Epilepsy Research 151 (2019) 24–30

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

# Electrical cortical stimulation for refractory focal epilepsy: A long-term follow-up study

Chun-Wei Chang[a], Shih-Tseng Lee[b], Siew-Na Lim[a], Mei-Yun Cheng[a,c], Ching-Yi Lee[b], Tony Wu[a,d,*]

[a] Section of Epilepsy, Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center and Chang Gung University College of Medicine, Taoyuan, Taiwan
[b] Department of Neurosurgery, Chang Gung Memorial Hospital Linkou Medical Center and Chang Gung University College of Medicine, Taoyuan, Taiwan
[c] Institute of Molecular Medicine, National Tsing Hua University, Hsinchu, Taiwan
[d] Department of Neurology, Xiamen Changgung Hospital, China

ARTICLE INFO

*Keywords:*
Refractory epilepsy
Cortical stimulation
Epilepsia partialis continua
Malformation of cortical development

ABSTRACT

*Objective:* To report the long-term seizure control and safety of open-loop electrical cortical stimulation in patients with refractory focal epilepsy of diverse etiologies.

*Methods:* Six patients who received a therapeutic trial of cortical stimulation were included retrospectively. The frequency of seizures was recorded before and after implantation. Surgical procedure- and stimulation-related adverse effects were also recorded.

*Results:* The mean reductions in seizures were 61% at 1 year, 68% at 2 years, and 80% at 3–7 years post-implantation. The median follow-up time was 54 months (range 36–156 months). The etiologies of epilepsy included polymicrogyria in two patients, post-traumatic in one patient, and periventricular heterotopia, post-encephalitis, and familial lateral temporal lobe epilepsy in the remaining three patients. Status epilepticus stopped immediately after stimulation in three patients with focal status epilepticus or epilepsia partialis continua at baseline, with a long-term reduction in seizures of more than 90% and improvements in conscious level. Tissue incompatibility with the connection wire was noted in one patient, which subsided after the system was removed.

*Conclusions:* Open-loop cortical stimulation of epileptic foci improved seizure control in our patients with refractory focal epilepsy of diverse etiologies. Electrical cortical stimulation stopped epilepsia partialis continua/focal status epilepticus immediately after the intervention and exhibited a sustained effect in reducing seizures. No procedure-related complications were observed. Further case cohort studies are needed to clarify which patients respond to open-loop cortical stimulation.

## 1. Introduction

Despite the availability of new antiepileptic drugs, approximately 30–35% of patients still have inadequate seizure control (Del Felice et al., 2010; Kwan et al., 2010). Some of these patients may benefit from surgical resection of the epilepsy-related brain area if it can be identified. However, surgical resection is not suitable for patients when the seizure foci reside in the eloquent cortex, are multifocal, difficult to localize and diffuse lesions defined by neuroimaging, or when permanent cognitive decline is a concern after resection surgery.

Deep brain stimulation (DBS) is a promising treatment option for drug-resistant epilepsy (Sprengers et al., 2017; Wu and Sharan, 2013). Various targets of stimulation have been investigated since the 1980s, including the anterior thalamic nucleus (ATN), centromedian thalamus, caudate, subthalamic nucleus, cerebellum, hippocampus, and motor cortex (Fisher and Velasco, 2014). Among these targets, randomized controlled trials of intermittent bilateral ATN stimulation and closed-loop responsive stimulation to foci (the RNS® system) have demonstrated sustainable efficacy and favorable safety profile for drug-resistant focal seizures (Bergey et al., 2015; Fisher et al., 2010; Morrell and Group, R.N.S.S.i.E.S., 2011; Salanova et al., 2015). Stimulation of other targets including the hippocampus (Lim et al., 2016; McLachlan et al., 2010), cerebellum (Cooper et al., 1973, 1976; Velasco et al., 2005), centromedian nucleus of the thalamus (Fisher et al., 1992), subthalamic nucleus (Chabardes et al., 2002), and caudate nucleus (Chkhenkeli et al., 2004) have also been shown to be effective for seizure control in smaller trials and case-control studies.

Furthermore, open-loop electrical stimulation to the cortex applied via a cyclic or continuous manner has shown encouraging results for refractory epilepsy with well-localized foci. In 2006, an early case

* Corresponding author at: 5, Fu-Hsin Street, Kwei-Shan, Taoyuan, 333, Taiwan.
*E-mail address:* tonywu@cgmh.org.tw (T. Wu).

https://doi.org/10.1016/j.eplepsyres.2019.01.003
Received 22 October 2018; Received in revised form 25 December 2018; Accepted 6 January 2019
Available online 09 January 2019
0920-1211/ 

report of chronic electrical cortical stimulation of the primary motor cortex showed a reduction in seizure frequency by more than 90% over 5 years of follow-up (Elisevich et al., 2006). In 2009, Velasco et al. reported a reduction in seizures by more than 90% in two patients who received stimulation to the motor cortex for 1.5 years (Velasco et al., 2009). A research group from King's College Hospital in London also reported that cortical stimulation effectively halted epilepsia partialis continua (EPC) in two patients with a sustained response over 2 years of follow-up (Valentin et al., 2015). In 2014, a research group from Mayo Clinic in Rochester reported three patients who responded to cortical stimulation (Child et al., 2014). This was followed by an analysis of 13 patients which found improvements in seizure severity and life satisfaction in 77% of patients who received stimulation, and significantly decreased interictal epileptiform discharges (Lundstrom et al., 2016). Moreover, no adverse effects were observed. Regarding stimulation frequency, both high (> 50 Hz) and low frequency (< 10 Hz) stimulation has been shown to be effective in suppressing seizures in human studies of neocortical stimulation (Child et al., 2014; Elisevich et al., 2006; Lundstrom et al., 2016; Valentin et al., 2015; Velasco et al., 2009). Several potential mechanisms for the antiepileptic effect of stimulation have been proposed, including sodium channel inactivation for high frequency stimulation, long-term depression for low frequency stimulation, and glutaminergic synaptic depression for both high and low frequency stimulation (Albensi et al., 2004; Goldin, 2003; Schiller and Bankirer, 2007). Despite the considerable number of patients who have received intermittent ATN stimulation and responsive cortical stimulation for epilepsy, relatively few patients have received open-loop chronic cortical stimulation (Vassileva et al., 2018). Therefore, more data are needed to validate the effectiveness and safety of open-loop chronic cortical stimulation under discrete clinical conditions.

In this study, we report the effect of long-term seizure control and safety outcomes of open-loop chronic cortical stimulation in six patients with refractory focal epilepsy, including three with EPC or partial status epilepticus, with diverse etiologies.

## 2. Material and methods

### 2.1. Subjects

This study was approved by the Institutional Ethics Board of Chang Gung Memorial Hospital, Linkou, Taiwan. All six patients with refractory focal onset epilepsy who received a therapeutic trial of cortical stimulation between February 2003 and October 2015 were included retrospectively. These patients either had EPC or chronic epilepsy for more than 2 years and failed at least two antiepileptic drugs (AEDs) before undergoing surgery (Kwan et al., 2010). Seizure classification was based on the 2017 operational classification of seizure types by the International League Against Epilepsy (ILAE) (Fisher, 2017). The preoperative evaluations included a detailed history of epilepsy, neurological examinations, AED use, video-EEG (vEEG) monitoring, brain magnetic resonance imaging (MRI), brain single-photon emission computed tomography, and fluorodeoxyglucose-positron emission tomography (FDG-PET) (Fig. 1A and B). Epilepsy-related cortical areas were identified by analysis of semiology, ictal scalp vEEG and corresponding structural and functional neuroimaging.

### 2.2. Surgical procedures and post-operative follow-up

All patients received pre-implantation electrocorticography (ECoG) for a total of 7 days with the placement of a subdural 32 or 64 grid covering the presumed epileptic area identified by presurgical scalp vEEG and the functional cortex (Fig. 1C). Three-dimensional CT (3D-CT) was performed after surgery to record the ECoG position. The protocol of cortical monitoring included 3 days of cortical monitoring to identify the epileptic foci, followed by a 4-day trial of electrical cortical stimulation using subdural contacts. Functional mapping and localization of the epileptic foci were identified intraoperatively and further confirmed by electrical cortical stimulation during the ECoG. The 4-day trial of electrical cortical stimulation was performed using subdural contacts covering the epileptic foci with 2 days of stimulation ON followed by two days of stimulation OFF. The initial lead coverage included possible pairs with the highest potential of being epileptic foci according to the ECoG. The initial parameters of stimulation were 1 V, 3 Hz, 90 us, bipolar, and cyclic stimulation (1 min ON and 5 min OFF). During the trial stimulation, adjustments of the stimulation parameters including increases in pulse amplitude to 2–3 V, and a shift from cyclic to continuous stimulation were allowed to gain better seizure control. Electrophysiological seizures were recorded, and the number of interictal epileptiform discharges were counted manually for the first 10 min of every hour recorded. The occurrence of seizures or a decrease in the number of interictal epileptiform discharges by more than 50% during the 2 days of stimulation ON compared to 2 days of stimulation OFF confirmed the appropriate selection of the contacts for seizure control. If poor seizure control or interictal discharges did not decrease, we changed the stimulation pairs and extended the trial stimulation for another 4 days using the same protocol until we found the best site and orientation of the quadripolar lead for the stimulation therapy.

Cortical stimulator implantation was performed under generalized anesthesia. According to the results of trial stimulation, one quadripolar lead for cortical stimulation (Resume II, model 3587 A, Medtronic, Minneapolis, MN, USA) was placed subdurally in the area with the best suppression of epileptic activities. The electrodes were often located on the seizure onset zone. Lead extensions (model 7482, Medtronic) were connected to a pulse generator (IPG; Synergy, model 7427, Medtronic) positioned in the infraclavicular area subcutaneously. Postoperative 3D-CT was performed and merged with the first CT image to visualize the relative position of the ECoG and the quadripolar lead (Fig. 1D). If the location of the quadripolar lead was not at the expected site, then the position was adjusted by the surgeon and follow-up 3D-CT was performed to obtain a second merged reconstruction imaging. Post-implantation vEEG was recorded for 7 days, including test stimulation from the third day postoperatively to identify the most suitable parameters to suppress seizures, and to monitor the occurrence of any stimulation-related adverse effects. Low-frequency stimulation (3–5 Hz) with a pulse amplitude of 1–2 V and pulse width 60–150 μs was used initially to preserve battery life with the smallest stimulus possible to effectively reduce seizures. Bipolar stimulation was used with the most anterior contact serving as the anode and the fourth contact serving as the cathode. Stimulation was applied in a cycling pattern, with 1 min on and 5 min off, or continuously. EEG recorded during stimulation OFF was used to evaluate the response to specific stimulation parameters if they were being cycled. If continuous stimulation was administered, the stimulation was turned off for 2 h to allow for adequate EEG data acquisition after a 2-hour stimulation session. After discharge, the patients were followed up monthly at neurologic clinics for the first 6 months, and then at 1-3-month intervals according to their clinical needs. To gain better seizure control, the parameters were adjusted in the clinics in a stepwise manner. The parameters were often changed when seizure frequency increased compared to last clinical follow-up, or when there was less than a 50% reduction in seizures compared to baseline seizure frequency before implantation. These changes included increasing the pulse amplitude by 0.5–1 V gradually to a maximum of 6 V, then shifting low-frequency stimulation to high-frequency stimulation (120–130 Hz), and then widening the pulse width to 150–210 μs. The daily usage of AEDs remained unchanged in the first 3 months after implantation. Subsequent adjustments of AEDs were based on the clinical response or adverse effects reported in the following periods.

### 2.3. Data analysis

Daily seizure diaries completed 3 months before electrode implantation served as seizure baseline data to compare with the

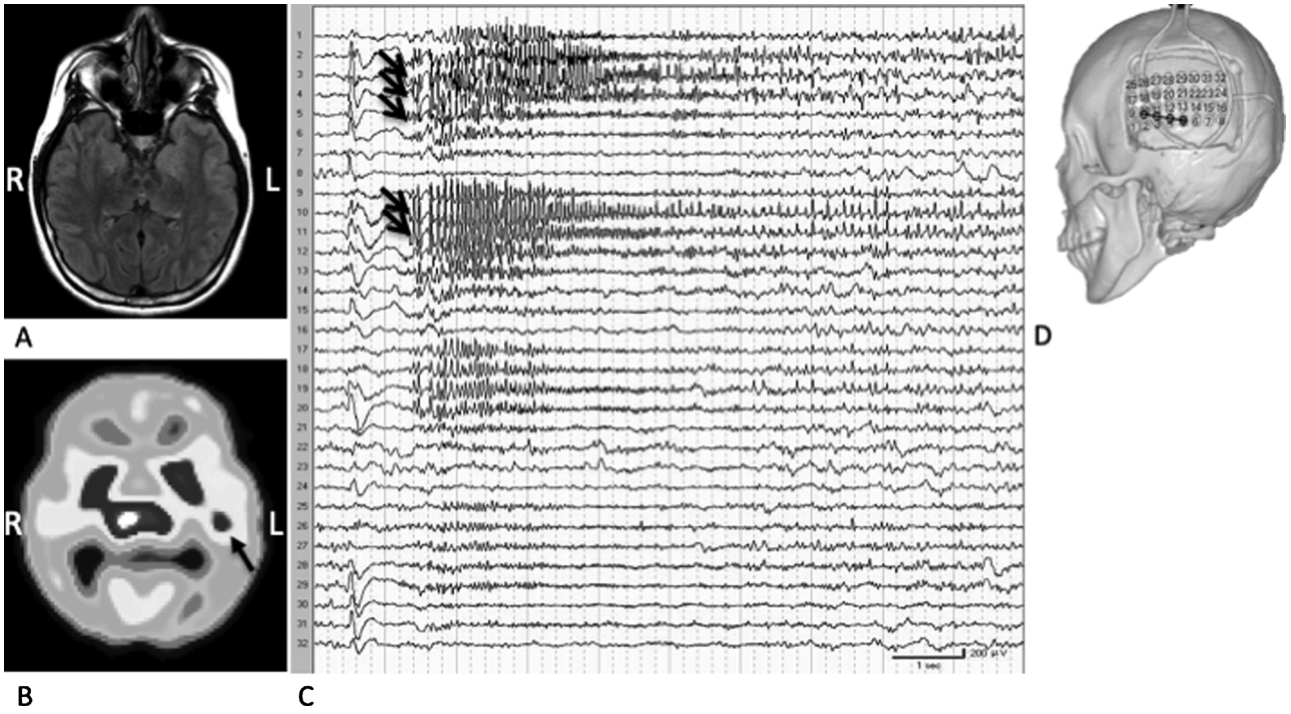


**Fig. 1.** (A) Pre-surgical brain MRI of patient 2 showed no structural lesion. (B) Brain single-photon emission computed tomography showed a possible ictal focus at the left temporal lobe (indicated by the black arrow). (C) Ictal electrocorticography (ECoG) showed seizure onset zone at lead 3, 4, 5, 10, and 11 (arrows). (D) The location of 8 × 4 grid ECoG and permanent subdural lead (the 4 oval-shaped dots) in a merged 3D-CT reconstruction imaging. R: right, L: left.

frequency of seizures after electrode implantation. Changes in seizure frequency at 1 and 2 years were calculated as the percentage change of monthly seizure frequency in the last 3 months compared to baseline. Changes in seizure frequency at 3–7 years after implantation were calculated as the percentage change of mean seizure count per month during 3–7 years post-implantation compared to baseline. Adverse effects directly related to surgical procedures and brain stimulation-related complications in the later period, including headache, wound infection/inflammation, focal neurologic symptoms, emotional problems, and cognitive deterioration were carefully monitored and recorded during each follow-up visit at the neurologic clinics.

## 3. Results

### 3.1. General results and seizure control

Table 1 shows the characteristics, pre-implantation surveys, stimulation parameters, outcomes, and implantation-related adverse effects of the patients who received cortical stimulation. Two men and four women were included, with an age ranging from 17 to 26 years. The etiologies of epilepsy included polymicrogyria in two patients, post-traumatic in one patient, and periventricular heterotopia, post-encephalitis, and familial lateral temporal lobe epilepsy in the remaining three patients. All six patients had partial seizures with a focal to bilateral tonic-clonic seizure pattern with focal interictal/ictal spikes identified by vEEG and ECoG. No surgical procedures prior to cortical stimulation were performed in any of the patients. Cortical stimulation was chosen due to concerns about possible postoperative permanent focal neurologic deficits after resection surgery, because the epileptic foci were located in functional areas involving motor function, vision, language, or memory. Three of the six patients (patients 1, 2 and 3) had focal status epilepticus at baseline. Patient 1 presented with right limb EPC with Todd's paralysis, patient 2 had episodic sensory aphasia lasting up to 2 h, and patient 3 had EPC involving the left arm and face twitching with secondary generalized tonic-clonic seizures with a baseline seizure frequency estimated to be more than 500 times per month. The initial stimulation mode was cyclic in five of the six patients. The remaining patient (patient 6) received continuous stimulation as the initial setting to achieve adequate suppression of frequent epileptic spikes, which was then shifted to cycling mode 4 months later because of a poor response to the continuous stimulation and to decrease battery consumption.

Table 2 demonstrates the effect of cortical stimulation for five patients (patients 1, 2, 4, 5 and 6) according to the change in seizure frequency during the whole follow-up period. The median follow-up time was 54 months (range 48–156 months), and the baseline seizure frequency was 8.3–346.7/month. The mean reductions in seizures were 61% at 1 year, 68% at 2 years, and 80% at 3–7 years post-implantation. Three patients (patient 1, 2 and 3) had focal status epilepticus or epilepsia partialis continua at baseline. In patient 1 and 2, cortical stimulation stopped status epilepticus immediately, and they were seizure-free at 1 month post-implantation (Fig. 2). Throughout the follow-up period, both patients had a mean reduction in seizures of more than 90% after cortical stimulation. EPC also stopped immediately in patient 3, who also had improvements in seizure control due to a remarkable decrease in the number of generalized tonic-clonic seizures and an improvement in conscious level from withdrawal motor response to being able to obey simple orders after stimulation.

Fig. 2 shows the temporal change in seizure frequency after stimulation for each patient. In general, there was an initial seizure reduction 1 month after implantation, followed by a transient increase in seizures from month 1-6. The seizure frequency then reduced again from month 6-60. In patient 5, there was an increase in seizure frequency of 60% for the first 3 months. After we increased the stimulation to 2 V and adjusted the AEDs, the seizure frequency started to decrease from month 6 post-implantation. The seizure frequency further decreased from month 6–18 after gradual titration to 4 V stimulation. A transient increase in seizure frequency again at month 24 possibly indicated breakthrough seizures triggered by extreme fatigue during her menstrual period, and she was stabilized without adjusting the stimulation parameters or AEDs.

**Table 1**
Demographics of the six patients.

| Characteristics | Patient no. | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Age (years) | 34 | 30 | 30 | 28 | 22 | 21 |
| Sex | M | F | M | F | F | F |
| Seizure onset age | 19 | 22 | 22 | 1 | 12 | 10 |
| Operation age | 21 | 26 | 25 | 23 | 19 | 17 |
| Etiology | Head trauma | Familial TLE | Post-encephalitis | Polymicrogyria | Polymicrogyria | Periventricular heterotopia |
| Seizure type | Rt limbs EPC, FBTCS | FIAS SE, FBTCS | Lt limbs and facial EPC, FIAS, FBTCS | FIAS, FBTCS, myoclonic, atonic | FIAS, FBTCS, | FIAS, FBTCS, |
| vEEG monitoring | | | | | | |
| Interictal EEG | Frequently clustered polyspikes at Lt F, SWC at Lt T-P | Frequent SWC at Lt T | Bilateral F and Rt T SWC | Rt T-P SWC | Lt T-O SWC | Bilateral T SWC |
| Ictal EEG focus | Lt F | FIAS SE: global aphasia for 2 hours, focus at Lt T | SE with focus at Rt T. | Rt T-O | Lt T-O | Rt T-O |
| Brain MRI | Encephalomalacia at Lt F-T-P and Rt F | Normal | Predominant atrophy at bilateral temporal lobes | Polymicrogyria at bilateral occipital. | Left parietal peri-sylvian polymicrogyria | Bilateral periventricular heterotopia |
| SPECT/PET | Decreased at Lt hemisphere. | Increased at Lt T cortex | Decreased diffusely | Decreased at Lt P cortex | Decreased at Lt P cortex | Decreased at Rt T-P-O cortex |
| Ictal ECoG focus | Lt F | Lt T | Multiple foci at Rt T | Multiple foci at Rt P-O | Lt P-O | Rt O |
| Stimulation parameters | | | | | | |
| Initial | Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 150μs, 5Hz | Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 5Hz | Cycling (1 min ON, 5 min OFF), bipolar, 2 V, 90 μs, 3 Hz | Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 150μs, 5Hz | Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 90 μs, 5Hz | Continuous, bipolar, 1 V, 90 μs, 3 Hz |
| Last | Cycling (1 min ON, 5 min OFF), bipolar, 1 V, 150μs, 5Hz | Cycling (1 min ON, 5 min OFF), bipolar, 5 V, 90 μs, 5Hz | Cycling (1 min ON, 5 min OFF), bipolar, 3 V, 90 μs, 3 Hz | Cycling (1 min ON, 1 min OFF), bipolar, 5 V, 150μs, 120Hz | Cycling (1 min ON, 5 min OFF), bipolar, 4 V, 90 μs, 5Hz | Cycling (1 min ON, 5 min OFF), bipolar, 5 V, 90 μs, 130Hz |
| Clinical/3 h EEG findings at 1st follow-up post-implantation | Rare minor focal jerking. 3 h EEG: continuous focal theta and delta at Lt hemisphere | Seizure free. 3 h EEG: Clusters of SWC over Lt T lasted for 0.8-1.6 s, prominently decreased compared to pre-operation EEG. | 3 FIAS and 1 FBTCS (triggered by fever) in 1 month. He became more alert in consciousness. 3 h EEG: decreased Rt T spikes. | One FIAS in 2 weeks, 3 h EEG: No more Rt T-O spikes. | 2012.10.9 f/u: 12 FIAS in 2 weeks, with improvement of her response. 3 h EEG: Frequent solitary spikes at Lt T | Seizure free. 3 h EEG: only one cluster of O2 spikes 7-8 Hz lasted for 3 s, and occasionally solitary spikes at Lt T. |
| Outcome | EPC and Todd's paresis resolved. Could click a mouse with the right hand. | FIAS SE stopped. Occasional CPS in the menstrual period. | EPC stopped. Brief facial motor seizures several times a day. Improved conscious level (motor response from M4 to M6). | No more falling seizures. Rare head nodding seizures. Tapering of some AEDs. | Decreased frequency of FIAS and FBTCS | Occasional FIAS and rare FBTCS. Currently working. |
| Surgery-related adverse events | No | No | Allergic reaction to the cable. Removed the DBS 4 years later. | No | No | No |

TLE: Temporal lobe epilepsy, FIAS: focal impaired awareness seizure, FBTCS: focal to bilateral tonic-clonic seizure, SWC: spike-and-wave complex, SE: status epilepticus, EPC: epilepsia partialis continua, Lt: left, Rt: right, F: frontal, T: temporal, P: parietal, O: occipital.

**Table 2**
Effects of cortical stimulation on seizure control.

| No. | Sex/operation age (year) | Seizure type | Baseline frequency (month) | Post-stimulation mean seizure frequency per month (% seizure frequency change) | | | Follow-up duration (month) |
|---|---|---|---|---|---|---|---|
| | | | | At 1 year | At 2 years | 3-7 years | |
| 1 | M/21 | EPC | 346.7 | 2 (-99%) | 0 (-100%) | 0 (-100%) | 156 |
| 2 | F/26 | FIAS SE | 48.3 | 4 (-92%) | 1 (-98%) | 0.5 (-99%) | 48 |
| 3 | M/25 | EPC FBTCS | 60.0 | 5 (-92%) | 0.7 (-99%) | 0.5 (-99%) | 54 |
| 4 | F/23 | FBTCS | 42.0 | 18.6 (-56%) | 19.3 (-54%) | 1 (-97%) | 60 |
| 5 | F/19 | FBTCS | 9.3 | 8.5 (-9%) | 9 (-3%) | 4 (-57%) | 36 |
| 6 | F/17 | FBTCS | 8.3 | 6.7 (-20%) | 3.5 (-58%) | 5.9 (-29%) | 48 |

M: male, F: female, EPC: epilepsia partialis continua, FIAS: focal impaired awareness seizure, SE: status epilepticus, FBTCS: focal to bilateral tonic-clonic seizure. For the patients with EPC or SE, seizures were counted as clusters because it is difficult to be confident in the exact number of such frequent events.

### 3.2. Complications

All of our six patients tolerated the surgical procedure and electrical cortical stimulation well. Postoperative brain CT did not show intracranial hemorrhage or prominent brain edema. One patient (patient 3) had recurrent post-implantation scalp inflammation due to an allergic reaction to the cable and needed surgical removal of the system 4 years after implantation. The seizure frequency did not increase after removal of the neurostimulation system. None of our patients experienced any emotional problems, cognitive deterioration, focal weakness/numbness, aphasia, or visual disturbance attributable to the implantation/stimulation.

## 4. Discussion

In this study, the mean reductions in seizures were 61% at 1 year, 68% at 2 years, and 80% at 3–7 years after open-loop electrical cortical stimulation. The median follow-up period was 54 months. Cortical stimulation stopped EPC and focal status epilepticus immediately with a sustained reduction in seizures after 4–6 years of follow-up. One patient had a cutaneous tissue inflammatory reaction to the connection wire which subsided after the system was removed. No other implantation- or stimulation-related adverse effects were noted. In previous large randomized-controlled trials of brain stimulation, open-loop stimulation to bilateral ATN achieved a median reduction in focal seizures of 40.4% at the end of a 3-month blinded phase, and a 41–69% median reduction in seizures during prospective follow-up for 1–5 years (Bergey et al., 2015; Salanova et al., 2015). For epilepsy with one or two well-localized epileptic foci, closed-loop stimulation (the RNS system) showed sustained efficacy with a median 41.5% reduction in seizures at the end of the 3-month blinded phase, a 44–53% median reduction during prospective follow-up for 1–2 years, and a 51–70% median seizure reduction for mesial temporal lobe and neocortical onset epilepsy after 6 years of follow-up (Bergey et al., 2015; Geller et al., 2017; Jobst et al., 2017; Morrell and Group, R.N.S.S.i.E.S., 2011). Our results demonstrated that chronic open-loop electrical cortical stimulation also appeared to be effective in decreasing seizures in patients with refractory focal epilepsy.

The etiology of our three patients with EPC and focal status epilepticus included post-traumatic, post-encephalitis, and non-lesional familial temporal lobe epilepsy. All of these patients had remarkable improvements after cortical stimulation including immediate cessation of status epilepticus, a sustained reduction in seizure frequency of 92˜100% over 3–7 years of follow-up, and improvements in conscious level. Several previous reports have reported that open-loop cortical stimulation is effective in suppressing seizures immediately in patients with EPC or partial status epilepticus (Child et al., 2014; Schrader et al., 2006), with a sustained reduction in seizures of 90–99% after 1–2 years of stimulation in patients with etiologies including birth trauma, intrauterine infarction and post-encephalitis (Child et al., 2014; Elisevich et al., 2006; Valentin et al., 2015). We believe that the findings of the current study support that open-loop electrical cortical stimulation can be used to control seizures rapidly with a sustained effect in reducing seizures in patients with EPC and focal status epilepticus of diverse etiologies.

Malformations of cortical development is a heterogeneous disorder which is frequently associated with refractory epilepsy and various types of neurological deficits (Raymond et al., 1995; Sisodiya, 2004). Several studies have reported that surgical resection led to seizure freedom in 50–60% of patients with polymicrogyria and focal cortical dysplasia (Guerrini et al., 2015; Wang et al., 2016). However, total resection of epileptic foci in patients with cortical malformations can be difficult when the foci are extensive or located in the eloquent cortex due to concerns over permanent post-surgical neurological deficits. Cortical stimulation is a possible alternative method to control seizures in these patients. One recent case series which included 13 patients

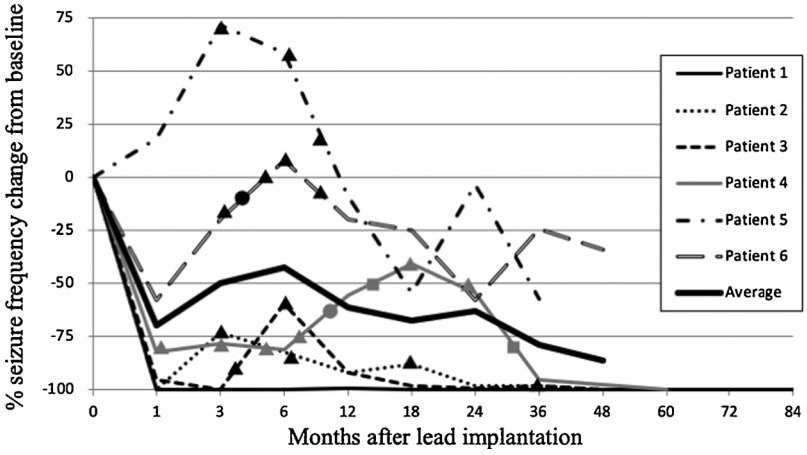


**Fig. 2.** Changes in seizure frequency after cortical stimulation. ▲ indicates increasing stimulation voltage; ● indicates shifting from low to high frequency stimulation; ■ indicates widening of pulse width.

with open-loop cortical stimulation to treat focal cortical dysplasia showed a mean seizure reduction of 80–85% with 3.3–74.6 months follow-up (Lundstrom et al., 2016). In the current study, three patients with polymicrogyria or periventricular heterotopia-related refractory seizures received open-loop cortical stimulation, and all of them demonstrated sustained improvements in seizure control. The patients with a polymicrogyria etiology (patients 4 and 5) showed a 57–97% reduction in seizures during 3–5 years of follow-up, and the patient with periventricular heterotopia (patient 6) showed a 29–57% reduction in seizures during 2–4 years of follow-up. Patient 5 was the only subject who had an increase in seizure frequency shortly after implantation. Polymicrogyria is considered to indicate highly epileptogenic lesions with a widespread epileptic network extending to an apparently normal cortex (Chassoux et al., 2008; Sethi et al., 2016). Implantation of a permanent subdural lead contacting a hyperexcitable cortex could trigger seizures in the early phase post-implantation due to local brain tissue edema. Another possible explanation is that the initial low stimulation parameter was not able to achieve adequate seizure control. We initially applied cyclic electrical cortical stimulation with 1 V in amplitude and 5 Hz in frequency to patient 5. After increasing the stimulation amplitude in a stepwise manner to 4 V, the seizures reduced over time and eventually reached a 57% reduction after 4 years of follow-up. Because of the limited number of cases in this study, further large case series including patients with epilepsy of different etiologies are required to elucidate the response of open-loop electrical cortical stimulation under discrete conditions.

In our analysis of the temporal pattern of seizure frequency after cortical stimulation, we found a noticeable reduction in seizures during the first month, followed by a transient increase in seizure frequency during the following 5 months, and after that a steady long-term reduction in seizures. Because all of our patients received stimulation within 2 weeks after internalization of the pulse generator, the therapeutic effect in the first month may be explained either by implantation of the cortical stimulation electrodes or active cortical stimulation. An “implantation effect” that temporarily ameliorates symptoms after DBS surgery has been reported in subthalamic nucleus stimulation for Parkinson’s disease and hippocampal stimulation for refractory mesial temporal lobe epilepsy, with the effect lasting for weeks to months after surgery (Chen et al., 2006; Tellez-Zenteno et al., 2006). This may be caused by short-term local brain tissue edema, which changes the impedance and neuronal activity at the electrode/tissue interface (Rosa et al., 2010). An implantation effect was also reported in several large trials of ATN stimulation and RNS for epilepsy (Fisher et al., 2010; Morrell and Group, R.N.S.S.i.E.S., 2011). Both studies showed similar reductions after implantation in patients randomized to sham and active stimulation groups. The steady improvement in seizure control over years may be explained by a neuromodulation effect produced by long-term neurostimulation. In addition to the current study, a long-term steady improvement has also been reported with other types of brain stimulation, including ATN stimulation, VNS, and RNS (Bergey et al., 2015; Orosz et al., 2014; Salanova et al., 2015). The neuromodulation effect of electrical cortical stimulation is further supported by the sustained seizure control in two of our patients (patient 1 and 3) after removal of the DBS system.

The most serious potential complication of DBS for epilepsy is intracranial hemorrhage, with reported incidence rates ranging from 1.2 to 2.1% for DBS and RNS (Morrell and Group, R.N.S.S.i.E.S., 2011; Sansur et al., 2007), with rare permanent neurological sequelae also being reported. None of our six patients experienced intracranial hemorrhage post-implantation. Infection is another common complication of DBS for epilepsy, which can develop postoperatively at the site of hardware implantation. In an anterior thalamic stimulation trial (the SANTE study) which included 110 patients, the incidence of implant site infection was 12.7%, none of which were parenchymal brain infections (Fisher et al., 2010). In the RNS trial, infections at the implant or incision site were reported in 5.2% of the subjects (Morrell and Group, R.N.S.S.i.E.S., 2011). Both trials reported that the implanted device was removed in about half of the patients. In the current study, one patient (patient 3) suffered from recurrent scalp inflammation due to an allergic reaction to the cable, and the stimulation system was subsequently removed without any long-term sequelae. The induction of seizures is a potential complication of direct electrical cortical stimulation (Kovac et al., 2016). A stimulation frequency in the range of 50–60 Hz has been reported to be associated with a higher risk of eliciting seizures, and therefore it should be avoided when the intention is to control seizures (Munari et al., 1993). In the current study, all six patients received low frequency stimulation at 3–5 Hz initially, and two patients (patient 4 and 6) were shifted to high frequency stimulation at 120–130 Hz to control seizures. None of our patients had stimulation-triggered seizures during the active stimulation period. Depression is another complication that has been reported in ATN stimulation (Fisher et al., 2010). Although formal psychiatric and neuropsychological assessments were not performed, none of our patients reported any emotional problems, cognitive deterioration, focal weakness/numbness, aphasia, or visual disturbance after implantation/stimulation. Our findings suggest that electrical cortical stimulation is a well-tolerated treatment modality in patients with refractory focal epilepsy.

Because our patients had either status epilepticus or very frequent focal seizures resistant to medical control before entering presurgical evaluation, active stimulation was applied within 2 weeks after implantation of the pulse-generator without sham stimulation. The seizure control may therefore also have been due to a placebo effect. In large trials of brain stimulation for epilepsy, including the anterior thalamic stimulation (SANTE) study and RNS study, the subjects with sham stimulation experienced a 9.4–28.7% seizure reduction during the first 3 months of stimulation, with the maximum seizure reduction observed in the second month after stimulation (Fisher et al., 2010; Morrell and Group, R.N.S.S.i.E.S., 2011). However, in both studies, there was still a more significant reduction in seizures in the active stimulation group compared to the sham group. Furthermore, a progressive reduction in seizure frequency was noted over time in the active stimulation group, which is compatible with our findings for open-loop electrical cortical stimulation. Therefore, even though we cannot completely exclude the possibility of a placebo effect, we still consider active stimulation to be effective in reducing seizures after cortical stimulation.

The limitations of the current study include the small number of patients, the non-blind retrospective design without a sham control group, and including relatively more patients with EPC. The results of our study cannot therefore be directly compared with the results from trials of ATN stimulation and responsive stimulation. Further controlled studies including more epileptic patients with more homogenous underlying etiologies are needed to clarify which patients respond to open-loop cortical stimulation. In addition, seizure frequency was based on seizure diary records, and the patients and their caregivers may not necessarily have known the exact number of seizures.

Despite these limitations, our long-term study showed that open-loop electrical cortical stimulation stopped EPC/focal status epilepticus caused by diverse etiologies immediately after the intervention, and had a sustained effect in reducing seizures throughout the follow-up period. Electrical cortical stimulation appears to be a viable option to control refractory focal seizures in patients with polymicrogyria or periventricular heterotopia. Furthermore, the procedure was generally safe, and a cutaneous tissue reaction to the connection wire noted in one patient subsided after removal of the system.

## Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

## Acknowledgements

This work was funded by the National Health Research Institutes, Taiwan (NHRI-EX97-9739NI), Ministry of Science and Technology, Taiwan (NMRPG3H0371) and Chang Gung Memorial Hospital, Taiwan (CMRPG3C0451).

## References

Albensi, B.C., Ata, G., Schmidt, E., Waterman, J.D., Janigro, D., 2004. Activation of long-term synaptic plasticity causes suppression of epileptiform activity in rat hippocampal slices. Brain Res. 998, 56–64.

Bergey, G.K., Morrell, M.J., Mizrahi, E.M., Goldman, A., King-Stephens, D., Nair, D., Srinivasan, S., Jobst, B., Gross, R.E., Shields, D.C., Barkley, G., Salanova, V., Olejniczak, P., Cole, A., Cash, S.S., Noe, K., Wharen, R., Worrell, G., Murro, A.M., Edwards, J., Duchowny, M., Spencer, D., Smith, M., Geller, E., Gwinn, R., Skidmore, C., Eisenschenk, S., Berg, M., Heck, C., Van Ness, P., Fountain, N., Rutecki, P., Massey, A., O'Donovan, C., Labar, D., Duckrow, R.B., Hirsch, L.J., Courtney, T., Sun, F.T., Seale, C.G., 2015. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology 84, 810–817.

Chabardes, S., Kahane, P., Minotti, L., Koudsie, A., Hirsch, E., Benabid, A.L., 2002. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord. 4 (Suppl 3), S83–93.

Chassoux, F., Landre, E., Rodrigo, S., Beuvon, F., Turak, B., Semah, F., Devaux, B., 2008. Intralesional recordings and epileptogenic zone in focal polymicrogyria. Epilepsia 49, 51–64.

Chen, C.C., Pogosyan, A., Zrinzo, L.U., Tisch, S., Limousin, P., Ashkan, K., Yousry, T., Hariz, M.I., Brown, P., 2006. Intra-operative recordings of local field potentials can help localize the subthalamic nucleus in Parkinson's disease surgery. Exp. Neurol. 198, 214–221.

Child, N.D., Stead, M., Wirrell, E.C., Nickels, K.C., Wetjen, N.M., Lee, K.H., Klassen, B.T., 2014. Chronic subthreshold subdural cortical stimulation for the treatment of focal epilepsy originating from eloquent cortex. Epilepsia 55, e18–21.

Chkhenkeli, S.A., Sramka, M., Lortkipanidze, G.S., Rakviashvili, T.N., Bregvadze, E., Magalashvili, G.E., Gagoshidze, T., Chkhenkeli, I.S., 2004. Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin. Neurol. Neurosurg. 106, 318–329.

Cooper, I.S., Amin, I., Gilman, S., 1973. The effect of chronic cerebellar stimulation upon epilepsy in man. Trans. Am. Neurol. Assoc. 98, 192–196.

Cooper, I.S., Amin, I., Riklan, M., Waltz, J.M., Poon, T.P., 1976. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. Arch. Neurol. 33, 559–570.

Del Felice, A., Beghi, E., Boero, G., La Neve, A., Bogliun, G., De Palo, A., Specchio, L.M., 2010. Early versus late remission in a cohort of patients with newly diagnosed epilepsy. Epilepsia 51, 37–42.

Elisevich, K., Jenrow, K., Schuh, L., Smith, B., 2006. Long-term electrical stimulation-induced inhibition of partial epilepsy. Case report. J. Neurosurg. 105, 894–897.

Fisher, R.S., 2017. The new classification of seizures by the international league against epilepsy 2017. Curr. Neurol. Neurosci. Rep. 17, 48.

Fisher, R.S., Velasco, A.L., 2014. Electrical brain stimulation for epilepsy. Nat. Rev. Neurol. 10, 261–270.

Fisher, R.S., Uematsu, S., Krauss, G.L., Cysyk, B.J., McPherson, R., Lesser, R.P., Gordon, B., Schwerdt, P., Rise, M., 1992. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33, 841–851.

Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., McKhann, G., Babu Krishnamurthy, K., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R., Graves, N., Group, S.S, 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51, 899–908.

Geller, E.B., Skarpaas, T.L., Gross, R.E., Goodman, R.R., Barkley, G.L., Bazil, C.W., Berg, M.J., Bergey, G.K., Cash, S.S., Cole, A.J., Duckrow, R.B., Edwards, J.C., Eisenschenk, S., Fessler, J., Fountain, N.B., Goldman, A.M., Gwinn, R.P., Heck, C., Herekar, A., Hirsch, L.J., Jobst, B.C., King-Stephens, D., Labar, D.R., Leiphart, J.W., Marsh, W.R., Meador, K.J., Mizrahi, E.M., Murro, A.M., Nair, D.R., Noe, K.H., Park, Y.D., Rutecki, P.A., Salanova, V., Sheth, R.D., Shields, D.C., Skidmore, C., Smith, M.C., Spencer, D.C., Srinivasan, S., Tatum, W., Van Ness, P.C., Vossler, D.G., Wharen Jr., R.E., Worrell, G.A., Yoshor, D., Zimmerman, R.S., Cicora, K., Sun, F.T., Morrell, M.J., 2017. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia 58, 994–1004.

Goldin, A.L., 2003. Mechanisms of sodium channel inactivation. Curr. Opin. Neurobiol. 13, 284–290.

Guerrini, R., Duchowny, M., Jayakar, P., Krsek, P., Kahane, P., Tassi, L., Melani, F., Polster, T., Andre, V.M., Cepeda, C., Krueger, D.A., Cross, J.H., Spreafico, R., Cosottini, M., Gotman, J., Chassoux, F., Ryvlin, P., Bartolomei, F., Bernasconi, A., Stefan, H., Miller, I., Devaux, B., Najm, I., Giordano, F., Vonck, K., Barba, C., Blumcke, I., 2015. Diagnostic methods and treatment options for focal cortical dysplasia. Epilepsia 56, 1669–1686.

Jobst, B.C., Kapur, R., Barkley, G.L., Bazil, C.W., Berg, M.J., Bergey, G.K., Boggs, J.G., Cash, S.S., Cole, A.J., Duchowny, M.S., Duckrow, R.B., Edwards, J.C., Eisenschenk, S., Fessler, A.J., Fountain, N.B., Geller, E.B., Goldman, A.M., Goodman, R.R., Gross, R.E., Gwinn, R.P., Heck, C., Herekar, A.A., Hirsch, L.J., King-Stephens, D., Labar, D.R., Marsh, W.R., Meador, K.J., Miller, I., Mizrahi, E.M., Murro, A.M., Nair, D.R., Noe, K.H., Olejniczak, P.W., Park, Y.D., Rutecki, P., Salanova, V., Sheth, R.D., Skidmore, C., Smith, M.C., Spencer, D.C., Srinivasan, S., Tatum, W., Van Ness, P., Vossler, D.G., Wharen Jr., R.E., Worrell, G.A., Yoshor, D., Zimmerman, R.S., Skarpaas, T.L., Morrell, M.J., 2017. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia 58, 1005–1014.

Kovac, S., Kahane, P., Diehl, B., 2016. Seizures induced by direct electrical cortical stimulation–Mechanisms and clinical considerations. Clin. Neurophysiol. 127, 31–39.

Kwan, P., Arzimanoglou, A., Berg, A.T., Brodie, M.J., Allen Hauser, W., Mathern, G., Moshe, S.L., Perucca, E., Wiebe, S., French, J., 2010. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51, 1069–1077.

Lim, S.N., Lee, C.Y., Lee, S.T., Tu, P.H., Chang, B.L., Lee, C.H., Cheng, M.Y., Chang, C.W., Tseng, W.E., Hsieh, H.Y., Chiang, H.I., Wu, T., 2016. Low and high frequency hippocampal stimulation for drug-resistant mesial temporal lobe epilepsy. Neuromodulation 19, 365–372.

Lundstrom, B.N., Van Gompel, J., Britton, J., Nickels, K., Wetjen, N., Worrell, G., Stead, M., 2016. Chronic subthreshold cortical stimulation to treat focal epilepsy. JAMA Neurol. 73, 1370–1372.

McLachlan, R.S., Pigott, S., Tellez-Zenteno, J.F., Wiebe, S., Parrent, A., 2010. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia 51, 304–307.

Morrell, M.J., Group, R.N.S.S.i.E.S, 2011. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 77, 1295–1304.

Munari, C., Kahane, P., Tassi, L., Francione, S., Hoffmann, D., Lo Russo, G., Benabid, A.L., 1993. Intracerebral low frequency electrical stimulation: a new tool for the definition of the "epileptogenic area"? Acta Neurochir. Suppl. (Wien) 58, 181–185.

Orosz, I., McCormick, D., Zamponi, N., Varadkar, S., Feucht, M., Parain, D., Griens, R., Vallee, L., Boon, P., Rittey, C., Jayewardene, A.K., Bunker, M., Arzimanoglou, A., Lagae, L., 2014. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 55, 1576–1584.

Raymond, A.A., Fish, D.R., Sisodiya, S.M., Alsanjari, N., Stevens, J.M., Shorvon, S.D., 1995. Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumour and dysgenesis of the archicortex in epilepsy. Clinical, EEG and neuroimaging features in 100 adult patients. Brain 118 (Pt 3), 629–660.

Rosa, M., Marceglia, S., Servello, D., Foffani, G., Rossi, L., Sassi, M., Mrakic-Sposta, S., Zangaglia, R., Pacchetti, C., Porta, M., Priori, A., 2010. Time dependent subthalamic local field potential changes after DBS surgery in Parkinson's disease. Exp. Neurol. 222, 184–190.

Salanova, V., Witt, T., Worth, R., Henry, T.R., Gross, R.E., Nazzaro, J.M., Labar, D., Sperling, M.R., Sharan, A., Sandok, E., Handforth, A., Stern, J.M., Chung, S., Henderson, J.M., French, J., Baltuch, G., Rosenfeld, W.E., Garcia, P., Barbaro, N.M., Fountain, N.B., Elias, W.J., Goodman, R.R., Pollard, J.R., Troster, A.I., Irwin, C.P., Lambrecht, K., Graves, N., Fisher, R., Group, S.S, 2015. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 84, 1017–1025.

Sansur, C.A., Frysinger, R.C., Pouratian, N., Fu, K.M., Bittl, M., Oskouian, R.J., Laws, E.R., Elias, W.J., 2007. Incidence of symptomatic hemorrhage after stereotactic electrode placement. J. Neurosurg. 107, 998–1003.

Schiller, Y., Bankirer, Y., 2007. Cellular mechanisms underlying antiepileptic effects of low- and high-frequency electrical stimulation in acute epilepsy in neocortical brain slices in vitro. J. Neurophysiol. 97, 1887–1902.

Schrader, L.M., Stern, J.M., Wilson, C.L., Fields, T.A., Salamon, N., Nuwer, M.R., Vespa, P.M., Fried, I., 2006. Low frequency electrical stimulation through subdural electrodes in a case of refractory status epilepticus. Clin. Neurophysiol. 117, 781–788.

Sethi, M., Pedersen, M., Jackson, G.D., 2016. Polymicrogyric cortex may predispose to seizures via abnormal network topology: an fMRI connectomics study. Epilepsia 57, e64–68.

Sisodiya, S.M., 2004. Malformations of cortical development: burdens and insights from important causes of human epilepsy. Lancet Neurol. 3, 29–38.

Sprengers, M., Vonck, K., Carrette, E., Marson, A.G., Boon, P., 2017. Deep brain and cortical stimulation for epilepsy. Cochrane Database Syst. Rev. 7 CD008497.

Tellez-Zenteno, J.F., McLachlan, R.S., Parrent, A., Kubu, C.S., Wiebe, S., 2006. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology 66, 1490–1494.

Valentin, A., Ughratdar, I., Cheserem, B., Morris, R., Selway, R., Alarcon, G., 2015. Epilepsia partialis continua responsive to neocortical electrical stimulation. Epilepsia 56, e104–109.

Vassileva, A., van Blooijs, D., Leijten, F., Huiskamp, G., 2018. Neocortical electrical stimulation for epilepsy: closed-loop versus open-loop. Epilepsy Res. 141, 95–101.

Velasco, F., Carrillo-Ruiz, J.D., Brito, F., Velasco, M., Velasco, A.L., Marquez, I., Davis, R., 2005. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46, 1071–1081.

Velasco, A.L., Velasco, F., Velasco, M., Maria Nunez, J., Trejo, D., Garcia, I., 2009. Neuromodulation of epileptic foci in patients with non-lesional refractory motor epilepsy. Int. J. Neural Syst. 19, 139–147.

Wang, D.D., Knox, R., Rolston, J.D., Englot, D.J., Barkovich, A.J., Tihan, T., Auguste, K.I., Knowlton, R.C., Cornes, S.B., Chang, E.F., 2016. Surgical management of medically refractory epilepsy in patients with polymicrogyria. Epilepsia 57, 151–161.

Wu, C., Sharan, A.D., 2013. Neurostimulation for the treatment of epilepsy: a review of current surgical interventions. Neuromodulation 16, 10–24 discussion 24.