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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 6250 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.

1. 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, 1999; Motamedi et al., 2002; Blume et al., 2004; Pouratian et al., 2004). Stimulating a cortical area can produce ADs, sometimes followed by clinical seizures, whether or not that region causes spontaneous seizures (Lesser et al., 1984b, 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 a 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.

2. Methods

2.1. Patients

We studied 13 patients, in whom subdural electrodes had been implanted for clinical testing, and in whom afterdischarges (ADs)

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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.

2.2. 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, CA).

2.3. 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).

2.4. 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 ms duration, repeated at 50 Hz and presented in trains lasting 4–5 s, with the first 0.3 ms positive pulse immediately followed by a 0.3 ms 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, 1994, 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, 1987, 1994, 1999; Jayakar et al., 1992; Jayakar and Lesser, 1997). 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 did not 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 h long, running from 13:00 to 16:00 h, 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.

2.5. 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 (Fig. 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, 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