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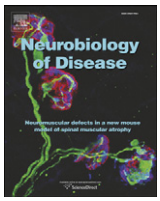

Review

Update on deep brain stimulation for neuropsychiatric disorders

Herbert E. Ward [a,*], Nelson Hwynn [b], Michael S. Okun [c]

[a] University of Florida Department of Psychiatry, McKnight Brain Institute, Movement Disorders Center, PO Box 100283, Gainesville, FL 32610-0383, USA
[b] University of Florida Department of Neurology, McKnight Brain Institute, Movement Disorders Center, Gainesville, FL, USA
[c] University of Florida Departments of Neurology, Neurosurgery, and Psychiatry, McKnight Brain Institute, Movement Disorders Center, Gainesville, FL, USA

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ABSTRACT

Deep brain stimulation (DBS) has proven a powerful treatment for medication refractory movement disorders. Success in this group of patients has allowed preliminary studies of DBS to proceed in severe and medication resistant cases of depression, obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). Pathophysiological and imaging studies along with attempts at lesioning the basal ganglia, have offered clues as to nodes in the circuitry that may be amenable to neuromodulation. DBS in neuropsychiatric illness has offered hope, but at this time rigorous screening by interdisciplinary and ethical teams should be employed when establishing treatment candidacy. A cautious approach to these disorders utilizing institutional review board approved research protocols will hopefully shed light onto patient selection and brain target(s) for each disorder. We need to keep an open mind as we move forward and especially that rational therapy may need to be patient and symptom specific. This review will summarize each disorder (depression, OCD and TS), review pathophysiology (both known and speculated), and update the current observations on DBS in each neuropsychiatric condition.

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Introduction

Deep brain stimulation (DBS) has emerged as an evidence based option for medication refractory basal ganglia abnormalities (Ardouin et al., 1999, Benabid et al., 1993, 1998, Cif et al., 2003, Coubes et al., 2000,

* Corresponding author. Fax: +1 352 265 7053.
E-mail address: hward@ufl.edu (H.E. Ward).
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2004, Krack et al., 2003, Kumar et al., 2000, Pollak et al., 2002, Rosenow et al., 2004, Lyons and Pahwa, 2004, Lozano and Mahant, 2004). The advent of DBS has opened the door for treatment of other disorders involving the basal ganglia circuitry. This circuitry is composed of a family of segregated motor and non-motor pathways (Alexander et al., 1986). We can now intervene or "neuromodulate" in these pathways in an attempt to alleviate motor and non-motor symptoms. Recently, neuromodulation utilizing DBS has been introduced for depression, obsessive-compulsive disorder, and Tourette's syndrome. In this review, we aim to update the reader on each of these disorders with a discussion on (1) the circuitry involved, (2) the results of best medical treatment, and finally (3) the rationale, patient selection, and current results of DBS.

DBS for depression

Depression

Major depressive disorder affects approximately 18 million people in the US and represents the fourth most disabling disease worldwide (Kessler et al., 2005, Lopez et al., 2006). In developed countries, depression has been ranked as the leading cause of disability by the Global Burden of Disease Study (Lopez and Murray, 1998). Symptoms may include depressed mood, anhedonia, low energy, under or over eating, disturbances of sleep, feelings of guilt, suicidal ideation and cognitive impairments. Quality of life can be compromised, and suicide may emerge as a major risk for patients with severe or treatment-resistant depression (Weissman et al., 1999, Dunner et al., 2006). In addition to the suffering inherent to the disorder itself, morbidity and mortality are increased when depression becomes coupled to medical conditions such as cardiovascular disease and diabetes (Ruo et al., 2003, Van Melle et al., 2004, Schulz et al., 2000).

The neurocircuitry of depression

It is generally accepted that the biological basis of depression will not be discovered in one neurotransmitter, or in one discrete brain region. Heterogeneity of clinical symptoms can best be explained on the basis of dysfunction in neural "networks" involving limbic-cortical pathways (Mayberg, 1997, 2003). Radiofrequency lesioning studies, including anterior capsulotomy, cingulotomy, subcaudate tractotomy and limbic leucotomy have all reveled benefits in treatment refractory depression (Greenberg et al., 2003). The anterior limb of the internal capsule, as one example of a structure that may play a role in depression circuitry, serves as a fiber link between the frontal lobe, thalamus, and basal ganglia circuitry. The nucleus accumbens as part of this extended limbic network is located in the ventral tier region of the striatum and plays an important role in both depression circuitry and reward circuitry. Accumbens receives projections from the orbitofrontal cortex, amygdala, and prefrontal cortex among other brain regions. Groups (Greenberg et al., 2003, Kopell and Greenberg, 2008, Abosch and Cosgrove, 2008, Hauptman et al., 2008) have hypothesized that intervention in these areas may be therapeutically beneficial.

The other area of recent interest regarding the treatment of depression has been Brodmann area 25 (subgenual cingulate) which has connections to the anterior cingulate cortex. Area 25 also projects to the caudate nucleus, amygdala, and thalamus. Subcortical structures, in turn, project to the orbitofrontal cortex, prefrontal cortex and cingulate cortex, forming a limbic loop. (Parent and Carpenter, 1996) The subgenual cortex has been hypothesized to play a role in circadian dysregulation seen in depression as well as disturbances in learning and memory. Stimulation in this area has interestingly been observed to reverse sadness. (Kopell and Greenberg, 2008, Abosch and Cosgrove, 2008).

The exact neural circuitry for depression and the specific involvement of the multiple basal ganglia structures and circuits remain cloudy; however, multiple imaging and physiology studies are currently aimed at answering these questions.

The results of best medical treatments for depression

There are currently over 20 common antidepressants used clinically. These antidepressants include heterocyclics, monoamine oxidase inhibitors (MAOI's), selective serotonin reuptake inhibitors (SSRI's), serotonin-norepinephrine reuptake inhibitors (SNRI's), and drugs with unique synaptic mechanisms. Treatment tailored to specific neurotransmitters has led directly and indirectly to a variety of augmentation strategies for treatment-resistant cases. Failure of remission with pharmacotherapy and psychotherapy often results in clinical teams turning to electroconvulsive therapy (ECT). Patients, however, often find the memory loss associated with ECT unacceptable. Additionally, the often transient benefit seen with ECT seems to require maintenance treatments (Gagne et al., 2000). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial provides prospective data that serves as a benchmark for clinicians treating depression. This study employed a five step sequence of treatments that included antidepressant monotherapy, cognitive behavior

Table 1
Effects of chronic DBS for treatment-resistant depression.

Study	*N*	Location of stimulation	Effects of chronic stimulation		
			Baseline	Post-DBS	Post-DBS
Lozano et al., 2008	20	Subcallosal cingulated gyrus	Baseline	12 months	
			HDRS-17 score 24.4 ± 3.5	12.6 ± 6.3	
			Mood subscore 11.9 ± 1.5	5.9 ± 3.7 (p<0.0001)	
			Anxiety subscore 3,8 ± 2.4	1.6 ± 1.9 (p<p 0.01)	
			Sleep subscore 3.6 ± 2.0	2.0 ± 1.3 (p<p 0.005)	
			Somatic subscore 4.9 ± 0.8	3.0 ± 1.4 (p<p 0.0001)	
			Baseline	1 week	1 month
Jiménez et al., 2007	1	Inferior thalamic peduncle	GAF 20		90
			HDRS ranged 33-42	3	8
			BDI 38	16	11
			Baseline	6 months	
Malone et al., 2009	15	VC/VS	HDRS-24 score 33.1	17.5	
			MADRS 34.8	17.9	
			Baseline	1 week	
Schlaepfer et al., 2008	3	NA	Baseline HDRS-24 33.7 ± 3.8	HDRS reduced to 19.7 ± 6.7	
			Baseline MADRS 35.7 ± 2.9	MADRS reduced to 24.7 ± 6.7	

Reported outcomes of deep brain stimulation for depression.
HDRS-17, Hamilton Depression Rating Scale (17 item); GAF, global assessment of functioning; BDI, Beck Depression Inventory; HDRS-24, Hamilton Depression Rating Scale (24 item); VC/VS, ventral capsule/ventral striatum; MADRS, Montgomery-Asberg Depression Rating Scale; NA, nucleus acumbens.