Summary

Deep brain stimulation (DBS) has shown efficacy in achieving significant seizure reduction in patients with refractory epilepsy not suitable for resective surgery. Based on the identification of several cortico-subcortical networks involved in epilepsy, several anatomical targets have been proposed for different epileptic syndromes. Among these targets, the most extensively investigated and also showing the most promising results are the anterior nucleus (ANT) as well as the centro-median (CMT) nucleus of the thalamus, and the hippocampus (Hipp). This paper provides a review of the literature in DBS for epilepsy focused on these targets with available data on efficacy as well as side effects. Technological advancements like responsive stimulation (RNS) are also underlined.

Although promising results were reported for these different targets in specific epileptic syndromes, only ANT and RNS were tested on larger series of patients and could reach class I evidence level of efficacy. Moreover, overall data suggest that seizure outcome improves over time.

We suggest that Hipp stimulation should be restricted to MTLE, whereas ANT stimulation could be performed also in multifocal seizures with predominant limbic involvement and CMT in generalized epilepsy. RNS should be proposed in focal epilepsy especially from extratemporal origin, even if closed-loop technology could be applied to propagation nodes, such as ANT, Hipp or CMT, thus extending its use to multifocal or even generalized epilepsy.

The complex physiopathology of seizure onset and propagation justifies further electrophysiologic and clinical research for the better understanding of the precise correlations existing between clinical manifestations and the structural and functional networks involved in the control of epileptogenicity. Together with a deeper understanding of the mechanisms of action of DBS at cortico-subcortical, this will certainly be helpful for the refinement of patient selection criteria, anatomical targets and stimulation parameters.

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Keywords: Deep brain stimulation, epilepsy, anterior nucleus, centro-median nucleus, hippocampus, closed-loop stimulation

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Tiefe Hirnstimulation bei Epilepsie: ein Update


Obwohl vielversprechende Ergebnisse für alle drei Zielpunkte für verschiedene spezifische Epilepsiesyndrome berichtet wurden, gibt es lediglich zur Stimulation des ANT und für die RNS grösse Untersuchungen und eine Klasse-1-Evidenz der Wirksamkeit. Darüber hinaus deuten die Zahlen darauf hin, dass sich die Anfallsergebnisse über die Zeit verbessern.

Wir schlagen vor, dass eine Stimulation des Hipp auf Fälle einer mesialen Temporallappenepilepsie beschränkt werden sollte, wohingegen die Stimulation des ANT im Falle einer multifokalen Epilepsie mit überwiegender Beteiligung des limbischen Systems angewendet und die Stimulation des CMT bei generalisierten Epilepsie durchgeführt werden sollte. RNS sollte für fokale Epilepsieformen mit überwiegendem Anfallsausbruch ausserhalb des Temporallappens vorgesehen werden, auch im Falle der Anwendung der adaptiven Stimulation im Bereich von Knotenpunkten der Anfallsausbreitung wie zum Beispiel der ANT, Hipp und CMT und damit einer möglichen Erweiterung der Anwendung im Bereich der generalisierten Epilepsie.
La stimulation cérébrale profonde: une revue de la littérature

La stimulation cérébrale profonde (DBS) a démontré son efficacité à réduire la fréquence des crises chez les patients souffrant d’épilepsie réfractaire et qui ne sont pas des candidats à la chirurgie ablative. Basé sur l’identification de différents circuits cortico-sous-corticaux impliqués dans le contrôle de l’épilepsie, plusieurs cibles anatomiques ont été proposées pour différents syndromes épileptiques. Parmi elles, le noyau antérieur (ANT) et le noyau centro-médian (CMT) du thalamus, ainsi que l’hippocampe ont été investigués de manière plus extensive et ont démontré les résultats les plus prometteurs. Ce travail propose une revue de la littérature concernant la DBS appliquée à l’épilepsie, focalisée sur ces cibles anatomiques, d’après les données sur les résultats et les effets secondaires de cette thérapie disponibles dans la littérature. Les avancées technologiques telles que la stimulation réactive (RNS) sont également soulignées. Bien que des résultats encourageants ont été rapportées pour ces différents cibles dans des syndromes épileptiques spécifiques, seules les stimulation du ANT et la RNS ont été testées à des séries de patients plus larges et ont pu ainsi atteindre un niveau d’évidence d’efficacité de classe I. De plus, l’ensemble des données suggère une augmentation de l’efficacité dans le temps.

Nous suggérons de réserver la stimulation hippocampique aux patients souffrant d’épilepsie réfractaire d’origine méso-temporale, alors que la stimulation du ANT peut être proposée lors d’épilepsies multifocales impliquant principalement le circuit limbique. Enfin la stimulation du CMT pour les épilepsies généralisées. La RNS devrait être proposée pour les épilepsies focales d’origine extratemporale, même si cette technologie pourrait être appliquée à différents noyaux de propagation, tels que le ANT, le CMT ou même à l’hippocampe, étendant ainsi son indication à l’épilepsie multifocale ou voire même généralisée. La physiopathologie complexe de l’origine et de la propagation des crises justifie la continuation de recherches électrophysiologiques et cliniques pour permettre de mieux comprendre les correlations existant entre les manifestations cliniques et les circuits structurels et fonctionnels impliqués dans le contrôle de l’épileptogénicité. De pair avec une meilleure compréhension des mécanismes d’action de la DBS au niveau cortico-sous-cortical, cette recherche sera certainement utile à la meilleure sélection des patients, des cibles anatomiques et des paramètres de stimulation.

Mots clés : La stimulation cérébrale profonde, épilepsie, noyau antérieur, noyau centro-médian, hippocampe, stimulation « closed-loop »

Introduction

Epilepsy is a potentially devastating neurological disorder affecting more than 50M people world-wide. People with uncontrolled epilepsy are subject to many consequences, such as falls and related injuries, driving restrictions, work limitations, lack of independence, the need of constant supervision, frequent medical consultations, hospital admissions and medically-related expenses. These result in a significant impact on the quality of life, leading to school absenteism, unemployment, depression and other psychiatric conditions, such as generalized anxiety and phobic disorder, often leading to social isolation and even suicide [1]. Antiepileptic drugs (AEDs) remain the first option for treating epilepsy. However, 20% to 40% of patients will suffer poor control from best medical treatment [2 - 4]. Standard care for drug-resistant epilepsies in case of focal seizure onset is resective surgery [5]. Seizure freedom can be achieved in 60 - 90% of MTLE, glioneuronal tumors, vascular malformations and focal cortical dysplasias [6, 7]. The success of resective surgery is highly dependent on the ability to detect and resect a focal epileptogenic lesion or epileptogenic brain area as well as to interrupt an epileptogenic network. Thus, up to 30 - 40% of medically resistant epileptic patients may not benefit from a resective surgical approach, due to multifocal epilepsy, or high risks of neurological deficits associated with lesion or cortex resection in highly eloquent brain areas. These patients may benefit from vagus nerve stimulation (VNS) in addition to continued medical therapy. VNS offers a mean seizure reduction of 28% for patients in whom it is employed with 23% of patients having a greater than 50% reduction in seizure frequency (Class 1 evidence) [8, 9].

Development of EEG signal analysis has improved our understanding in the neuronal pathways involved in seizure propagation, such as the limbic circuit of Papez [10 - 11] and the diffuse reticulo-thalamo-cortical pathway [12 - 14]. Consequently, the anterior thalamic nucleus (ANT), the hippocampus (Hipp) and the centromedian nucleus of the thalamus (CMT) have been proposed and investigated for Deep Brain Stimulation (DBS) in epilepsy. Other targets have been reported such as the subthalamic nucleus (STN), the caudate nucleus, the mamillothalamic tract, the nucleus ventro-oralis posterior (Vop) of the thalamus, the globus pallidus internus and the nucleus accumbens. Despite increasing interest in DBS for epilepsy, the exact mechanism of DBS is still poorly understood with regard to one specific target or specific network involved in a given epileptic syndrome. The mechanism of DBS induced attenuation of seizure activity possibly mimics that of high frequency DBS for movement disorders. Specifically, neurons adjacent to stimulating electrodes appear to undergo long term inactivation following stimulation, leading to interruption of pathologic network activity [15, 16].
This paper provides an update in DBS for epilepsy, with special attention on the most extensively investigated targets and showing the most promising results, i.e. the ANT, Hipp and CMT.

**Targets**

**ANT stimulation**

The ANT is an important hub within the circuit of Papez. It receives projections from the mammillary bodies via the mamillothalamic tract and projects to the cingulate, orbito-frontal and mesial prefrontal cortex [10, 17]. The role of ANT in seizure propagation was investigated in animal models of epilepsy [18]. Previous clinical studies have shown efficacy of high frequency bilateral ANT stimulation in achieving seizure reduction particularly in generalized tonic-clonic seizures (GTCS) as well as complex partial seizures (CPS) with or without secondarily generalized complex partial seizures (SGCPS) sustaining the hypothesis that ANT stimulation could interfere with ictal propagation rather than with seizure onset [19 - 23].

More recent studies conducted on larger series of patients have confirmed the efficacy of ANT stimulation in epilepsy [24 - 27]. The SANTE study group [26] investigated in a prospective double-blind trial the long-term effects of high frequency (145 Hz, 90 μs, alternating 1 minute on - 5 minutes off) bilateral ANT stimulation in a series of 110 refractory patients with partial seizures suggesting a focal onset, with or without secondary generalization (CPS in 92.7% and SGTCs in 77.3%), originating from different brain areas (TL in 60% and FL in 27.3%). The median seizure reduction was 49% at 1 year and 69% at 5 years follow-up. Accordingly, the responder rate (patients with > 50% seizure reduction) was increased in long-term follow-up (68% at 5 years vs. 43% at 1 year follow-up). These results confirmed that the ANT stimulation efficacy in drug-resistant epilepsy improves over time and that short-term responses may be predictive for long-term outcome. The study also suggested better outcomes in patients with TL (76%) and FL (68%) seizure onset compared to those with seizures originating in other lobes or multifocal epilepsy. Correlation between involvement of the limbic system in the epilepsy genesis/propagation and better seizure control was suggested and confirmed by other groups [22].

Krishna et al. have recently shown that the most efficacious site of stimulation appears to be in the anteroventral part of the nucleus [28].

**Hippocampal stimulation**

Interest in performing DBS directly in the hippocampus is related to the fact that

1. the hippocampus is a major component of the limbic system and the circuit of Papez [10, 11],
2. MTLE associated with hippocampal sclerosis is the most common cause of therapy-resistant epilepsy,
3. resection of the temporomesial structures is associated with the most favorable seizure outcome, and
4. resection of temporomesial structures have been reported to be associated with severe neuropsychological deficits [29 - 30].

High-frequency Hipp stimulation has been shown to significantly decrease afterdischarges duration in stimulated rats versus controls [31].

Velasco et al. were the first to report the effects of high-frequency Hipp stimulation in a series of 10 patients with refractory MTLE. Subacute stimulation (2 weeks) was delivered after invasive seizure recordings, through previously implanted recording electrodes, allowing the abolition of both CPS and SGTCs in 7/10 patients. The same group reported later the long-term effects (median follow-up: 18 months) of chronic Hf stimulation in 9 patients with refractory MTLE. The responder rate was 55% with a mean seizure reduction of 80%. The authors observed better responses in patients with normal MRI (4/5 of them became seizure free) compared to those with hippocampal sclerosis. They suggested that neuronal pauperization and/or higher impedance in sclerotic hippocampi could explain less favourable outcomes in this subcategory of patients [32, 33].

Subsequently, the Ghent group [34 - 36] as well as the Lausanne-Geneva group [37 - 38] confirmed long-term effects of Hipp stimulation. In the former group, the responder rate was 70% with a mean seizure reduction of 50% with an average follow-up period of 31 months and responder rate of 80% with mean seizure reduction of 70% after an average follow-up period of 96 months, also suggesting that the antiepileptic effects of Hipp stimulation may improve with time.

The latter group reported a series of 8 MTLE, with a follow-up period of 12 - 24 months with similar results on the seizure rate reduction. The subgroup of 2 patients with hippocampal sclerosis obtained a significant decrease (65 - 75%) in seizure rate only with higher voltage bipolar DBS (≥ 1 V) or with quadripolar stimulation compared to the group without hippocampal sclerosis. They also suggested that better efficacy may be correlated with a biphasic pulse waveform compared to pseudomonophasic stimuli in reducing interictal epileptiform activity during acute stimulation.

The only closed label trial examining hippocampal stimulation, by Tellez-Zenteno et al., included only four patients but imposed a rigorous randomization pattern
for stimulation that continued throughout the duration of seizure assessment [39]. Their results indicate a more modest improvement in seizure outcomes (overall 15% reduction, than the open label trials.

The optimal site of stimulation within the hippocampal structure is still not known. Velasco et al. observed that better seizure suppressive effects were reported in patients with stimulating contacts located in the anterior hippocampus/parahippocampal gyrus, through a possible polysynaptic inhibition on the CA1-CA4 epileptogenic neurons [32]. More recently, Bondallaz et al. [40] reported more favorable antiepileptic effects (seizure reduction > 50%) in patients with the active contacts located close (< 3 mm) to the subiculum, supporting the concept that DBS may rather modulate the epileptogenic network than playing a direct effect on the hippocampal neurons.

**CMT stimulation**

The rationale for CMT as a potential target for DBS in therapy-resistant epilepsy correlates with its role of important anatomical thalamic relay within the diffuse reticulo-thalamo-cortical activating system, with diffuse projections to the frontal cortex, which contribute to arousal and attention and participate to cortical excitability [41].

Fisher et al. [42] were the first to investigate the effect of bilateral CMT stimulation in a series of 6 patients with intractable focal or generalized onset seizures in a double-blind, sham stimulation controlled design study. The authors reported an average seizure reduction of 30% from baseline in on-stimulation condition (60Hz, 0.5-10V, 90 μs, a 1 min on - 4 min off, 2 h/day) compared to 8% decrease when stimulation was turned off. The results did not achieve statistical significance. Nevertheless, in an open-label extension of the trial with stimulation conducted for 24 h/day, 3/6 patients (50%) experienced a ≥ 50% reduction of seizures (GTCS).

Velasco et al. [43] observed a significant seizure reduction in patients suffering from Lennox-Gastaut syndrome (80% median seizure reduction after a mean follow-up period of 46 months). Subsequently, Cukiert et al. [44] reported effectiveness of CMT stimulation also in idiopathic generalized epilepsy (and Lennox-like syndrome with a 65 - 98% seizure reduction (mean 80%). Since all patients had received prior callosotomy, the authors were unable to clearly show the real impact of each procedure on seizure frequency.

Recently, Valentin et al. [45] investigated the effect of CMT stimulation in patients suffering from generalized seizures compared with frontal onset CPS (mean follow-up 24 months). They observed an average seizure reduction of 82% (with a 83% responders rate) in generalized seizures compared to 49% (20% responders rate) in frontal CPS.

**Specific side effects**

Assuming that inhibition of neural pathways could be the underlying mechanism of DBS for better controlling epileptic seizures, one could expect a deterioration of the specific function of the target/network modulated by the electrical current.

**ANT stimulation**

Oh et al. [27] studied the long-term neuropsychological outcomes in a series of 9 patients who underwent bilateral ANT DBS. The authors did not report any substantial cognitive impairment after chronic ANT stimulation (mean follow-up 34.6 months). They actually observed an improvement in word fluency and delayed verbal memory, suggesting a possible collateral positive effect of ANT stimulation on the limbic memory circuit.

The SANTE study group [26] recently reported subjective depression and memory impairment during the blinded phase in a minority of patients that were not accompanied by significant objective cognitive declines or worsening of depression scores, long-term neurobehavioral worsening either through the blinded phase or in open-label at 7 years. Higher scores were observed at 7 years on measures of executive functions and attention. The overall quality of life of stimulated patients was also improved. Nevertheless, they recommend monitoring and neuropsychological assessment of depression and memory from a theoretical standpoint and because more memory and depression adverse events occurred in the active stimulation than control group.

**Hippocampal stimulation**

Here also there is no evidence for a significant deterioration of the memory function, even in patients with bilateral implantation. Velasco et al. found a slight improvement in verbal and nonverbal memory [33, 35, 46].

**CMT stimulation**

Cognitive impairment is usually associated with Lennox Gastaut syndrome as well as idiopathic generalized epilepsy. The assessment of the real stimulation-induced neuropsychological effects may be more difficult. Interestingly, in this population, the seizure reduction was associated with improved ability scale scores and patients with normal development before the onset of epilepsy tended towards a better recovery of their abilities, suggesting that an early approach could allow better psychomotor outcome [43].
Closed loop stimulation (or responsive neurostimulation: RNS) is defined as the delivery of electrical current to a target, exclusively in response to a specific cue or command (seizure detection by a defined algorithm), compared to open-loop in which electrical current is delivered independently of seizure occurrence time. After a first pivotal study showing promising results [47] Bergey et al. [48] reported their long-term experience using NeuroPace RNS system (NeuroPace, Inc., Mountain View, CA, U.S.A.) on 256 patients. Approximately 1/3 had previous resective surgery and/or VNS. Mesial temporal onset was found in 111/256 of patients (bilateral in 72% of them) whereas neocortical in 126/256 cases (45% temporal and 38% frontal onset). Two epileptic foci had been identified in 48% of cases. Compared to the pivotal trial (37.9% seizure reduction), results at 6-year follow-up showed increased efficacy (mean seizure reduction of 66%).

The ability of reducing seizure rate was independent from seizure onset (neocortex vs. mesial temporal lobe), from the number of epileptic foci as well as from previous invasive recordings or surgical treatments. RS was approved by the US Food and Drug Administration (FDA) in November 2013 for the treatment of refractory partial seizures.

Conclusion

DBS represents a promising treatment option for a subgroup of carefully selected patients suffering from intractable epilepsy who are not candidates for resective surgery. So far, only ANT stimulation has achieved class I evidence of efficacy for partial onset seizures with or without secondary generalization. The small sample sizes reported prevents conclusive statements on efficacy of Hipp stimulation for MTLE and CMT stimulation for generalized epilepsy. Overall data suggest that seizure outcome improves over time.

As several distinct neuronal networks seem to be involved in the control of epileptogenesis, electrical stimulation delivered at different important nodes of these networks may, at least theoretically, show efficacy on seizure control. The complex physiopathology of seizure onset and propagation justifies further electrophysiologic and clinical research for the understanding of the precise correlations existing between clinical manifestations, epileptogenic brain pathologies, as well as structural and functional networks involved in the control of epileptogenesis. Furthermore, a deeper understanding of the mechanisms of action of DBS at cortico-subcortical levels will certainly be helpful for the refinement of patient selection criteria, anatomical targets and stimulation parameters. In addition, closed-loop technology could be applied to propagation nodes, such as ANT, Hipp or CMT, thus extending its use to multifocal epilepsy.

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