Deep brain stimulation (DBS) has opened new avenues in the treatment of degenerative diseases, such as Parkinson’s disease, essential tremor and dystonia, and new trials in obsessive compulsive disorder (OCD) and depression are being conducted with promising preliminary results. Epilepsy could also benefit from this new technique and controlled, double-blind clinical trials are being conducted worldwide with the purpose of coming up with robust positive data allowing the treatment of patients suffering from intractable epilepsy with DBS.

However, at this time, many questions are still unanswered and many options are still debated. What is the appropriate structure to stimulate or to inhibit? What is the most appropriate mode of stimulation and with what parameters? Which patients could benefit from DBS? This review will give an update of clinical data available in this field and will try to shed light on these questions.

Which Targets?

Two strategies are challenged: the first one, and the oldest, aims to modulate the cortical activity by stimulating or inhibiting nuclei that are involved in the remote anti-epileptogenic zone. The latter mainly includes the thalamus (centromedian (CM) and anterior nucleus (AN)), the basal ganglia (subthalamic nucleus (STN) and substantia nigra (SNr) and the cerebellum. Vagus nerve stimulation (VNS) belongs to this group. The second strategy aims to act directly on the epileptogenic zone (EZ) at the surface of the cortex or in the hippocampus.

The CM of the thalamus has been advocated as a potential therapeutic target mainly in generalised tonic-clonic seizure and complex partial seizure with falls. Long-term results seem to confirm the preliminary data with a mean reduction of seizure of more than 50% in all five patients, an effect that can occur several years after the surgery and that is more pronounced after changing anti-epileptic drugs (AEDs), raising the question of the mechanism of actions and the possibility that AN DBS may render the patients more sensitive to AEDs.

Based on these encouraging results, a double-blind, large multicentre control study is being conducted in North America and will give soon new insights into this field.

The role of basal ganglia (STN and SNr) in the control of epilepsy has been extensively studied in animals. The author’s group applied this concept for the first time in 2002 in a young patient suffering from motor epilepsy related to a dysplasia located in the motor cortex. Four other patients have been implanted, with three good responders out of five patients (more than 50% of seizure reduction).

Very recently, the author initiated a multicentre, crossover, double-blind study (STIMEP) to apply STN-SNr DBS on patients suffering from atypical absence, related or not to ring chromosome 20 and with Dopa positron emission tomography (PET) hypometabolism as a common feature. Others groups have confirmed that STN DBS could be a potential target for the treatment of severe epilepsy, but so far, no large, controlled studies have confirmed the potential therapeutic effect of such treatment.

Other nuclei that belong to basal ganglia have been used in the past, but to the author’s knowledge are not used any more.

The cerebellum has been regularly cited as a potential anti-epileptogenic centre since the 1970s, but its anti-epileptic effect has been debated. Very recently, Velasco et al. revisited this concept in five
patients with motor seizures and showed a mean reduction of approximately one-third.

The concept of direct cortical stimulation of the EZ is the second stimulation strategy. Indeed, it has been observed that current directly applied to the EZ could abort seizure in humans. Animal data are not numerous but seem to confirm this observation. Direct cortical stimulation has been applied in temporal and extra-temporal epilepsy and the preliminary and long-term outcome of this technique is promising. However, this was not confirmed by Tellez-Zenteno et al., who reported a mean reduction of seizure of around 15% after chronic hippocampal stimulation.

Which Mode of Stimulation?

Cycling mode versus continuous stimulation is still debated and the choice of each team is based on empirical knowledge rather than robust experimental data. Cycling mode may be a good strategy if one can be sure that it is as effective as continuous stimulation. The author prefers to test the best effect possible with a specific target and then tries to reduce the period of stimulation with the same good effect.

Some authors think that very short stimulation applied directly to the EZ just after or even just before the onset of seizure could abort it. This exciting strategy has been applied in humans with a very sophisticated closed loop device (Neuropace™), which consists of recording the electroencephalogram (EEG) activity within the EZ and delivering a current in response to spikes or seizure onset. Preliminary results showed about 40% of responders (more than 50% of seizure reduction) in a small series. This closed loop strategy is being investigated at the experimental level using the concept of an implantable EEG recording device coupled with a stimulator that delivers current to various deep nuclei.

Recently, a clinical trial has started in the US with the purpose of testing the efficacy of AN stimulation that can be activated by the patient himself when he feels the onset of the seizure (Intercept™, Medtronic).

Which Patients Could be Eligible for DBS?

In the US, it is anticipated that about one-third of the 2.3 million people suffering from epilepsy will not be cured by medications, and might be eligible for resective surgery (one-third) or alternative strategies such as VNS or DBS. So far, complex partial seizure, atypical absence and generalised tonic–clonic seizure seem to be the best candidates for such treatment. However, one of the main issues of many reported series is the lack of homogeneous population of epileptic patients with well defined epilepsy at the anatomical (frontal, insular, bi-frontal, bi-temporal, multi-lobar), clinical, radiological and genetic level. Recently, the author has started a French, multcentre, double-blind, crossover study to treat patients suffering from atypical absence, most of them with a ring chromosome 20, and that showed hypometabolism within the striatum in a pre-surgical [18F]fluoro-l-DOPA PET scan. This striatal dysfunction has been recently advocated as a reason of explaining the unusual, long-lasting seizures that are usually observed in this population of patients. The modulation of the basal ganglia through the STN, a small but pivotal nucleus in the basal ganglia circuitry, could be a welcome therapy to treat such devastating epilepsies.

References


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