Reduction of Seizure Frequency by Responsive Just-In-Time VNS in an Animal Model of Chronic Epilepsy

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Methods

This frequency during the ini-time VNS stimulation, in the animal lick-placophine model of epilepsy, VNS was applied only when brain dynamis were indicative of an impending seizure. This paradigm greatly reduced the amount of time under stimulation and led to a significant reduction in seizure frequency in eight rats.

Methods

Eight male Sprague-Dawley rats were induced to chronic epilepsy by the lick-placophine model of epilepsy [1]. Each rat was subsequently implanted with 8 Tungsten microelectrodes (two in centromedial thalamus, two in hippocampus and four on cortex). Rats were then implanted with two helical leads made of platinum-iridium coated with cyanoacrylate (Cyberonics, Inc., Houston, TX) wrapped around the left vagus nerve in the ventral cervical region for VNS electrical stimulation by programmable stimulators (A-M Systems Inc., Snoqualmie, WA). The experiment involved two phases per pair: stimulation (S) and no stimulation (NS). 4 to 5 days each in duration. During (S), VNS was administered upon warnings issued when analyzed EEG dynamics from critical pairs of brain sites were found to be significantly (p<0.05, t-test) entrained over the preceding 10 min interval (Figure 1). VNS stimulation was delivered until the critical pairs of sites desynchronized or up to a maximum of 1 hour after a warning. By design, the maximum rate that just-in-time (JIT) VNS stimulation could occur was once every 2 hours; in reality, the mean rate of JIT VNS was a fraction of this value, depending on each rat’s EEG dynamics. This closed-loop procedure was performed automatically and in real-time by our online, JIT seizure prediction software [2-4] (Figures 2 and 3). During (NS), no stimulation was administered at the issued warnings (control phase).

Results

Seizures occurred in both phases of the experiment and were detected by our in-house developed seizure detection algorithms. The frequency of seizures in each phase was then estimated and compared with each other and across rats. Cumulatively, across all rats, a statistically significant (p<0.05, t-test) reduction of the mean seizure frequency, from 8 seizures per 12 hours without stimulation to 2 seizures per 12 hours with stimulation, was observed over the experiment’s duration (Figures 4). Six of the eight rats showed a reduction in seizure frequency during the (S) phase compared with the (NS) phase (Figure 5).

Conclusion

Responsive, just-in-time, VNS was found to be effective in significantly reducing the seizure frequency in the lithium-platecarpine animal model of epilepsy. These results provide an initial supporting evidence for the use of closed-loop just-in-time VNS stimulation in the treatment of epilepsy. Just-in-time VNS stimulation greatly reduced the amount of time under stimulation potentially leading to an increase in stimulator battery life and a decrease in stimulation side-effects. Further studies with more rats and adjustment of the seizure prediction algorithm and maximum stimulation duration must be conducted to corroborate and improve these initial results.

References


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