Deep Brain Stimulation

a report by
Stéphan Charbardès

Staff Neurosurgeon, Neurosurgery Department, University Hospital, Grenoble

DOI:10.17925/ENR.2006.00.02.46

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 substancia 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 atypical absences[1-4] with relatively less effect in 'partial complex' seizure.[5] However, authors have recently focused on the AN to treat patients with complex partial seizure. The first preliminary results are promising[6,7] with four good responders out of five patients and with a best efficacy on secondary generalised tonic-clonic seizure and complex partial seizure with falls. Long-term results seem to confirm the preliminary data[8] 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.[9,10] The author's group applied this concept for the first time in 2002[11] 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).[11]

Very recently, the author initiated a multicentre, crossover, double-blind study (STIMEP) to apply STN-SNr DBS on patients suffering from atypical absence (see below), related or not to ring chromosome 20 and with Dopa positron emission tomography (PET) hypometabolism as a common feature.[12] Others groups have confirmed that STN DBS could be a potential target for the treatment of severe epilepsy,[13-15] 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.[16]

The cerebellum has been regularly cited as a potential anti-epileptogenic centre since the 1970s,[17-21], but its anti-epileptic effect has been debated.[22] Very recently, Velasco et al. revisited this concept[23] 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.[24] Animal data are not numerous but seem to confirm this observation.[25,26]

Direct cortical stimulation has been applied in temporal and extra-temporal epilepsy[27-29] and the preliminary and long-term outcome of this technique is promising.[30,31] However, this was not confirmed by Tellez-Zenteno et al.,[32] 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[33] 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[34] 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, multicentre, 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.[12] 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

1. *Velasco F, Velasco AL, Velasco G, Jimenez F, "Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity",* Epilepsia *(1993a);34: pp. 1065–1074.*
2. *Velasco M, Marquez I, Velasco G, "Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: II. Psychological performance and background EEG activity",* Acta Neurochirurgica – Supplementum *(1993b);58: pp. 201–204.*
3. *Velasco M, Velasco AL, Jimenez F et al., "Role of the centromedian thalamic nucleus in the genesis, propagation and arrest of epileptic activity. An electrophysiological study in man",* Epilepsia *(1995);36: pp. 63–71.*
4. *Velasco M, Velasco AL, Menez D, Rocha L, "Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures",* Stereotact Funct Neurosurg *(2001a);77: pp. 223–227.*
5. *Fisher RS, Uematsu S, "Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures,* Epilepsy Res Suppl *(1992);5: pp. 217–229.*
6. *Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM, "Chronic anterior thalamus stimulation for intractable epilepsy",*

Epilepsia *(2002);43: pp. 603–608.*

7. *Kerrigan JF, Litt B, Fisher RS et al., "Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy",* Epilepsia *(2004);45: pp. 346–354.*
8. *Andrade DM, Zumsteg D, Hamani C et al., "Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy",* Neurology *(2006);66: pp. 1571–1573.*
9. *Deransart C, Depaulis A, "The control of seizures by the basal ganglia? A review of experimental data",* Epileptic Disord *(2002);4(Suppl. 3): pp. S61–72.*
10. *Depaulis A, Moshe SL, "The basal ganglia and the epilepsies: translating experimental concepts to new therapies",* Epileptic Disord *(2002);4(Suppl. 3): pp. S7–8.*
11. *Chabardes S, Kahane P, Minotti L et al., "Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus",* Epileptic Disord *(2002);4(Suppl. 3): pp. S83–93.*
12. *Biraben A, Semah F, Ribeiro MJ et al., "PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy",* Neurology *(2004);63: pp. 73–77.*
13. *Handforth A, DeSalles AA, Krahl SE, "Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy",* Epilepsia *(2006);47: pp. 1239–1241.*
14. *Loddenkemper T, Pan A, Neme S et al., "Deep brain stimulation in epilepsy",* J Clin Neurophysiol *(2001);18: pp. 514–532.*
15. *Shon YM, Lee KJ, Kim HJ et al., "Effect of chronic deep brain stimulation of the subthalamic nucleus for frontal lobe epilepsy: subtraction SPECT analysis",* Stereotact Funct Neurosurg *(2005);83: pp. 84–90.*
16. *Chkhenkeli SA, Chkhenkeli IS, "Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy",* Stereotact Funct Neurosurg *(1997);69: pp. 221–224.*
17. *Cooper IS, Amin I, Gilman S, "The effect of chronic cerebellar stimulation upon epilepsy in man",* Transactions of the American Neurological Association *(1973);98: pp. 192–196.*
18. *Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP, "Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies",* Arch of Neurol *(1976);33: pp. 559–570.*
19. *Cooper IS, Amin I, Upton A et al., "Safety and efficacy of chronic cerebellar stimulation",* Appl Neurophysiol *(1977);40: pp. 124–134.*
20. *Cooper IS, Upton AR, "Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man",* Electroencephalogr Clin Neurophysiol Suppl *(1978): pp. 349–354.*
21. *Cooper IS, Upton AR, "Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus",* Biol Psychiatry *(1985);20: pp. 811–813.*
22. *Van Buren JM, Wood JH, Oakley J, Hambrecht F, "Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy",* J Neurosurg *(1978);48: pp. 407–416.*
23. *Velasco F, Carrillo-Ruiz JD, Brito F et al., "Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures",* Epilepsia *(2005);46: pp. 1071–1081.*
24. *Lesser RP, Kim SH, Beyderman L et al., "Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation",* Neurology *(1999);53: pp. 2073–2081.*
25. *D'Arcangelo G, Panuccio G, Tancredi V, Avoli M, "Repetitive low-frequency stimulation reduces epileptiform synchronization in limbic neuronal networks",* Neurobiol Dis *(2005);19: pp. 119–128.*
26. *Lian J, Bikson M, Sciortino C, Stacey WC, Durand DM, "Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro",* J Physiol *(2003);547: pp. 427–434.*
27. *Schrader LM, Stern JM, Wilson CL et al., "Low frequency electrical stimulation through subdural electrodes in a case of refractory status epilepticus",* Clin Neurophysiol *(2006);117(4): pp. 781–788.*
28. *Yamamoto J, Ikeda A, Satow T et al., "Low-frequency electric cortical stimulation has an inhibitory effect on epileptic focus in mesial temporal lobe epilepsy",* Epilepsia *(2002);43: pp. 491–495.*
29. *Zumsteg D, Lozano AM, Wieser HG, Wennberg RA, "Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy",* Clin Neurophysiol *(2006);117: pp. 192–207.*
30. *Velasco TR, Terra-Bustamante VC, Araujo D Jr et al., "Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report",* Epilepsia *(2001b);42: pp. 660–666.*
31. *Vonck K, Boon P, Achten E, De Reuck J, Caemaert J, "Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy",* Ann Neurol *(2002);52: pp. 556–565.*
32. *Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S, "Hippocampal electrical stimulation in mesial temporal lobe epilepsy",* Neurology *(2006);66: pp. 1490–1494.*
33. *Fountas KN, Smith JR, Murro AM et al., "Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note",* Stereotact Funct Neurosurg *(2005);83: pp. 153–158.*
34. *Worrel G, Wharen R, Goodman R et al., "Safety and evidence for efficacy of an implantable responsive neurostimulation (RNS) for the treatment of medically intractable partial onset epilepsy in adults",* American Epilepsy Society *(2005).*