NOVEL AND EMERGING USES OF DEEP BRAIN STIMULATION

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Introduction

Over the last twenty plus years, chronic deep brain stimulation (DBS) has become routine for several diagnoses in neurological practice (e.g., Parkinson disease (PD), dystonia, and essential tremor (PD)), and it has been utilized experimentally for select neuropsychiatric indications. In this American Academy of Neurology presentation I will focus on four novel and emerging uses of deep brain stimulation: 1- Tourette syndrome (TS), 2- obsessive-compulsive disorder (OCD), 3- depression, 4- epilepsy, and 5- Alzheimer's disease. During the oral presentation I may briefly review a few other indications.

Tourette syndrome

- Tourette syndrome is a complex neuropsychiatric disorder with a usual onset in childhood (mean age 7 years).
- The disorder is characterized by changing motor and vocal tics that must be present for at least one year and be marked by fluctuations in number, frequency and complexity.
- Patients frequently have associated behavioral abnormalities including anxiety, attention deficit hyperactivity disorder, self injurious behavior, and obsessive compulsive behavior which may persist into adulthood (even when motor and phonic tics decline or disappear).
- Only a small minority of patients diagnosed with TS progress to disabling refractory tic disorder or to malignant TS that is unresponsive to medical and behavioral therapy.
- A very select group of TS patients may be candidates for DBS.
- The heterogeneity of the patient populations and the small size of studies have severely limited the interpretation of reported successes and failures.
- Because of the special risks in this population, the Tourette Syndrome Association and European Society for the Study of Tourette Syndrome have published guidelines for selection of DBS candidates and for the preferred standardized outcome measures that should be employed if attempting these surgeries .
- The centro-median-parafascicular complex (CM-PF) of the thalamus, the GPi (both motor and non-motor territories), and the anterior limb of internal capsule have been most utilized as targets for DBS.
- To date, the GPi and the CM seem to have better efficacy than the anterior limb but more careful studies, including characterization of individual targets, will be needed.
- A large worldwide database-registry is underway and should help to guide the future of the therapy.

Obsessive Compulsive Disorder

- A relatively recent FDA approved DBS procedure (under a humanitarian device exemption) is obsessive-compulsive disorder (OCD).
- OCD has been characterized by recurrent intrusive thoughts or obsessions that may produce overwhelming anxiety. This anxiety may be relieved in some cases by the indulgence in ritualistic, compulsive behaviors.
- Functional neuroimaging has revealed hyperactivity within the ventral striatum (VS), medial thalamic region and the orbitofrontal cortex as potentially abnormal.
- A select group of patients who may be refractory to medical treatment or to behavioral approaches could be candidates for a neurosurgical intervention.
- Neurosurgical interventions have in the recent past involved lesioning of the anterior limb of internal capsule (ALIC), cingulotomies, leucotomies, as well as other approaches.
- High-frequency DBS of the bilateral anterior limb of the internal capsule/nucleus accumbens region may achieve remission in more than 50% of well-selected patients.

Depression

- Severe refractory depression is more common than any other current potential patient pool for DBS therapy. The loss of quality or life, the impact on lost work hours, and the suicide rate make DBS an attractive alternative therapy.
- DBS for medication refractory depression remains investigational and should only be considered when medication, psychotherapy and electrical convulsive therapy are not helpful, and when an institutional review board experimental protocol has been obtained.
- Experts have hypothesized that there is an abnormality in the cortico-striatal-thalalamic-cortical (CSTC) network in severely depressed humans and that by lesioning or neurmodulating at specific nodes, clinical symptoms may be reduced (e.g., anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy and limbic leucotomy).
- Though it has been reported that up to two thirds of well-selected patients may benefit, these data are highly preliminary and not inclusive of the entire population of depression patients, and there have been two recent trials of two different brain targets (ventral capsule/ventral striatum and area 25) that failed to meet the primary outcome.
- Neuromodulatory targets have been emerging and may include subgenual cingulate gyrus/outflow tract, ventral capsule/ventral striatum, nucleus accumbens, and the inferior thalamic peduncle.

Epilepsy

- Epilepsy has recently been addressed through neuromodulation techniques
- Bilateral anterior nucleus of the thalamus continuous DBS (SANTE trial)
- 110 patients, double blind and placebo controlled
- At 3 months 30% fewer seizures (active group)
- At 2 years 56% reduction in seizures
- Neuropace closed loop experience (Received FDA approval)
- Closed loop means that the device sensed the seizure (from a local field potential) and discharged in response to the electrical change
- 5 year followup showed a 65% reduction in seizures; 61% responder rate

Alzheimer's disease

- The recently completely ADVANCE study evaluated the safety of DBS of the fornix in people with mild Alzheimer's disease. Half of the patients were on active DBS and were randomized to implantation without activated DBS.
- Device and therapy related adverse events and an estimate of effect size was performed for a future trial.
- ADAS-Cog and CDR-SB scores were similar between groups.
- There was increased glucose metabolism in the activated group.
- Non-significant trend toward separation in ADAS-Cog13 and the CDR-SB scores in the older patients and this may inform a future trial (published as an abstract in Clinical Trials in AD meeting in Barcelona, 2015).
- There is another ongoing study of accumbens DBS for AD (clinicaltrials.gov NCT01559220).

Selected References (information from this brief syllabus was drawn from these sources with permission):

1- Valerie Rundle-González, M.D., Zhongxing Peng-Chen, M.D., Abhay Kumar, M.D., Michael S. Okun, M.D. Neurology in Clinical Practice. Elsevier. Chapter 37: Deep Brain Stimulation, 2015. These topics are all discussed in detail in this chapter.
2- Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med. 2012 Oct 18;367(16):1529-38.

3- Williams NR, Okun MS. Deep brain stimulation (DBS) at the interface of neurology and psychiatry. J Clin Invest. 2013 Nov 1;123(11):4546-56. doi: 10.1172/JCI68341. Epub 2013 Nov 1. Review. PubMed PMID: 24177464; PubMed Central PMCID: PMC3809784.