

**Debate: Should responsive neurostimulation be offered in preference to other forms of neurostimulation when a well defined focus is known?**

**Position: No**

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Multiple subcortical brain structures and cortical epileptogenic foci have been targeted for invasive – deep or subdural – brain stimulation in epilepsy. Most data on efficacy are derived from small, uncontrolled clinical studies hampering the significance of reported findings. Reliable data are available for continuous stimulation of the anterior nucleus thalamus and for responsive stimulation of the seizure onset zone in neo- or archicortical structures. Whether positive results of regulatory trials can be translated to the broad spectrum of difficult-to-treat epilepsies in the community, needs to be assessed at best by use of large international multi-centre registries. Prerequisite for successful invasive brain stimulation in epilepsy is ineligibility for possibly curative resective surgery and – most importantly – accurate phenotypisation of patients; different clinical forms of epilepsy may respond differently to individual targets and stimulation parameters.

The general concept of deep brain stimulation in epilepsy is continuous electrical stimulation in order to increase neuronal inhibition independent of the state of cortical excitability or seizure occurrence. An alternative approach is to continuously record electrocorticographically neuronal activity in the supposed seizure focus and to stimulate the epileptogenic zone responsively only in the case of abnormal activity. In clinical practise, induction of stimulation can be rather frequent, and up to 3,000 trains of stimulation have been observed within 24 h questioning the concept of responsiveness.

In a large randomised controlled trial on patients with intractable partial epilepsy, 109 adult patients from 17 centres in the U.S. underwent either 3-month bilateral electrical stimulation of the anterior thalamus or no stimulation starting 1 month after electrodes had been implanted (Fisher et al. 2010). Compared to a 3-month prospective baseline period, patients with stimulation on had a reduction of seizure frequency of 40.4% while patients with stimulation off had a reduction of 14.5%, indicating significant efficacy of chronic ANT stimulation. The two most common self-reported adverse effects were depression (14.8%) and memory impairment (13.0%), both of which were significantly more common compared to non-stimulated controls (1.8%, resp.). This regulatory clinical trial resulted in receipt of the CE certification (CE = *Conformité Européenne*) in the year 2010 in Europe that allows for ANT implantation in patients with refractory epilepsy. So far, there is no approval by the Food and Drug Administration in the U.S.

After the end of the 3-month blinded period, all patients were offered open-label ANT stimulation. One year after electrode implantation, median reduction in seizure frequency compared to baseline was 41%, and after 5 years, frequency reduction was 69% (Salanova et al. 2015). Along with reduced seizure frequency, clinical variables such as seizure severity, quality of life, and neuropsychological test composite scores including depression, anxiety, and subjective cognitive function significantly improved.

In another randomized controlled trial, eventually 191 patients underwent intracranial implantation of a neurostimulator directly addressing the seizure onset zone (Morrell et al. 2011). Responsive stimulation was successful, 3-month stimulation resulted in a significant reduction of median seizure frequency of 38% vs. 17% in the non-stimulated group. In four out of the 191 patients, the stimulation had to be explanted due to infections all of which involved soft tissue and not the brain or the skull. This

NeuroPace RNS® system has been approved by the U.S. Food and Drug Administration in 2013 but so far not in Europe. Recording and stimulation algorithms have not been disclosed by the above named company.

Long-term follow-up data confirm increased efficacy over time with reduction of median seizure frequency of 53% after 2 years and 63% of 4 years (Bergey et al. 2015). Along with decreased seizure frequency, quality of life improved.

To conclude, efficacy data on continuous deep brain stimulation and on responsive direct stimulation of the seizure focus seem to be similar. A clinical trial directly comparing the two approaches – in particularly in patients with well defined seizure focus – is desirable, but for various reasons this is unlikely to happen. Against this background, there is currently no indication to prefer craniectomy with implantation of the recording and stimulation system within the skull to the less invasive approach requiring only two small skull boreholes.

### References

Bergey GK, Morrell MJ, Mizrahi EM, et al. (2015) Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 84:810-817.

Fisher R, Salanova V, Witt T, et al. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51:899-908.

Morrell MJ; RNS System in Epilepsy Study Group (2011) Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 77:1295-1304

Salanova V, Witt T, Worth R, et al. (2015) Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 84:1017-1025.