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When Is Electrical Cortical Stimulation More Likely To Produce Afterdischarges?

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Abstract

Objective—To study when afterdischarges (ADs) are more likely to occur during cortical stimulation.

Methods—We examined 6,250 electrical stimulation trials in 13 patients with subdural electrodes, studying whether AD occurrence during a trial was influenced by electrode pair stimulated or AD occurrence during the previous trial. In total 545 electrodes were stimulated, 119 frontal (pre-perirolandic), 289 perirolandic, 36 parietal (post-perirolandic), 95 temporal, and 6 occipital.

Results—When the same electrode pair was stimulated as the prior trial, 19% produced ADs compared to 5% of trials when a different electrodes pair was stimulated ($p<0.0001$). When trials showed ADs, and the next trial stimulated the same electrode pair, ADs occurred in 46% of cases, compared to 13% of trials following trials without ADs ($p<0.0001$). AD probability decreased with increased inter-trial interval length only when the prior trial was at the same electrode pair and had produced an AD ($p=0.001$). AD probability increased with stimulation duration, whether the trial followed a trial with ($p<0.001$) or without ($p<0.0001$) an AD.

Conclusions—ADs were more likely to occur when an electrode pair showed ADs and was stimulated again, especially when stimulating after short inter-trial intervals or for longer duration.

Significance—When ADs occur, waiting about a minute before resuming stimulation might lessen the likelihood of AD recurrence.

Introduction

Afterdischarges (ADs) are characterized by distinctive rhythmic discharges of spikes and sharp waves that can occur as unwanted side effects after electrical stimulation of a cortical region (Lesser et. al., 1984b;Lesser et. al., 1999;Motamedi et. al., 2002;Blume et. al., 2004;Pouratian

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et. al., 2004). Stimulating cortical area can produce ADs, sometimes followed by clinical seizures, whether or not that region causes spontaneous seizures (Lesser *et al.*, 1984b;Lesser *et al.*, 1999;Blume *et al.*, 2004;Pouratian *et al.*, 2004). ADs can be used to study corticocortical functional connectivity, patterns of cortical activation (Lesser et. al., 2008), or as a model of human seizures (Lesser *et al.*, 1999).

We previously reported that the electrocorticographic responses to electrical stimulation can fluctuate considerably between repeated trials conducted within the same individual over short periods of time (Lesser *et al.*, 2008). In that study, we observed patterns of ADs over repeated trials and investigated how rapidly response patterns could vary in intact human brain. We found that occurrence of ADs could change within seconds. Also, ADs could occur at a given location during one trial but not the next and they could occur at electrodes adjacent or not adjacent to those directly stimulated.

In this study, we further examined short term changes of cortical responses following stimulation. We examined whether the probability of AD occurrence depended on (1) whether or not there was an AD at the prior trial or (2) whether the prior trial stimulated the same or different electrode pair. We also examined whether the probability of AD occurrence was affected by inter-trial interval length, duration of electrical stimulation, testing session, or by whether stimulated electrodes had shown ictal or interictal epileptiform discharges.

Methods

Patients

We studied 13 patients, in whom subdural electrodes had been implanted for clinical testing, and in whom afterdischarges (ADs) were noted after a run of electrical cortical stimulation given to assist in localizing motor, sensory, or language function. In keeping with our previous report, we call this localization stimulation (LS) (Lesser *et al.*, 1999). Subdural electrodes remained in place in their left hemispheres for several days, with patients in the epilepsy monitoring unit for video-electroencephalography for seizure recordings and for functional mapping using LS (Lesser et. al., 1994). Six patients were male and seven were female. Ages at seizure onset ranged from 14 months to 39 years, and ages at surgery were from 4.7 to 54 years. We previously have described other clinical details regarding these patients (Lesser et al., 2008).

Most testing, and all decisions regarding electrode placement, were based on clinical considerations. All research testing, and the analyses on which this report is based, were approved by our institutional review board.

Electrodes

The subdural electrode arrays we use are 1.5-mm-thick, soft Silastic sheets embedded with platinum-iridium disc electrodes (3-mm total diameter, 2.3-mm diameter exposed to the cortical surface) equally spaced with 1 cm center-to-center distances, in a rectangular or linear array (Adtech, Racine, WI, USA). Electrode position relative to the underlying cortex was determined by direct observation in the operating room (all patients) and by coregistration of pre-implantation volumetric brain magnetic resonance imaging (MRI) (1- to 1.8-mm coronal slice thickness) with post-implantation volumetric brain computed tomography (CT) (1-mm axial slice thickness) in 11 patients according to anatomic fiducials using Curry (Compumedics Neuroscan, El Paso, TX, USA). The electrode positions found with this were displayed with a brain surface rendering, with electrode labelling performed using Photoshop (Adobe Systems, San Jose, California)..

Electroencephalographic (EEG) Recordings

EEGs were recorded on a digital electroencephalogram (Telefactor Twin, Astro-Med, Inc., West Warwick, RI, USA) that could simultaneously record up to 128 channels, with 200 samples per second per channel. Low pass filter was set to 70 Hz and high pass to 0.3 Hz (−3 dB).

Electrical Cortical Stimulation

Testing of motor, sensory or language functions occurred over 1–5 sessions. One testing session was in the morning and another in the afternoon. Within each session, there was a sequence of trials, each trial characterized by electrical stimulation of a pair of electrodes followed by observation of the effects of this stimulation on the patient. Testing used biphasic, charge balanced, square wave pulses of 0.3 millisecond duration, repeated at 50 Hz and presented in trains lasting 4 to 5 seconds, with the first 0.3 millisecond positive pulse immediately followed by a 0.3 millisecond pulse of opposite polarity (Grass S12 stimulator; Astro-Med, Inc., West Warwick, RI). In general, stimulation was between pairs of adjacent electrodes, using methods previously described (Lesser *et al.*, 1984b;Lesser *et al.*, 1994;Lesser *et al.*, 1999;Pouratian *et al.*, 2004).

A total of 1156 electrodes had been implanted, 352 in frontal lobe anterior to the perirolandic region, 392 in the perirolandic region, 152 in the parietal lobe posterior to the perirolandic region, 252 in the temporal lobe, and 8 in the occipital lobe. Stimulation was performed on 545 electrodes, 119 frontal (pre-perirolandic), 289 perirolandic, 36 parietal (post-perirolandic), 95 temporal, and 6 occipital. A previous report found that AD thresholds differences vary considerably throughout the brain, by as much as 9.5, 8, and 12 mA between adjacent electrodes and by as much as 11, 8, and 12 mA in individual patients in the frontal, parietal, and temporal lobes respectively.(Lesser *et al.*, 1984b)

Although the characteristics of ADs are the focus of this paper, from the clinical perspective we hope to avoid their occurrence and minimize their duration (Lesser *et al.*, 1999). To do this, we start at 0.5 – 1 mA, increasing in steps of 0.5–1 mA until motor or sensory changes occur, but decreasing by 0.5 – 1 mA if ADs occur, in an effort to avoid further ADs.(Lesser et. al., 1984a;Lesser et. al., 1987;Jayakar et. al., 1992;Lesser *et al.*, 1994;Jayakar and Lesser RP, 1997;Lesser *et al.*, 1999) There was no precise timing for the interval between trials. This might increase, for example, if the patient had a question, or wanted to relax for a moment before resuming testing. It might also be longer if one of the testing personnel needed to adjust the testing equipment, or make notes about the testing. Finally, if ADs occurred, the next trial didn't occur until they stopped.

Only one of the 13 patients experienced an AD during the *first trial* of a session, and this only occurred during one out of four sessions for that individual. The remaining analyses therefore were restricted to *subsequent trials* only. For instance, if a session was 3 hours long, running from 13:00 – 16:00 hours, only the one at 13:00 was the first trial and all the others were subsequent trials, and these were the ones we further analyzed. We analyzed what occurs among all the testing sessions. For example, there could be session 1 on Monday morning, session 2 Monday afternoon, session 3 Tuesday morning.

EEG Analysis

We used previous definitions and descriptions of ADs (Lesser *et al.*, 1999;Blume *et al.*, 2004). In summary, ADs vary in morphology but can occur as spikes, polyspikes, spike-and-slow-wave complexes, or rhythmic sinusoidal or semi-sinusoidal discharges.(figure 1) We reviewed EEGs on a locally developed EEG viewer that displayed up to 128 channels simultaneously, and allowed us to mark the location of ADs and other events as precisely as

desired. Preliminary assessments of portions of the recordings were performed by several individuals, but one board certified electroencephalographer (RPL) performed the final markings of all recordings.

We found that there were times when it was difficult to decide whether a particular waveform was, or was not an AD. Because of this, although preliminary assessments of portions of the recordings were performed by several individuals, one board certified electroencephalographer (RPL) performed the final markings of all recordings. We discussed previously (Lesser *et al.*, 2008) that it can be difficult to decide whether an individual EEG waveform is, or is not, an AD, and there are a number of articles in the literature that describe difficulties in classifying individual events and findings, not only with EEG (Williams et. al., 1985;Williams et. al., 1990;Webber et. al., 1993) including computer based EEG analysis (Webber et. al., 1994), but also with polysomnography (Ferri et. al., 1989), electrocardiography (Eddy, 1988), radiologic imaging (Revesz and Kundel, 1977;Beam et. al., 2003), and clinical observation (Eddy, 1988;Groopman, 2007). Because of this, in our previous study, RPL marked the entire data set twice.(Lesser *et al.*, 2008) We found differences between the two reviews for 257 out of 11,944 events marked, but there were no differences in the conclusions with or without the 257 events. These differences, however, regarded whether there were ADs on a *particular channel.* There were no differences regarding whether ADs occurred at a *particular time*, and this was what we investigated in the present study.

After stimulation occurs, there can be “blocking,” saturation of the amplifiers for a period of time, and this can obscure any ADs that might be present. This could last for several seconds on the channels actually stimulated. For this reason we could not know whether ADs occurred on the stimulated channels until the saturation cleared.

Statistical Analysis

We calculated the number and percentage of trials that produced ADs by whether the trial was a first or subsequent trial in a session, and for subsequent trials, whether the prior trial stimulated the same or a different electrode pair and whether the prior trial produced an AD. We also recorded the sites where spontaneous epileptiform activity occurred, and determined whether such activity was more likely at sites where ADs occurred.

We used logistic regression to examine whether the probability of a trial producing any ADs depended on whether the same electrode pair was stimulated as the prior trial within a session and whether that prior trial produced ADs. Logistic regression models included the patient identification number as a fixed effect and were fit using generalized estimating equations (GEE) to take into account possible correlation among trials for which the same channel pair was stimulated (Lesser *et al.*, 1999).

Inter-trial interval length (length from end of immediately prior trial to start of current trial) and LS duration were calculated for each of the following conditions: (1) same electrode pair as prior trial, no AD at prior trial, (2) same electrode pair, AD at prior trial, (3) new electrode pair, no AD at prior trial, and (4) new electrode pair, AD at prior trial. We plotted the probability of an AD by the inter-trial interval length, with separate smoothed lines fit for each patient. We fit logistic regression models to examine whether the probability of a trial producing any ADs depended on inter-trial interval length or LS duration, conditional on whether the trial was at the same electrode pair as the prior trial or a new electrode pair and whether or not the prior trial produced ADs. Models included the patient identification number as a fixed effect, and were fit using GEE to take into account possible correlation among trials for which the same channel pair was stimulated.

We used logistic regression fit via GEE to examine whether there was an increase or decrease in the overall probability of ADs over testing sessions after adjusting for whether the prior trial stimulated the same or a different electrode pair and whether the prior trial produced an AD. We also used logistic regression fit via GEE to examine whether there was an increase or decrease in the overall probability of ADs when the stimulated channels were at locations where there were epileptiform discharges, compared to locations where there were no epileptiform discharges. We evaluated sites where epileptiform discharges were ictal only, interictal only, or both ictal and interictal,

All tests were two-sided with an alpha level of 0.05 used to determine statistical significance. From the logistic regression models, we report odds ratio (OR) along with 95% confidence intervals (CI) and *p*-values.

Results

The number of sessions per patient ranged from 1 to 5 and the number of trials per patient ranged from 71 to 1,206. Total testing time for the entire admission ranged from 48–370 minutes per patient. There were a total of 6,250 trials included for the analysis. Of these, 41 were the first trial of a session, and the other 6,209 were subsequent trials. Among all 6,250 trials, 18% produced ADs (Table 1A). For the 41 first trials of a session, ADs were observed during only 1 trial (2%).

We found that 43% of the 1,139 trials following a prior trial with an AD resulted in an AD compared to only 13% of the 5,070 trials following a prior trial without an AD (Table 1B, OR = 5.1, 95% CI = 3.4 to 7.8, $p<0.0001$). For the 6,209 subsequent trials within a session, ADs were more likely to occur if the same electrode pair was stimulated as during the prior trial or if the trial followed a trial that produced an AD (Table 1C). Among the 5,960 trials during which the same electrode pair was stimulated as the prior trial, 19% produced ADs compared to only 5% of the 249 trials during which a different pair of electrodes were stimulated compared to the prior trial (OR = 4.7, 95% CI = 2.4 to 9.1, $p<0.0001$).

Trials following a trial that resulted in an AD were significantly more likely to produce an AD if the same electrode pair was stimulated. We divided the 5,960 subsequent trials during which the same electrode pair was stimulated as in the prior trial into those where the prior trial did not produce an AD, and those where the prior trial produced an AD (Table 1D). For subsequent trials for which the same electrode pair was stimulated as the prior trial, 46% of the 1,076 trials following a prior trial with an AD resulted in an AD compared to only 13% of the 4,884 trials following a prior trial without an AD (OR = 5.4, 95% CI = 3.4 to 8.4, $p<0.0001$).

For the other 249 trials where a new electrode pair was stimulated compared to the prior trial (Table 1D), the odds of having an AD was almost twice as large if there was an AD at the prior trial; however, this was not statistically significant (8% of 63 trials with a prior AD vs. 4% of 186 trials without an AD, OR = 2.2, 95% CI = 0.62 to 7.8, $p=0.22$).

As might be expected, the length of inter-trial intervals (time from the end of one stimulation trial to the start of the next stimulation trial) was shorter when testing was performed at the same electrode pair as the prior trial and when the prior trial did not have an AD (Table 2A). When testing was performed at the same electrode pair, more than 95% of trials started less than a minute after the end of the prior trial, though trial lengths were somewhat longer when they followed a trial with an AD. For example, the inter-trial interval length was less than 10 seconds for 61% of trials at the same electrode pair when there was not an AD at the prior trial, compared to only 31% of trials when testing was done at the same electrode pair but there was an AD at the prior trial. When testing was performed at a new electrode pair, 30% of trials began 150 seconds or longer after the prior trial when there was no AD, compared to 43% of

trials following a trial with an AD. This is most likely because testers wait until the ADs stop before starting a new test, and this adds time to that taken to switch the electrode pairs.

Figure 2 and Table 2B show the probability of an AD by the inter-trial interval length, with separate lines for each patient. The probability of an AD depended significantly on the inter-trial interval length only when the prior trial was at the same electrode pair and had produced an AD (p=0.001) (Figure 2A). In this case, the probability of another AD decreased as inter-trial interval length increased (OR = 0.45, 95% CI = 0.25 to 0.79, p=0.005). For subsequent trials at the same electrode pair when the prior trial did not have an AD, the probability of an AD did not depend on the inter-trial interval length (p=0.16, Figure 2B). For trials at a new electrode pair, the probability of an AD did not depend on inter-trial interval length, regardless of whether the prior trial had an AD (p=0.58) or not (p=0.42) (Figure 2C).

The LS duration ranged from 1 to 5.5 seconds, and tended to be longer when the same electrode pair was stimulated following a trial with an AD as follows:

1. Same electrode pair, no AD at prior trial: median = 2.2, range = 1.0–5.5 seconds
2. Same electrode pair, AD at prior trial: median = 3.1, range = 1.0–5.4 seconds
3. New electrode pair, no AD at prior trial: median = 2.0, range = 1.0–4.8 seconds
4. New electrode pair, AD at prior trial: median = 2.0, range = 1.1–4.8 seconds

The probability of ADs increased with increasing LS duration most strongly for trials at a new electrode pair compared to the prior trial (OR = 4.5, 95% CI = 1.5 to 13.3, p=0.0068). This relationship did not depend on whether the prior trial produced ADs (p=0.78). In contrast, for trials performed at the same electrode pair as the prior trial, there was a significant interaction between the LS duration and whether the prior trial produced ADs (p=0.0015), where the positive association between the LS duration and the probability of an AD was stronger when the trial followed a trial *without* an AD (OR=1.70, 95% CI = 1.54 to 1.89, p<0.0001) compared to when the trial followed a trial *with* an AD (OR = 1.51, 95% CI = 1.33 to 1.72, p<0.001).

After adjusting for whether testing was done at the same or a different electrode pair as the prior trial and whether or not there was an AD at the prior trial, there was no association between the probability of an AD and the session during which the AD occurred either within a day (OR = 1.05, 95% CI = 0.81 to 1.35, p=0.74) or over all days (OR = 0.95, 95% CI = 0.85 to 1.06, p=0.37). There was no association between the probability of an AD and the trial number within a session (OR = 1.0, 95% CI = 0.998 to 1.001, p=0.29) or within a day (OR = 1.0, 95% CI = 0.9992 to 1.001, p=0.81).

ADs occurred more often when the stimulated channels were at locations where the only epileptiform discharges seen were ictal epileptiform discharges (OR vs. no discharges= 1.84, 95% CI = 1.08 to 3.16, p=0.026); however, there was no increased risk of ADs at locations with interictal epileptiform discharges only (OR vs. no discharges = 0.98, 95% CI = 0.62 to 1.15, p=0.93) or where both ictal and interictal epileptiform discharges occurred (OR vs. no discharges = 1.81, 95% CI = 0.85 to 3.92, p=0.13). At locations with only ictal epileptiform discharges, ADs occurred during 27% of the trials, compared to 21% of trials at locations with both ictal and interictal epileptiform discharges, 16% of trials at locations with only interictal epileptiform discharges, and 17% of trials with neither ictal nor interictal epileptiform discharges.

Discussion

Cortical stimulation is used clinically to localize regions important for motor, sensory, language or other functions. When setting up procedures for this, accuracy, safety and efficiency all are

important. For accuracy, testing to be done carefully, using optimized testing parameters. To improve safety, we would like to take care to avoid causing seizures with the electrical stimulation used for testing. However, efficiency implies that testing should be done as quickly as feasible. There are tradeoffs among these.

First, we found that, once ADs occurred during stimulation of a pair of electrodes, they were more likely to recur on the next trial at that pair. As mentioned in the Methods, our practice is to reduce stimulus intensity by 0.5 – 1 mA when ADs occur, but ADs could recur despite this. In a sense, each electrode pair served as its own control. There were no ADs at a given current intensity or set of intensities, then ADs occurred at another intensity, and when ADs occurred, they could continue to occur despite reduction in stimulation intensity. Second, in these cases, increasing the inter-trial interval helped to decrease the likelihood of AD recurrence. These two findings are consistent with the idea that cortical stimulation increased excitability, but also suggest that this increase was limited in duration. Third, increased stimulus duration increased the likelihood of ADs only when there hadn't been an AD during the previous trial. Put another way, this suggests that once the level of excitability had increased in the activated cortical region, to the point that ADs occurred, changes of stimulus duration, at least those within the range we used, didn't further increase excitability. They did not appear to be an additive effect for the coincidence of stimulating at the same electrode pair as during the previous trial, plus the occurrence of ADs during the previous trial. This could have been a sampling effect, since stimulating a new pair of electrodes was less common than stimulating the same pair of electrodes. Also, we begin stimulating a new pair of electrodes at low intensity, so ADs are less likely during the initial trial at an electrode pair in any case.

Changes in the level of activation of cortical cells, or in the occurrence of refractory periods, occur due to changes in ion channel activity and in the balance between intracellular and extracellular ion concentrations, these in turn occurring in large part due to neurotransmitter release, and resulting both in changes to the synaptic strength of existing connections and in the functional state of these connections, both locally and in multiple regions throughout the cortex (Buonomano and Merzenich, 1998;Sanes and Donoghue, 2000;Sjostrom and Nelson, 2002;Sheng and Kim, 2002;Nudo, 2003;Shu et. al., 2003;Destexhe and Marder, 2004;Abbott and Regehr, 2004;Chklovskii et. al., 2004;Feldman and Brecht, 2005;Pinto et. al., 2005;Haider et. al., 2007). The variations of excitability which we found can occur in awake humans under apparently stable conditions (Destexhe and Contreras, 2006;Haider *et al.*, 2007), and can occur in response to stimulation (Lee et. al., 2003;Lesser *et al.*, 2008). Normally these may be important in facilitating cortical plasticity (Duffau, 2006;Lesser *et al.*, 2008). In any case, it seems likely that all of these factors could have affected whether ADs occurred or did not occur during individual trials. In some cases, the tested regions might simply have been refractory to stimulation, due to the ADs that had just occurred. Also, other changes in the strength of connections within or between regions of the cortex might have resulted in changes in AD occurrence or recurrence.

The on-again, off-again, then on-again activation patterns we found seem best explained by alterations in neuronal excitability or refractory periods, in synaptic strengths of existing connections (Buonomano *et al.*, 1998;Abbott *et al.*, 2004;Chklovskii *et al.*, 2004), or in the functional state of the network as a whole (Buonomano *et al.*, 1998;Sanes *et al.*, 2000;Nudo, 2003;Haider *et al.*, 2007), and are consistent with the idea that rapid adaptive mechanisms can be present in the cerebral cortex of an awake human, even during apparently stable conditions (Destexhe *et al.*, 2006;Haider *et al.*, 2007) Perhaps neuronal activity can act as a gate or switch, preventing ADs on some occasions and allowing them on others. Changes in the neuronal processes underlying learning can occur over days or weeks. However, in theory, some adjustments in neuronal function should occur continuously, with adaptations to synaptic inputs occurring over seconds to minutes (Stemmler and Koch, 1999). The mechanisms

underlying these changes are unknown: they could be due to random fluctuations in thresholds of neuronal activity, a use dependent plastic process, or a deterministic process, not presently understood. Factors such as attention or activity levels, blood flow, cortical and subcortical neuromodulation, and metabolic fluctuations all could influence these changes.

Our principle findings should be taken in the context of the parameters actually used in our laboratory. Also, one should keep in mind that saturation of the amplifiers ("blocking") occurs for a period of seconds after stimulation, and ADs occurring during blocking might be missed. Because of this, our findings are relevant to circumstances in which ADs are seen, but might not be relevant to circumstances in which they are not seen. However, the parameters we used are similar to those reported by others, and so are likely to be applicable to cortical stimulation testing performed elsewhere.

It also would be important to assess the effects of current and voltage on ADs, but at the time these data were collected, we recorded current (the Grass S12 is a constant current stimulator) but did not assess voltage (which of course might vary), and both would be needed for proper analysis. We now have a system that records both current and voltage, and plan to report an analysis of the effects of these on AD occurrence in the future.

In summary, from the practical point of view, our findings suggest that, when ADs occur, and they don't respond to other means of terminating them, such as brief pulse stimulation, waiting about a minute before resuming stimulation-based testing might lesson the likelihood of AD recurrence.

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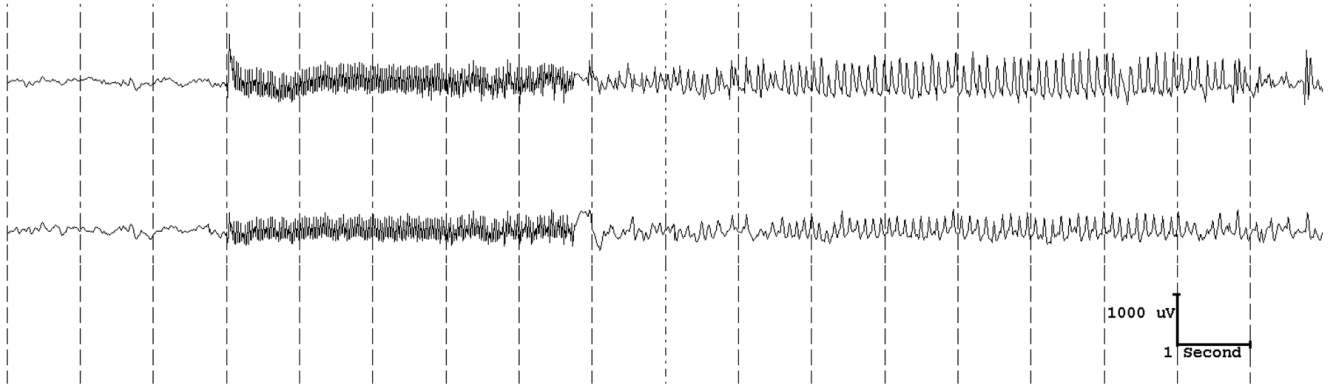
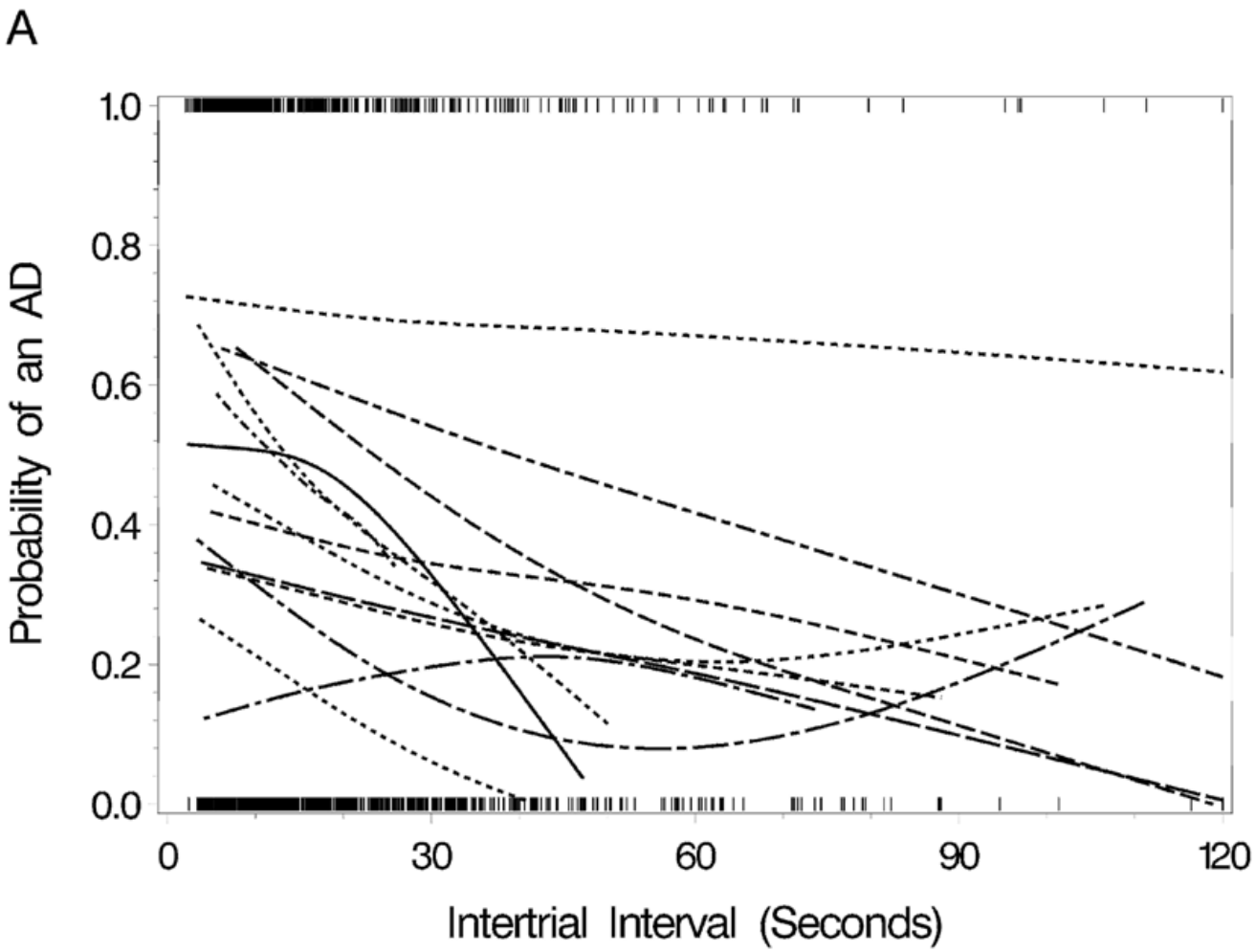


Figure 1.
Example of afterdischarges. The first three seconds show the baseline EEG. Then cortical stimulation occurs for slightly less than five seconds. Then ADs occur on both channels. Afterdischarges vary in morphology and examples of other morphologies have been published previously. (Lesser *et al.*, 1999;Motamedi *et al.*, 2002;Blume *et al.*, 2004)



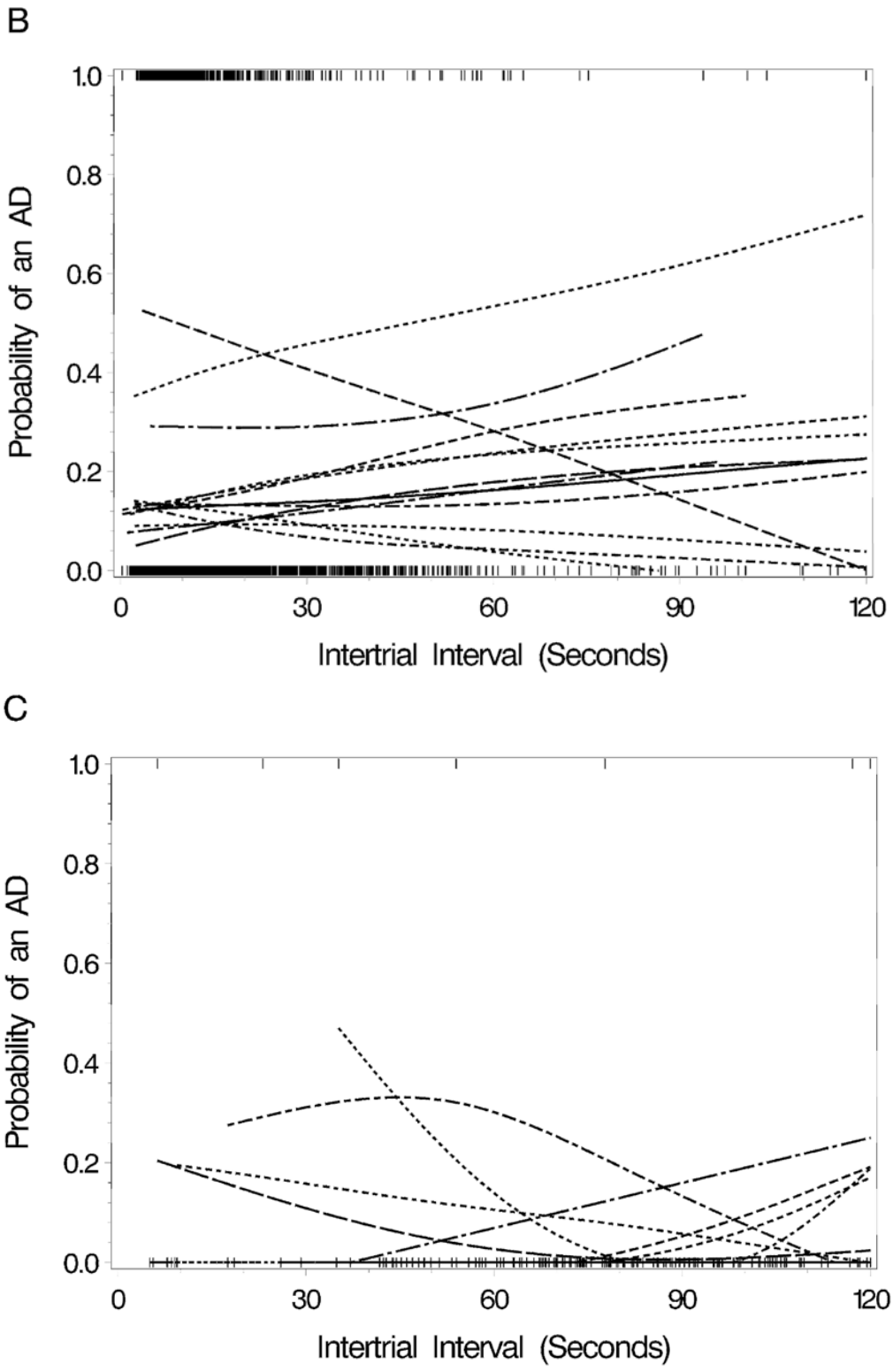


Figure 2.

Probability of an AD by the inter-trial interval length with separate lines for each patient. (A) Inter-trial interval with trials at the same electrode pair as during the immediately preceding

trial and an AD occurred at the previous trial, (B) inter-trial interval with trials at the same electrode pair as during the immediately preceding trial and when ADs did not occur at the previous trial, and (C) inter-trial interval when the electrode pair stimulated differed from the pair during the immediately preceding trial. Some lines in C have only or primarily zero values, and therefore overlap one another at the bottom of the figure. The lines were created using smoothing splines. The tics at the top and bottom of the graphs show each observation. A tic at the top of the graph corresponds to a trial with an AD, whereas a tic at the bottom of the graph corresponds to a trial without an AD.

Table 1

(A) Percentage of trials with ADs during all trials or during the first trials of testing sessions. (B) Percentage of subsequent trials with ADs, divided by those with and those without ADs during the immediately prior trial. (C) Percentage of subsequent trials with ADs, divided into those for which the same pair of electrodes was stimulated as during the immediately preceding trial and those during wich a different pair was stimulated. (D) Percentage of subsequent trials as in C, further separated into those with or without ADs during the immediately preceding trial.

A					**B**				**C**			
	Total		**First**		**AD prior trial**		**No AD prior trial**		**Subsequent - Same Pair**		**Subsequent - Different Pair**	
Patient	*N*	AD%	*N*	AD%	*N*	AD%	*N*	AD%	*N*	AD%	*N*	AD%
All	6,250	18%	41	2%	1,139	43%	5,070	13%	5,960	19%	249	5%
P#01	312	18%	4	0%	53	43%	255	13%	302	19%	6	0%
P#02	239	12%	1	0%	28	11%	210	12%	232	12%	6	0%
P#03	602	54%	3	0%	324	68%	275	38%	580	56%	19	5%
P#04	670	17%	5	0%	113	28%	552	15%	645	18%	20	10%
P#05	454	17%	2	0%	79	38%	373	13%	436	18%	16	13%
P#06	74	41%	1	0%	29	38%	44	43%	72	42%	1	0%
P#07	797	8%	5	0%	65	23%	727	7%	729	9%	63	3%
P#08	445	15%	5	0%	65	52%	375	9%	412	16%	28	7%
P#09	122	13%	4	0%	14	43%	104	10%	110	14%	8	13%
P#10	71	25%	1	0%	18	17%	52	29%	65	26%	5	20%
P#11	275	22%	2	0%	59	53%	214	14%	265	22%	8	13%
P#12	1,206	11%	4	0%	126	25%	1,076	9%	1,174	11%	28	0%
P#13	983	17%	4	25%	166	33%	813	14%	938	18%	41	0%

D								
	Subsequent - Same Pair				**Subsequent - Different Pair**			
	AD prior trial		**No AD prior trial**		**AD prior trial**		**No AD prior trial**	
Patient	*N*	AD%	*N*	AD%	*N*	AD%	*N*	AD%
All	1,076	46%	4,884	13%	63	8%	186	4%
P#01	49	47%	253	13%	4	0%	2	0%
P#02	27	11%	205	12%	1	0%	5	0%
P#03	311	71%	269	39%	13	0%	6	17%
P#04	106	29%	539	15%	7	14%	13	8%

D

	Subsequent - Same Pair				Subsequent - Different Pair			
	AD prior trial		No AD prior trial		AD prior trial		No AD prior trial	
P#05	75	37%	361	14%	4	50%	12	0%
P#06	28	39%	44	43%	1	0%	0	N/A
P#07	56	27%	673	7%	9	0%	54	4%
P#08	60	55%	352	9%	5	20%	23	4%
P#09	10	50%	100	10%	4	25%	4	0%
P#10	18	17%	47	30%	0	N/A	5	20%
P#11	57	54%	208	13%	2	0%	6	17%
P#12	120	27%	1,054	9%	6	0%	22	0%
P#13	159	35%	779	14%	7	0%	34	0%

Total = total number of trials.

First = first trial of each session (If a testing session lasted from 1300–1600 hours only the one at 1300 hours is the first trial).

Subsequent – trials that were not a session's first trial, as defined just above.

"Same Pair" / "Different Pair" = electrode pairs stimulated was same as / different from the immediately preceding trial.

N=number of trials;

AD% = percent of the trials listed under N with ADs, for example 18% of 6250 trials.

"AD prior trial", "No AD prior trial" refers to the immediately preceding trial.

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Table 2

(A) Intertrial interval length by whether the trial was at the same electrode pair as the immediately prior trial or a new electrode pair (same vs. new) and whether or not that prior trial produced ADs. (B) Relationship between intertrial interva

A														
	Same Electrode Pair													
Intertrial interval	<10 sec		10–19 sec		20–39 sec		40–59 sec		60–79 sec		80+ sec		All	<1 min
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No AD during prior trial	2,992	61%	1,282	26%	433	9%	111	2%	22	0.5%	44	0.9%	4,884	99%
AD during prior trial 3	337	31%	358	33%	251	23%	77	7%	34	3%	19	2%	1,076	95%
	New Electrode Pair													
	<30 sec		30–59 sec		60–89 sec		90–119 sec		120–149 sec		150+ sec		All	<1 min
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No AD during prior trial	11	6%	23	12%	52	28%	32	17%	12	6%	56	30%	186	18%
AD during prior trial 3	1	2%	2	3%	11	17%	12	19%	10	16%	27	43%	63	5%

B														
	Same Electrode Pair													
	<10 sec		10–19 sec		20–39 sec		40–59 sec		60–79 sec		80+ sec			
	N	AD%	N	AD%	N	AD%	N	AD%	N	AD%	N	AD%		
No AD at prior trial	2,992	12%	1,282	16%	433	15%	111	15%	22	32%	44	14%		
AD at prior trial	337	59%	358	47%	251	32%	77	34%	34	29%	19	42%		
	New Electrode Pair													
	<30 sec		30–59 sec		60–89 sec		90–119 sec		120–149 sec		150+ sec			
	N	AD%	N	AD%	N	AD%	N	N	N	AD%	N	AD%		
No AD at prior trial 3	11	18%	23	9%	52	0%	32	0%	12	0%	56	5%		
AD at prior trial	1	0%	2	0%	11	9%	12	8%	10	20%	27	4%		

Same / New Electrode Pair - same / new electrode pair, compared to the immediately prior trial.

Sec = second; min = minutes

No AD / AD during prior trial refers to the immediately prior trial.

All = all trials regardless of inter-trial interval. < 1 minute = all inter-trial intervals less than one minute.

Table 2(A) is simply descriptive and there is no statistical test performed, as the differences are simply due to how the testing occurs: we wait longer before starting the next trial when there are ADs.