Deep Brain Stimulation for epilepsy: knowledge gained from experimental animal models

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Abstract

Since the development of Deep Brain Stimulation (DBS) for Parkinson's Disease, DBS has been suggested as a treatment option for various other neurological disorders. Stimulation of deep brain structures for refractory epilepsy appears to be a safe treatment option with promising results. As research on the evaluation and optimization of DBS for refractory epilepsy may be difficult and unethical in patients, studies on animal models of epilepsy are indispensable. Various brain structures and specific nuclei such as the basal ganglia, the cerebellum, the locus coeruleus and temporal lobe structures have been investigated as target areas for DBS. Additionally, a wide variety of stimulation parameters are available, with a range of stimulation frequencies, pulse widths and stimulation intensities. This review provides an overview of the relevant literature on experimental animal studies of DBS for epilepsy. Knowledge gained from animal studies can be used to answer questions regarding the optimal brain targets and stimulation parameters in human applications.

Introduction

Each year, more than 50 to 70 new cases of epilepsy occur among every 100 000 people in the general population (Hauser, 1998). Despite the recent advent of new drugs, around 30% of the patients remains refractory to medical treatment and/or suffers from major side effects (Duncan and Sagar, 1987). Therefore, there is a continuous quest for new and better treatments.

Deep Brain Stimulation involves the intracranial implantation of one or more electrodes in a selected area. Via an implanted battery and a subcutaneous lead, electrical pulses are sent to specific parts of the brain to interfere with the neural activity of the target site. The use of electrical stimulation originates from the 1950s, as it was used to functionally locate and distinguish specific sites in the brain (Penfield, 1958). During this procedure, it was discovered that stimulation of certain brain structures could suppress abnormal electrical activity in the brain.

One of the first applications of chronic DBS was performed by Benabid and co-workers in Grenoble for the treatment of movement disorders (Benabid *et al.*, 1991). It is estimated that approximately 20.000 patients worldwide with movement disorders are currently being treated with DBS. Following this success, the number of neurological diseases in which the use of DBS is being investigated, is steadily growing.

Currently, also refractory epilepsy has been treated experimentally with DBS. Since 1988, intermittent stimulation of the left vagus nerve, known as vagus nerve stimulation (VNS), has been used as an approved therapy for epilepsy. Currently 30% of patients treated with VNS, do not experience any improvement (Handforth *et al.*, 1998). Despite its use in more than 30.000 patients, the exact mechanism of action of VNS is still to be clarified. It is suggested that through stimulation of the vagus nerve, deep brain structures such as the locus coeruleus, thalamus and cortex are indirectly influenced (Vonck *et al.*, 2001). In contrast with the extracranial stimulation of a peripheral nerve in order to indirectly influence brain structures, the direct stimulation of brain structures through DBS may exert stronger seizure suppressing effects. Therefore, DBS is a promising new technique in the search for alternative treatment options for refractory epileptic patients.

Despite the growing interest and increasing number of publications regarding the use of DBS for epilepsy, still many important questions remain unanswered. What are the optimal stimulation parameters? What is the optimal brain target? What

is the underlying mechanism of action? Does the effect of DBS depend on the type of epilepsy syndrome? To answer those questions, experiments on humans are difficult and restricted due to ethical considerations, the large patient groups needed and the variability among the patients. Studies on animal models for epilepsy are therefore indispensable.

The purpose of this review is to summarize the relevant animal studies that have been conducted in the field of DBS and epilepsy and to provide a better insight into the ongoing quest for optimal stimulation parameters and brain targets. For the ease of reading, the different animal studies are subdivided according to different brain targets.

Deep brain stimulation in animal models of epilepsy

1. Basal ganglia

The basal ganglia consist of a set of highly interconnected nuclei, including the putamen, the caudate nucleus (CN), the nucleus accumbens, the globus pallidus (GP), the subthalamic nucleus (STN) and the substantia nigra (SN). The SN pars reticularis (SNr) is the main output structure of the basal ganglia, and inhibition of the SNr leads to suppression of seizures in various animal models (Depaulis *et al.*, 1994; Gale, 1980; Iadarola and Gale, 1982). Based on these findings, the existence of a 'nigral control of epilepsy system' was postulated, with the STN, the caudate nucleus and the SN as key structures. Experimental animal studies demonstrated the presence of this nigral control system (Deransart *et al.*, 2001). Modulation of this subcortical control system through electrical stimulation of the STN, caudate

nucleus or SNr has been investigated in several animal models.

1.1. *Subthalamic nucleus*

Subthalamic nucleus stimulation (STN) has been extensively used as a treatment for movement disorders (Benabid, 2003). Drawn from this experience and based on the positive effects of modulation of the nigral control system on seizure suppression, STN stimulation has recently been introduced as a potential alternative treatment modality for refractory epilepsy (Table 1).

In Genetic Absence Epilepsy Rats from Strasbourg (GAERS), Verceuil *et al.* started five seconds of high frequency STN stimulation when a spike-and wave discharge (SWD) appeared at the EEG. Unilateral stimulation caused no interruption while bilateral stimulation interrupted the SWDs. The current intensity was kept below the threshold for motor behavior. Stimulation with the same intensity for ten minutes instead of five seconds, suppressed the SWD during the first two minutes (Vercueil *et al.*, 1998). A drawback from the inbred GAERS model is that the spontaneous SWDs (lasting for about 10s) can be interrupted by external stimuli such as clapping in the hands or blowing on the nose. Hence, it is difficult to establish whether the interruption of the SWDs in GAERS is to be attributed to the STN stimulation, or to the perception of an external stimulus associated with STN stimulation. In studies with another animal model, it was observed that the suppression of flurothyl-induced seizures due to STN stimulation appears frequency-dependent (Lado *et al.*, 2003). Only HFS (130 Hz) was able to significantly

Table 1

Animal experimental studies on DBS in the subthalamic nucleus: Parameters are frequency (Hz); intensity of stimulation (μA-mA); stimulation duration (ms-s); wave form and pulse width (ms)

Author	Animal model	Parameters	Target	Results
Vercueil (1998)	GAERS	130 Hz; 0-300 μA; 5 s and 10 min Pulse width 60 μs; uni- and bilateral	STN	Unilateral: no effect Bilateral: Stimulation during 5 s suppressed seizures, 10 min suppressed only short term
Lado (2003)	Flurothyl	130, 260 and 800 Hz; 200-500 μA Pulse width 60 μs; bilateral	STN	130 Hz increased the threshold for clonic seizures, 260 Hz had no effect and 800 Hz was proconvulsive
Usui (2005)	Kainic acid	130 Hz; 127 +/– 24 μA Pulse width 60 μs	STN	Decreased generalisation
Shehab (2006)	Electroshock	130 and 260 Hz; 175-300 μA; 30 min Pulse width 60 μs; bilateral	STN	No effect

increase the seizure threshold for clonic seizures. The latency for tonic-clonic seizures could not be increased due to HFS-STN. Stimulation with frequencies of 260 Hz did not show any difference with control rats and 800 Hz decreased the threshold for tonic-clonic seizures. A similar study in kainic acid treated rats was conducted by Usui *et al.* (Usui *et al.*, 2005). Unilateral STN stimulation with 130 Hz significantly reduced the duration of generalized seizures, although the total duration of (generalized and focal) seizures was unchanged. It can be concluded that STN stimulation suppresses secondary generalization of seizures. However, it needs to be remarked that comparison between the above-mentioned animal studies is limited by the fact that four distinct animal models are used. The underlying pathophysiology of the different types of epilepsy syndromes (eg. absence epilepsy versus generalized epilepsy) may need different types of stimulation. Furthermore, the 'epileptogenic' network may be situated elsewhere dependent on the animal model used.

The effect on the suppression of the secondary generalization of seizures is reflected in the results from clinical trials with STN stimulation. Two recent human studies in a small number of patients observed that bilateral STN stimulation in patients with refractory epilepsy is able to reduce the intensity and the frequency of seizures (Handforth *et al.*, 2006; Vesper *et al.*, 2007). Stimulation of the STN is a feasible and promising treatment for epilepsy but further research needs to be conducted to fully establish STN stimulation as an alternative treatment modality for refractory epilepsy patients.

1.2. *Substantia Nigra pars reticulata*

The first animal experimental evidence for the successful suppression of epileptic seizures due to substantia nigra pars reticularis (SNr) stimulation was given by Morimoto *et al.* (Morimoto and Goddard, 1987) (Table 2). Ipsilateral SNr stimulation preceding a kindling pulse during the kindling acquisition period delayed the appearance of stage 4 and 5 seizures and was able to decrease the afterdischarge (AD) duration. Bilateral antecedent stimulation in fully kindled animals prolonged the latency towards generalized seizures and decreased the AD duration. This effect was not repeated when SNr stimulation was switched on after forelimb clonus was already initiated. This suggests that SNr stimulation modulates the early aspects of seizure generalization in the kindling model (Morimoto and Goddard, 1987).

In adult rats postnatal day (PN) 60 challenged with flurothyl, both unilateral and bilateral high frequency (130 Hz) stimulation of anterior SNr increased the threshold for clonic seizures (Velisek *et al.*, 2002a). No effect was seen on the threshold for tonic-clonic seizures, neither following stimulation of the posterior part of the SNr. In PN15 rats bilateral SNr stimulation in both the anterior and posterior part of the SNr had anti-convulsive effects in tonic-clonic and clonic seizures (Velisek *et al.*, 2002a). Shi *et al.* treated fully amygdala-kindled rats with bilateral SNr stimulation immediately 1s after cessation of the kindling stimulus. They showed that DBS was able to block kindled seizures in 43.5% of rats. The suppressive effect lasted for up to 4 days (Shi *et al.*,

Table 2

Animal experimental studies on DBS in the Substantia Nigra pars reticulata

Author	Animal model	Parameters	Target	Results
Morimoto (1987)	Amygdala or piriform cortex kindling	100 Hz; 0-1.2 mA; 5 s Pulse width 0.5 ms; uni- and bilateral	SNr	Unilateral: decreased AD duration and slower progression to stage 4 and 5 Bilateral: decreased AD duration in fully kindled rats
Velisek (2002)	Flurothyl	130 Hz; 690 μA (PN 60)-870 μA (PN 15); 953 s (PN 60)-495 s (PN 15) Pulse width 60 μs; uni- and bilateral	Anterior SNr Posterior SNr	PN60: uni- and bilateral stimulation in the anterior SNr increased the threshold for clonic seizures PN15: bilateral stimulation had anti-epileptic effects. Unilateral stimulation had no effects
Usui (2005)	Kainic acid (ip.)	130 Hz; 188 +/– 41 μA Pulse width 60 μs	SNr	No effect in the majority of rats
Shi (2006)	Anrygdala-kindling	130 Hz; 100-200 μA; 20 s Pulse width 60 μs; bilateral	SNr	Complete blockade of kindling acquisition in 10 out of 23 rats
Feddersen (2007)	GAERS	5-500 Hz; 32.9 +/– 7.1 μA Pulse width 10-200 μs; uni- and bilateral	SNr	Bilateral 60 Hz with 60 μs pulse width was the most effective in blocking SWDs

2006). Optimization of SNr stimulation parameters was investigated in GAERS rats (Feddersen *et al.*, 2007). The optimal stimulation parameters to stop ongoing SWDs were 5 seconds of bipolar, monophasic, bilateral stimulation with a pulse width of 60 μs and a frequency of 60 Hz. On the contrary, chronic stimulation showed to be ineffective and even aggravated seizures in the GAERS model (Feddersen *et al.*, 2007). As mentioned above, the limitations intrinsic to the use of the GAERS model must be taken into consideration before making conclusions on the possible therapeutic effect of SNr stimulation.

No human studies have been undertaken to investigate the effect of SNr stimulation up to now. The risk of inducing extrapyramidal effects through stimulation or implantation of an electrode in this nucleus is a likely reason.

1.3. *Caudate nucleus*

Animal experimental studies on stimulation of the caudate nucleus (CN) have been published from the 1960's until the 1980's (Table 3). Later on, mainly human studies were conducted.

In rabbits, Costin *et al.* investigated the effect of CN stimulation on hippocampal ADs (Costin *et al.*, 1963). Caudate nucleus stimulation immediately following hippocampal stimulation prolonged the AD. Stimulation during or immediately preceding the hippocampal stimuli had no effect. In contrast to these negative findings, La Grutta reported a suppressive effect of CN stimulation in cats with focal paroxysmal activity in the temporal area (La Grutta *et al.*, 1971). Further, stimulation of the CN was observed to decrease the excitability of a cobalt –induced rhinencephalic seizure focus (Mutani and Fariello, 1969). Moreover, high frequency stimulation in the penicillin-induced cortical epileptiform activity in the cat was able to suppress the epileptiform spikes (Wagner *et al.*, 1975). Seizure frequency was decreased due to 10-100 Hz stimulation of the CN in an aluminium hydroxide seizure focus in the motor cortex in four out of six monkeys (Oakley and

Table 3

Animal experimental studies on DBS in the nucleus caudatus

Author	Animal model	Parameters	Target	Results
Costin (1963)	Hippocampal stimulation	15, 200, 300 Hz; 2-8 V; 10 or 170 s Pulse width 1 ms	Nucleus caudatus	The evoked AD was prolonged
Mutani (1969)	Cobalt (focal)	100 Hz; 5-30 V; 1 s Pulse width 0.6 ms	Head nucleus caudatus	Increase in number and duration of seizures
La Grutta (1971)	Amygdala stimulation	30 Hz; 0.2-1.5 mA; 5 s Pulse width 1.5 ms	Nucleus caudatus	Antecedent stimulation was able to block AD. No effect when DBS was given after or during seizure
Wagner (1975)	Penicillin (focal)	400 Hz; 0.3-0.9 mA; 1-9 s and 30-180 s Pulse width 0.5 ms	Nucleus caudatus	Penicillin induced spikes were suppressed
Amato (1982)	Amygdala stimulation	30-80 Hz; 4-12 V; 2-6 s Pulse width 0.1-1 ms	Nucleus caudatus, SN pars compacta, entopeduncular nucleus	Nucleus caudatus was the least effective in influencing AD durations
Oakley (1982)	Aluminium injection (focal)	10 and 100 Hz; 1-6 mA; 10 min on/off or continuous Pulse width 1 ms	Head nucleus caudatus	LFS: seizure frequency decreased HFS: seizure frequency augmented, mainly when stimulation was stopped
Psatta (1983)	Cobalt (focal)	5 Hz; 1-5 V; 1 s feedback stimulation; pulse width 0.3 ms	Nucleus caudatus	Decrease in interictal spikes
La Grutta (1986)	Penicillin (ip.)	30 Hz; 0.2-1 mA; 10-60 s Pulse width 0.5-1 ms	Nucleus caudatus	Decrease in interictal spikes
La Grutta (1988)	Penicillin (focal)	10 or 25 Hz; 0.1-0.5 mA; 30-180 s Pulse width 1 ms	Nucleus caudatus	Decrease in interictal spikes (short term). Long term stimulation was not effective (10 Hz)

Ojemann, 1982). However, when CN stimulation was stopped, an increase in seizure frequency was noticed and intermittent stimulation caused a status epilepticus in two out of six monkeys. This status could be interrupted by switching off the stimulator (Oakley and Ojemann, 1982). In a comparative study, the CN was observed to be the least effective stimulation target in fully kindled animals among the substantia nigra pars compacta, the entopeduncular nucleus and the nucleus caudatus (Amato *et al.*, 1982). However, no control group was mentioned here. Two studies also reported the effect of CN stimulation on interictal spikes. In the first study, feedback stimulation (5 Hz) in the CN was initiated whenever a spike was detected on the EEG (Psatta, 1983). Spike depression occurred instantly after onset of the feedback stimulation but this type of stimulation could not suppress an ongoing seizure. A second study reported that 10 Hz and 25 Hz CN stimulation were able to suppress hippocampal spiking activity induced by topical application of sodium penicillin in the cat (Sutula *et al.*, 1988). It is important to notice that the effect of CN stimulation on interictal spikes has not been proven to correlate with the effect of the same stimulation on spontaneous seizures in animals and humans (Gotman, 1991; Katz *et al.*, 1991). Therefore, some criticism is warranted when interpreting the results of studies on the effect of DBS on interictal spikes.

More recently, CN stimulation regained interest when Chkhenkeli *et al.* investigated this in patients (Chkhenkeli *et al.*, 2004; Chkhenkeli and Chkhenkeli, 1997). They demonstrated that 4-8 Hz stimulation of the head of the caudate nucleus was able to suppress the subclinical epileptic discharges and reduced the frequency of generalized seizures. However, more studies are needed to confirm the effect of CN stimulation in the suppression of epileptic discharges. It is hypothesized that activation of the substantia nigra pars reticulata is caused by stimulation of the caudate nucleus and therefore influences cortical epileptic activity (Chkhenkeli *et al.*, 2004; Deransart and Depaulis, 2002; Slaght *et al.*, 2002).

2. THALAMUS

The thalamus has been a site of interest for the treatment of epilepsy for many years. It is known to be involved in the initiation of generalized seizures, and is thought to be important in the propagation of partial seizures (Schaul, 1998). Due to its reciprocal connections to the cortex, stimulation of the thalamus may exert seizure modulating effects. The thalamus can be divided into four major anatomic nuclei: the anterior, the ventral, the mediodorsal and

the lateral nuclei groups. Mainly, the roles of the medial and the anterior nuclei have been investigated in animals and in humans as a potential target for neurostimulation in epilepsy. There is also one animal experimental report on the stimulation of the nucleus reticularis of the thalamus (Nanobashvili *et al.*, 2003).

2.1. *Centromedian nucleus*

The centromedian nucleus of the thalamus (CM) may control the physiological state of the thalamus via intrathalamic pathways, or may suppress seizure activity through excitatory connections to the striatum (Miller and Ferrendelli, 1990). In spite of the sparse animal experimental studies regarding the chronic stimulation of the CM, Velasco *et al.* successfully stimulated 13 patients with Lennox-Gastaut syndrome (Velasco *et al.*, 2006) and eighteen patients with intractable epilepsy (Velasco *et al.*, 1987; Velasco *et al.*, 2000a). These studies reported a significant improvement in seizure outcome. However, a more recent study by Andrade *et al.* showed no significant benefit following CM stimulation in two patients (Andrade *et al.*, 2004). Additionally, a placebo-controlled trial by Fisher *et al.* (Fisher *et al.*, 1992) found no statistically significant differences speculating that more animal and human studies are needed to demonstrate the efficacy of CM stimulation.

2.2. *Nucleus reticularis*

The nucleus reticularis of the thalamus is part of the thalamocortical system and different mechanisms can contribute to the influence of this nucleus on epileptic seizures (Bertram *et al.*, 1998; Cox *et al.*, 1997). Deep brain stimulation of this nucleus has only been investigated in one experimental study (Nanobashvili *et al.*, 2003) (Table 4). Stimulation with 60 Hz decreased the seizure severity and was able to decrease the duration of the AD during the kindling acquisition. In fully kindled animals, the number of generalized seizures was decreased (Nanobashvili *et al.*, 2003). No human studies on the stimulation of the nucleus reticularis have been conducted so far.

2.3. *Anterior thalamic nucleus*

The anterior nucleus of the thalamus (ANT) is a key structure in the circuit of Papez (Azzaroni and Parmeggi, 1968). The ANT receives input from the mammilary nuclei and projects to the cingulum bundle. The mammilary bodies receive input from the fornix, which in its turn receives projections from

Table 4

Animal experimental studies on DBS in the reticular nucleus of the thalamus

Author	Animal model	Parameters	Target	Results
Nanobashvili (2003)	Hippocampal kindlingn	60 Hz; 150 µA; 20 s Square wave; pulse width 0.5 ms	Reticular nucleus	Behavioural seizure scores were decreased during kindling progression. In fully kindled rats, the duration and the number of generalised seizures was decreased

the hippocampus. The cingulum bundle projects to the parahippocampal cortex, which in turn innervates the hippocampus. It has been documented that disrupting the ANT by lesioning or pharmacology increases the threshold for seizures (Hamani *et al.*, 2004; Mirski and Ferrendelli, 1984; Mirski and Ferrendelli, 1987). The effect of ANT-stimulation possibly mimics lesioning of the ANT and causes suppression of ongoing seizure activity due to disruption of the circuit of Papez.

Experiments in the early 1990's explored the effects of DBS in the mammilary nuclei and the ANT (Mirski *et al.*, 1994; Mirski *et al.*, 1997) (Table 5). Both studies reported that 100 Hz HFS was able to increase the clonic seizure threshold in the pentylenetetrazole model, while low frequency (8 Hz) stimulation decreased the threshold. Similar results were observed by Ziai *et al.* (Ziai *et al.*, 2005). Hamani *et al.* (Hamani *et al.*, 2004) recently investigated different ANT stimulation parameters in pilocarpine-induced seizures. Current intensities of 200 µA and 1mA elicited no significant effects. Bilateral ANT stimulation with 500 µA was most effective in increasing the latency for seizures, either with 20 Hz stimulation or 130 Hz stimulation, but stimulation was not able to stop ongoing seizures induced by pilocarpine. Despite the fact that all published studies agreed on the suppressive effect of ANT stimulation on epileptic seizures, Lado *et al.* (Lado, 2006) found that bilateral chronic ANT stimulation increased the seizure frequency in systemically treated kainic acid rats.

More recent animal experiments point to the fact that a lesion due to the implantation of the electrode can cause the observed effects on seizure suppression. Bilateral ANT stimulation in cortically kainic acid-injected rats caused abolishment of seizures whether the stimulation was on or off (Takebayashi *et al.*, 2007a). The same research group found similar effects in rats with intra-amygdala injection of kainic acid (Takebayashi *et al.*, 2007b).

Thanks to those initial animal experiments, it was possible to successfully investigate ANT stimulation in patients with refractory epilepsy (Hodaie *et al.*, 2002; Kerrigan *et al.*, 2004). Anterior nucleus of the thalamus stimulation is able to reduce the seizure frequency in patients with refractory partial and secondarily generalized seizures. Currently, a prospective randomized study on the Stimulation of the Anterior Nucleus for Epilepsy (SANTE) is being conducted in multiple centres across the United States (Halpern *et al.*, 2008).

However, similar to animal studies, the lesion effect due to implantation of the electrodes needs to be considered. Hodaie *et al.* (Hodaie *et al.*, 2002) observed a clear decrease in seizure frequency in five refractory epileptic patients, but the effects were probably caused by the insertion of the electrode as the benefits already became clear before the ANT stimulator was switched on.

The exact mechanism of action and the best stimulation parameters remain unknown and are the object for further research. So far, it seems that HFS is more prone to reduce seizures and LFS probably induces seizures.

3. CEREBELLUM

The main function of the cerebellum is to coordinate the execution of motor tasks and to maintain motor tone. The structure is highly interconnected with the cerebral cortex and brainstem and its efferent fibers project to the superior cerebellar peduncle (Ito *et al.*, 1964). Additionally, they make predominantly inhibitory connections to the thalamus. Because of these inhibitory connections, effects on seizure activity due to DBS in the cerebellum can be explained.

There are two main strategies for the electrical stimulation of the cerebellum. The most frequently used technique is to stimulate specific parts of the surface of the cerebellar cortex. Direct stimulation of cerebellar nuclei, such as the nucleus dentatus or the nucleus fastigii is another possibility (Table 6). Out of the eighteen cited animal experimental reports stimulating the cerebellar surface, ten studies suggest inhibition of seizures while eight studies clearly indicate that cerebellar stimulation has no effect or even a seizure facilitating effect. The available experimental studies can be subdivided following the

Table 5

Animal experimental studies on DBS in the anterior nucleus of the thalamus

Author	Animal model	Parameters	Target	Results
Mirski (1994)	PTZ	100 Hz; 30-200 µA	Mammilar nuclei	Higher seizure threshold, seizures interrupted
Mirski (1997)	PTZ	100 Hz and 8 Hz; 350-1000 µA Pulse width 0.1 ms	Anterior thalamic nuclear complex	HFS: higher seizure threshold LFS: proconvulsive
Hamani (2004)	Pilocarpine	100 Hz; 800 µA Pulse width 100 µs; uni- and bilateral	ANT	Unilateral: no significant alterations Bilateral: longer latency before seizure and status display
Ziai (2005)	PTZ	100 Hz; 150 µA; > 40 min Pulse width 0.1 ms; bilateral	ANT	Seizure threshold for first generalised seizure increased; lower incidence
Lado (2006)	Kainic acid (ip.)	100 Hz; 100-550 µA; cont./intermitt. Pulse width 100 µs; bilateral	ANT	Seizure incidence is increased
Takebayashi (2007)	Kainic acid (focal)	130 Hz; 140-500 µA Square wave; pulse width 0.1 ms; uni- and bilateral	ANT	Unilateral: significant decrease in seizure frequency Bilateral: no seizures developed Effects possibly caused by lesion
Nishida (2007)	PTZ	100 Hz; 150 µA uni-lateral; 80 µA bilateral; 10 s on/off Pulse width 300 µs	ANT Tuberomammillar nucleus Periformical urea	Unilateral in ANT; no effect Bilateral in ANT; decrease in latency and longer duration, but non-significant
Takebayashi (2007b)	Kainic Acid (amygdala)	130 Hz; 140-500 µA Square wave; pulse width 100 µs; uni- and bilateral	ANT	Seizure frequency decreased due to both uni- and bilateral stimulation
Hamani (2008)	Pilocarpine (ip.)	20 or 130 Hz; 1000, 500 or 200 µA; continuous Pulse width 90 µs	ANT	Both 200 µA and 1 mA were not effective 500 µA significantly increased the latency for seizures and status

animal model used. Most studies use the neocortical focally induced epileptic seizures model. These models are obtained by focal application of penicillin or metals such as alumina or cobalt directly on the surface of the brain. Other trials use the hippocampal or amygdala kindling model.

Cerebellar stimulation was reported to suppress neocortical focally induced epileptic seizures in two studies in the rat and cat (Dow *et al.*, 1962; Hutton *et al.*, 1972), while later experiments in the cat and monkey could not reproduce these results (Ebner *et al.*, 1980; Hablitz *et al.*, 1975; Lockard *et al.*, 1979; Reimer *et al.*, 1967; Strain *et al.*, 1978; Strain *et al.*, 1979). There is only one study that reported a prolongation of the seizure duration due to 10 Hz cerebellar stimulation in the cat with cobalt lesions in the sensorimotor cortex (Reimer *et al.*, 1967). On the contrary, five other studies (Ebner *et al.*, 1980; Hablitz *et al.*, 1975; Lockard *et al.*, 1979; Strain *et al.*, 1978; Strain *et al.*, 1979) found that 5-15 Hz stimulation in monkeys with chronic alumina-cream

epileptogenic foci was ineffective or even provoked electrographic seizures. In the penicillin-induced seizure models, the results of cerebellar stimulation on seizures are as conflicting as in the cobalt- or alumina-induced models. One study (Bantli *et al.*, 1978) found that seizure duration was significantly decreased by cerebellar surface stimulation, while three other studies in a similar animal model observed no suppression of any seizure manifestation (Godlevskii *et al.*, 2004; Hablitz, 1976; Myers *et al.*, 1975). The only changes that were reported, concerned suppression of interictal spikes (Godlevskii *et al.*, 2004; Hablitz, 1976), but the loose correlation between suppression of interictal spikes and suppression of seizure activity was already debated by Lockard *et al.* (Lockard *et al.*, 1979). This group observed that cerebellar stimulation decreased interictal spikes, but increased seizure frequency.

Epileptic seizures evoked by hippocampal stimulation were shown to be suppressed by cerebellar stimulation (Babb *et al.*, 1974; Iwata and Snider,

1959; Maiti and Snider, 1975; Mutani and Fariello, 1969). On the contrary, Myers *et al.* (Myers *et al.*, 1975) tested a range of stimulation parameters in four different animal models, but were unable to elicit any change in electrographic or clinical manifestation. Also Hemmy *et al.* could not significantly alter focal motor seizures induced by electrical stimulation (Hemmy *et al.*, 1977). And a recent report from Rubio *et al.* showed that in the amygdala-kindling model, cerebellar stimulation initially facilitated limbic seizures but impeded the secondary generalized seizures (Rubio *et al.*, 2004).

Only three studies have been published on the stimulation of the deep nuclei of the cerebellum, the nucleus dentatus and nucleus fastigii (Babb *et al.*, 1974; Hemmy *et al.*, 1977; Hutton *et al.*, 1972). Nucleus dentatus stimulation significantly prolonged the seizure duration in 2 out of 5 cats. Stimulation of the nucleus fastigii only decreased seizure duration in 1 out of 4 cats. Additionally, Hutton *et al.* described partial inhibition of seizure activity in 2 out of 7 cats due to nucleus dentatus stimulation, while nucleus fastigii stimulation had no effects. Electrically induced seizures could also not be suppressed with nucleus dentatus stimulation (Hemmy *et al.*, 1977).

The available human experimental trials also reflect these contradictory results seen in animal studies. Cooper was the first to successfully implant and stimulate patients with a complete cerebellar stimulation system. The intractable seizures of 18 out of 34 patients, and in a later study 23 out of 32 patients, were modified or controlled by chronic cerebellar LFS (10 Hz) and the seizure suppressing effect lasted up to 3 years (Cooper, 1973a; Cooper, 1973b; Cooper *et al.*, 1976; Cooper and Upton, 1978). Subsequent double-blind controlled trials, with a total of 17 patients, could not confirm these positive results (Van Buren *et al.*, 1978; Wright *et al.*, 1984). The work of Cooper *et al.* has therefore been criticized by many authors (Rosenow *et al.*, 2002; Strain *et al.*, 1978; Wright *et al.*, 1984). The effects that were observed in the uncontrolled studies were attributed to a powerful placebo effect. Furthermore, the placement of DBS electrodes was inconsistent and the used parameters varied, making it even more difficult to draw conclusions (Gwinn and Spencer, 2004). Recently, cerebellar stimulation for the treatment of refractory epilepsy patients, regained new interest. Velasco *et al.* (Velasco *et al.*, 2005) stimulated five patients in a double blind randomized control pilot study. Their results suggested that cerebellar cortex stimulation significantly decreased motor seizures. However, the small number of patients did not allow final conclusions on efficacy. Moreover, the safety

of the procedure was debated as three out of five patients underwent reimplantation due to electrode migration (Velasco *et al.*, 2005).

Despite the large number of animal and human experiments with cerebellar stimulation, results have been conflicting. This may have been due to the difference in animal models, the variation in stimulation parameters or the inconsistent stimulation locations. Predominantly LFS (10 Hz) was used, as the few reports of HFS (100 Hz) did not have a successful result. Nevertheless, the possible therapeutic role of cerebellar stimulation remains uncertain.

4. HIPPOCAMPUS AND AMYGDALA

The hippocampus and the amygdala are both located in the medial temporal lobe and are part of the limbic system, which is highly connected to the prefrontal cortex. Application of direct stimulation to the hippocampus or the amygdala can evoke seizures (i.e. kindling) (Goddard, 1983) but recently also DBS in the same structures is used as a way to suppress epileptic activity (Table 7). Early studies found that low frequency stimulation (LFS) in the amygdala and the hippocampus resulted into short term and long term seizure inhibition in fully kindled animals (Mucha and Pinel, 1977; Sainsbury *et al.*, 1978). The stimulation that was used, was in its turn able to evoke an afterdischarge (suprathreshold stimulation) (Gaito *et al.*, 1980). Later, subthreshold LFS was described to bring about long term seizure inhibition in fully kindled animals without evoking afterdischarges, making this a more applicable therapy (Shao and Valenstein, 1982). Early reports on the effect of LFS during the course of hippocampal or amygdala kindling, indicated that this could interfere with the generation of kindled seizures and was described to increase the AD threshold (Ullal *et al.*, 1989).

When Weiss *et al.* (Weiss *et al.*, 1995) published their findings, the interest for DBS in the mesial temporal lobe structures was increased. Low frequency stimulation (1 Hz) of the amygdala was reported to completely block the development and progression of afterdischarges during amygdala kindling, an effect that they called 'quenching'. The same authors later reported that a DC leakage of 5-15 μA originating from the stimulator was responsible for this 'quenching' effect (Weiss *et al.*, 1998). In later studies with both adult and immature rats, 1 Hz stimulation of 15 minutes in the basolateral amygdala was shown to delay the kindling acquisition process, to decrease the AD duration and to affect the seizure severity (Velisek *et al.*, 2002b). More recent studies on low frequency stimulation in the hippocampus

Table 6

Animal experimental studies on DBS in the cerebellum

Author	Animal model	Parameters	Target	Results
Iwata (1959)	Hippocampal stimulation	30 and 100 Hz; 7, 10 and 20 V Pulse width 0.1 ms	Vermis	Terminates ictal seizure activity
Dow (1962)	Cobalt (focal)	20-50 Hz and 200-400 Hz; 1-5 V; 1-3 ms Pulse width 0.3-1 ms	Lobus anterior	Inhibits epileptiform activity
Reimer (1967)	Cobalt (focal)	4-300 Hz; 1-7.5 V Pulse width 0.1 ms	Vermis	Seizures are prolonged when stimulation is applied during seizure activity
Mutani (1969)	Cobalt (focal)	100 Hz; 7 V Pulse width 0.6 ms	Lobus anterior	After seizure activity; inhibition
Hutton (1972)	Penicillin (focal)	200 Hz; 0.1-1 mA	Vermis, para-median lobuli, N, dentatus	All three targets induce inhibition
Babb (1974)	Cobalt (hippocampus)	30-500 Hz; 0.3-2.5 mA	N. fastigii, N. dentatus	N. fastigius: seizure stops N. dentatus: seizure longer
Meyers (1975)	Chloralose, PTZ, penicillin, enfluraan	1-250 Hz; 2.5 mA	Lobus anterior	No effect
Maiti (1975)	Hippocampal stimulation		Vermis	Decrease or interruption of AD
Hablitz (1975)	Aluminium hydroxide gel (focal)	5-15 Hz and 100 Hz; 1-10 V; 1-30 s Pulse width 1 ms	Vermis	LFS: no change in spontaneous cortical activity HFS: provokes seizures
Hablitz (1976)	Penicillin	10 and 100 Hz; 0.25-2 mA Square wave; Pulse width 1 ms	Median	LFS and HFS were both equally effective
Hemmy (1977)	Stimulation (focal)	4, 1à, 50 and 100 Hz; 10 mA Pulse width 1 ms	Cortex, N. dentatus	No effect
Bantli (1978)	Penicillin (focal)	10 Hz; 26 mA/cm^2 Pulse width 0.1 ms	Lobus anterior	Significant reduction in duration of seizures
Strain (1978)	PTZ and stimulation	10 Hz; 3 V Pulse width 1.5 ms	Cerebellar lobuli	No difference between DBS and pheno-barbital and diphenylhydandoine
Strain (1979)	Aluminium hydroxide gel (generalised)	10 Hz; 8-10 min on/off Pulse width ms	Paravermal cortex	No effect
Lockard (1979)	Aluminium hydroxide gel (generalised)	10 Hz; 2 mA; 10 min on/off Pulse width 1 ms	Anterior superior cerebellum	Seizure frequency increased and interictal spikes decreased
Ebner (1980)	Aluminium hydroxide gel (focal)	10 Hz; 1, 2 or 3x threshold for cortical response; 10 min on/off Pulse width 0.1 ms	Between vernis and lobuli	No effect on seizures
Godlevskii (2004)	Penicillin	10-12 Hz and 100-300 Hz; 20% of behavioural threshold Pulse width 0.25-0.5 ms	Paleocerebellar cortex	LFS: activation spike discharges and seizures HFS: spike suppression, decreased frequency, shorter duration
Rubio (2004)	Amygdala-kindling	100 Hz; 20 μA	Superior pedunculus	Electrode insertion causes decreased expression. Initially faster progression, but slower generalisation

Table 7

Animal experimental studies on DBS in the medial temporal lobe structures

Author	Animal model	Parameters	Target	Results
Mucha and Pinet (1977)	Amygdala-kindling	60 Hz; 20-, 40-, 60, 80 µA; 1 s	Kindlingfocus	Suppression (90 s-90 min) of AD
Gaito (1980)	Amygdala-kindling	3 Hz; 100-196 µA; 30 s Sine wave	Kindlingfocus	Higher seizure threshold and suppression of behavioural signs
Shao (1982)	Amygdala-kindling	60 Hz; until 54 µA; 1 s Sine wave	Kindlingfocus	Long-term inhibition
Ullal (1989)	Amygdala-kindling	4 Hz; $^1/_2$ of AD threshold Square wave; pulse width 125 ms	Hippocampus, Amygdala	Increased AD threshold during kindling acquisition and in fully kindled animals
Weiss (1995)	Amygdala-kindling	1 Hz; 15 min	Kindlingfocus	AD threshold increased
Weiss (1998)	Amygdala-kindling	1 Hz; 5-15 µA; 15 min Direct Current (DC)	Kindlingfocus	AD threshold increase caused by DC leakage
Bragin (2002)	Kainic Acid	1, 50 and 200 Hz; 10 min and 2 h	Perforant path	No significant change in spontaneous seizure rate
Velisek (2002)	Amygdala-kindling	1 Hz; 280 µA; 15 min Square wave; pulse width 200 µs	Kindlingfocus	Impaired progression towards fully kindled rats; decreased AD duration
Lopez-Meraz (2004)	Amygdala-kindling	1 Hz; 100-400 µA; 15 min Square wave	Kindlingfocus	Slower progression towards fully kindled rats
Goodman (2005)	Amygdala-kindling	1 Hz; 50 µA; 30 s Sine wave	Kindlingfocus	Decreased AD duration and behavioural score
Cuellar-Herrera (2006)	Amygdala-kindling	130 Hz; 120-660 µA; 1 h	Kindlingfocus	Non-responders and responders with no stage 4 or 5 seizures
Carrington (2007)	Amygdala-kindling	1 Hz; 100 µA; 30 s Sine wave	Kindlingfocus	Increased AD threshold
Wyckhuys (2007)	Alternate Day Rapid Kindling	130 Hz; 329 ± 52 µA; continuous Square wave; pulse width 60 µs	Hippocampus	AD threshold increased, AD latency and duration decreased
Mohammad-Zadeh (2007)	Rapid kindling	1 Hz; 50-150 µA Pulse width 0,1 ms	Perforant path	Slower progression towards fully kindled rats

and amygdala are all restricted to the kindling model. Lopez-Meraz *et al.* (Lopez-Meraz *et al.*, 2004) described a slower progression towards the fully kindled state but LFS did not prevent partial seizures. And Goodman *et al.* (Goodman *et al.*, 2005) found that the incidence of stage 5 seizures dramatically decreased due to precedent LFS in fully kindled animals. In another study, LFS seemed to increase the AD threshold, but changes on latencies and duration of the convulsions were not elicited in fully kindled rats (Carrington *et al.*, 2007). Additionally, application of LFS in the perforant path, which is the main gateway towards the hippocampus, was able to retard the kindling acquisition when applied immediately after termination of each kindling stimulus in the rapid kindling model (Mohammad-Zadeh *et al.*, 2007).

Remarkably, most of the animal experimental studies all describe low frequency stimulation in the kindling model. The first study using a spontaneous model, investigated the effect of 200 Hz high frequency stimulation and 1 Hz low frequency stimulation during two hours on the interictal spike rate and spontaneous seizures in kainic acid treated rats (Bragin *et al.*, 2002). They found no significant suppression of interictal events or spontaneous seizures by either HFS or LFS, but they argued that longer or continuous stimulation could be more suited to obtain a seizure-suppressing effect (Bragin *et al.*, 2002). The effect of HFS (130 Hz) was recently

investigated in the kindling model (Cuellar-Herrera *et al.*, 2006; Wyckhuys *et al.*, 2007). During the hippocampal kindling process, one hour of HFS applied immediately after each kindling stimulus was able to modify the epileptogenesis (Cuellar-Herrera *et al.*, 2006). In fully kindled animals, continuous HFS was reported to significantly increase the AD threshold, decrease the AD duration and AD latency (Wyckhuys *et al.*, 2007).

In line with these animal experiments on HFS, human trials were conducted to investigate its effect on spontaneous seizures. Velasco *et al.* (Velasco *et al.*, 2000b) were the first to use diagnostic depth electrodes to investigate the effect of 130 Hz stimulation in the hippocampus and amygdala. They noticed that unilateral HFS in ten presurgical candidates decreased interictal and ictal epileptiform activity during a two-week period. The most pronounced response was obtained with stimulating electrodes in or near the pes hippocampi. The positive effects of DBS were confirmed in later studies (Velasco *et al.*, 2007; Velasco *et al.*, 2001). Vonck *et al.* treated three refractory patients with amygdalo-hippocampal HFS for 3-6 months and reported a more than 50% reduction in seizure frequency and a significant reduction in seizure severity (Vonck *et al.*, 2002). These results were confirmed in a long-term study in 10 patients (Boon *et al.*, 2007). Further, two studies explored the efficacy of seizure-triggered responsive hippocampal DBS. Seizures were aborted (Kossoff *et al.*, 2004) or improved by 58% (Osorio *et al.*, 2005). Tellez-Zenteno *et al.* reported a median reduction of seizures of 15% in four patients with hippocampal DBS (Tellez-Zenteno *et al.*, 2006). Remarkably, most studies in refractory epileptic patients use the high frequency stimulation (HFS; 100 Hz -165 Hz). Only two research groups compared the effects of high frequency with low frequency (1-20 Hz) DBS in TLE patients (Boex *et al.*, 2007; Chkhenkeli *et al.*, 2004). Low frequency

stimulation (5 Hz) of the amygdala-hippocampal complex increased the epileptogenic interictal activity in 2 out of 3 patients (Boex *et al.*, 2007). Chkhenkeli *et al.* used LFS (1-20 Hz) in patients with mesiobasal temporal lobe foci and observed that stimulation with 1-3 Hz, and not 5-20 Hz, suppressed interictal discharges (Chkhenkeli *et al.*, 2004).

In conclusion, both the human studies and the animal experimental studies show promising results with DBS (especially with high frequency stimulation), but only few controlled studies have been conducted so far. Before the efficacy of stimulation of temporal lobe structures can be established, more controlled trials are needed.

5. PIRIFORM CORTEX

The piriform cortex is a structure between the lateral olfactory tract and the temporal lobe. Important in the context of epilepsy are its multiple connections to limbic nuclei (Gale, 1992). This structure is mainly involved in olfactory perception. Interest for the piriform cortex as a possible DBS target was raised by the discovery that a small central part is important in the generation and propagation of epileptic afterdischarges in the kindling model. It has been shown that the piriform cortex is activated early in the kindling process (Löscher *et al.*, 1995).

The effects of unilateral LFS of the central piriform cortex (cPC) on kindling progression and on afterdischarges in fully kindled animals were investigated (Yang *et al.*, 2006; Zhu-Ge *et al.*, 2007b) (Table 8). Ipsilateral and contralateral LFS (1 Hz) significantly inhibited the kindling process when LFS was given after termination of the daily amygdala kindling stimuli. The suppressive effects persisted for at least 10 days (Yang *et al.*, 2006). In fully amygdala-kindled animals, cPC-LFS resulted in decreased incidence of generalized seizures, decreased

Table 8

Animal experimental studies on DBS in the Substantia Nigra pars reticulata

Author	Animal model	Parameters	Target	Results
Yang (2006)	Amygdala-kindling	1 Hz; 50-150 µA; 15 min Pulse width 0.1 ms; bilateral	Central piriform cortex	Decreased AD duration and slower kindling progression. Ipsilateral more effect
Zhu-Ge (2007)	Amygdala-kindling	1 Hz; 50-150 µA; 15 min Pulse width 0.1 ms; bilateral	Central piriform cortex	Decreased AD duration. Ipsilateral more effect
Ghorbani (2007)	Piriform cortex-kindling	1 Hz; 1/4e of AD threshold-AD threshold or 3x AD threshold Pulse width 0.05-10 ms	Central piriform cortex	During kindling acquisition: decrease in stage 5 seizures; in fully kindled rats: number of stimuli to reach stage 1 or 2 is decreased

cumulative AD durations and increased AD threshold (Zhu-Ge *et al.*, 2007a). Ghorbani *et al.* (Ghorbani *et al.*, 2007) attempted to determine the effects of different stimulation patterns of monophasic square wave cPC-LFS on PC-kindled seizures. They observed that application of different patterns of LFS had no suppressive effect on seizure severity in fully kindled animals. During kindling acquisition however, LFS was shown to have anti-epileptogenic effects. The results reported by Ghorbani *et al.* are smaller than the ones reported by Yang *et al.* and Zhu-Ge *et al.*, possibly related to the use of a different animal model in both research groups (amygdala kindling versus PC-kindling). Secondly, in the latter study monophasic stimulation is used although biphasic stimulation is preferred to decrease the potential of tissue damage (Harnack *et al.*, 2004).

Before concluding that the piriform cortex is an interesting brain target for DBS, two major limitations have to be overcome. First, the limited studies in the field of DBS in the piriform cortex are all conducted in the kindling model. Before the relevance of PC stimulation for the treatment of refractory epilepsy can be confirmed, it would be interesting to investigate whether cPC stimulation is able to alter the seizure incidence in a spontaneous seizure model because the epileptogenic network may be different in the hippocampal kindling model, and in the spontaneous model, and it may also depend on where in the brain the responsible 'epileptogenic' networks are situated. Secondly, there is no direct proof that the PC in human epilepsy plays an evenly important role in the seizure initiation and propagation as it does in kindling (Löscher *et al.*, 1995). The role of the PC in human epilepsy should be investigated in more detail.

6. NUCLEUS OF THE SOLITARY TRACT

The nucleus tractus solitarii (or nucleus of the solitary tract) is situated in the medulla oblongata and receives afferent projections from the vagal nerve. Efferent projections from the nucleus tractus solitarii reach the hypothalamus and the cingulate gyrus, as well as other nuclei in the brainstem. Magdaleno-Madrigal *et al.* (Magdaleno-Madrigal *et*

al., 2002) investigated the effects of electrical stimulation of this nucleus one minute before a kindling pulse in the amygdala (Table 9). Stage 4 seizures were prevented and AD durations were decreased. It was concluded that stimulation of the nucleus of the solitary tract may have a hampering effect on the development of generalized seizures in the amygdala kindling model. Despite these promising results, no human trials or further animal experiments were conducted on stimulation in this nucleus.

Vagus Nerve Stimulation (VNS) is a widely accepted therapy for refractory epilepsy (Vonck *et al.*, 1999). As stimulation of the tenth cranial nerve may influence the nucleus tractus solitarii, direct stimulation of this nucleus may exert stronger effects on the modulation of epileptic seizures in comparison to VNS.

7. LOCUS COERULEUS

The locus coeruleus (LC) is located in the dorsal wall of the rostral pons. It is known that the main neurotransmitter released by the LC is norepinephrine, which acts to increase the seizure threshold (Feinstein *et al.*, 1989; Gwinn and Spencer, 2004). The main drawback is that the LC is a small nucleus, making stimulation in animal models very difficult. However, two experimental studies were performed (Table 10). Finch *et al.* (Finch *et al.*, 1978) implanted electrodes near the LC of adult cats. Following electrical stimulation of the LC, inhibition was measured using micropipets to record the activity of hippocampal neurons. Later, in the rat penicillin cortical model, it was shown that LC stimulation suppressed penicillin-induced focal epileptiform activity (Neuman, 1986).

The first human trial on LC stimulation for epilepsy in patients was conducted by Feinstein *et al.* (Feinstein *et al.*, 1989). Two patients were stimulated with 50-100 Hz LC stimulation and subsequently showed a reduction in incidence and severity of epileptic seizures. However, the small number of patients and the small number of animal experimental studies presently cannot confirm the efficacy of LC stimulation.

Table 9

Animal experimental studies on DBS in the nucleus of the solitary tract

Author	Animal model	Parameters	Target	Results
Magdaleno-Madrigal (2002)	Amygdala-kindling	30 Hz; 150-300 µA; 1 min Pulse width 0.5 ms	NTS	Significant slower progression towards fully kindled animals. Behaviour was affected by stimulation

Table 10

Animal experimental studies on DBS in the locus coeruleus

Author	Animal model	Parameters	Target	Results
Libet (1977)	PTZ	50-200 Hz; 40-100 µA; 20-40 min Pulse width 20-200 µs	Locus coeruleus	Suppressed epileptiform bursts caused by sub-convulsive dose of PTZ
Neuman (1986)	Penicillin (focal)	1-200 Hz; 40-137 µA Pulse width 0.1-0.5 ms	Locus coeruleus	Suppresses focal epileptiform activity

Conclusion

Three possible strategies have been put forward in the choice of a brain target for DBS in epilepsy. The electrode can be placed in a structure involved in seizure onset, in a nucleus involved in seizure generalization and/or propagation or in a structure that may modulate the activity of the 'epileptogenic network'. Structures known to be involved in seizure generalization or may modulate the network include the locus coeruleus, thalamic nuclei, the basal ganglia, cerebellum, nucleus of the solitary tract and piriform cortex. Stimulation of the STN is a highly promising technique as to suppress the ongoing generalization of seizures. This is confirmed in both animal and human experiments. The nucleus of the solitary tract and the locus coeruleus, although few studies have been conducted so far, are interesting targets to explore. In temporal lobe epilepsy patients, the hippocampal area can often be shown to be the region of seizure onset (Spencer, 2002). Therefore, hippocampal DBS aims at decreasing the probability of seizure occurrence, while DBS in specific nuclei involved in seizure propagation aims at interrupting ongoing seizures, or prevent their generalization. As to modulate seizure initiation, stimulation of the seizure focus through hippocampal and/or amygdala DBS with high frequencies is shown to be successful in both human and animal studies. However, DBS at the site of seizure onset can also be used to block already ongoing seizures, which is the goal of responsive stimulation or closed-loop stimulation (Sun et al., 2008): responsive neurostimulation aims to suppress epileptiform activity by delivering electrical stimulation immediately to the epileptogenic zone when the onset of ictal activity is detected.

Concerning the optimal stimulation parameters, variations in stimulation frequency (Hz), stimulus intensity, stimulus duration, pulse width, monophasic or biphasic stimulation, intermittent or continuous and mono- or multipolar stimulation modes can be applied to obtain seizure suppression. From the present study, it can be concluded that optimal DBS parameters strongly depend on the chosen target. For example, stimulation of the anterior thalamic nucleus is more successful with higher frequencies. Lower frequencies even tend to provoke seizures, while effects due to deep brain stimulation in the cerebellum are mainly accomplished with low frequency stimulation. In general, biphasic stimulation is recommended over monophasic stimulation as a build-up of charges in the latter can lead to tissue damage (Harnack et al., 2004). Concerning the stimulation intensities, amplitudes should be kept below the threshold for induction of seizures. Higher amplitudes can lead to the phenomenon of kindling (Corcoran and Cain, 1980).

Although DBS for uncontrolled epilepsy has been performed for many years, the best target and the most effective stimuli are presently unknown. This provides an impetus for further research to explore this exciting new approach to treat epilepsy and other brain diseases.

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