Responsive Neurostimulation for Drug-Resistant Epilepsy: Analysis of Device Configuration and Neuromodulatory Effects

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Introduction
Closed-loop neurostimulation is now an important treatment for drug-resistant epilepsy. Data informing treatment detection and stimulation parameters, however, are extremely limited. To overcome this barrier, we developed a novel platform for investigating responsive neurostimulation parameter space, event logging, and response to stimulation. Here, we describe the neuromodulatory effects of closed-loop stimulation on clinical and electrographic outcomes from the level of individual stimulation events.

Methods
Patient-reported outcomes in 12 subjects undergoing responsive neurostimulation were analyzed. In-depth analysis of parameter space and logging capabilities were undertaken using a novel computational platform, and seizure onset was marked in 14,394 90-second ECoG recordings by manual review. We then developed a method using weighted means to measure the bias created by the incompleteness of preserved ECoG recordings relative to overwritten and unstored recordings, as well as the existence of multiple seizure detection patterns. Finally, we performed a spectral analysis of ECoG recordings for each patient, aligned by seizure onset and grouped by time post-implant, to investigate the neuromodulatory effects of closed-loop stimulation.

Results
The average duration of responsive neurostimulation was 22 ± 10 months. The mean percentage of preserved ECoG recordings was 3% ± 7%. We found significant differences between weighted versus non-weighted means for accuracy, sensitivity, specificity, and latency of seizure detections. Spectral analysis revealed several modulatory effects, both transient and long-term, in response to electrographic ictal patterns (EIPs): frequency modulation of EIP oscillation, EIP fragmentation, increase of refractory epochs between consecutive discharges, decrease in mean EIP duration, and acute EIP inhibition.

Conclusions
Closed-loop parameter space and event logging is vast and complex. However, device configuration can be approached in a rational manner by evaluating settings using a weighted-mean methodology, which reduces the bias of ECoG reports. Furthermore, we identified, for the first time, several neuromodulatory mechanisms that may account for changes in clinical seizure manifestation.

References