Review article

Epileptic Disord 2009; 11 (2): 100-12

Manipulating the epileptic brain using stimulation: a review of experimental and clinical studies

Sandrine Saillet[1], Mélanie Langlois[1], Berend Feddersen[5], Lorella Minotti[1,2], Laurent Vercueil[1,2], Stephan Chabardès[1,3], Olivier David[1], Antoine Depaulis[1], Colin Deransart[1,2], Philippe Kahane[1,2,4]

[1] Institut des Neurosciences, INSERM U836-UJF-CEA, Grenoble
[2] Neurology Department
[3] Neurosurgery Department, Grenoble University Hospital, Grenoble, France
[4] Institute for Children and Adolescents with Epilepsy – IDEE, Hospices Civils de Lyon, France
[5] Department of Neurology, Klinikum Grosshadern, University of Munich, Germany

ABSTRACT – Neurostimulation represents an interesting alternative therapy for patients resistant to drug treatment or who cannot benefit from resective surgery. Theoretically, neurostimulation allows the control of seizures to be tailored to the individual patient and specific form of epilepsy. Here, we review both experimental and clinical studies that have reported the possible control of epileptic seizures by means of different approaches using electrical stimulation (vagus nerve stimulation, deep brain stimulation and repetitive transcranial magnetic stimulation). The rationale for targeting specific areas that have thus far been considered (*i.e.*, vagus nerve, cerebellum, anterior or centromedial thalamus, basal ganglia, cortex and temporal lobe) is addressed in the light of experimental data and clinical effectiveness in different models and forms of epilepsy. The type of seizures that can be considered for neurostimulation, as well as the optimal parameters such as stimulation frequency and modes of stimulation (chronic, continuous or adaptative), are discussed to determine the best candidates for such a therapeutic strategy. This review points out the need for improved knowledge of neural circuits that generate seizures and/or allow their propagation, as well as a better understanding of the mechanisms of action of neurostimulation.

Key words: neurostimulation, vagus nerve, cerebellum, thalamus, basal ganglia, cortex, hippocampus

Correspondence:
P. Kahane
Epilepsie et Malaises Neurologiques
Pavillon de Neurologie
CHU de Grenoble
BP 217X
38043 Grenoble cedex
France
<philippe.kahane@ujf-grenoble.fr>

About 30% of epileptic patients do not respond to antiepileptic drugs (Kwan and Brodie 2000), of which only a minority can benefit from resective surgery. Such a therapeutic option is considered only in patients who suffer from focal seizures with an epileptogenic zone that is clearly identified and may be removed safely. Therefore, patients with seizures arising from eloquent cortices, or which are multifocal, bilateral, or generalized, represent a particular challenge to "new" or "alternative" therapies.

doi: 10.1684/epd.2009.0255

For these patients, neurostimulation appears to be of great potential (Polkey 2003, Theodore and Fisher 2004). Different approaches to neurostimulation in epileptic patients now exist and depend on *(i)* the brain region which is targeted and *(ii)* the way the stimulation is applied (Oommen *et al*. 2005, Morrell 2006, Theodore and Fisher 2004, Vonck *et al*. 2007). The aim of neurostimulation in epilepsy is to reduce the probability of seizure occurrence and/or propagation, either by manipulating remote control systems (vagus nerve stimulation, deep brain stimulation), or by interfering with the epileptogenic zone itself (repetitive transcranial magnetic stimulation, cortical stimulation). In most cases, stimulation is delivered continuously or intermittently according to a scheduled protocol. In particular, new progress in biotechnology and EEG signal analysis now allows stimulation in response to the detection of electrographic seizures (*e.g*. closed-loop stimulation). Here, we review the various experimental and clinical attempts that have been made to control epileptic seizures by means of electrical stimulation.

Vagus-nerve stimulation

The vagus nerve, through the tractus solitarius and parabrachial nuclei, projects to autonomic and reticular brain structures as well as the thalamic and limbic areas (Henry 2002, Vonck *et al*. 2001). These widespread, bilateral, and multisynaptic projections may account for the multiple therapeutic mechanisms of vagus-nerve stimulation (VNS) in epilepsy. In animals, VNS has been studied in different models of seizures in different species (rat, cat, dog and monkey) and acute interruption of seizures was reported (see McLachlan 1993), as well as a chronic prophylactic effect on seizure frequency and severity (Lockard *et al*. 1990, Takaya *et al*. 1996, Chabardès *et al*. 2008). In human patients, the first open trial with VNS was done in 1988 and preliminary results showed that such a therapy was safe and potentially effective (Penry and Dean 1990). Later, five clinical trials were conducted (E01 to E05), including two double-blind, randomized, controlled studies (E03, E05) (Handforth *et al*. 1998, The Vagus Nerve Stimulation Study Group 1995). This has led to the approval by the European Community (1994) and FDA (1997) of VNS therapy for complex partial and secondary generalized seizures in patients over 12 years. To date, over 40 000 patients around the world have been treated with VNS.

The overall efficacy, as evaluated over three years from the five clinical trials, shows a median seizure reduction of 35-45% (Morris and Mueller 1999). Post-marketing experience, as provided by manufacturer-supported open databases, suggests that VNS reduces seizure frequency by 50% or more in 50-60% of the patients, whatever their type of epilepsy. Efficacy tends to improve over time (Handforth *et al*. 1998) and anti-epileptic drugs (AEDs) may be reduced in a number of cases (Labar 2002). Children seem to respond similarly to adults (Wheless and Maggio 2002). Beyond seizure control, VNS also reduces daytime sleepiness and promotes alertness (Malow *et al*. 2001). It improves mood (Harden *et al*. 2000) and memory (Clark *et al*. 1999), and leads to a global improvement in the quality of life (Dodrill and Morris 2001). It is also cost-effective, as suggested by a few European studies (Ben-Menachem *et al*. 2002, Boon *et al*. 1999). Serious complications are rare (Ben-Menachem, 2001) and there has been no evidence of increased mortality and overall morbidity in patients with VNS compared with uncontrolled epilepsy (Annegers *et al*. 2000). Side effects, which mainly include hoarseness, coughing, local paresthesia and dyspnea (Morris and Mueller 1999) are typically stimulation-related and transient, and generally resolve over time (Boon *et al*. 1999). No interference with AEDs has been found and there is no evidence of impaired fertility or teratogenicity due to VNS.

Overall, VNS appears as effective as AEDs in terms of seizure control and may bring additional benefits in terms of general health. A European multicentric phase IV post-marketing study (PULSE) currently aims at evaluating this aspect. Yet, with more than 40 000 patients implanted with VNS, no clear predictive factors for responders to VNS therapy have emerged, and the precise mechanisms of action of this treatment remain to be elucidated. Neuroimaging studies, including PET (Henry *et al*. 1998, 1999, Ko *et al*. 1996), SPECT (Van Laere *et al*. 2000, Vonck *et al*. 2000) and fMRI (Liu *et al*. 2003, Narayanan *et al*. 2002) suggest the involvement of thalamic nuclei in VNS efficacy.

Deep brain stimulation

For more than two decades, stimulation of a number of deep brain targets has been shown to be feasible, safe, and effective in humans suffering from different forms of movement disorders. This has led to the development of deep brain stimulation (DBS) in an increasing number of neurological and non-neurological diseases, including epilepsy (Benabid *et al*. 2001). Although the cortex plays a crucial role in seizure generation, accumulating evidence has pointed to the role of subcortical structures in the clinical expression, propagation and control of epileptic seizures in humans (Semah 2002, Vercueil and Hirsch 2002). Based on experimental findings, DBS has been applied to a number of targets, including the cerebellum, different nuclei of the thalamus and several structures of the basal ganglia system. Although encouraging, published results do not reach a definite conclusion and require further studies using animal models. Indeed, the study of the mechanisms of actions of such DBS on epileptic seizures is critical to understanding the transitions between normal and paroxysmal activities of the epileptic networks.

Cerebellum

During the 1950s and 1960s, cortical cerebellar stimulation was shown to have antiepileptic properties on different animal models of seizures, mostly penicillin and cobalt foci in cats (Cooke and Snider 1955, Dow *et al*. 1962, Mutani *et al*. 1969). Following this, and assuming cerebellar outflow is inhibitory in nearly all patients, Cooper and colleagues showed that seizures were modified or inhibited in 10 out of their 15 epileptic patients, without adverse effects (Cooper *et al*. 1973, 1976, Copper 1978). These data raised the issue of distant modulation of cortical epileptogenicity by electrical currents. More especially, this study showed for the first time the feasibility and safety of a therapeutic stimulation technique in epileptic patients. Later, a large open study on 115 patients reported that 31 became seizure-free and 56 were significantly improved by stimulation of the cerebellum (Davis and Emmonds 1992). Such promising results, however, were not confirmed in three controlled clinical trials involving 14 patients, of whom only two were improved (Krauss and Fisher 1993, Van Buren *et al*. 1978, Wright *et al*. 1984). Additional animal studies conducted in monkeys with cortical focal seizures induced by alumina cream, or in kindled cats, did not confirm previous experimental findings (Ebner *et al*. 1980, Lockard *et al*. 1979, Majkowski *et al*. 1980) and the interest for cerebellar stimulation in epilepsy disappeared for many years. Recently however, a double-blind, randomized controlled pilot study conducted in five patients suffering from intractable motor seizures has renewed the interest in such stimulation (Velasco *et al*. 2005). In this study, 10-Hz stimulations were applied to the upper medial surface of each cerebellar hemisphere, and parameters were adjusted to deliver a constant charge density of 2.0 microC/cm^2/phase. During the initial three-month double-blind phase, seizures were significantly reduced when the patients were stimulated. Over the following six-month open-label phase, where all the patients were stimulated, seizures were reduced by 41% (14-75%) and the difference was significant for tonic and tonic-clonic seizures. Effectiveness was maintained over two years and few complications occurred. Altogether, although cerebellar stimulation appears to possess antiepileptic effects in some patients and/or some forms of epilepsy, the rationale of such suppressive effects remains to be determined.

Thalamus

Since the 1980s, different nuclei of the thalamus have been studied to understand the physiopathology of epilepsy because many interactive pathways exist between these nuclei and the cortex. Several thalamic targets have been stimulated to suppress seizures, mainly the anterior nucleus and the centromedian nucleus. There is limited proof from animal studies that stimulation of these structures can influence seizure threshold. However, there is clinical evidence that continuous stimulation of these targets in epileptic patients reduces seizure frequency and severity.

Anterior thalamus

The anterior nucleus (AN) of the thalamus receives projections from the hippocampus via the fornix, the mamillary bodies and the mamillo-thalamic fascicle of Vicq d'Azir and has outputs to the cingulate cortex and, via the cingulum, to the entorhinal cortex and back to the hippocampus. It appears to closely interact with the circuit of Papez which is often involved in some forms of epilepsies (*e.g*. temporal lobe epilepsies). AN therefore is central in the network which underlies limbic seizures and, as such, represents an attractive target for DBS in epileptic patients. Cooper and his group, encouraged by their experience with cerebellar stimulation, were the first to direct their interest to this nucleus, based on the hypothesis that AN could act as a "pacemaker" for the cortex. They showed that bilateral chronic stimulation of AN in six epileptic patients resulted in 60% reduction of seizure frequency in five of them, as well as a decrease in EEG spikes (Cooper and Upton 1985). Using an experimental approach, it was later shown that AN and mamillary bodies were involved in the genesis of pentylenetetrazol-induced seizures and were activated during ethosuximide-induced suppression of these seizures (Mirski and Ferrendelli 1986a, 1986b). In addition, the section of the mamillo-thalamic bundle prevented pentylenetetrazol-induced seizures in guinea pigs (Mirsky and Ferrendelli 1984). Furthermore, it was reported that 100-Hz electrical stimulation of the mammillary nuclei and AN increased the seizure threshold of pentylenetetrazol in rats (Mirski and Fisher 1994, Mirski *et al*. 1997). These anticonvulsant effects were dependent on the intensity of the stimulation rather than frequency. On the contrary, low-frequency AN stimulation tended to be proconvulsive (Mirski *et al*. 1997). More recently, high-frequency AN stimulation suppressed focal cortical and limbic seizures induced by intra-cortical or intra-amydaloid kainic acid injections, respectively (Takebayashi *et al*. 2007a, 2007b) and delayed both status epilepticus and seizures induced by pilocarpine although without complete suppression (Hamani *et al*. 2004, 2008). Finally, 100-Hz AN stimulation was found to *aggravate* recurrent seizures observed following status epilepticus produced by systemic kainic acid (Lado, 2006).

These experimental data gave weight to the need for re-assessing the effect of AN stimulation in epileptic patients. Four open-label trials were reported showing that seizure frequency was reduced by 20-92%, being statistically significant in 12 of 18 patients (Hodaie *et al*. 2002, Kerrigan *et al*. 2004, Lim *et al*. 2007, Osorio *et al*. 2007). Two patients presented a complication (small frontal hemor-

rhage and extension erosion over the scalp), which did not result in major or permanent neurological deficit. One study showed that insertion of AN electrodes by itself could reduce seizures (Lim *et al.* 2007) and another that observed benefits did not differ between stimulation-on and stimulation-off periods (Hodaie *et al.* 2002), thus raising the issue of a lesional, placebo or carry-over effect. To address this question, a large multicenter prospective randomized trial of AN stimulation for partial and secondary generalized seizures (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy or SANTE) is currently under investigation in North America. Whether AN stimulation could be more effective in temporal lobe epilepsy (Zumsteg *et al.* 2006) and other components of the circuit of Papez, namely the mamillary bodies and mamillothalamic tract (Duprez *et al.* 2005, van Rijckevorsel *et al.* 2005), are possible targets for DBS and remain important issues for clinical trials.

Centromedian thalamus

In addition to the AN, attention was also directed towards one of the intralaminar nuclei of the thalamus, the centromedian nucleus (CM). This nucleus is part of the reticulothalamocortical system mediating cerebral cortex excitability (Jasper 1991), and has been suggested to participate in the modulation of vigilance states (Velasco *et al.* 1979). Although experimental findings remain rare (Arduini and Lary Bounes 1952), a first open-label study was conducted in five patients with bilateral CM stimulation at the end of the 1980s (Velasco *et al.* 1987). Initial results indicated an improvement of seizure frequency and EEG spiking over three months of chronic stimulation. Later, Velasco's group accumulated data in a cohort of 49 patients suffering from different forms of seizures and epilepsies (Velasco *et al.* 2001a, 2002). Among these patients, long-term follow-up studies of between five and 13 patients were performed (Velasco *et al.* 1993, 1995, 2000a, 2000b, 2006). Overall, the procedure was reported to be beneficial and generally well-tolerated, although a central nystagmus was induced in some cases (Taylor *et al.* 2000). A few patients were explanted because of repeated and multiple skin erosions (Velasco *et al.* 2006). It is interesting to note that a decrease of 80% of seizures were observed on average in patients with generalized tonic-clonic seizures and atypical absences of the Lennox-Gastaut syndrome, with a global improvement of patients in their ability scale scores (Velasco *et al.* 2006). By contrast, no improvements were found for either complex partial seizures or focal spikes in temporal regions. The best clinical results were seen when both electrode contacts were located within the CM on both sides and when stimulation at 6-8 Hz and 60 Hz induced recruiting responses and regional DC shifts, respectively (Velasco *et al.* 2000a). Two hours of daily 130-Hz stimulation sessions (one-minute on, four-minutes off), alternating the right and left CM, were used. However, continuous bilateral stimulation led to faster and more significant results (Velasco *et al.* 2001b). As for AN stimulation, persistent antiepileptic effects were found three months or more after discontinuation of the stimulation ("off effect"), and possible plasticity which develops during the stimulation procedure was suggested (Velasco *et al.* 2001b). No such seizure suppression was found in a small placebo-controlled study conducted in seven patients with mesial temporal lobe epilepsy. In this study, no statistically significant difference was observed in frequency of tonic-clonic seizures, relative to the baseline, when the stimulator was on versus off (Fisher *et al.* 1992). In the open-label follow-up phase, however, three of six patients reported at least a 50% decrease in seizure frequency.

Up to now, very few animal studies have examined the role of the CM or parafascicular nucleus (PF) of the thalamus, which have similar connections in the control of epileptic seizures. In a genetic model of absence epilepsy in the rat (GAERS), pharmacological activation of the PF was found to suppress spike-and-wave discharges (SWDs; Nail-Boucherie *et al.* 2005). More recently, 130-Hz stimulation of this structure was reported to interrupt focal hippocampal seizures in a mouse model of mesiotemporal lobe epilepsy (Langlois *et al.* in preparation). Because of their unique location between cortical and limbic structures and the basal ganglia (see below), the CM/PF nuclei could well constitute an interesting target for DBS. More animal studies are clearly required to understand the role of this structure in the modulation of epileptic seizures.

Basal ganglia

Since the beginning of the 1980s, experimental animal studies have suggested the existence of a "nigral control" of epileptic seizures (for review see Gale 1995, Depaulis *et al.* 1994). Inhibition of the Substantia Nigra pars Reticulata (SNR) has potent anti-epileptic effects in different animal models of epilepsy (Deransart and Depaulis 2002) and the GABAergic SNR output appears to be a critical relay in this control (Depaulis *et al.* 1990, Paz *et al.* 2005, 2007). Local manipulations of the basal ganglia that lead to an inhibition of the SNR neurons (*e.g.* activation of the striatum or pallidum, inhibition of the sub-thalamic nucleus) also had significant anti-epileptic effects (for review see Deransart and Depaulis 2002), suggesting that different striato-nigral circuits are involved in the control of epileptic seizures. In humans, EEG, clinical and imaging data also support the involvement of the basal ganglia in the propagation and/or control of epileptic discharges (Biraben *et al.* 2004, Bouilleret *et al.* 2008, Vercueil and Hirsch 2002). Altogether, experimental and clinical data suggest a privileged role for the basal ganglia in the control of generation and/or spread of epileptic discharges in the cortex. Paradoxically, the therapeutic relevance of such findings was rarely considered until the 1990s.

Caudate nucleus

Following experimental evidence that stimulation of the caudate nucleus (CN) has antiepileptic properties in different animal models of seizures (La Grutta *et al.* 1971, 1988, Mutani 1969, Oakley and Ojemann 1982, Psatta 1983), Chkhenkeli and his group, as well as Sramka and colleagues, were the first to suggest the beneficial effect of striatal low-frequency stimulation (below 50 Hz) in epileptic patients (Chkhenkeli 1978, Sramka *et al.* 1980). A decrease in focal and generalized discharges was observed in 57 patients bilaterally stimulated at low frequency (4-6 Hz) in the CN (Chkhenkeli and Chkhenkeli 1997). The study, however, was not controlled and the effects on seizures were not assessed. Interestingly, epileptic activity was worsened by stimulating the CN at higher frequency, a finding that was also reported in the aluminium-hydroxide monkey model of motor seizures (Oakley and Ojemann 1982). Therefore, if one assumes that low-frequency stimulation is excitatory and high-frequency stimulation is inhibitory, these clinical data are in agreement with animal data (see Deransart and Depaulis 2002). Indeed, activation of the striatum inhibits the SNR through GABAergic projections and therefore leads to seizure suppression (Deransart *et al.* 1998). Although further studies are needed, these results highlight the ability of the basal ganglia system to modulate cortical epileptogenicity.

Subthalamic nucleus

In 1998, Vercueil *et al.* (1998) were the first to show that 130-Hz stimulation of the subthalamic nucleus (STN) could interrupt absence seizures in GAERS, a well-established genetic model of absence epilepsy (Danober *et al.* 1998, Marescaux *et al.* 1992). Since then, high-frequency stimulation of the subthalamic nucleus has been reported to protect against seizures induced by local kainate injection in the amygdala (Bressand *et al.* 1999, Loddenkemper *et al.* 2001, Usui *et al.* 2005) or by fluorothyl inhalation (Veliskova *et al.* 1996). This is in agreement with the antiepileptic effects reported after pharmacological inhibition of the STN on seizures induced by amygdala kindling (Deransart *et al.* 1998), intravenous bicuculline or by focal application into the anterior piriform cortex (Dybdal and Gale 2000) and in GAERS (Deransart *et al.* 1996).

This led the group of Benabid at Grenoble University Hospital to perform the first STN stimulation in a five-year-old girl with pharmacologically-resistant inoperable epilepsy caused by a focal centroparietal dysplasia (Benabid *et al.* 2002). Later, 11 additional patients suffering from different forms of epilepsy received high frequency STN stimulation at different institutions (Chabardès *et al.* 2002, Loddenkemper *et al.* 2001, Vesper *et al.* 2007). Overall, seizure occurrence was reduced by at least 50% in seven out of 12 cases and stimulation was well tolerated. Good responders suffered from very different epilepsy types including focal epilepsy, Dravet syndrome, Lennox-Gastaut syndrome and progressive myoclonic epilepsy. Surgical complications occurred in two patients, including infection of the generator in one and a postimplantation subdural hematoma in another who later underwent surgical treatment, without sequelae (Chabardès *et al.* 2002). Bilateral stimulation appeared more effective than unilateral stimulation, in agreement with experimental data (Depaulis *et al.* 1994). However, whether this should be applied continuously or intermittently remains questionable (Chabardès *et al.* 2002). Furthermore, whether the optimal target in epileptic patients is the STN itself or, as is suggested in some patients, the SNR, remains an important issue (see below Chabardès *et al.* 2002, Vesper *et al.* 2007). A double-blind, cross-over, multicentric study is in progress in France (STIMEP) and aims to evaluate the clinical effect of 130-Hz stimulation of the STN/SNR in patients with ring chromosome 20 epilepsy. These patients suffer from very long-lasting epileptic seizures, evolving often into status epilepticus, which are difficult to control with antiepileptic drugs. They exhibit a deficit of dopaminergic activity in the striatum as compared with normal subjects (Biraben *et al.* 2004), a finding which is in accordance with the critical role of striatal dopamine in the control of seizures (Deransart *et al.* 2000).

Substantia nigra pars reticulata

In 1980, Gale and Iadarola were the first to correlate an increase of GABA in the Substantia nigra pars reticulata (SNR) with antiepileptic effects (Gale and Iadarola 1980). Later, they showed that the potentiation of the GABAergic neurotransmission within the SNR, by bilateral microinjections of GABAmimetic drugs, suppressed convulsions in various models of generalized seizures in the rat (Ladarola and Gale 1982). The possibility that seizures are controlled by the SNR also emerged from pharmacological studies in GAERS showing that a bilateral inhibition of SNR suppresses cortical SWDs (Depaulis *et al.* 1988, 1989, Deransart *et al.* 1996, 1998, 2001). Since then, several studies have confirmed that inhibition of the SNR has a potent anti-epileptic effect in different animal models of epilepsy (Depaulis *et al.* 1994, Deransart and Depaulis 2002, Paz *et al.* 2005, 2007).

In this context, it was shown that DBS applied to the SNR also suppressed generalized convulsive seizures induced by fluorothyl inhalation (Velisek *et al.* 2002), amygdala-kindled seizures (Morimoto and Goddard 1987, Shi *et al.* 2006), absence seizures in GAERS (Feddersen *et al.* 2007) and also focal seizures in kainate treated mice (Deransart and Depaulis 2004). In the model of generalized convulsive seizures induced by fluorothyl inhalation, bilateral and bipolar 130 Hz SNR stimulation had anticonvulsivant effects in both adult and infant rats (Velisek *et al.* 2002). In amygdala-kindling, such stimulations were shown to sup-

press epileptogenesis (Shi *et al*. 2006). In GAERS, bilateral, bipolar, and monophasic SNR stimulations at a frequency of 60 Hz and a pulse width of 60 µs were defined as the optimal conditions to interrupt ongoing absence seizures without motor side effects (Feddersen *et al*. 2007). The threshold for interrupting epileptic seizures was lower using SNR stimulation compared to STN stimulation, using the same model and stimulation parameters. However, this last study showed that continuous stimulation failed to control the occurrence of seizures, in agreement with previous reports (Vercueil *et al*. 1998) and suggested that a refractory period of about 60 seconds exists, during which time any stimulation is without effect. This study also showed that *continuous* stimulation of the SNR could even aggravate seizure occurrence. Adaptive stimulation may allow to alleviate this problem and to further specify the existence of a refractory period (see below).

Stimulation at seizure focus

Stimulating the epileptogenic cortex to interrupt epileptic seizures may appear paradoxical. Indeed, "stimulation" classically means "excitation" and epilepsies are characterized by a pathological hyperexcitability and hypersynchrony of cortical neurons. Furthermore, cortical stimulation is generally used to map functions in eloquent brain and, as such, produces clinical symptoms. Also, it is known that cortical stimulation can evoke focal afterdischarges, as well as electro-clinical seizures. The effects provoked by cortical stimulation, however, depend on the stimulation parameters used, the region which is stimulated, as well as the way that the stimulation is delivered (indirectly or directly). To date, a few studies have been conducted to evaluate the therapeutic effect of cortical stimulation, including a limited number of patients. Therapeutic results are equivocal at best.

Repetitive transcranial magnetic stimulation (rTMS)

A non-invasive way of electromagnetically stimulating the cortex is to use transcranial magnetic stimulation (TMS). TMS is widely used in neurophysiology for diagnostic purposes (*e.g*. measuring motor cortex excitability as a marker of underlying pathologies). It has also therapeutic uses in various brain diseases when delivered in series, or trains of pulses, a method known as repetitive TMS or rTMS (Kobayashi and Pascual-Leone 2003, Tassinari *et al*. 2003, Wassermann and Lisanby 2001). Low-frequency (0.5 Hz) rTMS was reported to have anticonvulsive effects against pentylenetetrazol-induced seizures in rats (Akamatsu *et al*. 2001), while high frequency rTMS had opposite results (Jennum and Klitgaard 1996). A recent study in rats suggests that EEG-guided rTMS can suppress kainate-induced seizures and that the effect is frequency-dependent (Rotenberg *et al*. 2008). In humans, low frequency rTMS reduces motor cortex excitability, while high frequency can lead to seizures, even in healthy subjects (Chen *et al*. 1997). rTMS therapy in epilepsy was tested for the first time at the end of the 1990s, using a round coil placed over the vertex in order to achieve global depression of excitability (Tergau *et al*. 1999). This open study showed that eight of nine patients submitted to five consecutive days of 0.33 Hz rTMS had a mean seizure reduction of 38.6%. Later, effects on rTMS were evaluated in three placebo-controlled studies, of which two failed to demonstrate any significant effect (Cantello *et al*. 2007, Theodore *et al*. 2002). In the remaining study, however, conducted in patients with cortical malformations, rTMS significantly decreased the number of seizures as compared to sham rTMS condition (Fregni *et al*. 2006). These data suggest that rTMS is more likely to be effective in patients with clearly identifiable foci in the cortical convexity, a finding also supported by another study showing greater effects in patients with neocortical foci than in those with mesial temporal lobe foci (Theodore *et al*. 2002). Other (uncontrolled) studies (Brasil-Neto *et al*. 2004, Kinoshita *et al*. 2005a, Santiago-Rodriguez *et al*. 2008), as well as anecdotal case reports (Menkes and Gruenthal 2000, Misawa *et al*. 2005), are also in line with this hypothesis. However, recent data have shown that rTMS did not always suppress seizures, and that stimulation site and structural brain lesions did not necessarily influence the seizure outcome (Joo *et al*. 2007). Thus, although most studies have found a significant decrease in interictal EEG epileptiform abnormalities, additional trials are needed to ascertain whether rTMS is an effective and convenient therapy for epilepsy. In that respect, a placebo-controlled study is in progress in Strasbourg (France), to evaluate the efficacy of rTMS in a specific group of patients suffering from drug-resistant seizures arising from the sensori-motor cortex.

Invasive cortical stimulation

Several preclinical studies have found potential antiepileptic effects of brain stimulation in animal models. Notably, low-frequency (1 Hz) stimulation applied after kindling stimulation of the amygdala was found to inhibit the development of after discharges, an effect named *quenching* (Weiss *et al*. 1995). This quenching effect seems effective in both adult and immature rats (Velisek *et al*. 2002). Interestingly, when applied immediately *before* the kindling stimulus, preemptive 1-Hz sine wave stimulation was also effective, thus suggesting some potential benefit for seizure prevention (Goodman *et al*. 2005). Other regions such as the hippocampus (Barbarosie and Avoli 1997), the central piriform cortex (Yang *et al*. 2006, Zhu-Ge *et al*. 2007) or the cerebral fastigial nucleus (Wang *et al*. 2008) may also appear as potentially effective targets for 1-Hz stimulation treatment of epilepsy. In general, these data suggest that 1-Hz

stimulation inhibits both acquisition and expression of kindling seizure by preventing afterdischarge generation and propagation in rats. Unexpectedly, such effects are also observed in the cerebral fastigial nucleus, suggesting that targets outside the limbic system may have a significant antiepileptic action.

In humans, both low- (1-Hz) and medium- (50 Hz) frequency stimulation have proven effective at reducing interictal epileptiform discharges (Kinoshita *et al.* 2005b, Yamamoto *et al.* 2002). Therapeutic stimulation, however, was applied at high frequency in almost all studies. The first attempt of therapeutic stimulation of temporal lobe structures was reported in 1980, in three patients, without clear benefit (Sramka *et al.* 1980). More recently, several investigators have tried continuous scheduled stimulation of epileptic foci, including hypothalamic hamartoma (Kahane *et al.* 2003), neocortical structures (Elisevich *et al.* 2006) and mostly, the mesio-temporal lobe (Tellez-Zenteno *et al.* 2006, Velasco *et al.* 2000c, 2007, Vonck *et al.* 2002). The first pilot study of mesio-temporal lobe stimulation, conducted in 10 patients studied by intracranial electrodes before surgery, showed that stimulation stopped seizures and decreased the number of interictal EEG spikes in the seven patients where the stimulated electrode was placed within the hippocampus or hippocampal gyrus (Velasco *et al.* 2000c). There were no side-effects on language and memory, and no histological damages were found in the stimulated tissue. Whether such an antiepileptic effect could be observed over a more prolonged stimulation procedure was later evaluated in a small open series conducted in three patients, all of whom exhibited more than 50% seizure reduction after a mean follow-up of five months, without adverse events (Vonck *et al.* 2002).

Following this, two additional trials of hippocampal stimulation were conducted, leading to opposite results. In one double-blind study, the seizure outcome was significantly improved in all nine patients over a long-term follow-up peroid (Velasco *et al.* 2007), which showed more than 95% seizure reduction in the five patients with normal MRI, and 50-70% seizure reduction in the four patients who had hippocampal sclerosis. No adverse events were found although three patients were explanted after two years due to skin erosion in the trajectory system. It was suggested that beneficial effects of stimulation were associated with a high GABA tissue content and a low rate of cell loss (Cuellar-Herrera *et al.* 2004). By contrast, seizure frequency was reduced by only 15% on average in the four patients of the double-blind, multiple cross-over, randomized study of Tellez-Zenteno *et al.* (2006). Additionally, effects seemed to carry over into the off period, thus raising the issue of an implantation effect. However, no adverse events were found. Overall, stimulation of hippocampal foci shows beneficial trends, but whether the effect is significant and of clear clinical relevance, remains debatable.

Currently, a randomized controlled trial of hippocampal stimulation for temporal lobe epilepsy (METTLE) is recruiting patients to determine whether unilateral hippocampal electrical stimulation is safe and more effective than simply implanting an electrode in the hippocampus without electrical stimulation, or treating with medical therapy alone. A prospective randomized controlled study of neurostimulation in the medial temporal lobe for patients with medically refractory medial temporal lobe epilepsy is also currently recruiting patients for a controlled randomized stimulation *versus* resection (CoRaStiR) study (www.clinicaltrials.gov).

Adaptative stimulation

Continuous scheduled brain stimulation, whatever the target (DBS, cortical stimulation), has appeared to be safe and of potential benefit in treating medically intractable epilepsies (see above). Limited, but growing data suggests that responsive (seizure-triggered) stimulation might also be effective (Morrel 2006). Such a strategy is distinct from continuous scheduled stimulation as it aims to block seizures when they occur, rather than chronically decrease cortical excitability. The reduced power consumption, paroxysmal nature of seizures and possible behavioural side-effects induced by chronic stimulations are all factors that have triggered interest in this strategy. Also, it has been suggested that continuous stimulations may aggravate seizures in animals (Feddersen *et al.* 2007). Seizure-triggered stimulation requires an implanted stimulating device coupled with real-time signal analysis techniques. Usually, a seizure detection algorithm allows the delivery of a stimulation to interrupt seizure prior to, or concomitantly with, the onset of clinical symptoms. A number of algorithms to detect seizures do exist (see for instance Osorio *et al.* 2002, Grewal and Gotman 2005). The main stumbling block, as for continuous stimulation, is to find, ideally following an automatic search, optimal stimulation parameters to abort seizures. To our knowledge, existing literature about automatic seizure-triggered stimulation in animal models *in vivo* is rather limited. Using similar techniques, such as VNS therapy, Fanselow and colleagues have shown a reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation (Fanselow *et al.* 2000). Interestingly, seizure-triggered stimulation was more effective than the stimulation protocol involving a fixed duty cycle, in terms of the percent seizure reduction per second of stimulation (up to 78%). Currently, a preliminary study in Grenoble (France) is testing a new technology based on stimulation combined to seizure-detection to interrupt absence seizures in GAERS (Saillet *et al.* 2009). This should allow better determination of the optimal target and parameters of stimulation required by such technology.

In humans, responsive stimulation can shorten or terminate electrically-elicited afterdischarges using brief bursts of 50-Hz electrical stimulation (Lesser *et al*. 1999), the effect being greater at primary sites than at adjacent electrodes (Motamedi *et al*. 2002). Preliminary trials of responsive stimulation, however, were not consistent with this paradigm (Kossof *et al*. 2004, Fountas *et al*. 2005, Osorio *et al*. 2005). The effects of responsive stimulation were first evaluated in four patients using an external neurostimulator, which proved effective at automatically detecting electrographic seizures, delivering targeted electrical stimuli and altering or suppressing ictal discharges (Kossoff *et al*. 2004). Another feasibility study confirmed these results using a cranially implantable device in eight patients (Fountas *et al*. 2005). Detection and stimulation were performed using electrodes placed over the seizure focus, and seven of the eight patients exhibited more than a 45% decrease in their seizure frequency, with a mean follow-up time of 9.2 months. In the third pilot study, conducted in eight patients, stimulation was delivered either directly to the epileptogenic zone (local closed-loop, n = 4), or indirectly through the anterior thalami (remote closed-loop, n = 4), depending on whether the epileptogenic zone was single, or multiple (Osorio *et al*. 2005). On average, a 55.5% and 40.8% decrease in seizure frequency was observed in the local closed-loop group and in the remote closed-loop group, respectively. Overall, none of the 20 patients enrolled in these three pilot studies had adverse events. Although promising, this new therapy needs further evaluation and a multi-institutional prospective clinical trial is underway in the USA. The Responsive Neurostimulation System (RNS), sponsored by NeuroPace Inc., is designed to continuously monitor brain electrical activity from the electrodes and, after identifying the "signature" of a seizure's onset, deliver brief and mild electrical stimulation with the intention of suppressing the seizure. The purpose of the RNS System Pivotal Clinical Investigation is to assess safety and demonstrate that the RNS System is effective as an add-on (adjunctive) therapy in reducing the frequency of seizures in individuals with partial onset seizures that are refractory to two or more AED medications. Whether closed-loop stimulators will be able to react using seizure-prediction algorithms in the near future represents a particularly challenging issue.

Conclusion

Neurostimulation in non-surgically remediable epileptic patients represents an emerging treatment. It has the advantage of reversibility and adjustability, but remains palliative and surgical resection remains the gold standard treatment for drug-resistant epilepsies, whenever this option is possible. VNS is the only approved stimulation therapy for epilepsy so far and, as such, it is licensed in many countries as an adjunctive therapy. Other stimulation techniques must be considered experimental although several controlled studies are currently under investigation. Notably, results of direct brain stimulation, although encouraging, are not conclusive and further investigations are required to evaluate the real benefit of this emerging therapy, in as much as the risks of haemorrhage and infection, although low (around 5%), do exist. However, pathological examination in post-mortem studies and temporal lobe resection, in Parkinson's disease or epilepsy, suggest that chronic stimulation does not induce neural injury and can be delivered safely (Haberler *et al*. 2000, Pilitsis *et al*. 2008, Velasco *et al*. 2000c). In any case, seizure types or epileptic syndromes which may respond to stimulation should be identified, as well as the type of stimulation that is likely to be of potential efficacy depending on the patient's characteristics. This requires improvement in our knowledge of the neural circuits in which seizures start and propagate, a better understanding of the precise mechanisms of the supposed effect of neurostimulation and a search for optimal stimulation parameters. The development of experimental research in this field, as well as rigorous clinical evaluation, is essential for further improvements in clinical efficacy. □

References

Akamatsu N, Fueta Y, Endo Y, Matsunaga K, Uozumi T, Tsuji S. Decreased susceptibility to pentylenetetrazole-inducded seizures after low frequency transcranial magnetic stimulation in the rat. *Neurosci Lett* 2001; 310: 153-6.

Arduini D, Lary Bounes GC. Action de la stimulation électrique de la formation réticulaire du bulbe et des stimulations sensorielles sur les ondes strychniques. *Electroencephalogr Clin Neurophysiol* 1952; 4: 502-12.

Annegers J, Coan SP, Hauser WA, Lesteema J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. *Epilepsia* 2000; 41: 549-53.

Barbarosie M, Avoli M. CA3-driven hippocampal-entorhinal loop controls rather than sustains in vitro limbic seizures. *J Neurosci* 1997; 17: 9308-14.

Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. *J Clin Neurophysiol* 2001; 18: 415-8.

Ben-Menachem E, Hellström K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. *Neurology* 2002; 59 (Suppl. 4): S44-7.

Benabid AL, Koudsié A, Benazzouz A, *et al*. Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. *J Neurol* 2001; 248 (Suppl. 3): III37-III47.

Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable

epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. *Neurosurgery* 2002; 50: 1385-91.

Biraben A, Semah F, Ribeiro MJ, Douaud G, Remy P, Depaulis A. PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy. *Neurology* 2004; 63: 73-7.

Boon P, Vonck K, D'Have M, O'Connor S, Vandekerckhove T, De Reuck J. Cost-benefit of vagus nerve stimulation for refractory epilepsy. *Acta Neurol Belg* 1999; 99: 275-80.

Bouilleret V, Semah F, Chassoux F, Mantzaridez M, Biraben A, Trebossen R, Ribeiro MJ. Basal ganglia involvement in temporal lobe epilepsy: a functional and morphologic study. *Neurology* 2008; 70: 177-84.

Brasil-Neto JP, de Arauja DP, Teixeira WA, Araujo VP, Boechat-Barros R. *Arq Neuropsiquiatr* 2004; 62: 21-5.

Bressand K, Dematteis M, Kahane P, Benazzouz A, Benabid AL. Involvement of the subthalamic nucleus in the control of temporal lobe epilepsy: study by high frequency stimulation in rats. *Soc Neurosci* 1999; 25: 1656.

Cantello R, Rossi S, Varrasi C, *et al.* Slow repetitive TMS for drug-reistant epilepsy: clinical and EEG findings of a placebo-controlled trial. *Epilepsia* 2007; 48: 366-74.

Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord* 2002; 4 (Suppl. 3): 83-93.

Chabardès S, Najm I, Luders HO. Vagus nerve stimulation and experimental data: a critical overview. In: Luders HO, ed. *Text book of Epilepsy Surgery*. Informa Healthcare, 2008.

Chen R, Classen J, Gerloff C, *et al.* Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997; 48: 1398-403.

Chkhenkeli SA. The inhibitory influence of the nucleus caudatus electrostimulation on the human's amygdalar and hippocampal activity at temporal lobe epilepsy. *Bull Georgian Acad Sci* 1978; 4/6: 406-11.

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: 221-4.

Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nat Neurosci* 1999; 2: 94-8.

Cooke PM, Snider RS. Some cerebellar influences on electrically-induced cerebral seizures. *Epilepsia* 1955; 4: 19-28.

Cooper I. *Cerebellar stimulation in man*. New York: Raven Press, 1978.

Cooper IS, Upton ARM. The effect of chronic stimulation of cerebellum and thalamus upon neurophysiology and neurochemistry of cerebral cortex. In: Lazorthes Y, Upton ARM, eds. *Neurostimulation: an overview*. New York: Futura, 1985: 207-11.

Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. *Arch Neurol* 1976; 33: 559-70.

Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans Am Neurol Assoc* 1973; 98: 192-6.

Cuellar-Herrera M, Velasco M, Velasco F, *et al.* Evaluation of GABA system and cell damage in parahippocampus of patients with temporal lobe epilepsy showing antiepileptic effects after subacute electrical stimulation. *Epilepsia* 2004; 45: 459-66.

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C. Pathophysiological mechanisms of genetic absence epilepsy in rat. *Prog Neurobiol* 1998; 55: 27-57.

Davis R, Emmonds SE. Cerebellar stimulation for seizure control: 17-year study. *Stereotact Funct Neurosurg* 1992; 58: 200-8.

Depaulis A, Vergnes M, Marescaux C, Lannes B, Warter JM. Evidence that activation of GABA receptors in the substantia nigra suppresses spontaneous spike-and-wave discharges in the rat. *Brain Res* 1988; 448 (1): 20-9.

Depaulis A, Snead 3rd OC, Marescaux C, Vergnes M. Suppressive effects of intranigral injection of muscimol in three models of generalized non-convulsive epilepsy induced by chemical agents. *Brain Res* 1989; 498: 64-72.

Depaulis A, Vergnes M, Liu Z, Kempf E, Marescaux C. Involvement of the nigral output pathways in the inhibitory control of the substantia nigra over generalized non-convulsive seizures in the rat. *Neuroscience* 1990; 39: 339-49.

Depaulis A, Vergnes M, Depaulis A. Endogenous control of epilepsy: the nigral inhibitory system. *Prog Neurobiol* 1994; 42: 33-52.

Deransart C, Depaulis A. The control of seizures by the basal ganglia? A review of experimental data. *Epileptic Disord* 2002; 4 (Suppl. 3): S61-72.

Deransart C, Marescaux C, Depaulis A. Involvement of nigral glutamatergic inputs in the control of seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 1996; 71: 721-8.

Deransart C, Lê BT, Marescaux C, Depaulis A. Role of the subthalamo-nigral input in the control of amygdale-kindled seizures in rat. *Brain Res* 1998; 807: 78-83.

Deransart C, Riban V, Lê BT, Marescaux C, Depaulis A. Dopamine in the nucleus accumbens modulates seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 2000; 100: 335-44.

Deransart C, Depaulis A. Le concept de contrôle nigral des épilepsies s'applique-t-il aux épilepsies partielles pharmacorésistantes? *Epilepsies* 2004; 16: 75-82.

Dodrill CB, Morris GL. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy. *Epilepsy Behav* 2001; 2: 46-53.

Dow RS, Ferandez-Guardiola A, Manni E. The influence of the cerebellum on experimental epilepsy. *Electroencephalogr Clin Neurophysiol* 1962; 14: 383-98.

Duprez TP, Serieh BA, Raftopoulos C. Absence of memory dysfunction after bilateral mammillary body and mammillothalamic tract electrode implantation: preliminary experience in three patients. *AJNR Am J Neuroradiol* 2005; 26: 195-7.

Dybdal D, Gale K. Postural and anticonvulsant effects of inhibition of the rat subthalamic nucleus. *J Neurosci* 2000; 20: 6728-33.

Ebner TJ, Bantli H, Bloedel JR. Effects of cerebellar stimulation on unitary activity within a chronic epileptic focus in a primate. *Electroencephalogr Clin Neurophysiol* 1980; 49: 585-99.

Elisevich K, Jenrow K, Schuh L, Smith B. Long-term electrical stimulation-induced inhibition of partial epilepsy. Case report. *J Neurosurg* 2006; 105: 894-7.

Fanselow EE, Reid AP, Nicolelis MA. Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *J Neurosci* 2000; 20: 8160-8.

Feddersen B, Vercueil L, Noachtar S, David O, Depaulis A, Deransart C. Controlling seizures is not controlling epilepsy: a parametric study of deep brain stimulation for epilepsy. *Neurobiol Dis* 2007; 27: 292-300.

Fisher RS, Uematsu S, Krauss GL, *et al.* Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia* 1992; 33: 841-51.

Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD. Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note. *Stereotact Funct Neurosurg* 2005; 83: 153-8.

Fregni F, Otachi PT, Do Valle A, *et al.* A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Ann Neurol* 2006; 60: 447-55.

Gale K. Chemoconvulsant seizures: advantages of focally-evoked seizure models. *Ital J Neurol Sci* 1995; 16: 17-25.

Gale K, Iadarola MJ. Seizure protection and increased nerve-terminal GABA: delayed effects of GABA transaminase inhibition. *Science* 1980; 208: 288-91.

Goodman JH, Berger RE, Tcheng TK. Preemptive low-frequency stimulation decreases the incidence of amygdala-kindled seizures. *Epilepsia* 2005; 46: 1-7.

Grewal S, Gotman J. An automatic warning system for epileptic seizures recorded on intracerebral EEGs. *Clin Neurophysiol* 2005; 116: 2460-72.

Haberler C, Alesch F, Mazal PR, *et al.* No tissue damage by chronic deep brain stimulation in Parkinson's disease. *Ann Neurol* 2000; 48: 372-6.

Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A Pilot Study of Mood in Epilepsy Patients Treated with Vagus Nerve Stimulation. *Epilepsy Behav* 2000; 1: 93-9.

Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. *Neurosurgery* 2004; 54: 191-5.

Hamani C, Hodaie M, Chiang J, *et al.* Deep brain stimulation of the anterior nucleus of the thalamus: effects of electrical stimulation on pilocarpine-induced seizures and status epilepticus. *Epilepsy Res* 2008; 78: 117-23.

Handforth A, DeGiorgio CM, Schachter SC. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology* 1998; 51: 48-55.

Henry TR, Bakay RA, Votaw JR, *et al.* Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy, I: acute effects at high and low levels of stimulation. *Epilepsia* 1998; 39: 983-90.

Henry TR, Votaw JR, Pennell PB, *et al.* Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology* 1999; 52: 1166-73.

Henry TR. Therapeutic mechanisms of vagus nerve stimulation. *Neurology* 2002; 59 (Suppl. 4): S3-14.

Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002; 43: 603-8.

Ladarola MJ, Gale K. Substantia nigra: site of anticonvulsant activity mediated by gammaaminobutyric acid. *Science* 1982; 218: 1237-40.

Jasper H. Current evaluation of the concepts of centrencephalic and cortico-reticular seizures. *Electroencephalogr Clin Neurophysiol* 1991; 78: 2-11.

Jennum P, Klitgaard H. Repetitive transcranial magnetic stimulations of the rat. Effect of acute and chronic stimulations on pentylenetetrazole-induced clonic seizures. *Epilepsy Res* 1996; 23: 115-22.

Joo EY, Han SJ, Chung S-H, Cho J-W, Seo DW, Hong SB. Antiepileptic effects of low frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. *Clinical Neurophysiology* 2007; 118: 702-8.

Kahane P, Ryvlin P, Hoffmann D, Minotti L, Benabid AL. From hypothalamic hamartoma to cortex: what can be learnt from depth recordings and stimulation? *Epileptic Disord* 2003; 5: 205-17.

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: 346-54.

Kinoshita M, Ikeda A, Begum T, Yamamoto J, Hitomi T, Shibasaki H. Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy – a pilot study. *Seizure* 2005a; 14: 387–92.

Kinoshita M, Ikeda A, Matsuhashi M, *et al*. Electric cortical stimulation suppresses epileptic and background activities in neocortical epilepsy and mesial temporal lobe epilepsy. *Clin Neurophysiol* 2005b; 116: 1291–9.

Ko D, Heck C, Grafton S, *et al.* Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging. *Neurosurgery* 1996; 39: 426-30.

Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurol* 2003; 2: 145-56.

Kossoff EH, Ritzl EK, Politsky JM, Murro AM, Smith JR, Duckrow RB, Spencer DD, Bergey GK. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia* 2004; 45: 1560-7.

Krauss GL, Fisher RS. Cerebellar and thalamic stimulation for epilepsy. *Adv Neurol* 1993; 63: 231-45.

Kwan P, Brodie M. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-9.

Labar DR. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy: a registry study. *Neurology* 2002; 59 (Suppl. 4): S38-43.

Lado FA. Chronic bilateral stimulation of the anterior thalamus of kainate-treated rats increases seizure frequency. *Epilepsia* 2006; 47: 27-32.

La Grutta V, Amato G, Zagami MT. The importance of the caudate nucleus in the control of convulsive activity in the amygdaloid complex and the temporal cortex of the cat. *Electroencephalogr Clin Neurophysiol* 1971; 31: 57-69.

La Grutta V, Sabatino M, Gravante G, Morici G, Ferraro G, La Grutta G. A study of caudate inhibition on an epileptic focus in the cat hippocampus. *Arch Int Physiol Biochim* 1988; 96: 113-20.

Lesser RP, Kim SH, Beyderman L, *et al.* Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. *Neurology* 1999; 53: 2073-81.

Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, Chang HW, Su YC, Wu T. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long term follow-up study. *Epilepsia* 2007; 48: 342-7.

Liu WC, Mosier K, Kalnin AJ. Marks D. BOLD fMRI activation induced by vagus nerve stimulation in seizure patients. *J Neurol Neurosurg Psychiatry* 2003; 74: 811-3.

Lockard JS, Ojemann GA, Congdon WC, DuCharme LL. Cerebellar stimulation in alumina-gel monkey model: inverse relationship between clinical seizures and EEG interictal bursts. *Epilepsia* 1979; 20: 223-34.

Lockard JS, Congdon WC, DuCharme LL. Feasibility and safety of vagal stimulation in monkey model. *Epilepsia* 1990; 31 (Suppl. 2): S20-6.

Loddenkemper T, Pan A, Neme S, *et al.* Deep brain stimulation in epilepsy. *J Clin Neurophysiol* 2001; 18: 514-32.

Majkowski J, Karli□ski A, Klimowicz-Młodzik I. Effect of cerebellar stimulation of hippocampal epileptic discharges in kindling preparation. *Monogr Neural Sci* 1980; 5: 40-5.

Malow BA, Edwards J, Marzec M, Sagher O, Ross D, Fromes G. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. *Neurology* 2001; 57: 879-84.

Marescaux C, Vergnes M, Depaulis A. Genetic absence epilepsy in rats from Strasbourg. *J Neural Transm Suppl* 1992; 35: 37-69.

McLachlan RS. Suppression of interictal spikes and seizures by stimulation of the vagus nerve. *Epilepsia* 1993; 34: 918-23.

Menkes DL, Gruenthal M. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. *Epilepsia* 2000; 4: 240-2.

Mirski MA, Ferrendelli JA. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. *Science* 1984; 226: 72-4.

Mirski MA, Ferrendelli JA. Anterior thalamic mediation of generalized pentylenetetrazol seizures. *Brain Res* 1986a; 399: 212–23.

Mirski MA, Ferrendelli JA. Selective metabolic activation of the mammillary bodies and their connections during ethosuximide-induced suppression of pentylenetetrazol seizures. *Epilepsia* 1986b; 27: 194–203.

Mirski MA, Fisher RS. Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. *Epilepsia* 1994; 35: 1309-16.

Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. *Epilepsy Res* 1997; 28: 89-100.

Misawa S, Kuwabara S, Shibuya K, Mamada K, Hattori T. Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia. *J Neurol Sci* 2005; 234: 37-9.

Morimoto K, Goddard GV. The substantia nigra is an important site for the containment of seizure generalization in the kindling model of epilepsy. *Epilepsia* 1987; 28: 1-10.

Morrell M. Brain stimulation for epilepsy: can scheduled or responsive neurostimulation stop seizures? *Curr Opin Neurol* 2006; 19: 164-8.

Morris 3rd GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. *Neurology* 1999; 53: 1731-5.

Motamedi GK, Lesser RP, Miglioretti DL, *et al.* Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. *Epilepsia* 2002; 43: 836-46.

Mutani R. Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencephalic epileptogenic focus, part 1: the role played by the caudate nucleus. *Epilepsia* 1969; 10: 337-50.

Mutani R, Bergamini L, Doriguzzi T. Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencephalic epileptogenic focus. Part 2. Effects of the paleocerebellar stimulation. *Epilepsia* 1969; 10: 351-62.

Nail-Boucherie K, Lê-Pham BT, Gobaille S, Maitre M, Aunis D, Depaulis A. Evidence for a role of the parafascicular nucleus of the thalamus in the control of epileptic seizures by the superior colliculus. *Epilepsia* 2005; 46: 141-5.

Narayanan JT, Watts R, Haddad N, Labar DR. LiPM, Filippi CG. Cerebral activation during vagus nerve stimulation: a functional MR study. *Epilepsia* 2002; 43: 1509-14.

Oakley JC, Ojemann GA. Effects of chronic stimulation of the caudate nucleus on a preexisting alumina seizure focus. *Exp Neurol* 1982; 75: 360-7.

Oommen J, Morrell M, Fisher RS. Experimental electrical stimulation for epilepsy. *Curr Treat Options Neurol* 2005; 7: 261-71.

Osorio I, Frei MG, Giftakis J, *et al.* Performance reassessment of a real-time seizure-detection algorithm on long ECoG series. *Epilepsia* 2002; 43: 1522-35.

Osorio I, Frein MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB. Automated seizure abatement in humans using electrical stimulation. *Ann Neurol* 2005; 57: 258-68.

Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. *Epilepsia* 2007; 48: 1561-71.

Paz JT, Deniau JM, Charpier S. Rhythmic Bursting in the Cortico-Subthalamo-Pallidal Network during Spontaneous Genetically Determined Spike and Wave Discharges. *J Neurosci* 2005; 25: 2092-101.

Paz JT, Chavez M, Saillet S, Deniau JM, Charpier S. Activity of ventral medial thalamic neurons during absence seizures and modulation of cortical paroxysms by the nigrothalamic pathway. *J Neurosci* 2007; 27: 929-41.

Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. *Epilepsia* 1990; 31 (Suppl. 2): S40-3.

Pilitsis JG, Chu Y, Kordower J, Bergen CD, Cochran EJ, Bakay RA. Postmortem study of deep brain stimulation of the anterior thalamus: case report. *Neurosurgery* 2008; 62: 530-2.

Polkey CE. Alternative surgical procedures to help drug-resistant epilepsy – a review. *Epileptic Disord* 2003; 5: 63-75.

Psatta DM. Control of chronic experimental focal epilepsy by feedback caudatum stimulations. *Epilepsia* 1983; 24: 444-54.

Rotenberg A, Muller P, Birnbaum D, Harrington M, Riviello JJ, Pascual-Leone A, Jensen FE. Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat. *Clin Neurophysiol* 2008; 119: 2697-702.

Saillet S, Charvet G, Gharbi S, Depaulis A, Guillemaud R, David O. Closed loop control of seizures in a rat model of absence epilepsy using the BioMEATM system. *IEEE Neural Eng* 2009 in press.

Santiago-Rodriguez E, Cardenas-Morales L, Harmony T, Fernandez-Bouzas A, Porras-Kattz E, Hernandez A. Repetitive transcranial magnetic stimulation decreases the number of seizures in patients with focal neocortical epilepsy. *Seizure* 2008; 17: 677-83.

Semah F. PET imaging in epilepsy: basal ganglia and thalamic involvement. *Epileptic Disord* 2002; 4 (Suppl. 3): S55-60.

Shi LH, Luo F, Woodward D, Chang JY. Deepbrain stimulation of the substantia nigra pars reticulata exerts long lasting suppression of amygdale-kindled seizures. *Brain Res* 2006; 1090: 202-7.

Sramka M, Fritz G, Gajdosova D, Nadvornik P. Central stimulation treatment of epilepsy. *Acta Neurochir Suppl* 1980; 30: 183-7.

Takebayashi S, Hashizume K, Tanaka T, Hodozuka A. The effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal cortical seizure status in rats. *Epilepsia* 2007a; 48: 348–58.

Takebayashi S, Hashizume K, Tanaka T, Hodozuka A. Anticonvulsant effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal limbic seizure in rats. *Epilepsy Res* 2007b; 74: 163–70.

Tassinari CA, Cincotta M, Zaccara G, Michelucci R. Transcranial magnetic stimulation and epilepsy. *Clin Neurophysiol* 2003; 114: 777-98.

Taylor RB, Wennberg RA, Lozano AM, Sharpe JA. Central nystagmus induced by deep-brain stimulation for epilepsy. *Epilepsia* 2000; 41: 1637-41.

Takaya M, Terry WJ, Naritoku DK. Vagus nerve stimulation induces a sustained anticonvulsant effect. *Epilepsia* 1996; 37: 1111-6.

Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology* 2006; 66: 1490-4.

Tergau F, Naumann U, Paulus W, Steinhoff BJ. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. *Lancet* 1999; 353: 2209.

Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol* 2004; 3: 111-8.

Theodore WH, Hunter K, Chen R, *et al*. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. *Neurology* 2002; 59: 560-2.

The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* 1995; 45: 224-30.

Usui N, Maesawa S, Kajita Y, Endo O, Takebayashi S, Yoshida J. Suppression of secondary generalization of limbic seizures by stimulation of subthalamic nucleus in rats. *J Neurosurg* 2005; 102: 1122-9.

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: 407-16.

Van Laere K, Vonck K, Boon P, Brans B, Vandekerckhove T, Dierckx R. Vagus nerve stimulation in refractory epilepsy: SPECT activation study. *J Nucl Med* 2000; 41: 1145-54.

van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Raftopoulos C. Deep EEG recordings of the mammillary body in epilepsy patients. *Epilepsia* 2005; 46: 781-5.

Velasco F, Velasco M, Cepeda C, Munoz H. Wakefulness-sleep modulation of thalamic multiple unit activity and EEG in man. *Electroencephalogr Clin Neurophysiol* 1979; 47: 597-606.

Velasco F, Velasco M, Ogarrio C, Fanghanel G. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsives seizures: a preliminary report. *Epilepsia* 1987; 28: 421-30.

Velasco F, Velasco M, Velasco AL, 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* 1993; 34: 1052-64.

Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long term studies. *Epilepsia* 1995; 36: 63-71.

Velasco F, Velasco M, Jimenez F, *et al*. Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. *Neurosurgery* 2000a; 47: 295–305

Velasco M, Velasco F, Velasco AL, Jimenez F, Brito F, Marquez I. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. *Arch Med Res* 2000b; 31: 304–15

Velasco M, Velasco F, Velasco AL, *et al*. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000c; 41: 158–69

Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I. Stimulation of the central median thalamic nucleus for epilepsy. *Stereotact Funct Neurosurg* 2001a; 77: 228–32

Velasco M, Velasco F, Velasco AL. Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. *J Clin Neurophysiol* 2001b; 18: 495–513

Velasco F, Velasco M, Jimenez F, Velasco AL, Rojas B. Centromedian nucleus stimulation for epilepsy. Clinical, electroencephalographic, and behavioral observations. *Thalamus & Related systems* 2002; 1: 387-98.

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: 1071-81.

Velasco AL, Velasco F, Jimenez F, *et al*. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. *Epilepsia* 2006; 47: 1203-12.

Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia* 2007; 48: 1895-903.

Velisek L, Veliskova J, Moshe SL. Electrical stimulation of substantia nigra pars reticulate is anticonvulsant in adult and young male rats. *Exp Neurol* 2002; 173: 145-52.

Velisek L, Velsikova J, Stanton PK. Low-frequency stimulation of the kindling focus delays basolateral amygdala kindling in immature rats. *Neurosci Lett* 2002; 326: 61-3.

Velísková J, Velsek L, Moshé SL. Subthalamic nucleus: a new anticonvulsant site in the brain. *Neuroreport* 1996; 7: 1786-8.

Vercueil L, Hirsch E. Seizures and the basal ganglia: a review of the clinical data. *Epileptic Disord* 2002; 4 (Suppl. 3): S47-54.

Vercueil L, Benazzouz A, Deransart C, *et al.* High-frequency stimulation of the sub-thalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res* 1998; 31: 39-46.

Vesper J, Steinhoff B, Rona S, Wille C, Bilic S, Nikkhah G, Ostertag C. Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy. *Epilepsia* 2007; 48: 1984-9.

Vonck K, Boon P, Van Laere K, *et al.* Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. *Epilepsia* 2000; 41: 601-9.

Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P. The mechanism of action of vagus nerve stimulation for refractory epilepsy. *J Clin Neurophysiol* 2001; 18: 394-401.

Vonck K, Boon P, Achten E, De Reuck J, Caemaert J. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann Neurol* 2002; 52: 556-65.

Vonck K, Boon P, Van Roost D. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy. *Acta Neurochir* 2007; 97 (Suppl.): 321-8.

Wang S, Wu DC, Ding MP, Li Q, Zhuge ZB, Zhang SH, Chen Z. Low-frequency stimulation of cerebellar fastigial nucleus inhibits amygdaloid kindling acquisition in Sprague-Dawley rats. *Neurobiol Dis* 2008; 29: 52-8.

Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001; 112: 1367-77.

Weiss SRB, Li XL, Rosen JB, Li H, Heynen T, Post RM. Quenching: inhibition of the development and expression of amygdala kindled seizures with low frequency stimulation. *Neuroreport* 1995; 4: 2171-6.

Wheless JW, Maggio V. Vagus nerve stimulation therapy in patients younger than 18 years. *Neurology* 2002; 59 (Suppl. 4): S 21-5.

Wright GD, Mc Lellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. *J Neurol Neurosurg Psychiatry* 1984; 47: 769-74.

Yamamoto J, Ikeda A, Satow T, *et al*. Low-frequency electric cortical stimulation has an inhibitory effect on cortical focus in mesial temporal lobe epilepsy. *Epilepsia* 2002; 43: 491-5.

Yang LX, Jin CL, Zhu-Ge ZB, Wang S, Wei EQ, Bruce IC, Chen Z. Unilateral low-frequency stimulation of central piriform delays seizure development induced by amygdaloid-kindled in rats. *Neuroscience* 2006; 138: 1089-96.

Zhu-Ge ZB, Zhu YY, Wu DC, *et al.* Unilateral low-frequency stimulation of central piriform cortex inhibits amygdaloid-kindled seizures in Sprague-Dawley rats. *Neuroscience* 2007; 146: 901-6.

Zumsteg D, Lozano AM, Wennberg RA. Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. *Epilepsia* 2006; 47: 1958-62.