Intracranial EEG Power Changes Resulting from Responsive Brain Stimulation in Epileptic Patients

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Abstract

Purpose
To determine if responsive neurostimulation alters the spectral power of intracranial EEG following detection of epileptiform activity.

Methods
Electrocorticographic (ECOG) segments were analyzed from 31 subjects implanted with a responsive neurostimulation system. During the time period analyzed, medications, epileptiform event detection settings, and stimulation settings remained constant for each subject. ECOG segments were divided into stimulation and control (no stimulation) groups. In the stimulation group one or two brief bursts (100 ms each) of high frequency stimulation (100-200 Hz) was delivered immediately after epileptiform event detection. In the control group, no stimulation was delivered. Power spectral density (PSD) was calculated for each 2-second window before and after event detection at the same time points for the stimulation and control groups. PSD differences were calculated for each ECOG segment by subtracting the pre-event PSD from the post-event PSD. The differences were then averaged for the control and stimulation groups.

Results
84% of subjects showed a lower average power difference in their stimulation datasets versus in the control. Across all subjects the stimulation group had an average reduction in total power of 12.49 $\mu V^2/Hz$ versus the control group reduction of 5.10 $\mu V^2/Hz$. This difference was significant ($p=0.0007$, two-tail paired t-test).

Conclusions
Responsive neurostimulation results in an acute reduction in the signal power of the ECOG in epileptic patients.

Keywords: brain electrical stimulation, responsive neurostimulator, power spectral analysis, neurostimulation, implantable device, intracranial EEG signal, postictal inhibition

Introduction

Epilepsy is a neurological disorder affecting around 50 million people world-wide (Jallon 1994). Treatment of epilepsy with antiepileptic medications, resective surgery, and open-loop chronic stimulation of the vagus nerve is well established. However, with these therapies as many as 50% of epileptic patients continue to have seizures, adverse medication side-effects, or both (Brown and Holmes, 2001;Morrell, 2006). The need for new treatments in epilepsy that target patients with medically intractable partial onset seizures who are not considered candidates for resective surgery has driven the development of state-of-the-art technologies utilizing direct brain stimulation, however there are not too many studies analyzing the acute effects of electrical stimulation in human subjects.

Two main modalities of brain stimulation are well known in the literature. Open-loop continuous or scheduled stimulation (Cooper et al. 1973; Cooper et al. 1977; VanBuren et al. 1978; Wright et al. 1984; Velasco et al. 2000; Velasco et al. 2005), and closed-loop responsive stimulation delivered in response to detected epileptiform discharges (Esteller et al. 2003; Kossoff et al. 2004; Fountas et al. 2005; Morrell et al. 2011);. In the past few years two technologies have come to market based on each of these stimulation modalities. The Medtronic Intercept™ Epilepsy Control System that provides open-loop stimulation of the anterior nucleus of the thalamus (Fisher et al. 2010), which is approved by numerous regulatory bodies outside of the U.S.; and the NeuroPace RNS® System that provides closed-loop responsive stimulation to the seizure focus when abnormal epileptiform activity is detected (Morrell et al. 2011; Heck et al. 2013), and is approved in the U.S.

The NeuroPace RNS System has become a treatment option for persons with medically-refractory partial onset seizures that arise from one or two epileptogenic foci. Results from a multi-center, randomized, sham-stimulation controlled pivotal study show that subjects receiving responsive stimulation have a significant reduction in seizures compared to those with no stimulation (Morrell et al., 2011). During the open-label period of the study, when all subjects had the opportunity to receive responsive stimulation, seizure reduction continued to improve. The median percent reduction in seizures was 44% at 1 year and 53% at 2 years post-implant compared to the pre-implant baseline (Heck et al., 2014).

Despite the clinical success of responsive stimulation, the underlying mechanism of responsive stimulation is not completely understood. A few acute studies have reported that brief bursts of electrical stimulation applied to the cortex during an after-discharge or at the onset of a seizure can disrupt the activity, suggesting that one mechanism of responsive brain electrical stimulation may be due to disruption of synchronous activity (Penfield and Jasper, 1954; Lesser et al., 1999; Kossoff et al., 2004; Osorio et al., 2005).

In this retrospective study, we aim to better understand the effects of responsive stimulation on the cortex by quantifying the change in the total spectral power of the ECOG activity as well as the change in power within different frequency bands immediately after responsive stimulation.

We investigated and quantified the acute effects of high frequency responsive neurostimulation in the power of ECOGs during detected seizure onsets or epileptiform discharges, aiming to

provide additional insight on the acute changes that may take place after responsive neurostimulation.

Methods

ECOG data were analyzed in subjects who were participating in the RNS® System (NeuroPace, Inc., Mountain View, CA) pivotal clinical investigation, which was multi-center, double-blind, randomized, sham-stimulation controlled investigational study of responsive stimulation as an adjunctive treatment for adults with medically intractable partial onset seizures originating from 1 or 2 foci (Morrell et al. 2011).

The RNS System includes a cranially implanted programmable neurostimulator, which is connected to 1 or 2 depth and/or cortical strip leads placed at the seizure focus (Sun et al., 2014). The neurostimulator continuously senses ECOG through the leads and provides responsive electrical stimulation through the leads when it detects abnormal patterns of activity. Physicians tailored detection settings to each subject based on review of both ictal and interictal ECOG data. Allowable stimulation frequencies ranged from 1–333 Hz, with burst durations of 10ms-5000ms, however stimulation was typically programmed at 100Hz or 200Hz, delivered in 100-200ms bursts, with charge densities typically in the range of 1-6 $\mu C/cm^2$ per phase based on subject tolerance and clinical response.

The neurostimulator can also be programmed to store ECOG segments based on triggers such as detection, responsive stimulation, or time of day. ECOG segments are bandpass filtered from 4 to 90 Hz using an analog anti-aliasing filter and digitized with a sampling rate of 250 Hz. Although storage in the neurostimulator is limited to about 6 minutes (per each of the four channels) at any time, ECOG segments stored in the neurostimulator can be transferred to and permanently stored in a centralized database using a programmer or a remote monitor.

The motivation for this analysis was to assess whether there is an acute effect on the ECOG signal power due to responsive stimulation. To accomplish this, a comparison of the ECOG signal power before and after detection of epileptiform events was conducted for stimulation and control (no stimulation) conditions.

Data

The ECOG data used in this analysis were identified and reviewed retrospectively; from the pivotal trial during which all the ECOG data were recorded. In order to conduct a controlled experiment and minimize potential biases, the subject ECOG data selected for inclusion in this analysis were required to meet the following rigorous criteria:

1) ECOG segments were recorded at least 8 weeks post-implant to minimize potential biases due to surgical recovery, edema resolution or tissue encapsulation.
2) Anticonvulsant medications were unchanged during the analysis period.
3) Detection and stimulation settings were unchanged during the analysis period to ensure the same types of events were detected in all segments analyzed.
4) Subjects must have a minimum of 20 ECOG segments during each analysis period (with stimulation disabled and enabled).

41 subjects met criteria 1-3. Ten of these forty-one subjects did not meet the fourth criterion mentioned above as they had fewer than 20 data samples for each analysis period. On average, these 10 subjects had 8 ECOG segments in the stimulation period (ranging from 2-16). It is shown in the results and discussion that the exclusion of these ten subjects did not bias the results of the analysis. Subjects analyzed had an average of 309 (range: 29-1105) and 193 (range: 22-2528) ECOG segments in the control and stimulation datasets, respectively. The ECoG data used spanned a post-implant average time of 5.8 months (median: 5.6, range: 5.3 – 7.7).

Analysis

To analyze power changes before and after detection of epileptiform events (with and without responsive stimulation), the ECOG segments were divided into windows of 2-second duration before and after detection of epileptiform events as shown in Figure 1. Three boxes depict 3 consecutive 2-second windows for control (1a) and stimulation (1b) ECOG segments. The first 2-second window precedes epileptiform event detection (red arrow) and will be referred to as the pre-event window. The 2-second window immediately following detection was not analyzed because when stimulation is enabled the amplifier is briefly turned off and a transient polarization artifact is present when the amplifier is turned back on. These distortions make immediate comparison following stimulation impossible. After 2-seconds the amplifier has stabilized, so the post-event segment was defined as the 2-second window that begins 2 seconds after detection.

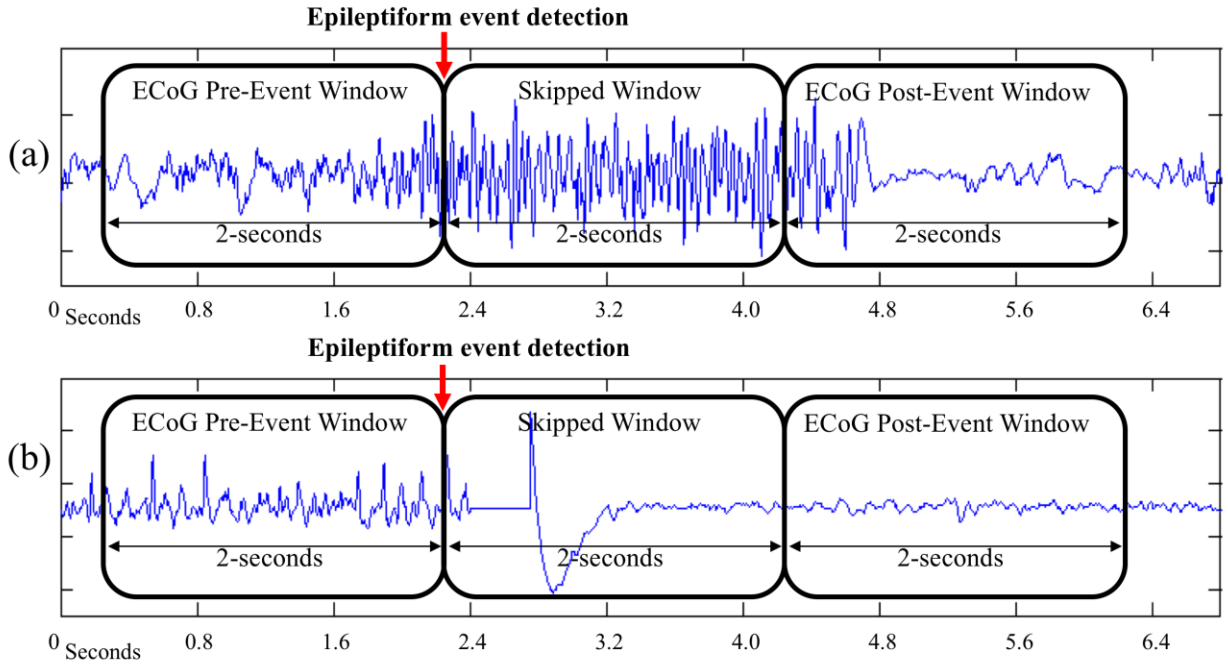

Figure 1: ECOG Analysis Window Definitions

The power spectral density (PSD) was computed for all pre- and post- event windows using Welch's method (Welch 1967) with a moving window length of 64 points, 50% overlap, and a 256-point FFT.

To calculate the difference in power between the pre- and post- event windows, the pre-event PSD was subtracted from the post-event PSD for each frequency bin. The PSD differences were then averaged across all events and for all frequencies for each subject to calculate average power differences for the stimulation and control datasets. Equation (1) summarizes the averaging conducted for treatment and control dataset of each subject:

$$Avg\ Power\ Difference = \frac{1}{M}\sum_{n}\frac{1}{N}\sum_{k}\left(postPSD(n,k) - prePSD(n,k)\right) \qquad (1)$$

where:

n is the ECOG event number
k is the frequency bin number
N is the total number of frequency bins (129)
M is the total number of ECOG events analyzed
prePSD is the power spectral density in the pre-event window
postPSD is the power spectral density in the post-event window

A paired t-test was used to compare the control vs stimulation sets across all subjects.

Results

Of the 191 subjects implanted in the RNS System Pivotal trial, 31 subjects had ECOG data that met the criteria outlined for this study. All 31 subjects had been randomized to the sham group in the pivotal study, which is expected given the criteria that subjects must have at least 20 ECOGs stored with no stimulation enabled after waiting 8 weeks post-implant.

Figure 2 presents the average power differences (equation 1) across all events for each subject. Blue bars correspond to the control dataset, red bars correspond to the stimulation dataset, and the black dots correspond to the PSD differences of the averaged power change in each condition (stimulation enabled minus control) for every subject. The blue and red horizontal lines show the average PSD change for the control and stimulation datasets respectively. The averaged PSD differences were lower in the stimulation dataset than the control dataset in 83.9% (26 out of 31) of the subjects. Across all subjects, the stimulation events had an average PSD reduction in total power of 12.49 $\mu V^2/Hz$ versus an average PSD reduction of 5.10 $\mu V^2/Hz$ in the control events. This corresponds to a difference in the average PSD reduction between stimulation and control events of 7.39 $\mu V^2/Hz$, which is significant at $p \leq 0.001$ (two-tail paired t-test) with a 95% confidence interval range of 3.58-11.20 $\mu V^2/Hz$. If all 41 subjects who met criteria 1-3 are analyzed, the stimulation events had an average PSD reduction in total power of -11.98 $\mu V^2/Hz$ compared to -3.97 $\mu V^2/Hz$ in the control events. This results in a difference in the power reduction of 8.01 $\mu V^2/Hz$ between stimulation and control events, which is significant at $p \leq 0.0001$ (two-tail paired t-test) with a 95% confidence interval from 4.54 to 11.48 $\mu V^2/Hz$.

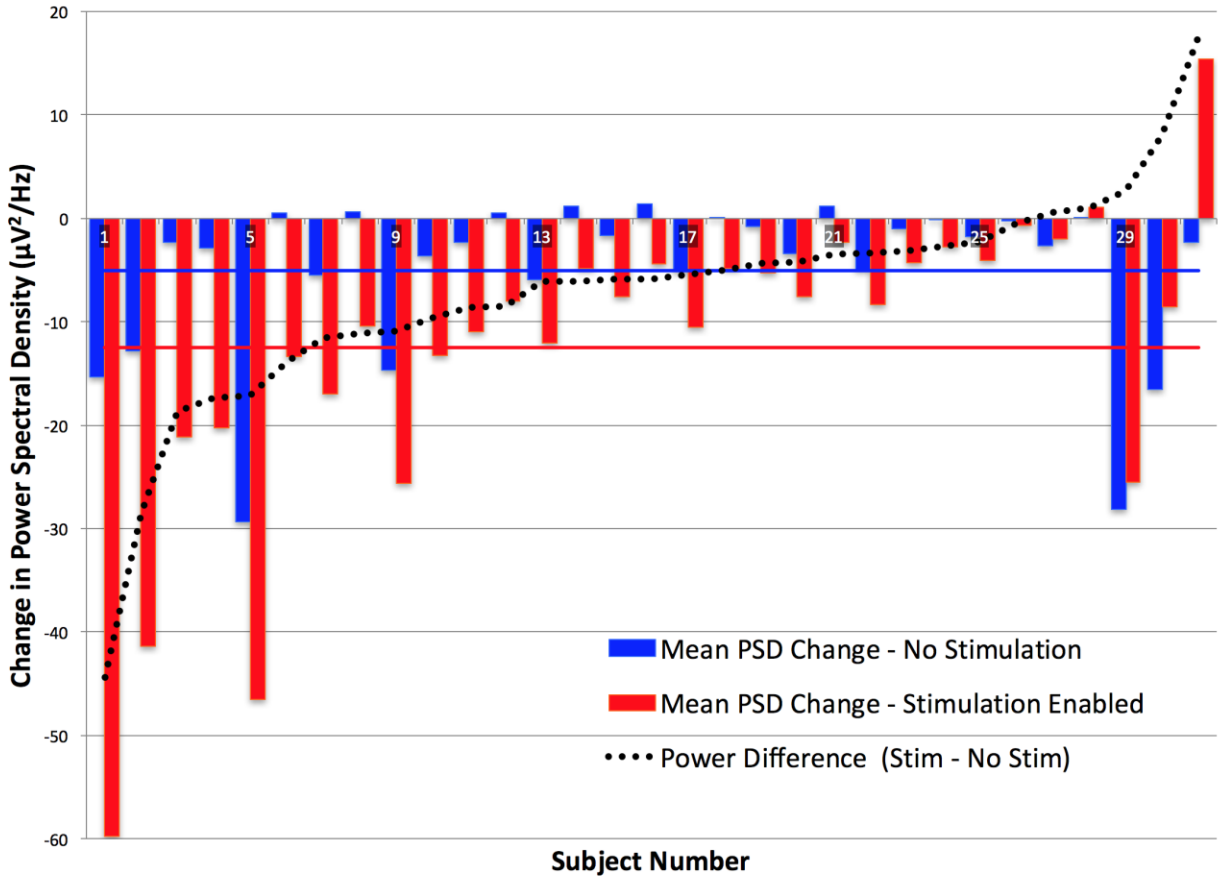

Figure 2: Average power difference for each subject in the treatment and control datasets

It is of interest to note that most of the control datasets also exhibited a decrease in power after detection. This is understandable since most epileptiform discharges are brief and only occasionally evolve into an electrographic seizure, so the tendency is for the power to decrease. However, this tendency was enhanced when stimulation was applied with the average power reduced by a factor of 2.45 compared to the control.

As part of this study, the changes in the power spectral content pre and post event were also analyzed. Figure 3 shows the average PSD differences for four subjects for control (blue) and stimulation (red) datasets. It was observed that there was a trend towards enhanced power reduction in the 5-20 Hz range following stimulation compared to the control dataset.

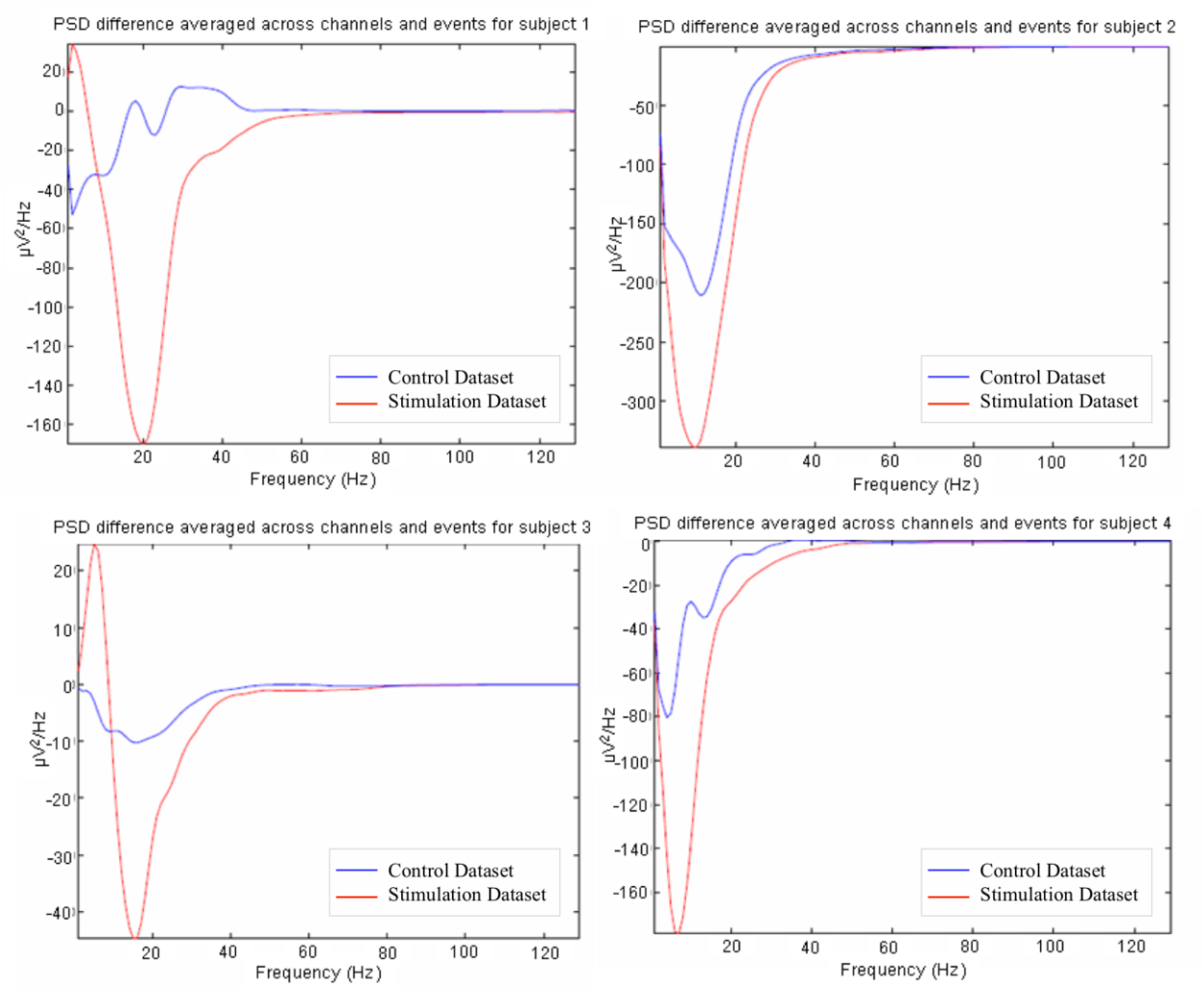

Figure 3: Average Power Difference for Subjects 1-4 in control and stimulation datasets

To further examine this effect, the averaged PSD differences from all 31 subjects underwent a second averaging to determine the mean PSD difference across all subjects. Figure 4 shows the mean PSD difference for all subjects for the stimulation (red) and control (blue) datasets. The PSD difference spectra for the stimulation condition show a larger drop in the 0-20 Hz range.

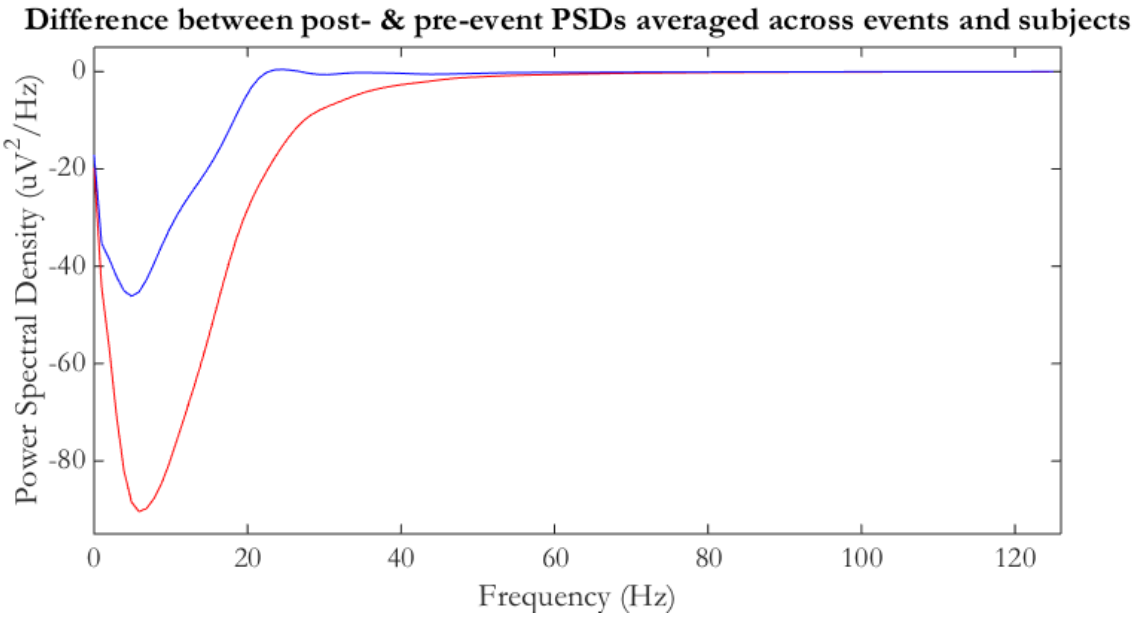

Figure 4: Power Difference in the frequency domain for each dataset averaged across all subjects

Discussion

The exploration of electrical brain stimulation for epilepsy started with Penfield and Jasper's work (Penfield and Jasper 1954). They observed an inhibition stage following stimulation induced afterdischarges that was characterized by lower excitability and slowing of the electrocorticographic activity. In 1983, Psatta applied responsive electrical stimulation when interictal spikes were detected in the caudate nucleus (CN) of epileptic cats and observed spike depression that was not obtained when random stimulation was applied to the CN or when contingent stimulation was applied to other structures such as thalamus, hypothalamus, and mesencephalic recticular formation (Psatta 1983). Takebayashi observed that electrical stimulation can suppress focal cortical clinical seizures similarly to lesioning of ANT (Takebayashi et al. 2007). Benazzouz and his colleagues (Benazzouz et al. 1995) described a post stimulation refractory period, Motamedi et al demonstrated that responsive stimulation shortens or terminates electrographic discharges (Motamedi et al. 2002), and Kossoff et al showed that responsive neurostimulation can alter and suppress electrographic seizures and improve baseline EEG, with no major side effects (Kossoff et al, 2004). Lee et al. (Lee et al. 2003) and Lado's group (Lado et al. 2003) reported post stimulation inhibition of neuronal firing in rats. Wagenaar et al showed that rapid stimulation of high density cultures reduces "burstiness" (Wagenaar et al. 2005). Sohal and Sun (Sohal and Sun, 2011) showed that intracranial responsive neurostimulation acutely suppresses long-range phase locking synchrony between gamma-frequency rhythmic activities in intracranial ECoG recorded from different locations. Benabid's group compared high frequency stimulation (HFS) and lesion effects and found that HFS may induce an inhibition-like process (Benabid et al. 2005). In Parkinson's disease HFS of the subthalamic nucleus specifically attenuates the beta band (Wingeier et al. 2006). All these studies coincide in reporting a quiet activity period following high frequency stimulation; however, they suggest different inhibition mechanisms as the cause of this post stimulation inhibition. The goal of this analysis was to determine the acute effects of high

frequency responsive neurostimulation on the power of the ECOG during detected seizure onsets or epileptiform discharges to provide additional insight on the mechanisms that lead to the post stimulation inhibition.

This analysis demonstrated an inhibition effect in the brain signal following responsive stimulation and characterized the reduction in the frequency domain. There was a greater reduction in total power in the ECOG signal with responsive stimulation as compared to the control condition (detection with no stimulation) in 83.9% of subjects. Across all 31 subjects, average signal power was significantly reduced ($p \leq 0.001$) with responsive stimulation (-12.49 $\mu V^2/Hz$) compared to the control condition (-5.10 $\mu V^2/Hz$). Furthermore, this same significant reduction in power ($p \leq 0.0001$) was equally demonstrated by the data from all 41 subjects who met the initial inclusion criteria (criteria 1-3 outlined above) with responsive stimulation (-11.98 $\mu V^2/Hz$) compared to the control condition (-3.97 $\mu V^2/Hz$), and an average reduction in power of -8.01 $\mu V^2/Hz$. The power reduction quantified in this analysis may be descriptive of cortical substrate changes responsible for the reduction in seizure frequency in the double-blinded randomized study described in (Morrell et al. 2011).

Spectral variation in power reduction with stimulation was most pronounced for frequencies below 40Hz. Reductions of 30 $\mu V^2/Hz$ or more occurred in the 0-20Hz band. This suggests that brief bursts of high frequency (100-200 Hz) responsive stimulation may acutely reduce the ability of neuronal tissue to synchronize, and this effect seems to be more pronounced for ECOG frequencies between 0-20Hz.

This analysis also characterized post-event power attenuation in the control condition that is milder and mainly occurs for frequencies lower than 20Hz. The post-event energy reduction is less pronounced in non-stimulated events and suggests an intrinsic mechanism of attenuation that may be triggered when abnormal epileptiform activity is present. For frequencies greater than 20Hz the energy decrease was small or increased slightly. We can conjecture that this low frequency power reduction is possibly an intrinsic "calming" mechanism restoring normal cell activity after the epileptiform event. Due to inherent data limitations in this retrospective study, we could not analyze whether there was a relationship between the power reduction and the seizure frequency changes in the subjects studied during the control (stimulation disabled) and treatment (stimulation enabled) periods. These time intervals were short in many instances, particularly for the treatment phase considered, mainly because therapy or detection parameters were changed within a few weeks of enabling stimulation. Only 7 of the 31 subjects had ECOG data spanning at least 4 weeks for each condition.
It is important to clarify there are limitations particular to this study that include the presence of potential biases regarding the timing for each condition analyzed and the types of ECOGs stored by the RNS® system. When considering the time delay between the control and treatment conditions, only patients in the sham group of the Pivotal investigation have control events meeting our study inclusion criteria, and in all these subjects, ECOGs in the control period preceded ECOGs in the treatment period. It is not clear if this time difference could have an impact in our results. The post-surgical effect reported in the literature [xx] decreases over time, therefore, its impact will be lesser in the stimulated events. The other potential bias comes from the type of ECOGs stored by the system, either epileptiform activity, seizure onset, or early onset events. Therefore, this study does not address whether the results observed are specific to

responsive stimulation or what would happen with the average power if stimulation is delivered during interictal times where no epileptiform activity is present.

This analysis demonstrates the use of spectral domain averaging techniques to unmask frequency specific power changes not apparent through ECOG review. These methods may help in understanding the mechanisms that operate during postictal periods and during electrical brain stimulation.

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Acknowledgement

The authors thank Felice Sun for the time and effort provided during her in-depth review and outstanding feedback to this work.