Commentary:
Treatment of Neurological and Psychiatric Disorders with Deep Brain Stimulation; Raising Hopes and Future Challenges

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ABSTRACT

The technology of Neural Stimulation in recent years has become the focus of the research and treatment, although it has been around for many years. The potential use of stimulating the brain and nerves ranges from the spinal cord stimulation to the implantations of cochlear and bionic eyes with a large discrepancy between the clinical readiness for these various uses.

Electrical high-frequency Deep Brain Stimulation (DBS) was developed as an alternative option to treat a few neurological disorders. However, with advancing in surgical procedures, technologies and safeties, the applications of DBS are expanding not only for therapeutic purposes but also for research. Although the exact mechanisms of action/s are not fully understood, the outcome of the ongoing research and clinical trials are promising. DBS has been used to treat the essential tremor since 1997, Parkinson's disease (PD) since 2002 and dystonia since 2003. It has also been used to treat various disorders, including major depression. The therapeutic effect of DBS in PD is well established but for other diseases such as epilepsy the outcomes are unclear and ambiguous. This article is a succinct review of the literature, focusing on PD, epilepsy and Obsessive Compulsive Disorder (OCD).

Introduction

Perhaps the ancient Romans and Greeks were the first to document the affect of the electrical pulses on nervous system. Torpedo nobiliana from the family of Torpedinidae was named by Romans (Rossi, 2003) for its ability to cause torpor. The same species was named by Greek narke for narcotizing its prey (Debru, 2006).

Claudius physician; Scribonius Largus, 47 AD., treated headache with the live ray. The same method was later on used for hemorrhoids, gout, depression, and epilepsy (Rossi, 2003). Although Avicenna (980-1037 AD.) had mentioned (Sharafkandi, 1997) the brain is not homogenous as it was thought to be but the breakthrough came by the observation and the subsequent experiment made by German neurologist Edward Hitzig 1864 who was assisted by an anatomist Fritsch, applying an electrical pulse to the exposed cerebral cortex of a dog without anaesthesia (Fritsch & Hitzig, 1992). Soon after the new era of brain stimulation has started with Cincinnati, Bartholow 1874 applying electrical current to a terminal patient whose scalp and cranium had eroded by basal cell carcinoma (Bartholow, 1982). these experiments went well, eliciting contralateral movements. A current DBS device has generally a quadripolar electrode inserted into the brain. The aligned extensions run behind the ear with an internal pulse generator implanted either on top of or deep to the pectoralis fascia. The current technology is advancing on daily basis and beyond imagination. The cochlear implant is already in use and some advances in

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bionic eyes have been made. Potentially DBS devices can be programmed through remote access by telephone or via internet as it is the case with the cardiac pacemakers (Schwalb & Hamani, 2008).

Parkinson's Disease

PD is the most common form of progressive neurodegenerative disease of the central nervous system (CNS). Approximately 10 million people are diagnosed by PD worldwide and that does not reflect the millions of cases that go undetected (De Lau & Breteler, 2006). Men are one and half times more likely to have PD than women. As many factors contribute to prevalence and incidence of PD, including gender, age, diagnostic criteria and medical facilities, therefore, the comparison of PD prevalence and incidence in different parts of the world has become very difficult (Friedman JH, et al., 2007) (Friedman & Friedman, 1993). The early symptoms of PD are motor-related that slows down the movement (bradykinesia), causes the resting tremor, muscular rigidity, shuffling, and flexed posture which are resulted from the death of dopaminergic neurons of the Substantia Nigra pars compacta (SNpc), a region of the midbrain with the appearance of the intracellular inclusions known as Lewy bodies (Vale, 2008). In the later stage of PD and sometimes during the early stage, a variety of non-motor-symptoms, including autonomic, sensory, sleep, cognitive, and psychiatric disturbances and also dementia may arise (Friedman & Friedman, 2001) (Alves, Wentzel-Larsen, & Larsen, 2004). The principle of neural stimulation is to restore the physiological function/s of the nerves or muscles by targeted and controlled delivery of electrical stimulation to the affected areas (Castrioto, 2011). Deep Brain Stimulation (DBS) has been used on the patients in the later stage of PD that pharmacological treatments offer them little to nothing and it has certainly improved locomotive ability and to some extent cognitions in patients with PD without dementia (Krack, 2003) (Liang, 2006).

In DBS electrical stimulation pulses are continuously applied to specific brain regions at high frequency by chronically implanted electrodes. These electrodes with lead extensions and a pulse generator are implanted surgically (Krack, 2003). A transdermal programming device is also used to allow different therapeutic options. Subthalamic nucleus (STN) and the globus pallidus internus (GPi), are thought to be over-activated in PD and they are the main target of DBS (Limousin, 1995). However, the ventralis intermedius nucleus of the thalamus is sometimes targeted, but STN is the most common target of DBS. While the mechanism of DBS is not fully understood, it appears to be due to modulation of neuronal activities, overriding the abnormal patterns in the basal ganglia, replacing them with less disturbing patterns (Limousin, 1995).

DBS has provided an alternative treatment for sever PD. It is widely used and known to greatly improve the symptoms of PD, including pain relief and cognitive deficit to some extent, but not dementia associated with PD.

Epilepsy

Epilepsy is a diverse set of chronic neurological disorders associated with recurrent seizures (Chang & Lowenstein, 2003). Epileptic seizure must be repeated at least twice or one single seizure with brain alterations which could increase the chance of future seizure (Fisher, 2005).

Excessive, abnormal or hypersynchronous neuronal activity in the brain causes epileptic seizure (Fisher, 2005). Over 50 million people worldwide have epilepsy, predominantly in developing countries (Brodie, Elder & Kwan 2009) (Holmes, Thomas, Browne & Gregory, 2008). About 70% of the epileptic seizures can be controlled with medication for the other 30%, medication offers little to nothing. Surgery or DBS therefore, may be considered (Cascino, 1994).

Electrical stimulation of the vagus nerve (VNS) is performed in the treatment of refractory epilepsy patients who are not suitable for surgery, and medications offer them no benefit.

The mechanism of action (MoA) of VNS in treatment of seizure suppression is not clear. Vagal afferent synapses use excitatory neurotransmitters, inhibitory neurotransmitter, acetylcholine and a variety of neuropeptides. Majority of vagal afferent synapses are received by Nucleus Tractus Solitarius (NTS). The NTS projects to other brainstem nuclei, including the LC and raphe magnus, and thus modulates norepinephrine and serotonin release, respectively. These neurotransmitters have ultimately effects the limbic, reticular, and autonomic centers of both cerebral hemispheres (Zabara, 1985). Hypothetically, afferent vagal synapses attenuate seizure activity through neurotransmitter modulation (Miller, 1992). An implanted device administrates electrical pulses at the cervical level of the neck. Intracranial and brainstem structures along the anatomical pathway from point of stimulation towards the cortex play a key func-

tional role in VNS's MoA; including the locus coeruleus, thalamus, NTS and limbic structures (Vonck, Herdt, Sprengers, & Ben-Menachem, 2012).

Obsessive Compulsive Disorder

OCD is an anxiety disorder, the disorder of the brain and behavior, characterized by disturbing thoughts, uneasiness, fear, apprehension and worries that lead to repetitive behaviors to reduce the associated anxiety; or by a combination of such obsessions and compulsions. The repetitive behavior includes excessive washing or cleaning, checking, hoarding and preoccupation with sexual, violent or religious thoughts. Notwithstanding, daily life routines, religious rituals and practices and repetitive learning activities are not compulsions. It seems that OCD caused by abnormalities of the cortico-striato-thalamocortical (CSTC) circuit involving the ventral-mesial pre-frontal cortex (PFC), dorsal anterior cingulate cortex, orbitofrontal cortex (OFC) and their associated basal ganglia and thalamus connections (Lyons, 2011). OCD has a prevalence of 2% worldwide in which approximately 20-40% of those affected, have persistent symptoms, leading to chronic functional impairment (Mian, Campos, Sheth, & Eskandar, 2010). The current treatments (including selective serotonin reuptake inhibitors, cognitive behaviour therapy and ablative surgery) are effective, however, approximately 10% of the patients do not respond to these treatments. These patients are good candidates for DBS and they may benefit from it (Huff, 2010).

The target of stimulation is currently STN and the anterior limb of the internal capsule, the ventral capsule/striatum (VC/VS) and inferior thalamic peduncle (ITP) are also the sites of interest in future studies (Lyons, 2011). There are advantages/disadvantages with each site that required more studies and trials. Stimulation of the STN may reduce surgical complications as this is a common procedure in the treatment of Parkinson's disease and it has been well established (Mian, Campos, Sheth, & Eskandar, 2010). On the other hand, the stimulation of VC/VS requires lower stimulation energies, thus allowing a longer battery life, reducing any side-effects caused by surgery. The outcome of this treatment is promising, in two different studies, four out of six patients had significant reduction in Y-BOCS scores (Yale-Brown Obsessive Compulsive Scale), but more thorough investigation and clinical trials should be carried out to determine the efficacy and the safety of the treatment (Goodman et al., 2010) (Mayberg, Lozano, Voon, McNeely, & Seminowicz, 2005).

Other Brain Disorders

Some other brain disorders may benefit from DBS such as; Tourette syndrome (also called Tourette's syndrome, Tourette's disorder, Gilles de la Tourette syndrome, GTS or just Tourette's or TS) which is an inherited neuropsychiatric disorder with onset in childhood. This neuropsychiatric disorder is characterized by multiple physical (motor) tics and at least one vocal (phonic) tic. However, as the procedure is invasive and Tourette's is more common in pediatric populations, therefore, it is only recommended for treatment-refractory cases (Malone DA, & Pandya MM 2006). There have also been some successful clinical trials of DBS for patients with Lesch-Nyhan syndrome in France, Switzerland and Japan (Cif et al 2007). Other disorders such as Phantom limb pain, severe depression, sever pain/s and perhaps the most predominant neurodegenerative disease Alzheimer's could benefit from DBS (Hardenacke et al. 2012).

Future Challenges Facing DBS

We still have a long way ahead as lots of clinical trial has not been finished or published yet. The so called neuromodulatory therapies for brain disorders have raised more questions than hopes and answers. Some of these therapies such as spinal cord stimulation for pain relief and PD, cochlear implant and severe depression have been well established and some others such as; Attention deficit-hyperactivity disorder and Alzheimer's have not. The science of neuromodulatory therapies itself has yet to be established. Although neuroanatomy and neurophysiology has advanced very well, the best target for treating a disorder yet to be determined. There are technical and clinical questions that yet to be addressed such as; what are the most effective parameters for stimulatory frequencies and rates and which patients will most benefit and the duration of the stimulation (Schwalb & Hamani 2008). The long term side effects of DBS have not been clearly identified. The legal and ethical responsibilities also should be addressed and need to be regulated.

Conclusion

The implantable neuromodulatory devices have been very beneficial to patients and their therapeutic usages are rapidly expanding. Their efficacy and potential in the treatment and management of brain disorders have been validated by numerous clinical cases and trials (Schwalb & Hamani 2008). The knowledge and experiences have been gained has leveraged DBS into the other area of medicine, psychology and nutrition. The accurate regula-

tion of neurotransmission and downstream neurochemical cascades via both invasive, DBS, and non-invasive such as trans cranial magnetic stimulation proved to be a serious challenge ahead. Variety methods of stimulations are facilitated by these devices of which they have the ability to target highly specific foci in the CNS. This can be in the form of both inhibitory and/or excitatory action (Schwalb & Hamani 2008).

DBS has emerged to a new therapeutic level with the aid of functional imaging with MRI or positron emission tomography. The advances in surgical procedures have decreased infections and surgical complications. Nevertheless, it is an invasive procedure and the risk of surgical complications, particularly in vulnerable patients do exist. DBS today is considered an alternative therapy for not only psychiatric disorder but also as a potential therapy for non-psychiatric disorder such as hypertension, obesity, and eating disorders. Autonomic changes have been reported in patients with chronic pain receiving periaqueductal/periventricular grey (PAG/PVG) (Schwalb & Hamani 2008). DBS has created a new field in which specialized physicians and nurses need to be trained and the field continues to expand.

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