# Intracranial Stimulation for Children with Epilepsy

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# Abstract

**Objectives:** This is a pilot study to evaluate the efficacy of intracranial stimulation to treat refractory epilepsy in children.

**Methods:** This is a retrospective analysis on all 8 children who had intracranial electrical stimulation for the investigation and treatment of refractory epilepsy at King's College Hospital between 2014 and 2015. Five children (one with temporal lobe epilepsy and four with frontal lobe epilepsy) had subacute cortical stimulation (SCS) for a period of 20-161 hours during intracranial video-telemetry. Efficacy of stimulation was evaluated by counting interictal discharges and seizures. Two children had thalamic deep brain stimulaton (DBS) of the centromedian nucleus (one with idiopathic generalized epilepsy, one with presumed symptomatic generalized epilepsy), and one child on the anterior nucleus (right fronto-temporal epilepsy). The incidence of interictal discharges was evaluated visually and quantified automatically.

**Results:** Among the three children with DBS, two had >60% improvement in seizure frequency and severity and one had no improvement. Among the five children with SCS, four showed improvement in seizure frequency (>50%) and one chid did not show improvement. Procedures were well tolerated by children.

**Conclusion:** Cortical and thalamic stimulation appear to be effective and well tolerated in children with refractory epilepsy. SCS can be used to identify the focus and predict the effects of resective surgery or chronic cortical stimulation. Further larger studies are necessary.

# Highlights

1.      Cortical and thalamic stimulation appear to be effective and well tolerated in children with refractory epilepsy.

2.      SCS can be used to identify the focus and predict the effects of respective surgery.

3.      Further larger studies are necessary.

# Keywords

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# Author Agreement/Declaration

All the authors certify that they have seen and approved the final version of the manuscript being submitted. The article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

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None of the authors has any conflict of interest to disclose

# INTRODUCTION

Around 0.4% of children under the age of 16 have epilepsy[1] and approximately 35% are not satisfactorily controlled by medical treatment. Children with refractory epilepsy are very difficult to manage, they consume substantial health resources, often have major disabilities and social disadvantage, and have higher risk of death from accidental causes, status epilepticus or Sudden Unexpected Death in Epilepsy (SUDEP), reaching up to 1% per annum[2]. Resective surgery is only considered as a treatment option when the area causing seizures can be removed without causing unacceptable neurological or cognitive deficits. In some cases, resective surgery is not an option due to proximity to eloquent cortex, presence of multiple foci, bilateral or generalized epilepsy.

Neurostimulation is an alternative for refractory patients who are not candidates for resection[3] This technique delivers electrical pulses to specific areas of the nervous tissue with the intention of reducing the number and/or the severity of seizures (neuromodulation). In contrast to resective procedures, the technique is, at least potentially, both adjustable and reversible.

## Deep Brain Stimulation

The effects of deep brain stimulation (DBS) on pharmacoresistant epilepsy have been under scrutiny since the 1970s[4], and several structures have been targeted throughout the years[5]. The efficacy of thalamic stimulation depends on the epilepsy type. Stimulation of the anterior nucleus has proved to be effective for partial epilepsy showing that 54% of patients had seizure reduction of at least 50% after a 2 years follow up (Stimulation of the Anterior Nucleus of Thalamus for Treatment of Refractory Epilepsy (SANTE) trial[6]). Other studies have showed that the centromedian nucleus stimulation appears to be effective in generalised epilepsies[7] [8] [9].

A low number of minors have been recruited with DBS. Seven children between four and 15 year old were implanted in the centromedian nucleus of the thalamus[10]; two children in the anterior nucleus of the thalamus[6] [11], one in the hippocampus[8], and one in the subthalamic nucleus[11]. Authors reported that skin erosion might be of particular concern in children under eight years of age as a result of the relatively large size of the pulse generator and leads, originally designed for an adult population[12]. Reports elsewhere in this edition suggest that these issues may not be insurmountable.

## Cortical Stimulation

Interest in cortical stimulation as a therapeutic mean to reduce seizure activity began when Lesser et al. reported that during functional cortical mapping for potential resective surgery, epileptiform discharges could be terminated by brief electrical stimulation of the focus point[12]. In 2006 a case was published where, for the first time, continuous cortical stimulation was applied to the motor cortex in one patient for the treatment of focal epilepsy[13]. Ictal origin was within a functional area of the primary motor cortex, and consequently resective surgery was contraindicated. Assessment of stimulation though various electrode pairs surrounding ictal onset identified the most effective set of stimulation parameters in reducing interictal discharges. The patient's seizure frequency improved significantly over time, and after 4 years it decreased from 20-30 daily events to just one every other day, with no evidence of tissue injury or other adverse effects.

Regarding cortical stimulation, several studies have shown that hippocampal stimulation could be a useful alternative to surgical resection[14 15 16 17 18]. Another study randomized controlled trial has shown efficacy of responsive (closed loop) neurostimulation of different cortical structures[19 20 21]. Chronic cortical stimulation of the primary motor cortex has been reported in only seven adults to date[13 22 23 24]. A recent article reported that a 4-day period of cortical stimulation in a 6 year old child with frequent seizures from multiple foci over the lateral temporal cortex, became seizure-free for 2 years after subacute cortical stimulation[25]. We have found no other report on the efficacy of cortical stimulation for the treatment of epilepsy in children.

**King's College Hospital experience in neuromodulation in epileptic children**

In the present study we discuss our preliminary experience with neuromodulation in 8 children with epilepsy. Three patients underwent electrode implantation for chronic thalamic deep brain stimulation (DBS). Five patients had a short period of cortical electrical stimulation during intracranial recordings in the video telemetry unit (hereafter called subacute cortical stimulation or SCS) with the purpose of identifying the candidate regions for further surgical treatment. The main aim of SCS is to identify the epileptogenic cortex in order to optimize future chronic treatment (resection, thermocoagulation or chronic stimulation). Given the significant long-term effects of chronic childhood epilepsy on educational attainment, employment, marital status, and psychological health into adulthood, this study may offer the potential to significantly improve the long-term quality of life of children with refractory epilepsy.

# MATERIALS AND METHODS

## Patients

This is a retrospective analysis on all 8 children treated with cortical and thalamic electrical stimulation for the investigation and treatment of refractory epilepsy at King's College Hospital between 2014 and 2015. EEG recordings and seizure assessment during the period of video-telemetry were performed as part of standard clinical practice, and thus formal ethical approval was not required under National Health Service (NHS) research governance arrangements. All families gave written consent for the surgical procedures.

## Subacute cortical stimulation (SCS)

Among the eight children included in this study, five were admitted for intracranial video-telemetry to elucidate the location of the epileptogenic focus and identification of eloquent motor cortex. After sufficient seizures had been recorded for clinical purposes, a SCS period of 20-161 hours was performed with different combinations of stimulation parameters and cortical locations. The cortical locations for SCS were chosen based in the following criteria: a) abnormal responses to single pulse electrical stimulation (SPES)[26]; b) areas involved in seizure onset[27]; c) areas showing most frequent interictal discharges or areas close to interictal focal slow activity[28] and d) areas showing an MRI lesion.

Efficacy of stimulation was evaluated by visually counting interictal discharges and seizures recorded in the pre-stimulation, stimulation and post-stimulation periods. If the initial combination of parameters appeared not to be efficacious, a different combination was tried. Although the duration of the evaluation was relatively short, patients were intensively monitored during video-telemetry, providing a reliable estimate of efficacy for the different cortical stimulation parameters. Patients with improvement in the frequency of seizures and interictal discharges during this study

were considered for surgical resection or chronic cortical stimulation of the areas whose stimulation had been most effective in reducing the frequency of seizures and interictal discharges. A preliminary MatLab analysis developed by our team was used to identify and quantify EDs, comparing the results with the visual EDs counting. The data was segmented into one hour epochs and the Teager energy was computed for each sample point[29][30] . The best threshold was selected for each channel individually from the Receiver Operating Curve (ROC) plot as shown as an example in Fig 1F. We calculated sensitivity as TP/(TP+FN) and false detection rate as FP/(TP+FP) to measure the goodness of automatic detector versus the gold standard of visual detection. The best threshold value and filter type (Threshold=1.5; Frequency band=1-30 Hz) were selected based on the highest sensitivity and lowest FDR.

## Thalamic DBS

Under a general anaesthetic, a stereotactic frame (Leksell Coordinate Frame G, Elekta, Stockholm, Sweden) was applied and target coordinates (bilateral centromedian in two children, bilateral anterior thalamic in another) acquired using the Stealth Framelink 5 software (Medtronic, Minneapolis, USA). Four-contact electrodes (K-3387/K-3389, Medtronic) were then implanted through bilateral frontal burr holes, their position confirmed on computed tomography.

The effects of DBS stimulation was studied at the longest clinical follow up in each case.

# RESULTS

## Patients

Table 1 shows the electroclinical characteristics of patients. The study included 8 children, 4 females and 4 males, aged between 6 and 15 years.  Three patients had thalamic DBS and 5 patients SCS. Among the three patients with thalamic DBS, one patient had idiopathic generalized epilepsy, one patient had presumed symptomatic generalized epilepsy, and one had probable right fronto-temporal epilepsy.  Among the five patients with cortical stimulation, four patients had frontal lobe epilepsy, and one had temporal lobe epilepsy. The two patients with idiopathic or presumed symptomatic generalized epilepsies had normal imaging. Among the frontal patients, one had tuberosclerosis, one had an area of cortical dysplasia over the left superior frontal gyrus and precentral gyrus, spanning the precentral sulcus, and three had normal imaging.

All patients showed drug resistant epilepsy with daily seizures. Among the patients with DBS, one patient had idiopathic generalized epilepsy, one patient had presumed symptomatic epilepsy, and one had frontotemporal epilepsy. The 5 patients with subacute cortical stimulation had frequent complex partial seizures (with or without secondary generalization) and simple partial seizures. Seven of the eight patients were on polytherapy. The patient with IGE had a very severe allergic reaction to many antiepileptic drugs which significantly limited the use of anticonvulsant medication.

## Deep brain stimulation

Two patients had chronic DBS of the centromedian nucleus of the thalamus (Figure 2B). One case was associated with >90% improvement in seizure frequency and severity (36 months follow up), but after 1-6 months, stimulation parameters and location had to be changed to maintain the improvement, as otherwise stimulation efficacy decreased. The second patient had no significant improvement in seizure frequency, with a slight worsening in seizure severity (12 months follow up). The child with chronic DBS in the anterior nucleus of the thalamus showed an improvement in

seizure frequency (>60%; 6 months follow up) and severity, but associated with worsening in the daily behaviour (Figure 2A).

## Subacute cortical stimulation

Among the five children with SCS, under the best combination of stimulation parameters four showed improvement in seizure frequency during the period of SCS (>50% in all four cases, 1 case seizure free for 20 months after SCS[25]), severity of seizures (shorter and less distressing) and interictal epileptiform discharges (estimated >75% reduction in all four cases). In two patients, a short period after SCS in the video telemetry unit showed a return to the baseline seizure frequency. One patient showed no clear improvement in seizure frequency and severity was noted.

As described in table 1, two patients became seizure free after SCS, one after removal of electrodes without any further surgical procedure (26 month follow up), and another one after an ECoG guided resection of the previously successfully stimulated region in the supplementary cortex (8 month follow up) (Figure 2C). Two patients had >90% improvement in seizure frequency, one after a limited thermocoagulation of the successfully stimulated region in the primary motor cortex of the leg and the other patient after resection of the successfully stimulated frontal tuber (Figure 2D). One patient did not improve after SCS and VNS was implanted

## Safety and side effects

The surgical procedure and electrical stimulation were well tolerated by all children. No patient showed postsurgical haemorrhage or oedema in the post-insertion CT.

# Discussion

There are a number of stimulation/neuromodulation techniques which are becoming established for the treatment of epilepsy. None of these techniques have been widely applied in adults, and the experience in children at present is very limited. Their safety and surgical techniques for implantation have become more standardised in children. Larger studies will be required to demonstrate efficacy both in adults and children, but earlier intervention for severe epilepsy clearly improves long term outcome physically, psychologically and socially.

The mechanisms of action of the neuromodulation techniques are still speculative, and probably some differ between deep brain stimulation (DBS) and cortical stimulation (CS). Both techniques could have similar basic mechanisms of action involved in modulation of neuronal activity and long-lasting change in local excitability such as kindling[31], long-term potentiation[32][33] and DSE (modulating presynaptic release by endocannabinoids)[34]. However, Wyckhuys et al have demonstrated that seizure frequencies normalise back to baseline after the paroxysmal depolarization shift (PDS) is terminated, thus refuting the first two mechanisms by arguing against any long lasting effects in PDS[35]. They suggested that neurons are able to adjust to a range of magnitudes of their functional intrinsic currents due to homeostatic scaling mechanisms of membrane excitability and/or synaptic strength[36]. Neurons are also potentially able to adjust and modulate their synaptic strength[37] in response to the overall level of synaptic input activity[38].

**Possible mechanisms of action of DBS**
Modulation of distal cortex is a theory supported by the SANTE trial where stimulation of the anterior nucleus of the thalamus was associated with a 69% improvement in seizure frequency in adult patients with focal epilepsy and a minimum follow-up of 5 years[39]. More recently, Gibson et al demonstrated that DBS of the anterior thalamic nucleus (ATN) showed strong activation of

ipsilateral Papez structures including entorhinal cortex, hippocampus, parahippocampal gyrus, cingulate and inferior temporal gyrus. They also suggested that prefrontal and eloquent cortical areas might be stimulated by ATN DBS[40]. Similar distal effects have been reported during DBS of the centromedian thalamic nucleus[41 7] and subthalamic nucleus[42].

Stimulating with a Poisson distributed (i.e. random) paradigm might cause disruption of synchrony[15]. Behavioral effects of high frequency electrical stimulation of the hippocampus on electrical kindling in rats[43] in some patients, and why we have observed in some patients the need for frequent changes of settings to maintain control of seizures.

## Possible mechanisms of action of CS

It has been suggested that stimulation provokes a reversible functional lesion, inhibiting the generation and/or propagation of epileptic activity over the area of stimulation[3]. Indeed, cortical stimulation with single pulses provokes periods of suppression in cellular firing lasting for up to 1.3 seconds in 26% of neurons[44] suggesting that repetitive stimulation at the correct frequency may be able to permanently suppress cortical activity stimulation[45 46 47 48 49].

It can also cause activation and enhancement of inhibitory pathways mainly via partial inactivation of voltage-gated sodium channels, change of extracellular potassium concentration[52] or induction of long term synaptic depression in excitatory synapses[50 51 52 53]. This may explain why high and low frequencies can show varying degrees of efficacy in different patients[23]. There may be disease or patient-specific factors which determine how stimulation parameters affect seizures in each patient. It has also been suggested that subthreshold high frequency stimulation can suppress intrinsic firing from the cell soma. On the other hand, low frequency stimulation is thought to elicit long term synaptic inhibition. Moreover, long-term depression (LTD) and γ-aminobutyric acid (GABA) receptor mediated mechanisms may be responsible for a reduction in cortical excitability following electrical stimulation [9 54 55]. Other suggested mechanisms of action are modification of non-synaptic activity[59], postsynaptic signalling and plasticity mechanisms[56 57], depotentiation of synaptic responses[49], receptor desensitization or downregulation[56 58], increase in neuronal synchronization[56 59 60] or desynchronisation of network activity[51], neurotransmitter build up and loss of information transfer[56 60].

Consequently, the efficacy of cortical stimulation depends on multiple parameters such as stimulation site, intensity, pulse duration and frequency. One practical difficulty in implementing cortical electrical stimulation as a treatment for epilepsy is to establish a paradigm to identify the best stimulation parameters among the enormous number of parameter combinations available. A visual analysis of interictal epileptiform discharges and clinical/subclinical seizures is performed as initial clinical assessment of stimulation. However, as not all stimulation parameter/positions are effective, automatic analysis of stimulation effects on the number of seizures and epileptiform discharges would be desirable for future assessment. A preliminary MatLab analysis is been developed by our team with promising preliminary results (Figure 1).

In this retrospective analysis of children who had subacute cortical (SCS) and thalamic stimulation at King's College Hospital, we have found that both techniques appear to be effective and well tolerated in children with focal or generalised epilepsy. Among the 5 children with SCS, the technique helped to determine a precise surgical target in three cases, allowing limited resection/coagulation of eloquent brain. In one patient, a period of four days with SCS days was associated with a long period of 30 months of seizure freedom. Regarding the three children undergoing thalamic stimulation, in two cases there was an improvement in seizure frequency and/or severity without significant side effects.

Our study suggests that in children where a possible single focus could be identify and intracranial recordings are carried out, SCS can help in localizing very precisely the epileptogenic cortex. If this is the case, the patients could benefit of a limited resection/thermocoagulation of the area, or if the risk of surgery is too high due to eloquent cortex, they could have implanted a chronic CS. In cases when the epileptogenic focus can't be localised or they have generalised epilepsy, it would be reasonable to consider a centromedian or anterior nucleus DBS implantation.

The future of neuromodulation with intracranial stimulation for medically refractory epilepsy is encouraging and will hopefully provide an important alternative for children with debilitating seizure disorders. However, caution is required to adapt brain stimulation to a developing central nervous system, and further research would be required to find the most suitable and less disruptive stimulation parameters in the child population.

**Table 1 Abbreviations:** y=year; m=month; m=male; f=female; TC=tonico-clonic; abs=absences; sz=seizure; AED=Antiepileptic drug; CPS=Complex partial seizures; ANT=anterior thalamic nucleus; CM=centromedian thalamic nucleus; SMA=supplementary motor area; FEF=frontal eye field; pCG=precentral gyrus; VNS=vagal nerve stimulation; Stim=stimulation; * - no further surgery as subacute stimulation resulted in seizure freedom; ** - Taylor's cortical dysplasia type 2b

**Figure 1.** Example of the efficacy of subacute cortical stimulation treatment in patient SC3. A) anterior posterior X-ray showing four 8-contact depth and three 8-contact subdural strips electrodes; B) lateral X-ray; C) intracranial EEG recording showing typical interictal epileptiform discharges in a baseline period with a common average reference; D) intracranial EEG recording after cortical stimulation at contacts 1 and 2 of the depth superior central electrode (D SC) with a common average reference; E) Number of interictal discharges (IEDs) before and during cortical stimulation in 5 hour wakeful EEG. The number of IEDs has reduced 10 times during cortical stimulation in comparison to pre-stimulation; F) Performance curves of automatic detector at channel 7 of the subdural post central strip (SD PC). Comparisons were made for four different frequency ranges, and 18 threshold values on the bases of sensitivity and False Detection Rate (FDR). Sensitivity vs. false detection rate with different δ and filter types. In this patient and this channel, detection of spikes with δ = 1.5 and FIR filter 1-30 Hz allows for sensitivity of 81% with false detection rate of 0.19 per minute. IEDS=Interictal epileptiform discharges; ST= Strip; D=Depth; A=Anterior; P=Posterior; I=Inferior; S=Superior; C=Central; FIR= Finite impulse response filter; FDR=False discovery rate.

**Figure 2.** Examples of surgical procedures. A) Lateral X-ray showing the DBS implantation in the anterior nucleus in patient D01; B) Lateral X-ray showing the DBS implantation in the centromedian nucleus in patient D03; C) Superimposed photograph of the small resection over a 3D pre implantation MRI in patient SC5. The black arrow points at the resected area; D) Lateral MRI showing the thermocoagulated region in patient SC3.

**Figure 3.** Efficacy of subacute cortical stimulation on average counting of clinical seizures during the telemetry recording in all 5 patients with SCES. Periods pre-SCS, SCS ON and post-SCS are included when available. Note that Patient DD did not have clinical seizures during periods SCS ON and OFF, and that patients SC2 and SC3 did not have period post SCS.

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**Figure 1**
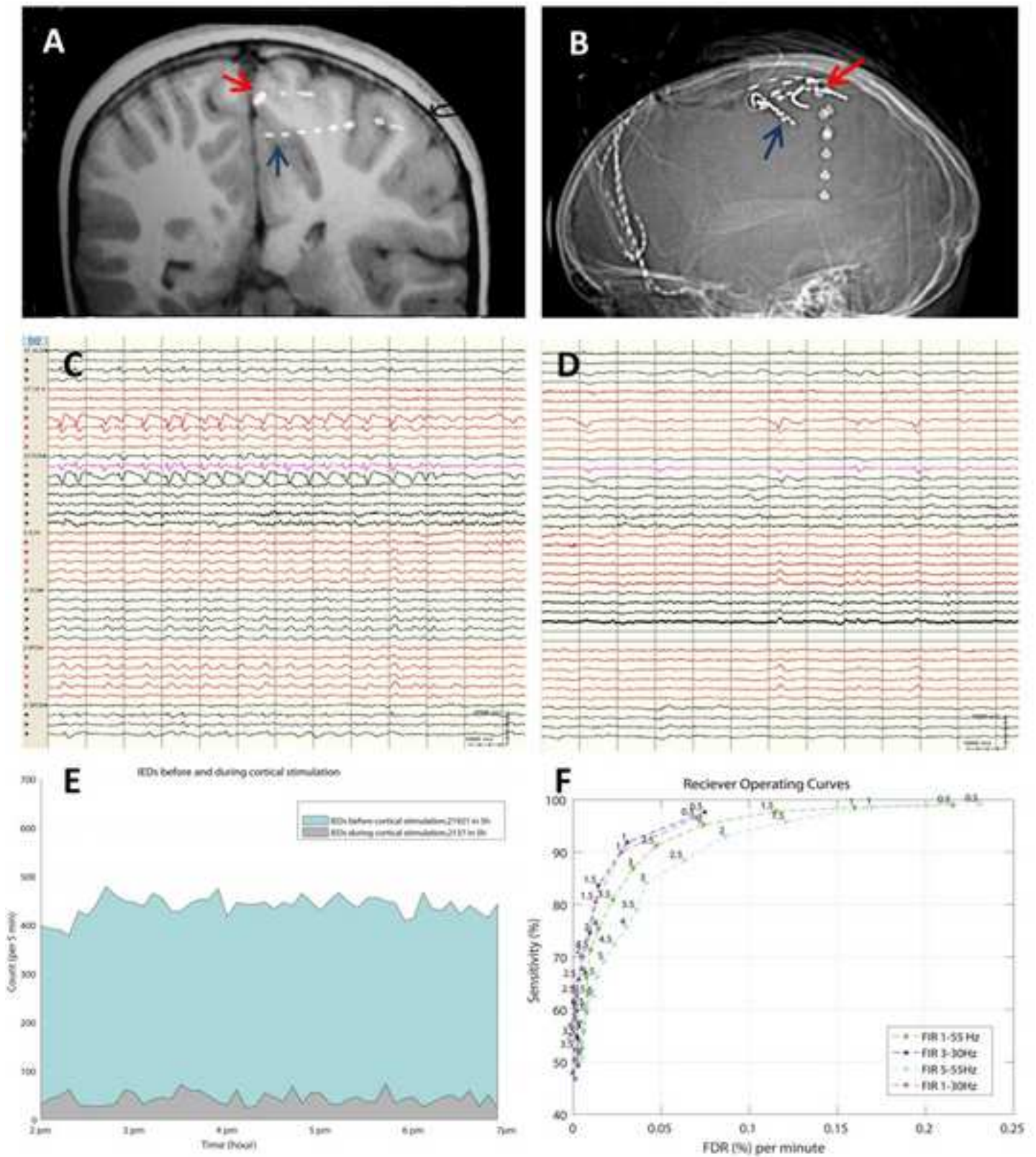**Click here to download high resolution image**

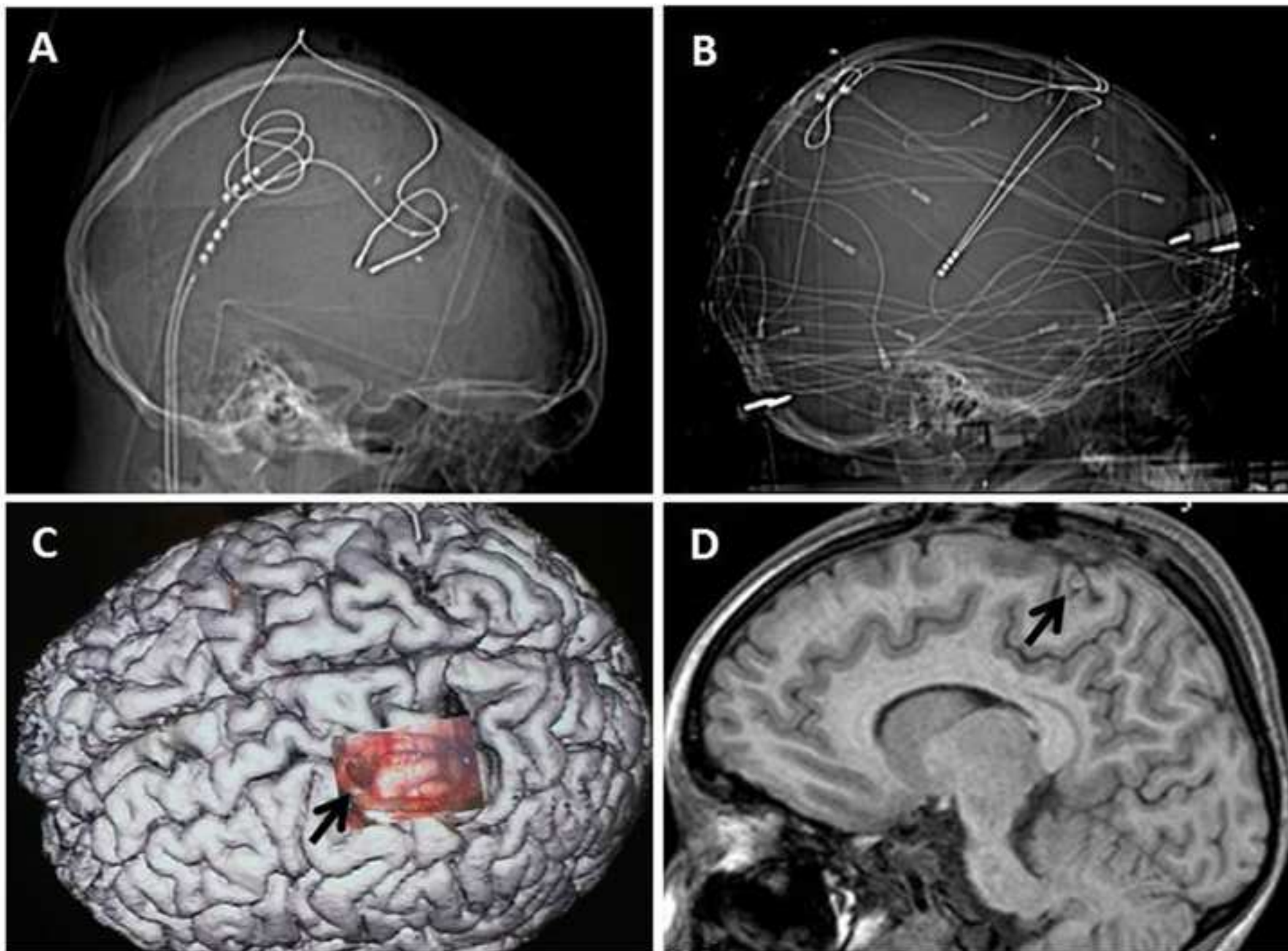**Figure 2**
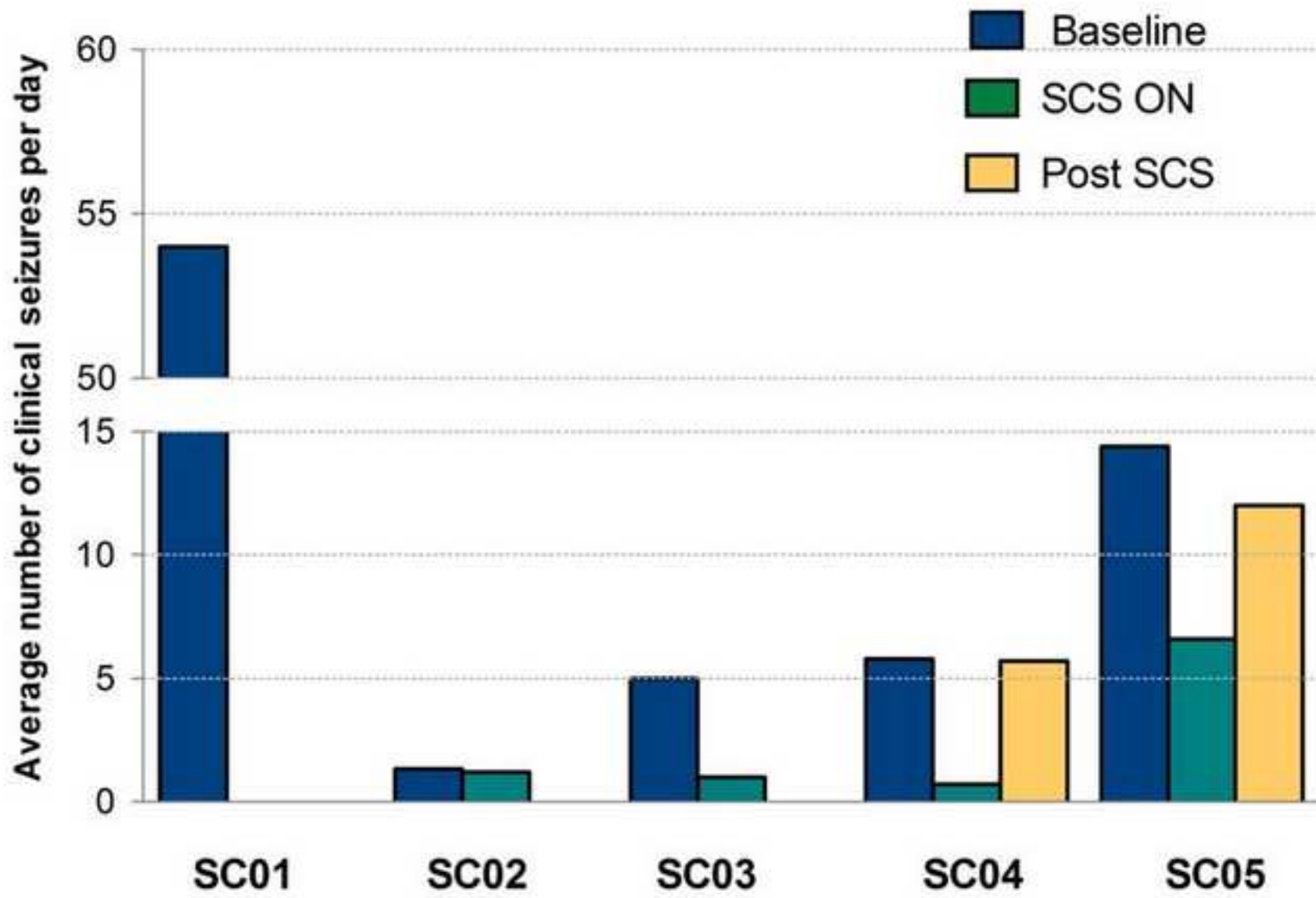**Click here to download high resolution image**

Figure 3

**Table 1**

| | Patient | Age surgery | Gender | Epilepsy type | Seizure type | Number of clinical szs | MRI | electrodes | position | stimulating area | Stim. time | CS result | surgical procedure | outcome | follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **subacute cortical stimulation** | SC01 | 7y3m | M | Structural | Focal motor | >50/day | Cortical lesion left mid temporal sulcus | Subdural | Left temporoparietal | Lateral temporal | 36 h | sz free | No resection* | Engel 1a (AEDs stopped) | 30 m |
| | SC02 | 7y8m | M | Unknown | Focal motor | 1,5/day | Normal | Subdural | Left frontotemporal | lateral frontal | 20 h | no change in szs/IEDs | No resection | Engel 4 (VNS inserted) | n/a |
| | SC03 | 7y6m | F | Unknown | Focal motor | 5/day | Normal | Subdural + depth | Left parcentral lobule | paracentral lobule | 161 h | >75% sz reduction | Thermocoagulation SCS area | Engel 1b (on AEDs >95% seizure reduction) | 8 |
| | SC04 | 9y5m | F | Structural | Focal motor | 6/day | Multiple tuberosclerosis | Subdural | Right frontoparietal | lateral anterior frontal | 29 h | >85% sz reduction | frontal tuber resection SCS area | Engel 1b (on AEDs >90% seizure reduction) | 14 |
| | SC05 | 15y5m | F | Structural | Focal motor / bilateral tonic clonic | 14/day | Left precentral cortico displasia | Depth + subdural | Left SMA/FEF/pCG | medial/lateral primary frontal | 83 h | >50% sz reduction | lesionectomy SCS area** | Engel 1a (on AEDs) | 10m |

| | Patient | Age surgery | Gender | | Epilepsy type | Number of clinical szs | MRI | electrodes | position | outcome | follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **DBS ANT** | D01 | 14y7m | M | Structural | Focal motor | 10/month | Normal | Depth implant | Bilateral ANT | Engel 3 (>60% seizure reduction); increased aggession | 12 |
| **DBS CMN** | D02 | 9y6m | M | Unknown | generalised Abs, atonic, TC | TC 60/day, atonic 10/day, abs 100/day | Normal | Depth implant | Bilateral CM | Engel 3 (>60% seizure reduction) | 4 y |
| | D03 | 8y3m | F | Genetic | Generalised, myoclonus, abs | 30/day | Normal | Depth implant | Bilateral CM | Engel 4 (DBS stopped at 18 months) | 18m |