Responsive Neurostimulation Suppresses Synchronized Cortical Rhythms in Patients with Epilepsy

Vikaas S. Sohal, MD, PhD[a,b,c,*], Felice T. Sun, PhD[d]

KEYWORDS

• Synchrony • Gamma rhythms • Phase locking • Stimulation • Neocortex • Hippocampus

Well established as a modality for the treatment of Parkinson disease, deep brain stimulation and other direct stimulations of neural tissues are increasingly being investigated to treat several neurologic and psychiatric conditions, including epilepsy (for review see[1]), depression,[2] obsessive-compulsive disorder,[3,4] and Tourette syndrome.[5] Despite this increasing potential clinical utility, the mechanisms by which deep brain stimulation and other forms of neurostimulation, including electroconvulsive therapy, transcranial magnetic stimulation, and vagus nerve stimulation, modulate neuronal activity remain unknown. Deep brain stimulation and other forms of intracranial neurostimulation require mechanistic explanation at multiple levels: (1) how does neurostimulation affect directly stimulated neurons and their processes, (2) how do these direct local effects of stimulation acutely affect patterns of large-scale activity in populations of neurons, and (3) how do these effects ultimately alter macroscopic activity in brain regions over the long term. Recent work suggests that deep brain stimulation in the subthalamic nucleus may alleviate the symptoms of Parkinson disease by exciting axons from distant, possibly cortical, structures.[6] Imaging work suggests that in depression, deep brain stimulation in axons near the subgenual cingulate (Cg25) may ultimately lead to downregulation of activity in the Cg25 and consequent changes in other interconnected regions.[7] In this article, we focus on how intracranial neurostimulation affects synchronous rhythmic activity in populations of neurons. Disrupting synchronous activity may be an important therapeutic mechanism for deep brain stimulation in Parkinson disease[8] and is also likely to be critically important for the treatment of epilepsy, which is, almost by definition, characterized by abnormal neural synchrony. We describe the effects of neurostimulation on rhythmic activity recorded intracranially from the neocortex and hippocampus in patients

Disclosure: V.S. Sohal was a paid consultant for NeuroPace, Inc from 2006 until 2010. F.T. Sun is an employee of NeuroPace, Inc.

V.S. Sohal is supported by the Staglin Family and the International Mental Health Research Organization (IMHRO).

[a] Department of Psychiatry, University of California, San Francisco, 401 Parnassus Avenue, San Francisco, CA 94127, USA

[b] Keck Center for Integrative Neuroscience, University of California, San Francisco, 401 Parnassus Avenue, San Francisco, CA 94127, USA

[c] Sloan-Swartz Center for Theoretical Neurobiology, University of California, San Francisco, San Francisco, CA 94127, USA

[d] NeuroPace, Inc, 1375 Shorebird Way, Mountain View, CA 94043, USA

* Corresponding author.

E-mail address: vikaas.sohal@ucsf.edu

Neurosurg Clin N Am 22 (2011) 481–488

doi:10.1016/j.nec.2011.07.007

1042-3680/11/$ – see front matter

with epilepsy participating in a clinical investigation of an implantable responsive neurostimulation (RNS) system (RNS System, NeuroPace, Inc, Mountain View, CA, USA). We found that responsive stimulation acutely suppresses phase locking between gamma-frequency rhythmic activities recorded at different locations.

METHODS

Electrocorticographic Recordings

Electrocorticographic (ECOG) signals were recorded from 65 patients participating in a feasibility clinical trial of the responsive stimulation System. This was a multicenter trial conducted between 2004 and 2007 designed to demonstrate adequate safety and provide preliminary evidence for effectiveness. The trial was approved by the Food and Drug Administration and investigational review boards of each center, and informed consent was obtained from all patients.

The responsive stimulation System provides responsive cortical stimulation via a cranially implanted programmable neurostimulator connected to 1 or 2 recording and stimulating depth and/or subdural cortical strip leads that are surgically placed in the brain according to the seizure focus. The neurostimulator continually senses ECOG activity and is programmed by the physician to detect abnormal ECOG activity and then provide stimulation. Forty-one subjects had leads implanted in the neocortex, 19 had leads implanted in the hippocampus, and 5 had leads implanted in the hippocampus and neocortex. In total, 95 patients had leads located in the neocortex, and 29 had leads in the hippocampus. Two channels of bipolar recordings were available for each lead. Whenever recording sites or the recording montage changed, data from that patient were treated as a new data set, resulting in 146 data sets.

The cranially implanted neurostimulator processes the signals in real time, using detection parameters that were unique to each patient and adjusted over time to detect epileptiform activity. When stimulation was enabled, detection events were followed after a short latency (typically 60–300 microseconds) by electrical stimulation (typically high frequency; >90% of stimulation occurred at frequencies between 100 and 333 Hz, delivered pulses that were 120–200 microseconds wide, and lasted 100–200 milliseconds). ECOG records (sampled at 250 Hz and typically 60–180 seconds in duration) were stored in response to preprogrammed events (such as an individual detection event or multiple consecutive detection events).

Selection of ECOG Data

Some ECOG records contained multiple detection events, each of which would be followed by stimulation if stimulation was enabled. To minimize effects from one stimulation that might affect the analysis of later stimuli, we only analyzed data corresponding to the first stimulation event in each ECOG record. The wavelet analyses described later occurred at discrete time points, which were defined relative to the detection event. In ECOG records containing responsive stimulation, these time points were always measured relative to the detection event immediately preceding the stimulation. This measurement allowed us to compare activity at corresponding time points in ECOG records that contained stimulation (after detection events) and those containing detection events only. During the period immediately following stimulation, signals could be saturated or blanked (ie, no signal available for analysis) or contain transient low-frequency (<1 Hz) artifacts. To ensure that our results were not affected by these sorts of stimulation artifacts, we verified that ECOG signals from every recording channel were nonzero and nonsaturated throughout a window surrounding each time point. This window was large enough to include all time points that might contribute to the analysis via temporal filtering and the wavelet transformation. Any ECOG records that did not meet these criteria were excluded from the analysis. We only analyzed data sets in which a minimum of 10 ECOG records with and without stimulations were available to calculate the phase-locking statistic.

Wavelet Analysis

To study rhythmic activity, we first computed the discrete wavelet transform of activity in each channel at each time point. We based our analysis on a previously described approach.[9] Specifically, for each frequency, *f*, we first band-pass filtered recordings between $f \pm 2.5$ Hz (**Fig. 1**B) and then convolved the filtered signal with a wavelet of frequency *f* to obtain an amplitude and a phase given by

$$e^{-t^2/2\sigma^2} e^{2\pi i f} \quad \textbf{(1)}$$

where $\sigma = 4/3f$ and *f* is the frequency.

Measuring Phase Locking

Following the approach described by Lachaux and colleagues,[9] we used phases obtained from the discrete wavelet transformation described earlier to calculate a measure of phase locking. For each pair of recordings from each data set, we computed phase differences, converted these to unit vectors in the complex plane (see **Fig. 1**C),