Clinical Neurophysiology 125 (2014) 1324–1338

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Dynamic mechanisms underlying afterdischarge: A human subdural recording study

Giridhar P. Kalamangalam [a,*], Nitin Tandon [b], Jeremy D. Slater [a]

[a] Department of Neurology, University of Texas Health Science Center, Houston, TX, USA
[b] Department of Neurosurgery, University of Texas Health Science Center, Houston, TX, USA

ARTICLE INFO

Article history:
Accepted 27 November 2013
Available online 4 December 2013

Keywords:
Partial epilepsy
Electroencephalogram
Cortical stimulation mapping
Fourier analysis
Weiner–Winfree–Kuramoto model

HIGHLIGHTS

- We outline a mechanism explaining how afterdischarges may arise following electrical stimulation of the brain – a phenomenon that has remained unexplained for >75 years.
- We achieve a unifying link between the neurobiology of brain stimulation and the physics of coupled nonlinear oscillators.
- Our findings offer potentially new insight into the process of neural synchronisation underlying focal seizure disorders.

ABSTRACT

Objective: No synoptic understanding exists of how and why afterdischarges (ADs) occur following electrical stimulation of the cerebral cortex. Based on human observations, we formulated a general mechanism for the emergence of ADs.
Methods: We retrospectively analysed spectra of AD time-series and control segments of the resting electrocorticogram (ECoG) in 15 epilepsy patients who underwent cortical stimulation mapping. The observations led to the development of phenomenological models for AD emergence and morphology.
Results: An analytical relationship exists between the spectrum of the baseline ECoG and the ensuing AD, characterised by 'condensation' of the main baseline spectral cluster, with variable inclusion of higher harmonics of the condensate.
Conclusions: ADs arise by synchronisation of pre-existing local field potentials, likely through temporary inactivation of inhibitory interneurons from repetitive stimulation-induced depolarization. The appearance of higher harmonics indicates that ADs are further modulated by recurrent feedback, likely from the entrained activity of single units.
Significance: For the first time, a putative mechanism is suggested for AD emergence following electrical stimulation of the cerebral cortex. Insight is also offered into several empirical observations regarding ADs, detailed in the main text. More generally, a novel conceptual synthesis emerges between the behaviour of electrically-excited cortex and the physics of nonlinearly coupled multi-oscillator systems.

1. Introduction

First observed by (Adrian, 1936), stimulation-induced afterdischarges (ADs) are paroxysms of local epileptiform activity that follow focal electrical stimulation of cerebral cortex. ADs are visually striking on the electroencephalogram (EEG) directly recorded from brain surface (the electrocorticogram; ECoG), appearing as large-amplitude, well-organised rhythms that stand out from the baseline. Early simultaneous microelectrode and surface EEG recording (Gerin, 1960) established that ADs are rhythmic large-scale fluctuations of the local field potential that, at onset, are independent of individual neuronal action potentials but later synchronously entrain single units.

ADs are observed in several different experimental preparations; in human subjects they are commonly observed during cortical stimulation mapping (CSM) carried out for localisation of eloquent function prior to resective surgery for refractory focal epilepsy or brain tumours (Blume et al., 2004; Lesser et al., 2008, 1984; Pouratian et al., 2004; Tandon, 2008). Stimulation parameter

* Corresponding author. Address: Department of Neurology, University of Texas Health Science Center, 7.102 MSB, 6431 Fannin, Houston, TX 77030, USA. Tel.: +1 713 500 7117; fax: +1 713 500 7120.
E-mail address: Giridhar.P.Kalamangalam@uth.tmc.edu (G.P. Kalamangalam).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.11.027

prerequisites for ADs are, in general, sufficient current intensity (amperage) and stimulus duration (Pinsky and Delisle Burns, 1962). In patients with partial epilepsy, as in animal experiments, ADs are readily elicited over normal brain areas, but are seen at lower stimulation thresholds in proximity to epileptic foci (Wyler and Ward, 1981). In addition, seizure-like symptoms may be seen with ADs occurring over eloquent cortex (Carreno and Lueders, 2008).

Despite their immediacy to processes underlying localisation-related epilepsy, and a wealth of observation since Adrian's original report, ADs remain poorly understood. Stimulus thresholds for eliciting ADs show high degrees of inter- and intra-subject variability (Lesser et al., 2008)). Essentially, the intrinsic features of the baseline brain state predisposing to ADs following stimulation remain unknown, apart from the single observation (Lesser et al., 2008) that areas of greater low-frequency content in the baseline ECoG (i.e., brain areas with focal slowing) are more prone to AD than others. Why this should be – the authors' dataset otherwise documented the complete *un*predictability of AD occurrence – is unclear. Early observations in humans (Jasper, 1954) established that ADs adopt certain stereotypic waveforms, confirmed and reclassified more recently (Blume et al., 2004). The reason for these distinct morphologies, and whether they represent distinct neurophysiological processes, is uncertain. In the setting of focal epilepsy, a reliably predictive relationship between AD thresholds and sites of spontaneous ictogenesis remains controversial (Bernier et al., 1990; Blume et al., 2004; Jasper, 1954; Weiser et al., 1979). At root, these multiple knowledge gaps reflect the lack of a fundamental understanding of ADs; no synoptic understanding exists for why and how ADs occur following electrical stimulation.

We performed a systematic review of ECoG AD data acquired in 15 epilepsy patients undergoing extra-operative cortical stimulation mapping over the left hemisphere with subdural grid electrodes. We regarded ADs as the dynamic response of the normal brain to electrical stress; that is, behaviour exhibited by the cortex operating physiologically, but under extreme conditions (or 'parameter regimes': (Glass and Mackey, 1987)). We asked whether signatures of such cortical response existed under less extenuating conditions, i.e., with sub-threshold stimuli. Based on pilot observations, we hypothesised the existence of an observable continuum of transitions from baseline ECoG recordings to AD-like patterns following cortical stimulation at increasing strengths. The abrupt appearance of ADs in an 'all-or-none' fashion at threshold, we surmised, represented the crossing of a critical point in the continuous transition. We further hypothesised that the various AD morphologies represented 'waypoints' on the transition – that is, variants along a spectrum of fundamentally similar latent behaviours. Our conceptual framework suggested a unifying proposal regarding the neurophysiology of ADs.

2. Methods

2.1. Definition

Afterdischarges (ADs) were defined as rhythmic stereotypic slow waveforms at or above 1 Hz, or repetitive spike discharges at or above 1 Hz, or waveforms of mixed slow/sharp morphology at or above 1 Hz, that lasted least 2 s following the offset of electrical stimulation and stood out clearly from the baseline. A single spike, slow, or spike-wave discharge was not treated as an AD in the present study.

2.2. Data

Fifteen patients (3 males, 12 females; median age 32 years) with medically refractory left hemispheric fronto-temporal epilepsy were studied. All patients underwent subdural grid electrode implantation, performed by a single surgeon (NT) for the purposes of localisation of ictal onset and mapping of eloquent function. Subdural electrodes were platinum–iridium discs with 3.5 mm in contact with the pia and 10 mm inter-electrode distance, embedded in silastic (PMT Corporation, Chanhassen, MN, USA). Sets of electrodes forming rectilinear grids or strips were placed subdurally during craniotomy. Location and numbers of electrodes implanted were determined by clinical criteria; most patients nevertheless received fairly stereotypic coverage of the temporal and frontal brain areas. Numbers of contacts per patient varied from 94–147 (mean 118). Postoperatively, cranial CT scans were obtained and co-registered with pre-implantation cranial MRI. Electrodes were localised on the CT scan and projected onto a cortical surface model generated by FREESURFER (Dale et al., 1999) using in-house software and visualised in SUMA (Saad and Reynolds, 2012). Locations were manually verified using intraoperative photographs (Pieters et al., 2013). Patients subsequently underwent several days of continuous video-EEG monitoring (Nihon-Kohden, Inc., Foothills Ranch, CA, USA; EEG sampling frequency either 200 or 1000 Hz, corresponding to analogue data pre-filtered in the passband 0.3–70 or 0.3–300 Hz) with their antiepileptic medications reduced to enable recording of habitual seizures. Medications were then reintroduced and patients were additionally administered fosphenytoin prior to CSM being carried out in sessions lasting 1–3 h each, over a 24–48 h hour period.

Stimuli were delivered via a Grass S88X dual output square pulse stimulator (Grass Technologies, Warwick, RI, USA) using biphasic, charge-balanced pulses of 0.5 ms duration at a frequency of 50 Hz, in trains lasting 3 s. Electrodes were sequentially stimulated in a contiguous bipolar fashion, always progressing from lower current strengths (0.5–1 mA) to a maximum of 10 mA, with standardised testing (Tandon, 2008) for motor, sensory and language function conducted during stimulus delivery. Since the objective of mapping was to delineate eloquent cortex, testing of an electrode was considered complete once function of any type was unequivocally identified at particular stimulus strength; higher stimulus strengths were not employed. Thus, not all electrodes were tested at maximum current strengths. For clinical reasons, only a proportion (30–50%) of all electrodes implanted required testing; these were usually those over the lateral and basal temporal surfaces (for language), and over the lateral frontal contacts (for sensorimotor function and language). The ECoG was concurrently inspected for ADs following each stimulus. Electrode pairs eliciting brief, self-terminating ADs at particular stimulus strengths were re-challenged at the same strength after a $\sim$10 s interval in an attempt to continue mapping. Mapping was however abandoned at electrode pairs exhibiting repeated or prolonged ADs. Occasionally, in an attempt to halt a prolonged AD, a second stimulus was delivered over the ongoing discharge. The manoeuvre variably changed the visual character of the AD, occasionally aborting it.

Raw CSM ECoG data were reviewed offline in an average reference montage. The first author, a board-certified electroencephalographer, marked all instances of ADs, noting stimulus strengths, electrode contacts stimulated, electrodes involved in the AD, and AD duration. AD epochs, as well as multiple length-matched ECoG segments representing stimulus-free baseline conditions and segments following sub-threshold stimuli were archived. ADs of duration 7 s or greater were flagged. The data were subjected to further independent review by another author (JDS), also a board-certified electroencephalographer. The latter was blinded to the results of initial review and re-reviewed all the data for AD occurrences and their duration. There was agreement between the two reviewers in all except seven instances (three pertained to the diagnosis of a post-stimulus waveform as an AD; four concerned the labelling of ADs being greater than or less than 7 s). Only ADs that were agreed upon by both reviewers were studied further.