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

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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

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.
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 (Oomen 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 electrophysiological 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 (Penny 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 epileptogenesis 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/cm²/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, whereas 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 Viaq 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 (Mirs and Ferrendelli 1986a, 1986b). In addition, the section of the mamillo-thalamic bundle prevented pentylenetetrazol-induced seizures in guinea pigs (Mirs and Ferrendelli 1984). Furthermore, it was reported that 100-Hz electrical stimulation of the mammary nuclei and AN increased the seizure threshold of pentylenetetrazol in rats (Mirs 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 (Mirs et al. 1997). More recently, high-frequency AN stimulation suppressed focal cortical and limbic seizures induced by intra-cortical or intramydloid 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 reassessing 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 mammillothalamic 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 reticulothalamicocortical 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; Nall-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 (Danobe 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 (Chabardés 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 ladarola were the first to correlate an increase of GABA in the Substantia nigra pars reticulata (SNR) with antiepileptic effects (Gale and ladarola 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 afterdischarges, 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 fissi- tigial 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 period (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).

**Adaptive 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 pentylentetrazole-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 (Kossoff 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. □

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