procedure, and while it is non-ablative in nature and theoretically reversible with interruption of stimulation, evidence supporting its use in psychiatric disorders is limited to the experiences observed for approximately 50 OCD patients worldwide and even fewer for MDD.

8. PERSPECTIVE

8.1. Long-term follow-up

For any surgical intervention for psychiatric illness, a key issue is long-term outcome. Treatment decisions, particularly when surgical intervention is required, need to be made based on the probability that therapeutic effects will be durable, and that the balance of potential side effect burden and efficacy is reasonable. Patients with severe, chronic, and highly resistant psychiatric illness typically require multiple treatment modalities to support their daily struggles and process of recovery. Particularly with DBS, frequent and long-term (i.e. over 5 of more years) follow-up visits are necessary to adequately assess the extent of clinical response across multiple symptomatic and functional domains. Particular attention should be placed on feelings of hopelessness that may arise in patients undertaking investigational treatments thought to represent "last resort" measures. Suicide has been reported in patients placed on waiting lists for psychiatric neurosurgery and for an OCD patient who did not experience improvement in an investigational trial of DBS.

8.2. Research protocols for investigational treatment with DBS

An interdisciplinary group of collaborators, which began to systematically study the effectiveness and safety of DBS in psychiatric illness in the late 1990s, has set forth recommendations for psychiatrists and neurosurgeons contemplating use of DBS for psychiatric indications. Until FDA approval, treatment with DBS should be limited to that delivered in approved research protocols which are subjected to initial and ongoing review by an institutional review board (U.S.) or ethics committee.

In the U.S., there is additional review of IRB-approved DBS studies required by the FDA, via the Investigational Device Exemption (IDE) mechanism. Careful psychiatric assessment with regard to diagnosis, illness severity and suitability of a candidate for inclusion in a DBS protocol, is essential. Procedures for establishing a history of resistance to standard therapies also should include detailed consideration of the adequacy and quantity of past and ongoing psychosocial/behavioural, pharmacological, and somatic treatment approaches undertaken for each individual subject. It has also been proposed that potential candidates for psychiatric DBS also undergo independent consideration by an interdisciplinary review committee with appropriate expertise, including bioethics. DBS research is optimally conducted at a specialized academic centre with expertise in the treatment of patients with the neuropsychiatric condition being studied, and with a neurosurgical team experienced in DBS procedures. Recent experience with DBS in psychiatry has produced updated recommendations and guidelines for research teams (47). In anticipation of gradual expansion of research and clinical uses of DBS in psychiatry, issues of training and interdisciplinary collaborations are starting to be addressed (8).

8.3. Summary

DBS as an investigational treatment in neuropsychiatry has generated considerable interest. Preliminary data with OCD and MDD patients are encouraging. The pathophysiology of these conditions is poorly understood, leading to investigation of therapeutic effects at several different DBS targets. Although its mechanisms of therapeutic action are not completely understood, DBS can precisely target regions and circuits deep within the brain that are hypothesized to be centrally involved in neuropsychiatric disorders. Relative to surgical lesion therapies, DBS offers the advantages of reversibility and adjustability, which might permit effectiveness to be enhanced or side effects to be minimized. While results from pilot studies suggest DBS may offer a degree of hope for patients with severe and highly treatment-resistant neuropsychiatric illness, controlled trials have not yet been conducted to fully evaluate efficacy and safety. Research to realize the potential of DBS in this domain requires a considerable commitment of resources and time across disciplines including psychiatry, neurosurgery, neurology, neuropsychology, bioengineering, and bioethics. Limited evidence available at present suggests that, with the appropriate multidisciplinary work, cautious optimism about the role of DBS in psychiatric treatment is justified.

9. ACKNOWLEDGMENTS

We would like to thank Cynthia Read, M.A. for her generous editorial assistance.

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Key Words: Deep brain stimulation, DBS, Depression, Ventral Anterior Capsule, Ventral Striatum, Neurosurgery, Psychiatry, Review

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