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Deep brain stimulation of hippocampus in treatment of refractory temporal lobe epilepsy

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ABSTRACT

Introduction. Temporal lobe epilepsy (TLE) is the most common cause of focal onset seizures, affecting 40% of adolescents and adults with epilepsy. TLE is also one of the most common drug resistant forms of epilepsy. Surgical resection remains the treatment of choice for TLE, but not all patients with TLE are suitable candidates for resective neurosurgery. For such patients, deep brain stimulation (DBS) of the hippocampus remains a reversible and efficient treatment alternative.

State of the art. We undertook a systematic review of the literature on hippocampal DBS efficacy and safety in the management of patients with TLE. A search using two electronic databases, the Medical Literature, Analysis, and Retrieval System on-line (MEDLINE) and the Cochrane Central Register of Controlled Trials (CEN-TRAL), was conducted.

Clinical implications. We found 14 articles related to hippocampal DBS for the treatment of TLE. The responder rate (defined as at least 50% reduction in seizure frequency) for all patients was 83.4%, Of 99 patients treated by hippocampal DBS, 82 were regarded as responders, and 17 as non-responders.

Future directions. Hippocampal DBS appears to be a safe and efficacious treatment alternative for patients who are not candidates for temporal lobectomy or selective amygdalohippocampectomy due to serious postoperative cognitive deficits. In selected patients with TLE, this neuromodulatory therapy may be very safe and efficacious.

Keywords: deep brain stimulation, hippocampal stimulation, temporal lobe epilepsy, hippocampal sclerosis, neuromodulation

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Introduction

Epilepsy is one of the most common neurological disorders, affecting 0.5-1% of the general population [1]. Despite available antiseizure medications (ASMs), epilepsy remains poorly controlled in 30% of patients [2]. Based on the seizure origin, epilepsy can be distinguished into focal-onset or generalised. Among focal-onset epilepsy, temporal lobe epilepsy (TLE) is the most common, affecting 40% of adolescents and adults [3]. The underlying pathological changes predominantly involve hippocampal sclerosis (HS), which has been associated with increased drug resistance [4, 5].

Early resective surgery including anteromesial temporal resection is associated with a good clinical outcome and

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reduction of the deleterious effects related to longstanding drug resistant epilepsy (DRE) including cognitive dysfunction, and the risk of premature death [6, 7]. However, even with resection, 20–30% of patients fail to show clinical benefit [8]. The most common causes of TLE surgery failure include insufficient resection of epileptogenic mesial temporal structures, relapse on the contralateral mesial temporal lobe, lateral temporal neocortical epilepsy, coexistence of HS and a neocortical lesion (dual pathology), and extratemporal lobe epilepsy mimicking TLE or temporal plus epilepsy [8, 9]. A subgroup of patients with bilaterally located epileptic foci, poor seizure localizations, memory decline concerns, and personal preference might not be good candidates for temporal lobe resection [10]. Also, patients with continuing seizures originating from the contralateral temporal lobe are considered not good candidates for temporal lobe resection [11]. These patients remain intractable due to persistent DRE, and constitute natural candidates for non-resective, adjustable, and reversible neuromodulatory techniques such as hippocampal DBS but also responsive neurostimulation (RNS) or vagus nerve stimulation (VNS) [12, 13]. The hippocampus is a highly epileptogenetic structure and represents the main epileptogenetic area in patients with HS and non-lesional TLE. In non-resective cases, direct hippocampal DBS, RNS, and VNS may represent the available treatment modalities [14, 15].

The strength of this comprehensive review is the presentation of all-important clinical data of patients treated by hippocampal DBS for drug resistant TLE. The information given in individual studies includes the stimulated area within the mesial temporal lobe structures, the number of patients with non-lesional or lesional HS (unilateral versus bilateral HS), the seizure type, as well as the responder rate. Moreover, detailed information is provided about preoperative invasive neurophysiological monitoring by the utilization of subdural grids or strips as well as the electrodes used for stereoencephalography (sEEG) before permanent DBS leads placement. The types of DBS leads are also provided with stimulation settings including detailed information of permanent unilateral or bilateral hippocampal DBS. The stimulation mode and polarity used in individual studies are also presented, with follow-up times. Information collected in supplementary material reports details of all encountered adverse events and neurobehavioral changes after hippocampal DBS seen in patients with MTL epilepsy. This comprehensive review represents an up-to-date and detailed assessment of knowledge regarding the clinical efficacy and safety of hippocampal DBS for TLE.

Methods

A systematic literature search for publications regarding hippocampal DBS for TLE was conducted spanning a period from January 2000 to January 2024. The search algorithm included the following key words: 'deep brain stimulation', 'hippocampal stimulation', 'mesial temporal epilepsy', and 'temporal lobe epilepsy'. The following electronic databases were consulted: the Medical Literature, Analysis, and Retrieval System on-line (MEDLINE) and the Cochrane Central Register of Controlled Trials (CEN-TRAL). The search algorithm followed the PRISMA guidelines (Fig. 1) [16]. We considered only research articles published in English restricted to clinical studies involving only humans. No limitations were made regarding the study design or the number of individuals included in the study.

Exclusion criteria included animal studies, studies that included treatment of TLE without DBS, preclinical studies, review articles, and letters to the editor. The exclusion criteria also included articles describing patient populations other than those with TLE and reports that mainly dealt with aspects related to the surgical technique. A search using the two databases and the aforementioned key words yielded 14 articles eligible for further analysis. A cumulative 99 patients treated by hippocampal DBS were identified. Among these 99 patients, 60 were diagnosed with HS, and the remaining 39 had non-lesional TLE.

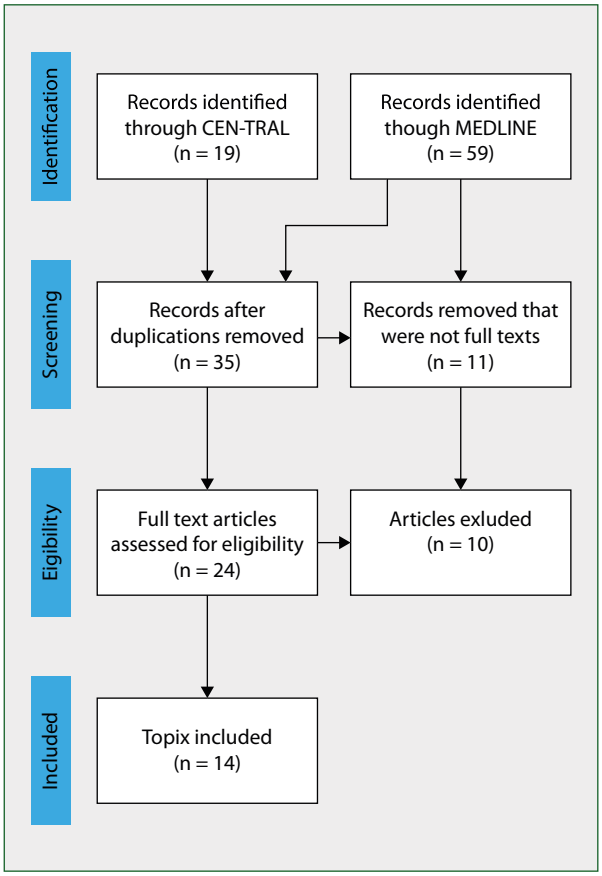

Figure 1. Selection of articles reporting outcomes of hippocampal DBS for TLE

Indications and contraindications for hippocampal DBS for TLE

Hippocampal DBS is not yet an FDA-approved procedure for the treatment of TLE. Patients referred for hippocampal DBS should have epilepsy resistant to two ASMs. Video-EEG and MRI findings should be consistent with TLE. Patients with bilateral temporal ictal onset, or patients at risk of postoperative memory decline, are considered good candidates for hippocampal DBS but also for RNS [17]. Patients after temporal lobectomy with continuing seizures coming from the contralateral temporal mesial structures can be also regarded as good candidates for hippocampal DBS or RNS [17]. Moreover, patients should keep a seizure diary, and be on stable ASMs for at least three months before hippocampal DBS. The abovementioned indications for DBS are nearly the same as for RNS. RNS was approved in 2013 in the United States [18]. Especially patients with bilateral HS may benefit from RNS, and in this scenario RNS may be preferable to other neuromodulation modalities because of recording capacities that may guide an eventual resection after confirming the strong unilateral predominance of seizures originating from MTL structures [19, 20].

The contraindications for hippocampal DBS are the same as for other neuromodulation targets used in epilepsy. Patients are generally excluded if they have been diagnosed with psychogenic pseudoepileptic seizures, depression, or memory deficit, suicide attempts, or psychosis unrelated to epilepsy. Patients with severe, progressive systemic disease are excluded from hippocampal DBS. Patients with resectable pathology involving the hippocampus such as brain tumour, cavernoma, arteriovenous malformations, Rasmussen encephalitis, and cortical dysplasia are not included for hippocampal DBS implantation. Other contraindications constituting non-compliance include non-attendance at postoperative scheduled follow-up visits and recent status epilepticus.

Results

Clinical efficacy of hippocampal DBS for treatment of TLE

Velasco et al. reported the antiseizure effects of transient hippocampal stimulation performed in 10 patients through implanted depth electrodes or subdural grids placed in the subtemporal region for a topographic diagnosis of the site and extent of the epileptic focus before a temporal lobectomy [21]. In 7 patients whose stimulation electrodes were located in the hippocampus or hippocampal gyrus, stimulation decreased seizure frequency and the number of interictal EEG spikes at the focus after 5-6 days. The most striking antiseizure effect was associated with stimulation of the anterior pes hippocampus close to the amygdala or the anterior parahippocampal gyrus close to the entorhinal cortex [21]. Light microscopy analysis revealed that transient hippocampal stimulation appeared to be a safe procedure that could suppress temporal lobe epileptogenesis [22]. Based on these results, Vonck et al. implanted separate electrodes into the amygdala and hippocampus in 3 patients with TLE [15]. In all , unilateral amygdalohippocampal stimulation was performed, and all patients were clear responders, with a more than 50% monthly seizure reduction [23].

In 2006, Tellez-Zenteno at el. performed the first double blind multiple cross-over randomised controlled trial (RCT) in 4 patients with TLE. The median seizure reduction between postoperative 'OFF' and 'ON' periods was 15%. Compared to baseline in postoperative period in the 'ON' phase, the average seizure frequency decreased by 26% [24]. Subsequent RCTs have brought contradictory results [25–28]. Velasco et al. presented the long-term outcome in 9 patients after hippocampal DBS. In 5 patients without HS, the seizure frequency decreased by 95% and in 4 patients with HS the seizure frequency decreased by 50-70% [25]. In 2007, Boon et al. reported 10 patients after hippocampal DBS achieving a responder rate of 70% with a mean follow-up of 31 months [19]. Also, Boex et al. presented good outcomes of hippocampal DBS in patients with and without HS [29].

In 2013, Cukiert et al. presented the outcomes on 9 patients with refractory TLE treated by hippocampal DBS resulting in mean seizure reduction of 86.5% [30]. Subsequent studies reported excellent long-term results of hippocampal DBS for TLE [31, 32]. Cukiert et al. subsequently published the largest prospective, controlled randomised, double blind study of hippocampal DBS, providing evidence that TLE responds to hippocampal DBS in an active group compared to a control group [33]. Half of patients in the active group became seizure-free. The focal impaired awareness seizures (FIAS, complex partial seizures) responded more favorably to hippocampal DBS than focal aware seizures (FAS, simple partial seizures) [33]. In a subsequent observational open label study with long term follow-up, Cukiert et al. reported that 32% of patients were seizure-free [34]. Other authors, mostly in observational single-centre studies, have shown further benefit of hippocampal DBS for TLE [35–41]. All clinical data regarding the number of patients, the stereotactic target chosen within hippocampal formation or mesial temporal lobe structures for permanent stimulation, as well the responder rates/seizure frequency reduction, and stimulation parameters, are set out in Table 1.

Among 14 studies reporting the outcomes of hippocampal DBS, the responder rate (defined as at least a 50% decrease of postoperative seizures in an individual patient compared to baseline seizure count) has varied between 60% and 100%. The mean responder rate for all these studies was 83.42%. Among 99 patients, 17 were regarded as non-responders, indicating that 82 patients were regarded as responders to hippocampal DBS [23–41].

Table 1. Clinical studies reporting the outcome of hippocampal DBS for TLE

Authors and year of publication	Number of patients	Brain region targeted	Patients with uHS/ /bHS and NLE	Seizure type	Responder rate	Invasive electrophysiology DBS electrode implanted for permanent stimulation	Uinlateral /Bilateral Stimulation	Stimulation parameters	Mode of stimulation and polarity of stimulationm	Follow–up months
Vonck et al. 2002 [23]	3	Amygdala and anterior hippocampus	3 Pts NLE	FIAS	100%	Subdural grids or strips. Two electrodes in each hemisphere Electrode Model 3387 Medtronic	US 3 Pts	130 Hz–2 Pts 200 Hz–1 Pt 450 us 1 V	C/B	3–6 months mean 5
Tellez–Zenteno et al. 2006 [24]	4	Pes and body of hippocampus	2 Pts uHS 2 Pts bHS	FIAS and FBTC	75%	Depth electrodes Electrode Model 3487A	US 4 Pts	190 Hz 90 us individualized stimulation V	C/M	9 months
Velasco et al. 2007 [25]	9	Amygdalo–hippocampal junction [anterior hippocampus]	3 Pts uHS 1 Pt bHS 5 Pts NLE	9 Pts had FIAS 7 Pts had FBTC	100%	Bilateral depth electrodes [AD–TECH] Electrode Model 3378 Medtronic	US 6 Pts BS 3 Pts	130 Hz 450 us 3 V	I/B	18–84 months mean 37 months
Boon et al. 2007 [27]	10	Amygdala and anterior hippocampus	2 Pts uHS 1 Pt LE 7 Pts NLE	10 FIAS and FBTC	60%	Subdural grids or strips Two electrodes in each hemisphere Electrode Model 3387 Medtronic	US 9 Pts BS 1 Pt	130 Hz or 200 Hz 450 us 2–3 [mean 2.3] V	C/B	12–52 months mean 31
Mc Lachalan et al. 2010 [28]	2	Hippocampus	1 Pt bHS 1 Pt NLE	FIAS and BTCS	Seizure frequency decrease by 33% during stimulation	Electrodes Mode 3487 3 mm in lenths with 6 mm interdistance	BS 2 Pts	185 Hz 90 us individualized stimulation V	C/M	9 months
Boex et al. 2011 [29]	8	Amygdala and hippocampus	2 Pts MTS 6 Pts NLE	FIAS and BTCS	75%	In 5 Pts depth electrodes 5 Pts Medtronic Pisces–Quad 3478 [3 mm lenth 6 mm spacing] 3 Pts Medtronic Sub Compact Octad 3876	US 8 Pts	130 Hz 450 us 1 up to 3 V	C/M Pts with uHS C/B Pts with NLE	12–74 months mean 43.5 months
Vonck et al. 2013 [32] previously reported by Boon et al.	11	Amygdala and anterior hippocampus	3 Pts uHS 7 Pts NLE 1 Pts LE	FIAS BTCS	91%	Subdural grids or strips Two electrodes in each hemisphere Electrode Model 3387 Medtronic	US 8 Pts BS 3 Pts	1 30 Hz or 200 Hz 450 us 2–3 [mean 2.3] V	C/B	67–120 months mean 102 months
Cukiert et al. 2013 [30]	9	Hippocampal head	2 Pts uHS 4 Pts bH 3 Pts NLE	FIAS FBTC	78%	Electrode Model 3387 Medtronic	US 7 Pts BS 2 Pts	130 Hz 300 us 1–3.5 V	I/B	15–50 months mean 30.1 months

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Table 1. cont. Clinical studies reporting the outcome of hippocampal DBS for TLE

Authors and year of publication	Number of patients	Brain region targeted	Patients with uHS/ /bHS and NLE	Seizure type	Responder rate	Invasive electrophysiology DBS electrode implanted for permanent stimulation	Uinlateral /Bilateral Stimulation	Stimulation parameters	Mode of stimulation and polarity of stimulationm	Follow–up months
Min et al. 2013 [36]	2	Amygdalo-hippocampal stimulation	1 Pt uHS 1 Pt bHS	FIAS FBTC	100%	Depth electrodes Electrode Model 3146 St Jude Medical	BS 2 Pts	130 Hz 450 us 3.1 V	C/M	18–36 months mean 27 months
Jin et al 2016 [37]	3	Parahippocampal gyrus and Hippocampal head	3 Pts NLE	IAS BTCS	100%	Depth electrodes Electrodes 3487 A Medtronic	US 2 Pts BS 1 Pt	130–170 Hz 450 us up to 3.5 V	C/B	26–43 months mean 34.7 months
Lim et al. 2016 [38]	5	Hippocampal head	1 Pt uHS 1 Pt bHS 3 Pts NLE	FIAS FBTC	60 %	Electrode Model 3387 Medtronic	Unilateral 2 Pts Bilateral 3 Pts	5–145 Hz 150 us 1 V	I/B	30–42 months [mean 38.4 months]
Cukiert et al. 2017 [33]	16	Hippocampal head	11 Pts uHS 3 Pts bHS 2 Pts NLE	FAS FIAS	Responder rate [87,5%] [active phase]	Electrode Model 3391 Medtronic	US 10 Pts BS 6 Pts	130 Hz 300 us 2 V	C/B	6 months
Vazquez–Barron et al. 2020 [39]	6	Subiculum	5 Pts uHS 1 Pt bHS	FIAS FBTC	83%	Depth electrodes [AD-TECH],Electrode Model 3387 Activa	US 5 Pts BS 1 Pt	130 Hz 300 us 3 V	I/B	24 monts
Saucedo et al. 2021 [40]	6	Parahippocampal cortex	2 Pts uHS 4 Pts bHS	FAS FIAS FBTC	60%	Deep electrodes Electrode Model 3391 Medtronic	BS 6 Pts	130 Hz 450 us 2.5–3 V	C/B	12 moths
Cukiert et al. 2021 [34]	25	Hippocampal head	11 Pts uHS 8 Pts bHS 6 Pts NLE	FAS FIAS	FAS reduced by 66% FIAS reduced by 91%	Electrode Model 3391 Medtronic	US 10 PTs BS 15 PTs	130 Hz 300 us 3.0 V	C/B	13–75 months 57 months
Wang et al. [41] 2021	7	Hippocampal head	3 Pts uHS 3 Pts bHS 1 Pt NLE	FIAS FBTC	85.7%	Depth electrodes 2 Pts Electrode Model 3146 St Jude Medical 5 Pts Electrode Model L303 Beijing PINS Medical	BS 7 Pts	128 Hz 350 us 1.5– 3.0 V	I/M	mean 48 months

uHS — unilateral hippocampal sclerosis; bHS — bilateral hippocampal sclerosis; NLE — non–lesional epilepsy; LE — lesional epilepsy; I — intermittent stimulation mode; C — continuous stimulation mode; M — monopolar stimulation; B — bipolar stimulation; DBS — deep brain stimulation; TLE — temporal lobe epilepsy; Pt — patient; Pts — patients; US — unilateral stimulation; BS — bilateral stimulation; FAS — focal aware seizures; FIAS — focal impaired awareness seizures; FBTC — focal bilateral tonic clonic seizures

Discussion

Preoperative invasive electrophysiology for localisation of ictal onset zone

The candidates considered for hippocampal DBS in the treatment of TLE represent a unique population of patients with poorly localised and bilateral temporal ictal onset zones or bilateral HS. This was the reason to incorporate the invasive electrophysiology using sEEG or subdural grids or strips to properly localise the ictal onset zone before accomplishment of the temporal lobectomy [21]. Most authors before implanting permanent DBS leads performed stereotactic placement of stereo-EEG electrodes, and after confirmation of the ictal onset zone(s), unilateral or bilateral DBS lead placement followed [23–25, 27, 29, 37–41]. Vonck et al. performed simultaneous placement of DBS leads with subdural grids or strips over the frontal and temporal neocortex which were subsequently removed [23, 27, 28]. Another approach in hippocampal DBS for TLE is represented by investigators who did not use invasive monitoring before hippocampal DBS implantation [33, 34, 36, 38]. The decision to implant the DBS electrodes is based on preoperative work-up including interictal and ictal electroencephalography and high resolution 1.5 Tesla magnetic resonance imaging (MRI) [33, 34]. Patients with bilateral ictal onset and bilateral HS are implanted with bilateral DBS leads [33, 34]. The advantage of using the sEEG implanted along the long axis of the hippocampus and amygdala is the determination of the exact location of the ictal zone [39-41]. This region of the ictal zone within the amygdalohippocampal complex is thereafter overlapped with the implanted DBS electrode [25, 31, 37, 39–41]. Another advantage of sEEG is the limitation of the implanted DBS hardware. It has been shown that the clinical outcome is independent of unilateral or bilateral stimulation, meaning that the shift from unilateral to bilateral hippocampal DBS is not automatically associated with better seizure frequency reduction [33, 34]. Another approach was presented by a research group from Belgium who implanted separate electrodes in the amygdala and hippocampus on each side, but the results were similar to other studies reporting the outcomes of hippocampal DBS [27, 32]. Compared to transient sEEG monitoring, the RNS has the unique advantage of having the ability to record automatically and store electrocorticographic data. This monitoring is the most important evaluation method for decision making in the diagnosis and treatment of DRE especially involving MTL structures. The sEEG monitoring performed in an epilepsy monitoring unit (EMU) is limited to one or two weeks, and circumstances are different from those pertaining in daily life.

On the other hand, RNS provides electrocorticographic data over months, or even years, under ordinary conditions. The study by Hirsch et al. provides the best evidence of MTL resections guided by chronic ambulatory intracranial EEG in patients with evidence of bilateral mesial temporal lobe epilepsy [42]. In this study, of 157 patients treated by the RNS with bilateral MTL leads due to presumably bitemporal epilepsy, 25 (16%) underwent subsequent MTL resection. Nine out of these 25 patients had exclusively unilateral temporal seizures. At the most recent follow-up, 15/25 (71%) were seizure-free. Most patients after MTL resections continued RNS therapy. The subgroup of patients with bilateral HS or bilateral non-lesional temporal epilepsy may gain greater seizure reduction by the use of RNS due its aforementioned capabilities [42–44].

Hippocampal DBS for non-lesional TLE and TLE due to hippocampal sclerosis

Hippocampal DBS has been performed for non-lesional TLE and lesional TLE due to unilateral or bilateral HS. Among 14 studies reporting 99 patients with hippocampal DBS, 39 patients had non-lesional TLE, 34 had unilateral HS, and 26 had bilateral HS. Most studies have reported that hippocampal DBS is more effective in patients without HS than in patients with HS [25, 30, 40]. HS is associated with severe neuronal loss, which may represent a less satisfactory tissue for neuromodulation [25]. This observation is supported by the study by Velasco et al., who reported in 4 HS patients a 50–70% reduction in the total number of seizures (FIAS and FBTCS) at 18 months after DBS, compared to a more than 95% seizure reduction in 5 patients with non-lesional TLE [25].

Another possibility is that sclerotic tissue has high impedance and requires higher stimulation settings. Boex et al. in 8 patients (2 with HS and 6 with non-lesional TLE epilepsy) showed that in patients with HS quadripolar stimulation was necessary to achieve 65-75% seizure reduction, whereas in non-lesional TLE epilepsy, a bipolar stimulation mode was sufficient to reduce seizures [29]. The authors conclude that a large zone of stimulation would be required in HS patients, as opposed to a limited zone of stimulation or even a microlesional effect that could be sufficient in non-lesional TLE patients [29]. The stimulating parameters and mode of stimulation should be taken into account when assessing the efficacy of hippocampal DBS due to underlying TLE (non-lesional versus HS). Moreover, the sclerotic hippocampus is atrophic and firmer, which might cause the DBS electrode to depart from the stimulating target [39]. On the other hand, RNS has proven its efficacy regardless of lesional or non-lesional MTL epilepsy. One study of RNS has shown greater seizure reduction in lesional epilepsy than non-lesional epilepsy: Jobst et al. provided the clinical data of 126 patients with neocortical epilepsy onset [44]. Subsequent reports have brought contradictory findings [14]. Geller et al. presented the results in 111 patients with MTLE after RNS treatment [14]. At the long-term follow-up (6.1 ± 2.2 years), the mean seizure reduction reached 70% [14]. In this study, no difference in seizure control was observed among patients with or without HS, bilateral MTL seizure onset, previous resective surgery, invasive monitoring, and prior VNS [14].

Unilateral or bilateral DBS implantation for TLE

In 14 clinical articles, a cumulative number of 99 patients after hippocampal DBS has been reported. 75/99 patients underwent bilateral hippocampal DBS implantation, whereas 24 had unilateral DBS hippocampal implantation. In the postoperative period, 41 patients were stimulated bilaterally and 58 unilaterally. This observation has shown that 34 patients despite bilateral DBS implants had one active DBS lead, achieving a good clinical outcome.

This observation suggests that half of the patients implanted with bilateral DBS leads can be sufficiently stimulated unilaterally, saving the DBS hardware and prolonging IPG life. Invasive electrophysiology has shed light on the bilateral effects of unilateral hippocampal sEEG stimulation [26]. In the report by Boex et al. using three orthogonally sEEG implanted electrodes in 2/3 patients, unilateral amygdalohippocampal stimulation provided effects in the contralateral mesial temporal lobe structures [26]. These effects are related to strong connectivity between bilateral limbic structures. Contralateral propagation of the epileptogenic activity is strongly related to a close functional relationship between both temporal lobes. These observations are supported by subsequent examinations including PET, SPECT, MRI volumetry, and MRI spectroscopy [26].

Bilateral stimulation is not superior to unilateral hippocampal stimulation. This assumption is proved by the study of Cukiert et al. [30]. This observation highlights the fact that bilateral hippocampal DBS is not necessary to achieve a good clinical outcome in patients with refractory TLE [30, 33, 34], but it also suggests further assessment in larger and prospective studies. The same conclusions have been drawn in patients with RNS, where Hirsch et al. showed that RNS-guided MTL resections may be a valuable option in patients previously thought to have bitemporal MTL epilepsy onset [42].

Search for ideal target in hippocampal DBS for TLE

Enough evidence exists to suggest that TLE is initiated from, and propagated through, hippocampal formation. This hippocampal formation encompasses the dentate gyrus, the hippocampus proper, and the subiculum. Clinical evidence shows that ictal and interictal epileptiform EEG activity occurs first in the hippocampus [45]. Moreover, several studies have also highlighted the role of the dentate gyrus and CA1 region in TLE models [46, 47]. Temporal lobectomies that involve the hippocampus have reduced seizures more than those in which the hippocampus has been spared [48]. These observations indeed initiated hippocampal DBS for TLE in the early 21st century [21, 23–25].

More recent studies have demonstrated that the subiculum and parahippocampal gyrus play an active role in the generation and propagation of temporal lobe seizures, but not the hippocampus itself, even in non-sclerotic hippocampal tissue [31–41]. Bondallaz et al. reported on 8 patients with refractory TLE in whom invasive recordings done in 5 patients enabled placement of a permanent DBS lead in the vicinity to the ictal focus [31]. The authors found that most active contacts were localised close to the CA1 field of the hippocampus and subiculum [31]. All responders had active contacts localised less than 3 mm from the subiculum [31]. This observation suggests that the efficacy of DBS might be associated with the involvement of the subiculum, which also carries the axons of the perforant pathway – the main output pathway of the hippocampal formation [31].

To date, there has been no data underlying the direct neuromodulatory effect of electrical stimulation on the subiculum in refractory MTL epilepsy. Studies regarding the changes in GABAergic signaling in MTL epilepsy have pointed to the hyperexcitability of GABAergic excitation of early development in the subiculum or to vulnerability of GABAergic interneurons that give raise to input specific impairment of inhibition [49, 50]. These mechanisms are thought to underlie the development of MTL epilepsy at a cellular level. Taking all this into account, DBS may increase the inhibitory effect of GABAergic pathway on the generation and propagation of MTL epilepsy [50]. Future clinical studies may prove this concept of an antiseizure effect of subiculum DBS.

Vazquez-Baron et al. found that subiculum stimulation is effective for FBTC seizures in patients with MTL epilepsy in the course of HS, suggesting that the subiculum mediates the generalisation rather than genesis of MTL seizures [39]. In patients with HS, cell loss may be severe in the hippocampus, but it is not common in the subiculum [39]. Aside from its intrinsic functions, the subiculum is considered as an input and output gateway between the hippocampus and cortical and subcortical structures. Velasco et al. compared the role of the subiculum to the centromedian nucleus (CMN) for the treatment of primary generalised tonic-clonic seizures [39]. Moreover, a sclerotic process in patients with HS is evident in the hippocampus sparing the subiculum, which is easier to influence on a cellular level [39]. As the parahippocampal cortex and subiculum escape the sclerotic process in patients with MTL epilepsy, consecutive pilot studies were performed to explore the antiseizure effects of subicular and parahippocampal DBS in patients with refractory MTL epilepsy [39, 40]. The intrinsic connectivity between hippocampal formation and the parahippocampal cortex may play an essential role in the neuromodulation of this target. The parahippocampal cortex sends projections to all hippocampal formation subfields [51]. These projections originate from neurons in II and III layers of parahippocampal gyrus, with a few projections from deeper layers that probably form a feedback inhibitory system [52].

On the other hand, studies on parahippocampal cortex subacute stimulation through subdural grids or strips for defining the seizure onset zone have demonstrated that high-frequency stimulation of the seizure-onset zone decreases

interictal discharges, increases post-discharge thresholds, and decreases regional blood flow [21]. In patients with HS and cell loss in CA1 and CA4, stimulation of the parahippocampal cortex seems promising in terms of offering faster and adequate control of FIAS, BTCS and focal aware seizures (FAS) than hippocampal DBS [41].

On the other hand, Cukiert et al. analysed the exact location of the implanted DBS leads in the hippocampus and found no correlation between lead location and outcome [34]. The same conclusions were reported using RNS in the study by Geller et al. [18]. Seizure reduction in that study was not dependent on the location of depth leads relative to the hippocampus. Considering the diameter and volume of tissue activated elicited by depth electrodes, it is possible that as contacts are located in the hippocampus, the outcome might be similar. The relatively large stimulating parameters used for permanent DBS may obscure the correlation of the exact location of active contacts regarding the clinical outcome [39]. Theoretically, patients with non-lesional TLE may benefit from hippocampal DBS with leads implanted within the hippocampus proper, and those with lesional-TLE epilepsy may benefit from subicular or parahippocampal DBS [34, 39, 40].

Stimulation parameters, polarity, and mode of hippocampal DBS

Seizure reduction in MTE with high-frequency stimulation (130-200 Hz) has been shown to be effective in several reports [27–41]. Boex et al. curried out a comparative study of subacute amygdalohippocampal stimulation with low (5 Hz) and high (130 Hz) frequency stimulation in non-lesional TLE [26]. They showed that high frequency, but not low frequency, was associated with interictal spike reduction and the absence of clinical seizures [26]. The EEG desynchronisation induced by high-frequency stimulation produces an antiepileptic action [26]. Most authors use 130-145 Hz stimulation frequency [27–41].

The initial stimulation voltage for hippocampal DBS is relatively low, around 3 volts, even in studies with longer follow-ups [27, 29, 33, 34, 39]. The pulse width for hippocampal DBS shows a very wide range, from 60 to even 450 microseconds [27–41]. The relatively long pulse width of hippocampal DBS is related to the homogenous volume of the amygdala and hippocampus surrounded by cerebrospinal fluid of the temporal horn. Regarding the stimulation mode, most studies have reported the use of a continuous rather than a cycling stimulation mode [25, 38, 39]. Continuous stimulation may be related to higher scores for mean seizure frequency reduction and larger percentages of responders [27, 33, 34, 37, 40, 41]. However, some authors have used a cycling mode of stimulation with good results [25, 38, 39].

Although the number of patients treated for DRE with DBS is not large, with just 99 cases reported in the world literature, certain conclusions can be drawn regarding the setting of the initial neurostimulation parameters. All authors use initial high frequency stimulation of above 130 Hz and even up to 200 Hz [27–41]. The initial voltage of the stimulation current ranges from 1-3 volts. The stimulation pulse width shows the greatest variability, ranging from 50 to 450 microseconds [27–41]. In most studies on hippocampal DBS, the type of stimulation is continuous; only three studies have used intermittent stimulation, which is more widely used in ANT stimulation in the treatment of DRE [27–41, 56]. Bipolar stimulation is used much more often than monopolar stimulation in the literature [15–17, 19–22, 24–33]. The more distal contacts of the implanted DBS leads placed usually in the amygdala or hippocampal head are set as cathodes [22, 24–26, 29–31]. The detailed stimulation parameters, polarity, and mode of stimulation are set out in Table 1.

Adverse events related to hippocampal DBS procedures

Among the 99 patients reported in the world literature after hippocampal DBS there were only 2 cases of intracranial haemorrhage [26, 27]. One resulted in transient mild hand weakness, and the other was clinically silent. Compared to the SANTE trial (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy), the haemorrhage rate was higher, affecting 4.5% of patients, but all haemorrhagic complications were clinically silent and detected incidentally by neuroimaging [55]. The most common complication in TLE patients treated by hippocampal DBS was infection [25, 26, 30, 34]. DBS hardware infections resulted in explantation of the entire DBS system in 6 patients, which was later reimplanted in some patients [25, 26, 30, 34]. There were 2 DBS lead fractures that needed revision surgeries [31, 39].

Regarding memory function and quality of life, most studies have reported the subjective improvement of daily living without deleterious effect on neuropsychological functioning [24, 26, 39]. On the other hand, more neuropsychological adverse events were reported in the early phase of the SANTE study, especially depression and memory problems [55].

Wang at al. found that bilateral hippocampal DBS did not influence verbal and performance intelligence (FSIQ), visual and verbal memory (Auditory Memory Index [AMI] and Visual Memory Index [VMI]). For all patients, there were no significant differences in FSIQ, AMI, and VMI [41].

Overall, based on existing studies, hippocampal DBS does not seem to have a significant effect on memory [25, 26–41]. According to previous reports, patients after anterior temporal lobectomy (ANL) display a wide range of deficits across verbal and visual memory domains. These permanent memory deficits may be found in 20-50% of patients after ANTL [53, 54]. All adverse events related to hippocampal DBS surgery along with stimulation-induced and neuropsychological side effects are set out in Table 2. Recently, an interesting observation has appeared regarding ophthalmological symptoms in patients with Parkinson's Disease (PD) assessed by the Visual Impairment in Parkinson's Disease Questionnaire (VIPD-Q)

Table 2. Adverse events including procedural, hardware and stimulation-related complications as well as cognitive/emotional outcomes following hippocampal DBS in patients with TLE

Authors and year of publication	Procedural-related adverse events intracranial hemorrhage	Hardware-related adverse events or other complications	Stimulation--related adverse events	Behavioral/cognitive changes	Activities of daily living
Vonck et al. 2002 [23]	No	No	No	No neuropsychological deterioration	NR
Tellez-Zenteno et al. 2006 [24]	No	No	No	No worsening during on period regarding depression, no neuropsychological differences between on and off periods No subjective memory differences between on and off periods	No worsening in on period regarding QoL, clear improvement when compared to off period
Velasco et al. 2007 [25]	No	3 patients were explanted after 2 year of stimulation due to skin erosions and infection that started 24-26 months after surgery, Skin erosions and infections started at the mastoid bone [connection side]	NR	No memory decline under unilateral or even bilateral DBS	NR
Boon et al. 2007 [27]	1 Pt had asymptomatic hemorrhage along the trajectory of depth electrodes	No	No	No changes in neurophysiological testing	No
MacLachlan et al. [28]	No	No	No	Worse neuropsychological assessment in 1 Pt	NR
Boex et al. 2011 [29]	No	1 electrode displacement needed revision 1 electrode fracture requiring replacement	No	Verbal and visual memory normal, psychiatric assessment revealed no changes No cognitive or psychiatric impairments	NR
Vonck et al.2013 [32] previously reported by Boon et al.	1 Pt had asymptomatic hemorrhages along the trajectory of depth electrodes	A revision of a connection cable,IPG removal due to infection	Acute seizure induction due to high output voltage	No impairments in neuropsychological performance	NR
Cukiert et al. 2013 [30]	No	1 Pt had explanation of the device due to infection related to trauma	No	No self-reported memory deterioration	NR
Min et al. [36]	No	No	No	NR	NR
Jin et al. 2016 [37]	No	No	No	No postoperative neuropsychological deterioration	NR
Lim et al 2016 [38]	No	No	No	No disturbances in sleep patterns and behavioral changes	NR
Cukiert et al. 2017 [33]	No	2 Pts with local skin erosions treated by antibiotics	No	NR	NR
Vazquez-Barron et al. 2021 [39]	No	1 DBS electrode fracture with reimplantation	Transient preserving ideas in 1 Pt	Neuropsychological evaluation not changed	In 4 among 6 Pts positive influence on daily living activities
Saucedo-Alvarez et al. 2021 [40]	No	No	Paresthesia over V2 branch of trigeminal nerv due to gasserian ganglion stimulation	Improvement in all neuropsychological tests	No significant changes in QOLIE-89 2 Pts unemployed before surgery return to work
Cukiert et al. 2021 [34]	No	IPG infection and explanation 23 months after surgery	No	Lack of formal neuropsychological data	NR
Wang et al. [41] 2021	No	No	No	No significant decreases in intelligence or verbal and visual memory	NR

NR — not reported; Pt — patient; Pts — patients; QoL — quality of life; QOLIE-89 — Quality of Life in Epilepsy Inventory; IPG — implantable pulse generator

[56]. This study aimed to assess the prevalence of ophthalmological symptoms in PD depending on the type of treatment used i.e. pharmacological or subthalamic nucleus deep brain stimulation (STN DBS). The prevalence of ophthalmological symptoms differed significantly between both groups. A burning sensation or a gritty feeling in the eyes occurred more often in patients in the STN DBS group, but patients treated by pharmacological agents experienced an inability to read plain text on a coloured or grey background, and had problems with rapid changes of light intensity [56]. Ophthalmological symptoms, or vision in general, did not worsen in patients undergoing hippocampal DBS for DRE, but visual field deficits are well known complications after resective surgery including anterior temporal lobectomy (ANL) [53, 54].

Various diagnostic as well as pharmacological issues of DRE have been discussed in recent reports [57–59]. One interesting finding is the suggestion that generalised epilepsy is associated with cortical epileptogenic focus, but distinguishing between focal and generalised epilepsy can still be difficult. The solution may be the detection of differences between default mode function in patients with idiopathic generalised epilepsy. Moving from a 'generalised theory' of epilepsy to a 'focused theory' by investigating characteristics of default mode function could bring insights into the pathophysiology of generalised epilepsy with new pharmacological as well as neurosurgical treatment options [57]. One of the pharmacological treatment options for patients with generalised DRE may be the use of cannabidiol (CBD) [58]. CBD has been an effective drug in DRE, particularly in Dravet Syndrome, Lennox-Gastaut Syndrome, and seizures associated with tuberous sclerosis complex. Some of these syndromes have been treated by neuromodulation therapies including DBS, RNS or VNS [59]. A special situation in the treatment of focal DRE pertains to pregnancy and the breastfeeding period. In the last case series report, it has been shown that lacosamide (LCM) monotherapy during pregnancy and breastfeeding remains a safe treatment option [60]. Despite this, patients with DRE should be provided with the best possible conditions for pharmacological and other forms of neuromodulatory therapies including hippocampal DBS.

Conclusions and future directions

Hippocampal DBS is one neuromodulatory treatment modality available for MTL epilepsy. It is reserved for patients not suitable for standard classic anterior temporal lobectomy due to the fear of postoperative side effects. Patients with bilateral ictal temporal onset zones and bilateral HS constitute the preferred target population for DBS, but also for RNS. DBS is an open-loop neurostimulation system, unlike RNS which is a closed-loop neurostimulation system. The advantage of RNS is the capacity to monitor the electrocorticographic activity. This may guide further resection in patients previously thought to suffer from biltareral MTE epilepsy onset.

Hippocampal DBS has no negative influence on cognitive functions. The mean seizure frequency reduction in 14 reported studies is estimated at 83.4%. FIAS and BTCS respond more favorably than FAS. Future directions of hippocampal DBS should be aimed at recruiting a larger number of patients with MTL epilepsy who are not candidates for resective surgery. The comparative studies of DBS and RNS for MTL epilepsy are warranted. The search for the ideal target within the hippocampal formation or parahippocampal gyrus should continue with the establishment of clinically optimal stimulating settings. Further research is needed in the field of neuromodulation for drug resistant MTL epilepsy.

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