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Intra-stimulation discharges: An overlooked cortical electrographic entity triggered by direct electrical stimulation

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HIGHLIGHTS

- Intra-stimulation discharges (IDs) can occur during language mapping and before after-discharges (ADs).
- High stimulus intensities, long stimulation durations, and presence of baseline epileptiform discharges at the stimulation site increase the probability of triggering IDs, and consequently, ADs.
- Attention to IDs may improve the safety and precision of neurophysiologic mapping.

ABSTRACT

Objective: Intra-stimulation discharges (IDs) can occur during language mapping, are largely unrecognized, and may precede the occurrence of after-discharges (ADs) and seizures. This study aimed to identify predictors of ID occurrence and determine whether IDs increase the probability of triggered ADs.
Methods: A total of 332 stimulation events performed during language mapping were analyzed in 3 patients who underwent intracranial EEG recordings during evaluations for epilepsy surgery. IDs were identified in 76 stimulation events. The relationships between IDs and the stimulus current intensity, stimulation duration, and proximity to regions of abnormal cortical excitability [characterized by the presence of baseline epileptiform discharges (BEDs)] were determined using regression analysis.
Results: The presence of BEDs in close proximity to stimulation, an increase in stimulus intensity by 1 mA, and an increase in stimulation duration by 1 s independently increased the odds of triggering IDs by 7.40, 1.37, and 1.39 times, respectively. All IDs were triggered during stimulations in the temporal lobe. The occurrence of IDs increased the odds of triggering ADs 5-fold.
Conclusions: Longer stimulations, higher currents, and the presence of BEDs at the stimulation site increase the probability of ID occurrence, which in turn increases the probability of triggering ADs.
Significance: Attention to IDs may improve the safety and precision of neurophysiologic mapping.

1. Introduction

Accurate identification of language areas is essential for safe and adequate resection of many supra-tentorial lesions. Visual recognition of anatomic regions highly associated with language function, such as the inferior frontal lobe or posterior superior temporal gyrus, is insufficient due to significant inter-individual variability of language representation (Mani et al., 2008; Ojemann et al., 1989), structural displacement from mass effect, and lesion-induced cortical re-organization (Lubrano et al., 2010).

Despite the availability of sophisticated neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and diffusion tensor imaging (DTI), mapping based on direct electrical cortical stimulation (Penfield, 1957; Penfield and Rasmussen, 1950) remains the gold

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standard procedure for identifying functional cortex. Its application has been shown to minimize post-operative neurological deficits, while allowing for optimal lesion resection (Duffau et al., 1999).

Direct application of electrical currents, however, can unexpectedly increase cortical excitability beyond a certain threshold and thus trigger unwanted epileptiform discharges, known as after-discharges (ADs). ADs occur after the cessation of stimulation and may propagate and organize into seizures. Seizures pose a significant safety risk to the patient, particularly when they occur intraoperatively or are associated with convulsions. ADs can also result in false localization of functional cortex and seizure foci, as the discharges may occasionally occur remotely from areas of baseline cortical irritability and/or spread beyond the stimulation site, resulting in clinical manifestations not representative of the stimulated cortex (Blume et al., 2004; Jasper, 1954). Therefore, Blume et al. (2004) advocated for the prompt identification of ADs by the use of concurrent electrocorticographic recordings (ECoG) during functional mapping requiring electrical stimulation.

Contrary to ADs, intra-stimulation discharges (IDs) have drawn significantly less attention (Ishitobi et al., 2000). These authors found a strong correlation between language disruption and IDs triggered at a distance from the stimulating electrodes, occurring in areas well known to support language function. We have previously reported our experience with IDs (Simon et al., 2010). Although typically obscured by stimulation artifact, we found that IDs are commonly recorded on intra- or extra-operative ECoG recordings during functional mapping and seem to precede the occurrence of ADs. In agreement with Ishitobi et al., we cautioned regarding their potential implications for patient safety, as well as the risk for false localization of eloquent cortex.

In this study, we describe this less recognized entity and identify factors that increase its probability of occurrence, as well as investigate the association between IDs and ADs. Finally, we propose potential areas for future research.

2. Methods

2.1. Subjects

We evaluated 3 male patients with non-lesional refractory epilepsy, with a mean age of 27 years (range: 20–33), who were implanted with subdural electrodes as part of their phase II evaluations for epilepsy surgery. The subdural electrode arrays were composed of platinum–iridium electrodes of 2.3 mm exposed diameter, embedded in a plastic sheet with 1-cm center to center distance. Their location was determined by the clinical scenario and was confirmed with co-registration of pre-implantation MRI with post-implantation CT. Each patient underwent extra-operative language mapping in the Epilepsy Monitoring Unit (EMU).

2.2. Stimulation and recording

The Penfield stimulation method was used; repetitive pulses, each of 1 ms width, at a frequency of 60 Hz, were applied to the cortex via two adjacent electrodes of the grid, connected to an XLTEK/NATUS stimulating device. Concomitant ECoG recordings were obtained from the remaining electrodes, using referential (referenced to the contralateral mastoid) and bipolar montages. The stimulus intensity was slowly increased, in 0.5 mA increments, from 1 mA up to 12 mA (mean: 4.9 mA). Stimulation of all areas of interest was performed. If stimulation of these regions did not produce any language disruption, the stimulus intensity was gradually ramped up in 0.5 mA increments until it resulted in language impairment or ADs. The stimulation was performed in epochs of 3–11 s duration (mean: 5.8 s). By using a notch filter, IDs could also be identified during the stimulation epochs. IDs and ADs were present in isolation, or in runs of epileptiform discharges, induced during and immediately after the stimulation respectively, and clearly distinguishable from the baseline epileptiform activity or any associated stimulus artifact. An area was considered safe for future resection if, when stimulated up to 12 mA, no language disruption was triggered. If language disruption was triggered by stimulation, the response was considered to be reliable if it was reproducible (i.e., the same language deficit was recorded upon repeated stimulations of the same region) and was obtained in the absence of ADs and/or IDs. Patient 1 was stimulated in the left temporal and frontal lobes, patient 2 in the left temporal, frontal and parietal lobes, and patient 3 in the left temporal lobe. All patients were on antiepileptic drugs at the time of stimulation.

A summary of the patient characteristics, stimulation parameters, and mapping results are provided in Table 1.

2.3. Variables

For each stimulation, the following variables were recorded: (1) subject (e.g., patient 1); (2) order (e.g., the fifth stimulation); (3) duration of stimulation (seconds); (4) intensity (mA); (5) location of stimulation (temporal, frontal or parietal); (6) presence or absence of triggered IDs and their duration (seconds); (7) field of IDs in relation to the stimulation site (at or beyond the "stimulation site," defined as the area where the stimulation contacts and their immediately adjacent neighbors reside); (8) presence or absence of baseline interictal and ictal epileptiform activity (BEDs) at the stimulation site; (9) presence or absence of language disruption; (10) presence or absence of ADs; (11) the field of ADs in relation to the stimulation site.

2.4. Statistical analysis

We used multivariate logistic regression to evaluate the impact of stimulation intensity, duration, and proximity to regions of increased baseline cortical excitability on the probability of triggering IDs, adjusting for additional subject specific variability. The latter was represented as three category variables (P), each category representing the individual properties for each patient (i.e., P1 for patient 1, P2 for patient 2, and P3 for patient 3). The stimulation intensity and duration were introduced in the model as continuous variables. Presence of increased cortical excitability at the stimulation site was represented as a dichotomous variable (i.e., presence or absence of BEDs). The lobar location of the stimulation was not included in the logistic regression model, as all of the stimulations that triggered IDs were in the temporal lobe regions. The outcome was represented as a dichotomous variable (i.e., presence or absence of triggered IDs).

Univariate logistic regression analysis was used to determine whether stimulations that triggered IDs had an increased probability of eliciting ADs when compared to stimulations that did not trigger IDs. Statistical analysis was performed in SAS, version 9.3 (North Carolina).

3. Results

A total of 332 stimulation events were performed and analyzed during language mapping. IDs were identified in 76 events (23% of all stimulation events), with an average duration of 4.3 s (range: 1–8 s). Sixty-four out of the 76 IDs (84.21%) had an electrical field beyond the stimulation site and 57 out of 76 (75%) were not followed by ADs. All IDs were exclusively triggered by the stimulation