ELECTROCONVULSIVE THERAPY FOR SEIZURE CONTROL: PRELIMINARY DATA IN A NEW SEIZURE GENERATION AND CONTROL MODEL

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1. ABSTRACT

Electroconvulsive therapy (ECT) effect upon seizure cessation was studied in five male Wistar rats using a penicillin intracisternal injection model (which did not damage the cranial vault). Animals were observed both clinically and electrographically for seizure development. ECT was applied at varying times following onset of seizure, at varying parameters (frequency, pulsewidth, and duration). ECT affected EEG seizure pattern in several different stimulation parameter-dependent ways: (1) modulation to different pattern; (2) increased interictal time; and (3) seizure cessation. Stimulation with higher, sustained current (50 mA) led to changes in seizure amplitude; stimulation at pulses of current led to seizure frequency dimunition, and at certain characteristic pulses "capture" was seen as the EEG activity mimicked the ECT-inducing stimulation pattern. Interictal time was usually increased by sustained, continuous (rather than pulsatile) stimulation. Seizure activity was completely stopped in several instances using parameters of 800 pulses at a frequency of 200 Hz, with 2.56 ms pulsewidth and 50 mA of current (in consecutive iterations for one specimen). No ECT-related adverse effects were noted. Analogous to the heart, pacing or defibrillating the brain using external scalp electrodes may have a role in the control of otherwise intractable seizures.

2. INTRODUCTION

A seizure is a disease process which can be defined clinically by specific, observed behavior, and electrographically by contemporaneously recorded abnormality. In many seizures (especially as observed from animal models), there is a time period where sharp spikes are noted at gradually increasing frequency, until a continuous spike train and subsequent spike-and-wave phenomenon occurs which may clinically correlate with repetitive movement in some cases.(1) Hence, to oversimplify, in many cases a seizure may be viewed as "regular brain activity recording" whereas normal brain activity is not generally rhythmic for a given population of cells.

In contradistinction, the human heart is repetitive and relatively constant in its periodicity. Electrographically, (electrocardiogram) recordings do display a specified rhythm. Absence of this rhythm (as seen in ventricular fibrillation, for example) is treated in some cases by applying electrical energy to "shock" the heart into rhythm. A cardiac pacemaker, for example, will "capture" the rhythm of the heart into periodicity (2).

Electroconvulsive therapy (ECT) is used routinely in the treatment of mood disorders (primarily

depression) in psychiatry. Notwithstanding initial social stigma, it can presently be performed in a relatively safe, efficacious fashion in many cases.(2).

Based upon these observations, the question arises, can the brain be electrically "paced" out of a seizure by applying the opposite wave phase that would be applied to a heart which is "paced into normal rhythm?" Additionally, what sorts of changes can be effected upon the brain's rhythm to facilitate seizure termination, or lower the threshold for seizure termination?

3. MATERIALS & METHODS

3.1. Development of a new epilepsy model

Induction of seizures was sought via a model which would allow quick onset, allow both partial and generalized seizure activity (at varying concentrations), and allow numerous seizures to occur. The agent penicillin has been used previously for this purpose, but the modes of administration in rats were limited to either intravenous, intraperitoneal, or cortical application (3). Because great care was needed to not violate the integrity of the skull (which may interfere with electroconvulsive therapy (ECT) administration), we developed a new model for this procedure. The intracisternal (IC) penicillin model in the rat has only recently been described by our group, and no previous accounts exist in the world literature (PubMed search using "rat intracisternal penicillin seizure", 2/27/2005). After anesthetizing a rat intraperitoneally using a mixture of alpha-chloralose and urethane and performance of a tracheostomy (with the rat placed on a ventilator), a 27-gauge bent needle was passed through the exposed occiptoatlantal membrane and cerebrospinal fluid and an equivalent amount of cerebrospinal fluid was removed and replaced with the penicillin solution. Seizure recording, or electroencephalography (EEG), was conducted using needle electrodes (A.D. Instruments, Colorado, U.S.A.) placed into the scalp, and has relatively quick onset according to our work.

3.2. Electroconvulsive Therapy (ECT) Administration

Earbar electrodes were placed upon the rats, and all stimulation activity was recorded contemporaneously with EEG, using a single system (A.D. Instruments, Colorado, U.S.A). A varying amount of time was allowed between recording of seizure activity and initiation of ECT. Hence, each animal served as both (1) its own control; and (2) a control for the group. Spontaneous resolution of seizure activity was carefully documented as well. Parameters used for ECT administration were varied as well to determine effects related to frequency, current, pulsewidth, and time of stimulation.

4. RESULTS

4.1. Seizure onset

Seizure onset following intracisternal penicillin model occurred in an average of 13 minutes, 42 seconds following penicillin injection (range 4:30 to 23:20) for the intracisternally (IC) injected group. 96 total separate seizure episodes were seen with electrographic and clinical

correlation, ranging from 3 to 540 seconds. Epileptic activity could be seen in all IC-injected rats, lasting over 1 hour into the study.

4.2. Response to Electroconvulsive Therapy

ECT affected the seizure pattern on EEG in several different ways, dependent upon stimulation parameters: (1) modulation to a different pattern; (2) increasing the interictal time; (3) stopping a seizure. Stimulation with higher, sustained current (50 mA) led to changes in seizure amplitude (voltage); stimulation at pulses of current led to decrease in frequency of the seizures, and at characteristic pulses, e.g. frequency of 2 Hz, current 5 mA, "capture" was noted, whereby the electrical seizure mimicked the ECT-inducing stimulation pattern. Interictal time was usually increased by sustained, continuous (rather than pulsatile) stimulation. Seizure activity was completely stopped in several instances using parameters of 800 pulses at a frequency of 200 Hz, with 2.56 ms pulsewidth and 50 mA of current (in consecutive iterations, in one specimen). Importantly, spontaneous seizure activity was noted prior to stimulation, to ensure that the effect was not from spontaneous resolution of seizures but rather from the intervention itself. No adverse effects directly resulting from ECT were identified. Figures 1-3 depict and respectively discuss examples of responses actually noted following ECT.

5. DISCUSSION

5.1. Electroconvulsive therapy

The marriage of techniques used in neurosurgery, neurology, cardiology, and psychiatry in this single technique of using ECT for seizure control has promise, based upon this pilot study. Each of the three types of effects that ECT had upon the EEG (and seizure control) in individual trials are depicted and discussed here (as opposed to the "Results Section" where these would normally be presented, so that individual cases could be discussed more clearly).

5.1.1. Modulation to different pattern

Desynchronization of the EEG resulting in seizure generation has been proposed by previous investigators(4). There is also evidence that increased complexity of the seizure waveform as observed on EEG routinely precedes seizure termination(5). The mechanism of seizure termination, as observed by some of the prior investigations, is postulated to involve a "desynchronization of the EEG," implying that a change in waveform (whether intrinsic or induced) may facilitate cessation of a seizure (Figure 1).

How can simply changing a seizure's electrical appearance lead to seizure control? One answer may be by changing the *threshold* at which the seizure can subsequently be terminated using medications. While the first line of therapy for epilepsy is medications, many patients who are considered "refractory" to medical therapy have often failed multiple medications. This suggests that certain electrical activity is simply refractory to the neurochemical/electrical changes induced by those

Electroconvulsive therapy for seizures
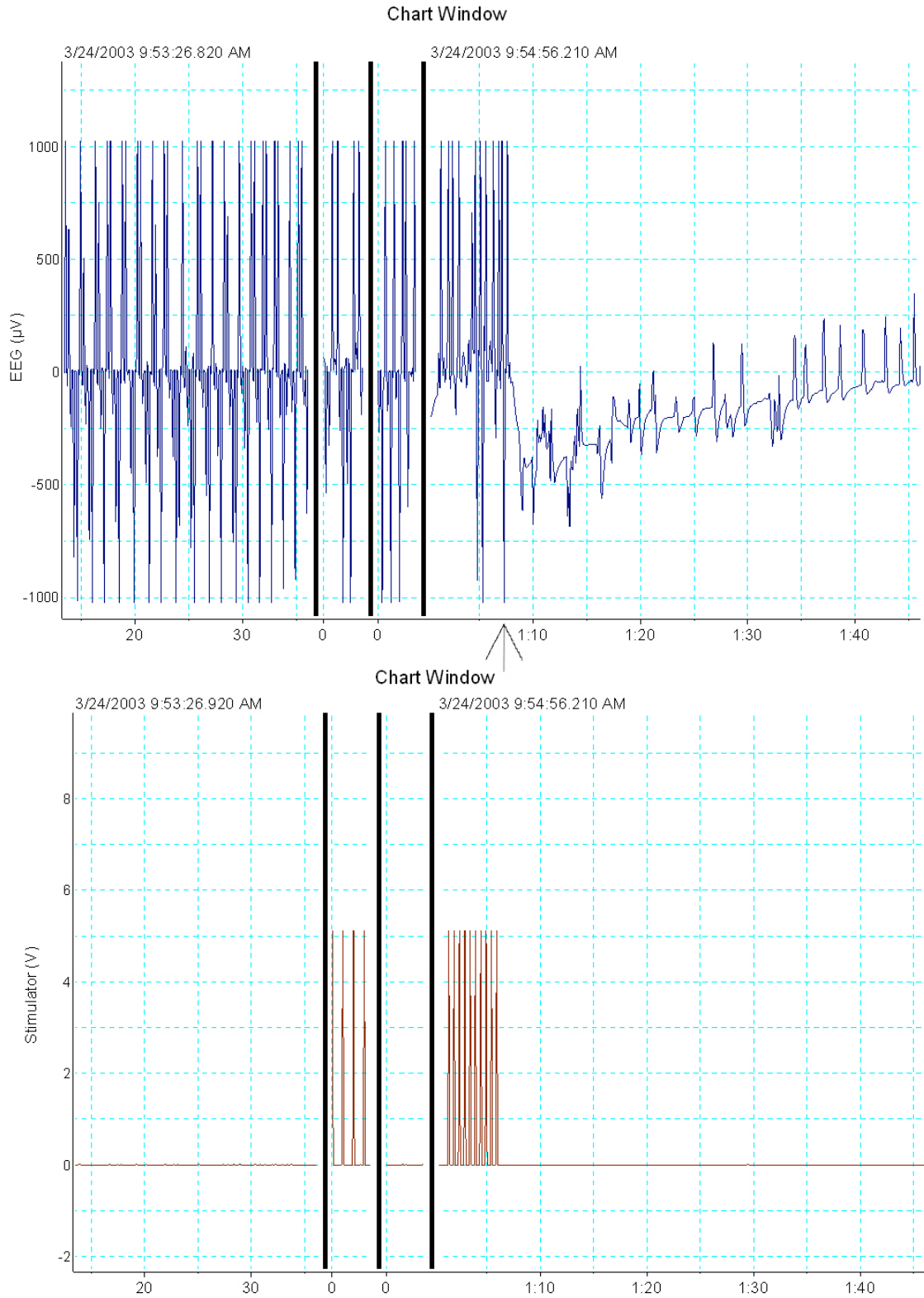
Figure 1. Modulation to a different seizure electrical pattern is indicated by EEG (top graph) and stimulus delivered (bottom graph), with change in pattern denoted by the arrow on EEG.

medications. However, a seizure with a different electrical pattern may not be so refractory. Hence, a change in the seizure pattern may well allow a seizure to no longer be as medically refractory, leading to seizure cessation with medication. This illustrates a case where it is necessary but not sufficient for either medication or electrical stimulation to terminate a seizure; however, in combination, the seizure may be terminated.

5.1.2. Increase in interictal time

Interictal time represents the seizure-free time between epileptic attacks. Some studies have correlated improvement in quality of life for subtypes of epilepsy with decreased frequency of seizures(6). For example, mothers of children who suffered over 100 seizures per day noticed a dramatic improvement following vagal nerve stimulation in not only seizure reduction, but also playfulness and interactivity of the children in many instances (Patwardhan *et al*, unpublished data, 1999). In a canine model, Patwardhan *et al* showed that ninth cranial nerve stimulation resulted in increased interictal time; 40% of the animals subsequently became seizure-free, with seizure control occurring in 75% of cases (7) (Figure 2).

One observed electrographic phenomenon during the interictal period is the interictal spike. The significance of this is debated – some suggest that progressive increase in interictal spikes results in a seizure (7), whereas others debate that the spike is generated by a different population of neurons and may confer a protective effect in an otherwise epileptogenic region(8). Based upon previous data (7,9) and the present study, spikes preceded seizures electrographically – while this does not necessarily imply causality, circumstantial evidence is at best present.

Hence, for a given period of time, an increase in interictal time should (by definition) decrease the seizure duration. The observed increase in interictal time following ECT in this study may well portend a decreased threshold for seizure cessation.

5.1.3. Termination of seizure

While changing the electrical pattern of a seizure and increasing the interictal time may allow eventual seizure control as noted, there are some studies which suggest that quality of life is dependent upon the frequency of seizures and not the interictal time (10). Hence, the ultimate goal of any antiepileptic therapy should not simply be facilitation of seizure reduction via changing the seizure pattern or increasing interictal time, but actually stopping the seizure (Figure 3).

Seizure termination in our study occurred in consecutive iterations, where the same frequency parameter was used. This lends credence to the hypothesis that "desynchronization" using a regular waveform could effectively cancel a seizure, leading to an observed irregular pattern on EEG (void of regular seizure activity preceding stimulation) and clinical absence of movement associated with a seizure.

The key question concerning parameters of stimulation is applicable to many neurosurgical stimulators in present-day use. For example, vagal nerve stimulation underwent a trial comparing low vs. high stimulation, with the result showing greater benefit with higher stimulation (11). Deep brain stimulation (DBS) has also recently replaced lesioning as a method for control of tremor, rigidity, and/or dyskinesia in many cases – the frequency of stimulation for DBS is hypothesized to inhibit rather than excite neurons. The exact mechanisms for electrical stimulation (and hence successful alterations to optimize efficacy) remain largely unknown (12).

The crux of our study relies upon interruption of the seizure pattern electrographically, which should correlate with a similar such pattern clinically. To this extent, introduction of a destructive electrographic wave which "cancels" an existing epileptic waveform must be created effectively. Data from this animal study shows that seizure termination clearly occurred – based upon this data, a device has been created which can clearly record and "cancel" the seizure using special electrodes and a recording/feed-forward system.

5.2. Clinical Application

There has been only one anectodal report of ECT use in medically intractable seizures in human patients: one patient experienced "change in a seizure pattern with cessation at higher intensity," while the other experienced "decrease in spontaneous seizure frequency." (13) Surprisingly, no further studies to investigate this methodically in an animal model similar to our study (nor in a human clinical series) are found in a search of the world literature (as of March 1, 2003). This is the first stepwise approach in the scientific process, to our knowledge, to determine whether this technique can have widespread use as part of standard of care.

6. SUMMARY

This pilot study shows promise in the use of stimulation similar to electroconvulsive therapy in the control of seizure activity of the brain, much like an external pacemaker or cardiac defibrillator does for the heart. This idea can easily be modified to create an internalized "pacemaking" or seizure cessation apparatus. Alternatively, both external and internal components can be used.

Based upon the idea of this system and initial encouragement from the successes in this small population, a device capable of electrographically modulating seizure activity using ECT-based principles has been devised (patent pending, with further testing to occur) for use in the control of seizures in humans.

7. ACKNOWLEDGMENT

Electroconvulsive therapy for seizures
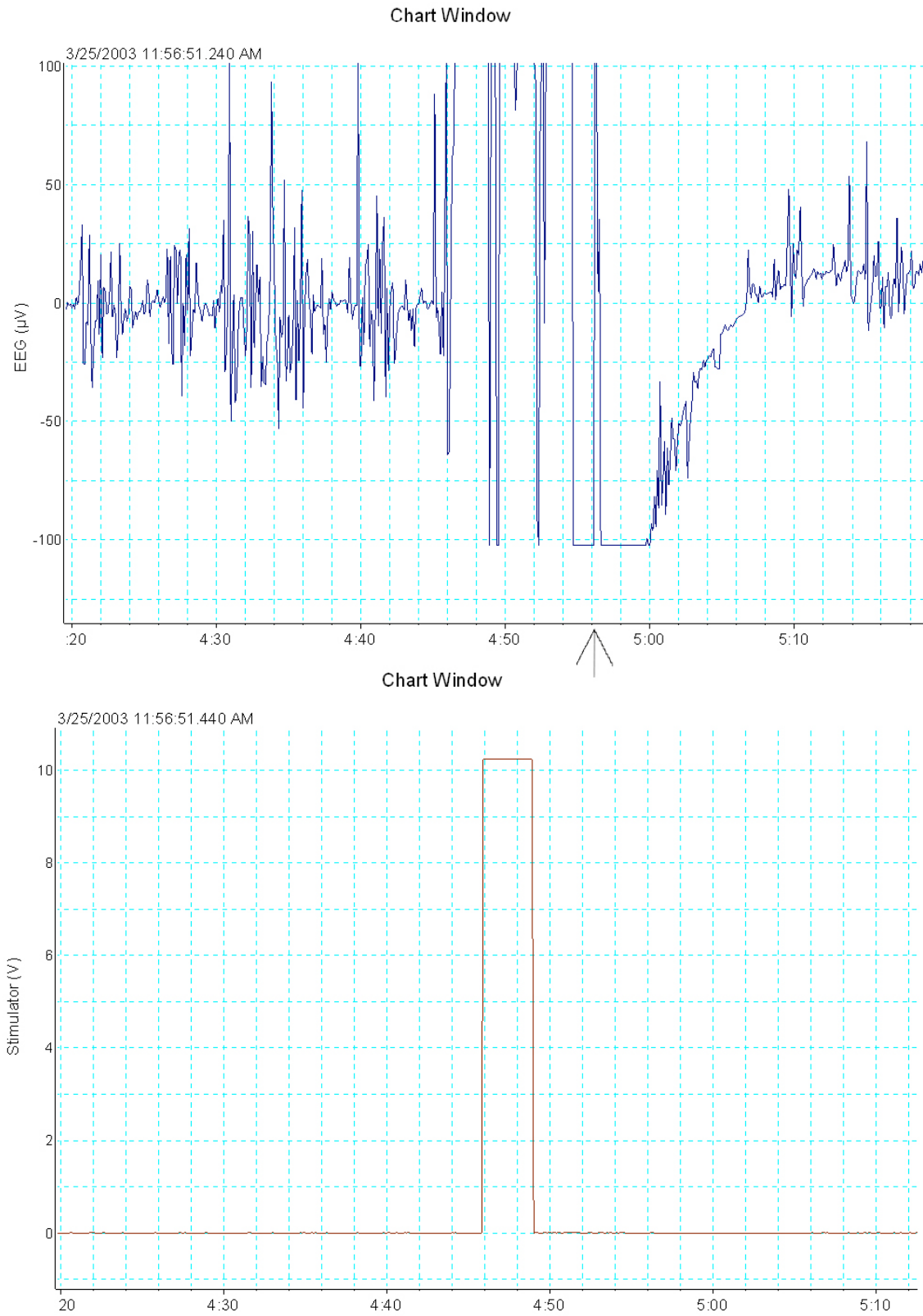
Figure 2. Increase in interictal time is noted on EEG (top graph) following stimulation (bottom graph), denoted by the arrow on EEG.

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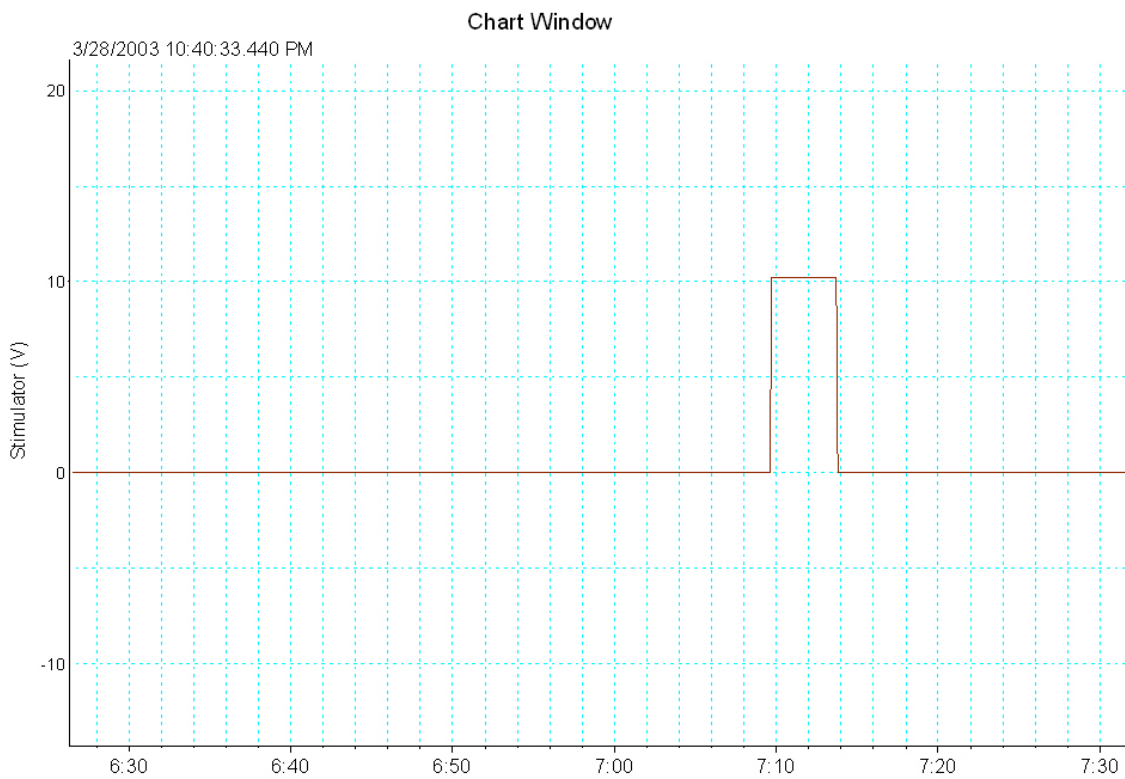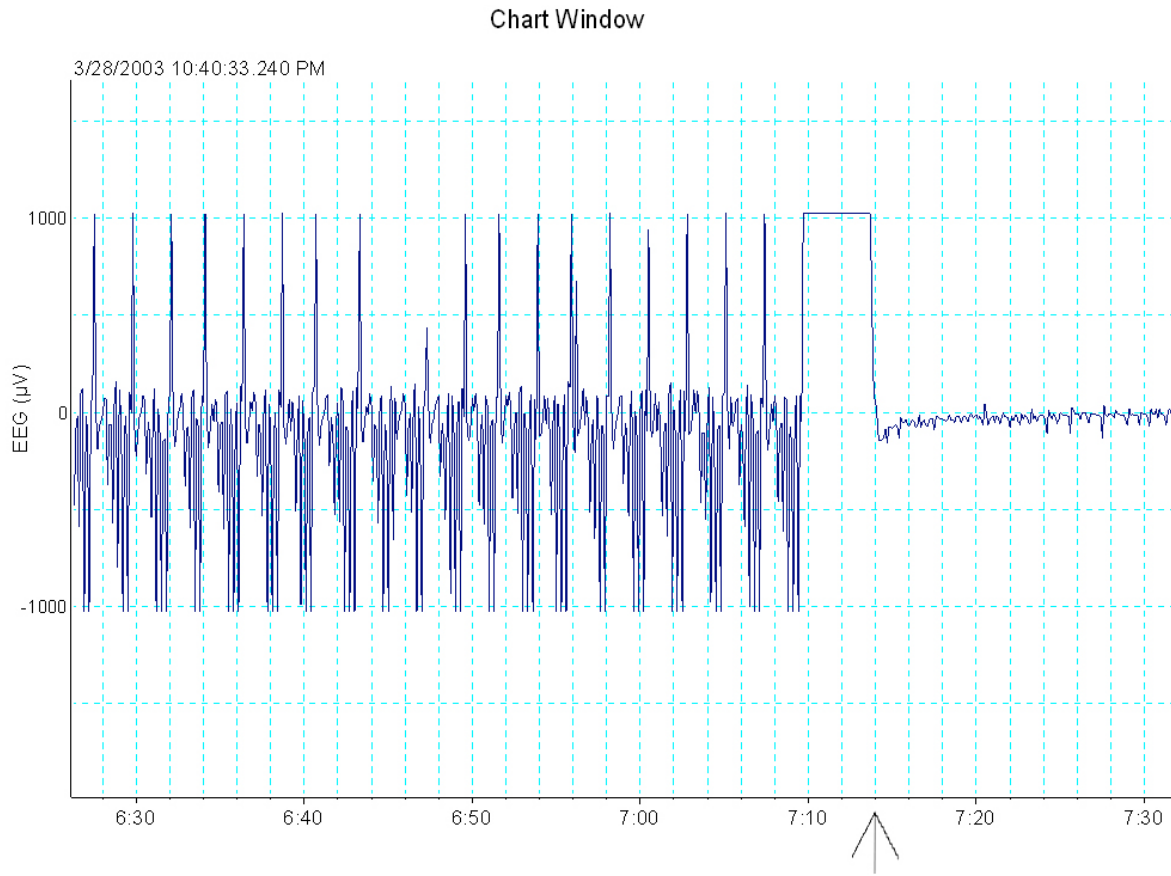### Chart Window

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Figure 3. Cessation of a seizure (EEG, top graph) following stimulation (bottom graph) , denoted by the arrow on EEG.

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