Understanding and evaluating responsive neurostimulation: A rational approach.

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Editorial

Closed-loop brain stimulation is being utilised more often at level 4 epilepsy clinics, despite a lack of understanding of how the device works on a daily basis. This lack of understanding is impeding the advancement of closed-loop treatment and, eventually, understanding why some patients never achieve seizure reduction. The goal was to assess the accuracy of closed-loop seizure detection and stimulation on the RNS device by extrapolating data from carefully reviewed ECoG recordings and extensive device logging data. A custom-built software package was used to collect, evaluate, and analyse RNS System event recording data. To compare adjusted and non-weighted (standard method) findings, a weighted-means approach was devised and tested to compensate for bias and incompleteness in event logs using Bland-Altman plots and Wilcoxon signed-rank tests. Twelve individuals who had been implanted for an average of 21.5 (interquartile range 13.5-31) months were evaluated. The mean reduction in seizure frequency after RNS implantation was 40.1% (interquartile range 0%-96.2%). There were three primary levels of event logging granularity identified (ECoG recordings: 3.0% complete (interquartile range 0.3%-1.8%); Event Lists: 72.9% complete (interquartile range 44.7%-99.8%); and Activity Logs: 100% complete (completeness measured with respect to Activity Logs). The Bland-Altman interpretation revealed non-equivalence with unexpected magnitude and direction deviations. Wilcoxon signed rank tests revealed significant (p<10-6) differences in accuracy, sensitivity, and specificity for extrapolated *vs* standard findings at >5% absolute mean difference. To derive metrics for detector performance and stimulation, device behaviour documented by the RNS System should be utilised in conjunction with a careful analysis of stored ECoG data.

Penfield described the modulatory effects of electrical stimulation on seizures using Electrocorticography (ECoG) as early as 1954. Based on these findings, the NeuroPace RNS System was created as a closed-loop brain modulation device capable of detecting and responding to abnormal brain activity by delivering programmable stimulation targeted to seizure foci, with the goal of disrupting epileptic form activity before a seizure occurs. The device's capacity to respond to aberrant brain activity is dependent on how well the physician-selected combination of detection parameters is suited for the specific seizure onset pattern(s) identified in each patient's ECoG recordings. Several multi-center outcomes studies have shown that the RNS System is effective, with a median 55% of patients seeing a 53% decrease in seizure frequency after two years and a median 70% of patients experiencing a 78% seizure frequency reduction after six years. The fact that the responder rate and seizure reduction have increased over time begs the question of why some patients respond faster and more effectively than others. Examining the characteristics of responders versus non-responders is one way to tackle this topic. However, because of the variability of device behaviour among patients, this method is unable to distinguish whether poor patient response is related to suboptimal settings or fundamental patient features. The interplay between the detection and stimulation settings, as well as each individual patient's unique neurophysiological onset patterns causes this variability. As a result, we propose that the first step toward bettering closed-loop therapy is to develop quantitative methods for assessing device behaviour, which is defined by the type of neurophysiological event being stimulated, the timing of stimulation relative to event onset, and the rate of stimulation. This technique goes well beyond the capabilities of the NeuroPace Patient Data Management System's (PDMS) present analytic tools.

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