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Neurophysiological effects of continuous cortical stimulation in epilepsy – Spike and spontaneous ECoG activity

Karin Westin [a,b], Brian N. Lundstrom [c], Jamie Van Gompel [c], Gerald Cooray [a,b,*]

[a] Clinical Neurophysiology, Karolinska University Hospital, Stockholm, Sweden
[b] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[c] Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, Sweden

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HIGHLIGHTS

- Stimulation over the seizure onset zone reduced background activity and interictal spike rate.
- Changes in power of background activity and spike rate showed a clear positive correlation.
- Possible causal relationship between spectral power, coherence and interictal spikes.

ABSTRACT

Objective: The effect of continuous subthreshold cortical stimulation (CSCS) over the seizure onset zone (SOZ) in epilepsy was analyzed to delineate the affected physiological processes.
Method: ECoG data was recorded over SOZ and adjacent regions in patients (n = 7) with refractory-epilepsy. Data was reviewed before and during 2 Hz cortical electrical stimulation. Group differences were estimated using ANOVA and correlation with Pearson's r.
Results: CSCS reduced background ECoG power at SOZ ($p < 0.05$), increased spectral coherence ($p < 0.05$) and reduced spike rate ($p < 0.01$) over all recorded sites. Spectral power and coherence ($p < 0.01$) correlated with spike rate at SOZ but not with each other at any location. Spike morphology correlated with spike-rate over all recorded sites ($p < 0.0001$) and with spectral power and coherence at SOZ ($p < 0.01$).
Conclusion: This study shows changes in cortical electrophysiology during CSCS over the SOZ where spike rate reduction correlated with two independent electrophysiological parameters, background power and coherence. These results suggest the possibility of a causal relationship between spectral power, coherence and interictal spikes which may be related to seizure rate.
Significance: Improved understanding of the effect of electrical stimulation on epileptic tissue could suggest improvements in stimulation paradigms to reduce seizure frequency.

1. Introduction

Epilepsy constitutes a wide range of brain disorders characterized by a predisposition of developing seizures. Approximately thirty percent of patients with focal epilepsy do not respond adequately to antiepileptic drugs and develop pharmacoresistant epilepsy, sometimes experiencing multiple daily seizures (Abramovici and Bagic, 2016), as well as an increased risk of premature death, neurological deficits and reduced quality of life (Chen et al., 2016). Amongst focal drug-resistant epilepsies, surgical resection of the epileptogenic zone provides a good outcome in a majority of cases (West et al., 2016). If the seizure onset zone (SOZ) is located within eloquent cortex, surgery is in certain cases not feasible due to possibly serious adverse effects. For such patients, other treatment options are needed. Both central and peripheral electrical neurostimulation has proven effective in treatment of these patients (Edwards et al., 2017). Peripheral vagus nerve stimulation as a treatment of intractable seizures has been approved by the FDA since 1997 (Dalkilic, 2017). Deep brain stimulation is a safe and established option for movement disorders (Lozano et al. 2018), but the technique has also been used in epilepsy care. In 2010, convincing evidence of the effect of deep brain stimulation of the anterior nuclei of the thalamus was presented in the SANTE study (Salanova et al., 2015). Here, stimulated patients experienced

* Corresponding author at: Clinical Neurophysiology, Karolinska University Hospital, Stockholm, Sweden.
E-mail address: gerald.cooray@ki.se (G. Cooray).

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a clear, long-lasting reduction of seizures without serious adverse effects (Fisher et al., 2010). In a recent Cochrane review, hippocampal stimulation significantly reduced seizure frequency (Cukiert et al., 2017). Despite the many aetiologies of epilepsy, seizure propagation often occurs along the cortical-strial-thalamic or limbic network, which is why these pathways typically are targeted in deep brain stimulation (Laxpati et al., 2014). Electrical stimulation in response to seizure initiation has also proven effective. The responsive focal cortical stimulation system senses electrocortical activity and provides stimulation pulses to the seizure onset zone (SOZ) in response to seizure initiation (Geller et al., 2017). In a randomized, multi-center, double-blind controlled trial (the Responsive Neurostimulation System, RNS, Pivotal trial), responsive stimulation significantly reduced seizure load (Heck et al., 2014).

Recent evidence suggests a novel neurostimulation technique using chronic subthreshold cortical stimulation (CSCS) is promising (Lundstrom et al., 2016; Kerezoudis et al., 2018, Lundstrom et al., 2017). Patients with frequent, disabling seizures and SOZs located in eloquent or near eloquent cortex received continuous electrical stimulation directed towards the SOZ. Stimulation is directed towards the epileptic focus where initiation of the ictal event occurs, not the pathway along which the seizure propagates, as is targeted in deep brain stimulation (DBS). In contrast to RNS which only stimulates in response to putative seizure activity, CSCS delivers continuous stimulation to the SOZ. One of the challenges with RNS is to define appropriate patterns using electrocorticography (ECoG), triggering electrical stimulation in order to terminate nascent seizures (Baldassano et al., 2016). With CSCS, 77% of patients reported both a reduction in seizure frequency and improvement in quality of life, and approximately 40% of patients were free of disabling seizures (Lundstrom et al., 2016; Kerezoudis et al., 2018). The approach has been safe (Kerezoudis et al., 2018). Also, the amount of interictal epileptiform activity was significantly reduced during acute stimulation (Lundstrom et al., 2016, Lundstrom et al., 2018). The mechanism underlying the clinical effect of electrical neurostimulation on seizure burden is largely unknown (Yamamoto et al., 2006). However, it is established that stimulation parameters such as pulse frequency, amplitude and width can play an important role in determining clinical outcome (Laxpati et al., 2014).

In this study, we investigated the neurophysiological effects of CSCS on the SOZ as well as surrounding cortical tissue. We analysed ECoG data recorded at baseline and during stimulation from seven patients with focal epilepsy who underwent continuous stimulation. Our aim was to quantify any change in both background and spiking activity in order to give a first insight into the changes induced in a cortical network surrounding the SOZ by ongoing electrical stimulation. Such changes might provide clues to the mechanism behind inhibition of seizure development and progression, as seen in clinical studies of electrical neuromodulation (Kinoshita et al., 2005; Lundstrom et al., 2016; Geller et al., 2017).

2. Method and material

2.1. Patients

ECoG-data was collected from de-identified patients with drug-resistant focal epilepsy with approval by the Mayo Clinic Institutional Review Board. As part of evaluation for surgical resection, patients had subdural electrodes implanted over potential seizure onset zones. Epilepsy surgery was not feasible in any of the patients included in this study due to the location of the epileptogenic zone. They were offered a therapeutic trial of continuous subthreshold cortical stimulation from electrodes placed over the SOZ. Details of the patients and the CSCS have been presented previously (Lundstrom et al., 2016, Kerezoudis et al., 2018).

2.2. Chronic subthreshold cortical stimulation (CSCS)

Patients were reviewed retrospectively before and after initiation of continuous subthreshold cortical stimulation over the SOZ. ECoG was recorded from subdural grid electrodes during 6–7 days prior to stimulation onset. Data were analysed from a 4×4 grid (1 cm spacing) of electrodes that included the SOZ. Six blocks of 15 minute registration of data were collected between 8 pm and 6 am during the first or second night of their hospital stay. After the baseline period patients received a biphasic (charge balanced) 2 Hz electrical stimulation (pulse width 90–450 microseconds, inter-pulse delay 500 ms, amplitude 1–6 V) over the predefined clinically determined SOZ via adjacent strip and occasional depth electrodes in the region of seizure onset (Lundstrom et al., 2017). Further ECoG data was retrieved again overnight from 8 pm to 6 am during the first or second night following initiation of stimulation. The stimulation amplitude was set to a level that would not cause any immediate clinical manifestations (e.g. motor or sensory manifestations) i.e. clinically subthreshold. The stimulation was provided using off-label FDA approved Medtronic devises for which voltage clamp is standard for clinical purposes e.g. DBS for tremor and Parkinson disease (Deuschl et al., 2013). However, in experimental paradigms voltage control is less optimal than current control as the physiological effect is dependent on delivered charge (Merrill et al., 2005).

2.3. Analysis

Stimulation artefacts were identified and 50 ms of recording before and after the centre of the stimulation artefact were removed (leaving 400 ms segments of data). The stimulation artefact induced only small changes of activity in the interstimulus window (400 ms segment of data). The artefacts caused changes of the activity in the interstimulus window less than 0.01 of the amplitude of the background activity. This was estimated by comparing the variation of the background activity in the interstimulus window in comparison to the stimulus averaged activity. When analysing the effect of epileptic transients on the background activity it is important to remove the parts of the ECoG activity contaminated by spikes and any spike induced slow waves. To remove this confounding effect of spikes on background activity we studied only segments between electrical stimulation (500 ms) without spikes when estimating the power and coherence of the background activity. The remaining data was band-pass filtered between 4 and 40 Hz using a Butterworth filter of order 5. Pre-stimulation data was segmented into 400 ms segments and pre-processed in the same way.

In order to analyse spiking activity, a previously validated method for automated spike detection was used (Barkmeier et al., 2012). Possible spikes were located by a threshold based on standard deviations (SD coefficient) of the absolute amplitude of filtered ECoG signal. Each of the sixteen channels were then normalised using the median value of the average absolute amplitude across the grid. After normalisation spike amplitude was measured in normalised units of amplitude taking into account, at least partly, for confounding effects of lead field differences between ECoG electrodes. Spikes were identified using shape characteristics such as amplitude, width and slope. Ten minutes of ECoG data from all channels from each patient were visually analysed for spikes (by Clinical Neurophysiology Consultant, GC) and compared to the spike detection of the algorithm with different thresholds (400, 600, 800, 1200, 1400, 1600 and 1800). The Youden's J statistic was calculated from the false and true positive rate and found to be

greatest (0.7) for a threshold of 1400. The algorithm's default values were used in the spike detection except for the threshold which was set at a higher level of 1400 μV (total amplitude of both half-waves; equivalent to 10 normalized units of the median grid amplitude) similar to what we used previously on this data set (Lundstrom et al., 2018).

The number of spikes was estimated per minute (spike rate) for each channel. The coherence between spike rate was estimated between each pair of the sixteen channels. Recorded data was divided into segments (400 ms duration with no electrical stimulation) with and without spikes. Segments without spikes were used for analysis of spectral power and coherence. The electrode positions were also subdivided into different recording site groups, those at the SOZ, as per clinical evaluation, (SOZ), those lying within 1 cm of the SOZ (BRIDGE), and electrodes further away from the SOZ (non-SOZ, NSOZ). The estimated measures of spectral power, coherence, spike-rate and spike-morphology (amplitude and duration) were estimated for each recording site group or pair of recording site groups (SOZ, BRIDGE or NSOZ).

In order to determine the spectral power of the signal from each channel before and during stimulation, the autospectral density was calculated for pre-stimulation and stimulation data. Segments without spikes were used for spectral analysis (remove the confounding effect of spike activity on background activity) The following was used to calculate the autospectral density:

$$S_{xx}(\omega) = |F_x(\omega)|^2$$

where $F_x(\omega)$ is the fourier transform of the recorded time signal $x(t)$. S_{xx} was estimated for each spike free segment of data and then averaged over all analysed segments. The average autospectral density of each patient and channel was calculated. We also determined the coherence, pairwise between each two pairs of channels as a measure of connectivity. The following was used to calculate the absolute coherence:

$$G_{xy}(\omega) = \frac{\left|F_x(\omega)\overline{F_y(\omega)}\right|}{|F_x||F_y|}$$

These results were used to estimate the average power and coherence at recording site group and between recording site groups (SOZ, BRIDGE or NSOZ) before and during stimulation. Spectral-amplitude of the background activity was quantified as the square root of the autospectral density.

2.4. Statistics

All statistical estimations were done in MATLAB. Several distributions were non-gaussian, however, after a logarithmic transformation they showed Gaussian distributions. P-values were estimated using ANOVA or T-tests. Correlation between estimated parameters was tested using both Pearson's and Spearman's r (resulting in similar findings). Results estimated using Pearson's r are given in the results section.

3. Results

3.1. Patients

Data from seven patients were analysed (age at start of permanent stimulation 14–56, median age 20). Four patients had one or several sites of focal cortical dysplasia located in the frontal (n = 2), temporal (n = 2) and parietal lobes (n = 1). Three patients had encephalomalacia, posttraumatic (n = 1) and ischemic (n = 2). SOZ was located in motor (n = 5), language (n = 1) and visual (n = 1) cortices for which reason these patients did not qualify for resective surgery. Seizure types included focal dyscognitive seizures (n = 4), reflex seizures (n = 1) and focal motor seizures (n = 2), see Table 1. Further details on the demographics and clinical effect of cortical stimulation is presented in (Lundstrom et al., 2018; Kerezoudis et al., 2018).

3.2. Spectral and coherence analysis

Pre-stimulation data showed differences in spectral power between recording site groups SOZ (n = 24), BRIDGE (n = 43) and NSOZ (n = 45) with significant differences in spectral power between the three groups for 4–8 Hz and 8–12 Hz ($p < 0.05$, ANOVA after logarithmic transformation). Greatest power was seen over recording site group SOZ and the lowest over NSOZ, Table 2.

Onset of cortical stimulation resulted in a marked reduction of spectral power across channel types where differences between electrode recording sites were no longer statistically significant, see Fig. 1 and Table 2. There was a significant reduction in activity over SOZ (n = 24) and BRIDGE (n = 43) electrodes for 4–8 Hz ($p < 0.05$), 8–12 Hz ($p < 0.01$) and 12–40 Hz ($p < 0.01$) activity. Cortical stimulation led to increased average spectral coherence between all channel pairs, Fig. 2 and Table 3. Greatest changes were seen for SOZ-SOZ electrode pairs with an increase in coherence (stimulated – pre-stimulated) of 0.41. Furthermore, we found statistically different changes in spectral coherence when comparing recording site group SOZ (n = 23, increase of 0.41), BRIDGE (n = 43, increase of 0.18) and NSOZ (n = 45, increase of 0.02). ANOVA was used to estimate a $p < 0.0001$.

3.3. Spike-rate

Spike-rate was measured for SOZ, BRIDGE and NSOZ group electrodes from the pre-stimulation and stimulation data. Before stimulation SOZ electrodes showed the highest spike rate (4.8 per min) while NSOZ (1.5 per min) had the lowest. There were significant differences in spike-rate when comparing the three channel types (SOZ, BRIDGE and NSOZ) during pre-stimulation ($p < 0.01$) but not during stimulation. Moreover, cortical stimulation resulted in a decrease in spike rate over all recording site groups with a statistical significance of $p < 0.05$ (t-test), Table 4 and Fig. 3.

3.4. Spike morphology

Analysis of spike amplitude showed significant changes between pre-stimulation and stimulation data for SOZ electrodes and nonsignificant changes for BRIDGE and NSOZ electrodes, Figs. 3 and 4. Mean spike amplitude decreased after stimulation most clearly for recording site group SOZ (24 electrodes with a mean reduction of −2.1 units, $p < 0.01$) while BRIDGE (43 electrodes with a reduction −0.2 units $p < 0.1$) and NSOZ (45 electrodes with a reduction −0.1 units $p < 0.1$) showed smaller nonsignificant changes ($p < 0.10$). P-values were calculated after logarithmic transformation of the data using t-tests. Furthermore, reduction in spike duration was noted; however, these changes were not significant as p-values > 0.05 but less than 0.1 for all three regions of electrodes (SOZ, BRIDGE, NSOZ). Further analysis of spike morphology from each recording site group was done using a discrete cosine decomposition using 5 components. The spikes were normalized for amplitude before comparison. A trend was seen in the changes in the first component (t-test, $p < 0.10$) when comparing pre-stimulation with stimulation spikes for all three recording sites (SOZ, BRIDGE and NSOZ). This component is related to the duration of the spike and similar results were seen on direct comparison with spike duration.

Table 1
Demographic and etiologic description of patients at stimulation trial together with lesion type and seizure type. FCD – Focal cortical dysplasia, FDS – focal dyscognitive seizure. *Reflex seizures were induced by ambulation on or direct sensory stimulation of the right foot with unilateral focal sensory and motor symptoms.

Case	Age at Op	Sex	Lesion	Seizure type
1	15	F	Cortical left post ischemic temporal encephalomalacia	FDS
2	26	M	Left frontal and temporal FCD	FDS
3	56	M	Post traumatic right frontal and temporal, mainly cortical encephalomalacia	Reflex seizure*
4	27	F	Right temporal FCD	FDS
5	14	M	Right parietal FCD	Focal motor
6	19	M	Cortical left post ischemic parietal occipital encephalomalacia	FDS
7	20	F	Right frontal FCD	Focal motor

Table 2
Spectral power (mV^2) during pre-stimulation and stimulation. Mean and 95% confidence intervals are given for three frequency bandwidths. Changes between recording site groups for stimulation and pre-stimulation (p-values) were estimated using ANOVA after logarithmic transformation.

	Recording site group			
	SOZ (N = 24)	BRIDGE (N = 43)	NSOZ (N = 45)	p-value
Frequency bandwidth (Hz)	*Pre-stimulation*			
$4 \leq f < 8$	1.0 [0.6–1.7]	0.5 [0.3–0.8]	0.4 [0.2–0.6]	<0.05
$8 \leq f < 12$	7.1 [3.8–13]	3.4 [2.1–5.5]	2.5 [1.4–4.4]	<0.05
$12 \leq f < 40$	2.5 [1.3–4.7]	1.3 [0.8–2.1]	0.9 [0.5–1.5]	ns
	Stimulation			
$4 \leq f < 8$	0.3 [0.2–0.6]	0.3 [0.2–0.4]	0.2 [0.1–0.4]	ns
$8 \leq f < 12$	1.5 [0.7–3.1]	1.2 [0.7–2.0]	1.2 [0.6–2.2]	ns
$12 \leq f < 40$	0.6 [0.3–1.3]	0.5 [0.3–0.9]	0.5 [0.3–0.9]	ns

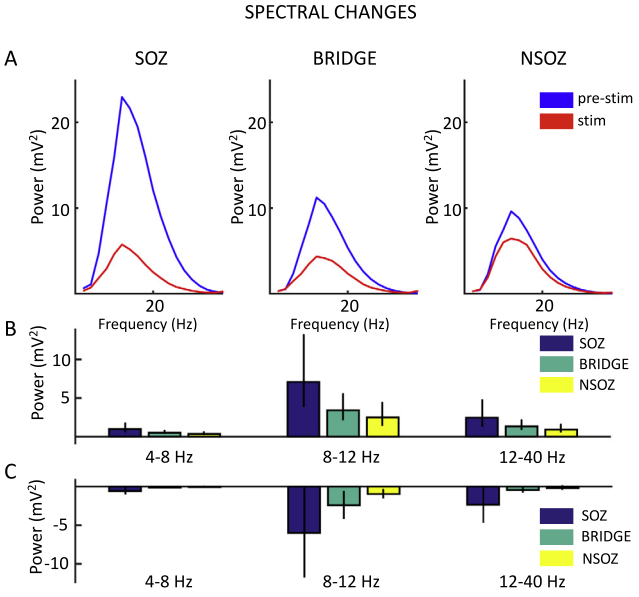

Fig. 1. Stimulation effects on spectrum of ECoG activity. (A) Panels show average power for each recording site group. SOZ (n = 24) to the left, BRIDGE (n = 43) in the middle and NSOZ (n = 45) to the right. Blue line depicts power during pre-stimulation and red depicts power during stimulation. (B) Mean power in frequency bands 4–8, 8–12 and 12–40 Hz for recording site groups during pre-stimulation. The 95% confidence interval of the mean is given by a black bar next to each column. (C) The change in power after onset of stimulation in the frequency bands 4–8, 8–12 and 12–40 Hz for the three recording site groups (SOZ-blue, BRIDGE-green, NSOZ-yellow). The 95% confidence interval of the mean is given by a black bar next to each column. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.5. Correlation between spike and background activity.

Spike-rate and power of the background activity decreased following onset of cortical stimulation while spectral coherence increased. Electrodes at recording site SOZ showed a significant positive correlation when comparing changes in spike-rate (stimulation – pre-stimulation spike-rate) with changes in background power (stimulation – pre-stimulation background power), Fig. 5. Changes in spectral coherence correlated negatively with changes in spike-rate (Pearson's r, $p < 0.01$) for recording site group SOZ (n = 24) and BRIDGE (n = 43) but did not correlate with change in spectral power at any of the recording site groups (SOZ, BRIDGE and NSOZ). Change in spike morphology (spike amplitude and spike duration) correlated with change in spectral power (SOZ, BRIDGE) and change in spike-rate (Pearson's r, $p < 0.01$) Fig. 5.

4. Discussion

Chronic subthreshold cortical stimulation is a novel technique for treatment of drug resistant epilepsy when epilepsy surgery is not an option often due to the epileptogenic focus being located in or near eloquent cortex. Clinical studies have shown promising outcomes with seizure reduction and improved quality of life without serious adverse effects (Lundstrom et al. 2016, Kerezoudis et al., 2018). Here, data were analysed from 2 Hz electrical stimulation applied to the SOZ via a 4 × 4 subdural grid of intracranial electrodes. We found that the stimulation had a neuromodulating effect on the electrophysiology of the cortex in the stimulated regions. Primary results were that stimulation led to a: (1) Decrease in spectral power (4–40 Hz) and increase in background coherence for all recording site groups: SOZ, BRIDGE and NSOZ, (2) Decrease in spike rate that was more pronounced in the SOZ than NSOZ, and (3) Decrease in spike amplitude for the SOZ. There was a positive correlation between the reduction in spike-rate and reduction in spectral power and increase in coherence.

The mechanisms of induced electrophysiological changes due to continuous electrical stimulation over the cortex are not fully understood. However, we found that spontaneous activity and spiking activity was attenuated by stimulation. We found the greatest changes over the seizure onset zone or adjacent regions. Reduction in spike-rate and reduction in background power has been described previously (Yamamoto et al., 2002, Kinoshita et al., 2005). Studies investigating changes in background power have investigated changes post-stimulus over the seizure onset zone and non-epileptic areas during ongoing stimulation and we

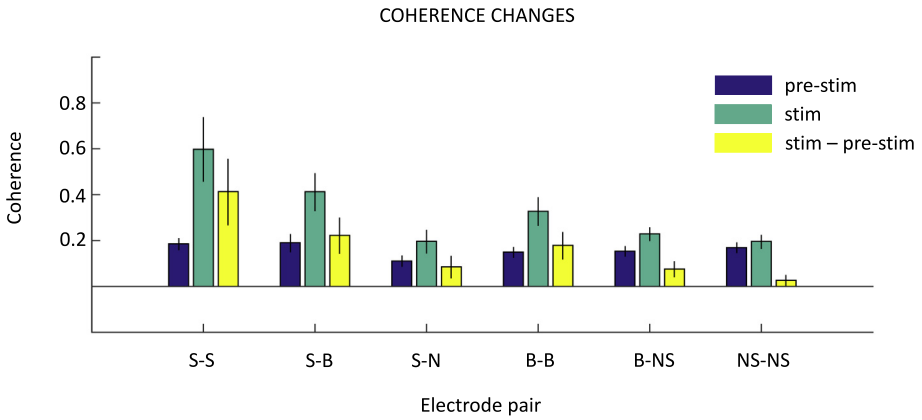

Fig. 2. Stimulation effects on coherence of ECoG activity. Average coherence (Pearson's r) was calculated between electrodes for each recording site group (SOZ n = 24, BRIDGE n = 43 and NSOZ n = 45) for pre-stimulation, stimulation and the change between stimulation and pre-stimulation data. The 95% confidence intervals are given as black lines. Data was first transformed using a logarithmic transformation before estimating 95% confidence intervals. See Table 2 for precise information regarding correlation and statistical significance. S = SOZ recording site group, B = BRIDGE recording site group, N = NSOZ recording site group.

Table 3
Spectral coherence (within 4–40 Hz) during pre-stimulation and stimulation. Mean and 95% confidence intervals are given for pairs of electrodes from different recording site groups. Changes between recording site groups for stimulation and pre-stimulation (p-values) were estimated using ANOVA after logarithmic transformation.

Recording site group pair	Prestimulation	Stimulation	p-value
SOZ-SOZ	0.19 [0.16–0.21]	0.60 [0.46–0.73]	$p < 0.001$
SOZ-BRIDGE	0.19 [0.15–0.23]	0.41 [0.33–0.50]	$p < 0.001$
SOZ-NSOZ	0.11 [0.09–0.13]	0.19 [0.15–0.25]	$p < 0.05$
BRIDGE-BRIDGE	0.14 [0.13–0.17]	0.33 [0.27–0.39]	$p < 0.01$
BRIDGE-NSOZ	0.15 [0.13–0.18]	0.23 [0.20–0.26]	$p < 0.05$
NSOZ-NSOZ	0.17 [0.15–0.19]	0.19 [0.17–0.23]	$p < 0.05$

see in this study similar but greater changes in background power and spike rate. Spike-rate and background power were also closely correlated with a seemingly linear fit when comparing the induced change in spectral activity and spike-rate. The greatest effects were seen in the alpha band over all three electrode regions (SOZ, BRIDGE and NSOZ) during stimulation. Alpha band activity in deeper layers of the cortex have been shown to modulate activity in more superficial layers of the cortex (Spaak et al., 2012, Moran et al., 2013, Maier et al., 2010). This would suggest that the stimulation process modulates directly or indirectly the deeper cortical layers which in turn modulate superficial layers. Previous studies on electrical stimulation of the cortex to reduce seizure activity have investigated the causal mechanisms in-vivo and in-vitro. Several different paradigms have been investigated with different suggested modes of action. Direct Current (DC) hyperpolarizing has shown reproducible effects on attenuation of seizure generation in-vitro and in-vivo (Ghai et al., 2000, Gluckman et al., 1996). Moreover, these paradigms have been developed into an adaptive seizure control paradigm which has shown seizure reduction effect in-vitro (Gluckman et al., 2001). Further study is required to investigate if the stimulation process in the present study resulted in hyperpolarization of pyramidal cells causing a change in their background activity resulting in a modulation of cortical column activity. This would require the measurement of the extracellular potentials using microelectrodes before and after stimulation. Paradigms using non-invasive repetitive TMS have suggested physiological/synaptic changes involving NMDA-receptors where repeated stimulation results in long term depression like changes (Huang et al., 2007). Furthermore, the time constant of the NMDA-receptor is in the range of 100 ms indicating that its resonant oscillatory activity lies in the range of alpha band activity which showed greatest attenuation during electrical stimulation (Moran et al., 2011). Moreover, it might be possible that changes seen in this study were caused by several different electrophysiological processes.

The spontaneous activity recorded by the ECoG subdural electrodes is dominated by the postsynaptic currents induced in the dendritic trees of cortical pyramidal cells (Niedermeyer, 2005). This activity can be considered a driving force on the pyramidal cells causing the generation of action potentials. As the subdural ECoG electrodes view a volume of approximately 1 cm^3 (Hill et al., 2012), this driving force would be a mesoscopic approximation of the local pyramidal driving force and is often assumed to be the net effect of afferent inputs from elsewhere on the pyramidal cells of a given cortical column. In the present study the above was augmented with continuous 2 Hz electrical stimulation (Jansen and Rit, 1995; Marreiros et al., 2008, Bastos et al., 2012). This input will feed through the neural circuit of the cortical column reaching the dendritic tree of the pyramidal cells where the spectral response will be altered depending on the time constants of the intervening synapses. We suggest that a modulation of the input in the cortical columns (resulting in a decreased gain of the input) caused a decrease in epileptiform spike-rate as measured from the pyramidal dendritic tree. The mechanism of this modula-

Table 4
Spike rate (min^{-1}, mean and 95% confidence interval) measured at different recordings sites (SOZ, BRIDGE and NSOZ). There was a significant difference between the three groups when comparing spike rate at pre-stimulation (p-value was calculated using ANOVA after logarithmic transformation of the data).

	Recording site group			
	SOZ (N = 24)	BRIDGE (N = 43)	NSOZ (N = 45)	p-value
	Pre-stimulation			
Spike-rate (min^{-1})	4.8 [2.6–8.8]	3.0 [1.6–5.7]	1.5 [0.8–3.1]	0.01
	Stimulation			
Spike-rate (min^{-1})	0.05 [0.02–0.15]	0.07 [0.02–0.21]	0.09 [0.03–0.3]	ns

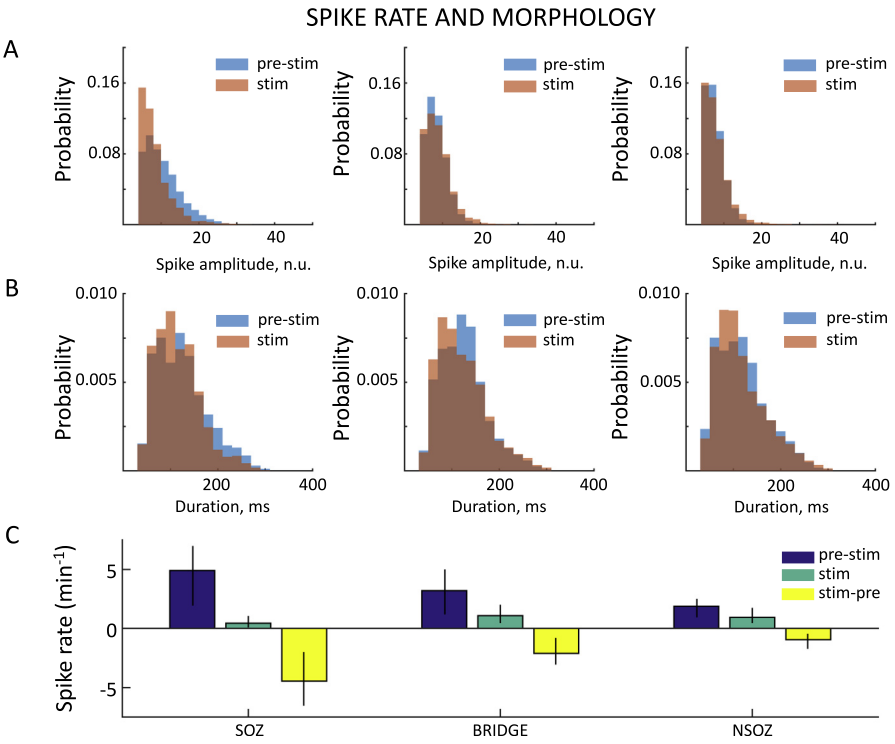

Fig. 3. Stimulation effects on spike rate and morphology. (A) Probability distribution of spike amplitude for recording site group SOZ (n = 24) to the left and BRIDGE (n = 43) in the middle and NSOZ (n = 45) to the right. Pre-stimulation is given in blue and stimulation in red. (B) Probability distribution of spike duration for electrode group SOZ (n = 24) to the left, BRIDGE (n = 43) in the middle and NSOZ (n = 45) to the right. Pre-stimulation is given in blue and stimulation in red. There were no significant changes after stimulation. (C) Average spike-rate measured at the three recording site groups (SOZ, BRIDGE and NSOZ) during pre-stimulation (blue), stimulation (green) and difference between the two states conditions (stimulation – pre-stimulation). There was a significant difference in spike-rate when comparing pre-stimulation data between the three groups of electrodes ($p < 0.01$, ANOVA). Furthermore, all three groups showed a significant reduction in spike-rate after stimulation (t-test, $p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

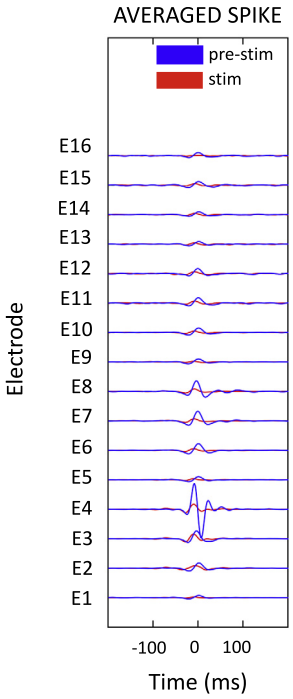

Fig. 4. Averaged spike morphology from pre-stimulation and stimulation recording for patient 1, indicating a clear reduction in spike amplitude. Blue – pre-stimulus and red – stimulus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tion is speculative at this moment but previous studies have suggested hyperpolarising changes in membrane potential (Ghai et al., 2000; Gluckman et al., 1996). Analysis of spike morphology did show that continuous stimulation did affect amplitude and duration of spikes. This further constricts our hypothesis of the causal relationship between background activity and spike (epileptiform) activity, where increased background activity might increase the probability of spikes, i.e. increases spike rate, and also change the mechanism of the spike generation (as seen by the changes in spike morphology).

Stimulation increased spectral coherence over all recording site groups and was negatively correlated to spike-rate but did not show any relation to spectral power. This suggests that spectral power and coherence are two independent factors affected by stimulation. We found three main factors that were affected by stimulation, one of them spike rate. The underlying mechanism of these changes cannot be delineated in this study. However, they do allow for the generation of a hypothesis on the mechanism involved in these changes. The primary effect of CSCS could be on any one of these factors with secondary effects on the other two components. With regard to the possible electrophysiological mechanisms and the complex dynamics they involve as discussed above, a plausible explanation could be a primary effect on both spectral power and coherence and secondary effects on spike rate. The mechanisms for this would be increased perturbation of stable systems, where each region sampled by an ECoG electrode would be represented by a cortical column (stable system) interconnected to the other sampled regions. Further modelling work might shed further light on the relation between spectral coherence and spike rate, which is not evident, while the relation between increased perturbation and spike rate is less disputable.

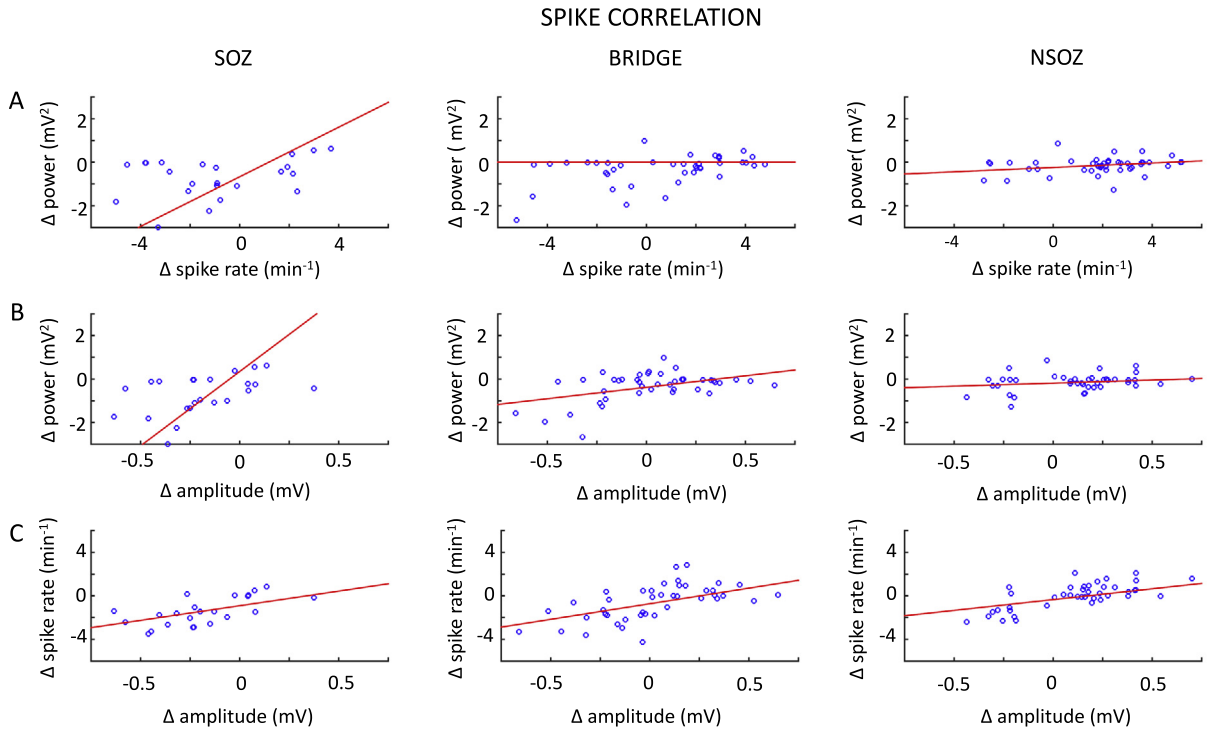

Fig. 5. Relation between changes induced by stimulation on spectral power, spike-rate and spike amplitude. (A) Scatterplot between change in spike-rate and total power of the full band width 4–40 Hz for recording site group SOZ (left, n = 24, Pearson's r = 0.5, p < 0.05) BRIDGE (middle, n = 43, non-significant correlation) and NSOZ (right, n = 45, non-significant correlation). (B) Scatter plots between change in spike amplitude and total power of the full band width 4–40 Hz for recording site group SOZ (left, n = 24, Pearson's r = 0.8, p < 0.0001) BRIDGE (middle, n = 43, Pearson's r = 0.5, p < 0.001) and NSOZ (right, n = 45, non-significant correlation). (C) Scatter plots between change in spike rate and amplitude for electrode group SOZ (left, n = 24, Pearson's r = 0.7, p < 0.0001), BRIDGE (middle, n = 43, Pearson's r = 0.6, p < 0.0001) and NSOZ (right, n = 45, Pearson's r = 0.6, p < 0.0001). The line of best fit is drawn in red for each scatter plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Spike morphology showed strong correlations with spike rate and showed similar relations with the other parameters (spectral power, coherence, etc.) as spike rate did. Spike morphology is generated at a later time point than the initial spike generation so it is assumed that spike-rate is not causally dependent on spike morphology. However, morphology of spikes is dependent on the characteristics of the system generating them, which could be used in understanding changes in the system induced by stimulation.

Prior studies have examined the effect of chronic cortical stimulation on spike rate (Velasco et al., 2000; Lundstrom et al., 2016, 2018) We use a relatively simple spike detector (Barkmeier et al., 2012) that has the benefit of straightforward criteria for detecting putative spikes, although some spikes may not be epileptiform (Lundstrom et al, 2018). One of the challenges of spike detection is dealing with stimulus artifact. Due to dynamic thresholding intrinsic to this method of spike detection, relative thresholds are higher when stimulus artifacts have high amplitudes. This affects all contacts similarly, and the total number of spikes detected during stimulation should be uniformly underestimated. Conversely, stimulation does lead to background suppression, which tends to decrease detection thresholds. In the end, we analyzed the data with several methods, including a method that completely removed spiking artifacts prior to spike detection, and found qualitatively similar results regardless: stimulation leads to decreased spiking and this decrease is greater for SOZ compared to NSOZ contacts.

In this study we analyzed the acute changes of stimulation and not its chronic effects. Stimulation will affect the physiology and function of nearby tissue but also more distant regions which network with the stimulated region (Sunderam et al., 2010). The stimulation would hopefully reduce clinical seizures (in intensity and frequency) but could also have other adverse or beneficial effects on cognitive function. These clinical changes would need to be analysed in a separate study. However, analysis of the acute changes are of great importance as these effects are those used to tune the different parameters of the stimulation for optimization or used for adaptive (stochastic) control of seizure activity (Gluckman et al., 2001). In this study we did see changes in the spontaneous activity of the cortex and not only in the rate of interictal spikes (possible proxy for seizure frequency) i.e. evidence of changes in both epileptic and non-epileptic physiology/function.

This study has revealed a close relation between power of background cortical activity and spike rate (assumed to be a proxy of seizure severity). Certain patients will have sparsely occurring seizures which requires a more frequently occurring electrophysiological proxy such as interictal spikes. However, even these could be sparse for which reason a proxy that is present continuously might be of great importance in control strategies for epilepsy especially adaptive control (Berényi et al., 2012; Sunderam et al., 2010). We suggest a causal dependency of spike rate on background activity but further studies are required to confirm the relation between these changes in background power and seizure occurrence during stimulation. Once this causal dependency has been confirmed it would be possible to tune the stimulation parameters (e.g. intensity and frequency) so as to increase the reduction in background power. This would then cause an optimal reduction in spike-rate and hence a maximum reduction in seizure frequency. This would be an important improvement in the practical application of CSCS where the stimulating parameters could be set to be, at least partly, patient specific. However, further studies are required where seizure frequency is measured during different stimulation settings to validate the method.

In the article on seizure initiation by Jirsa (2013), variations in slow time variables are considered to be one of the main factors contributing in pushing a normal brain state into seizure initiation via a transition state, or bifurcation. It is conceivable that the same fluctuations in variables resulting in seizure development also contribute to the generation of interictal transient activity. A decrease in transient activity, as seen in our results, might thus reflect a general reduction of such brain activity fluctuations that might result in seizure development. Thus, it is reasonable to propose that the stimulation exerts its action by increasing the overall brain state stability.

5. Conclusion

Continuous electrical stimulation over epileptic tissue has been shown in animal and human studies to reduce seizure frequency and epileptic activity. The mechanism of this effect is still unknown, however, we have seen in this study several electrophysiological parameters affected by stimulation with an internal substructure of dependence that we could partly uncover. An understanding of the mechanisms of this internal substructure of relations could help in understanding the mechanism of CSCS in epilepsy. We hypothesize that reduced spike rate is independently related to spectral amplitude and coherence. Future work could test this hypothesis using computational modelling of spike generation under the influence of electrical stimulation. With an improved understanding of continuous electrical stimulation better stimulation paradigms might be developed for improved suppression of seizure frequency.

Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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