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Dynamic mechanisms underlying afterdischarge: A human subdural recording study

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Abstract

Objective: No synaptic 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.

Keywords

Partial epilepsy; Electroencephalogram; Cortical stimulation mapping; Fourier analysis; Weiner-Winfree-Kuramoto model

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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 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 localization-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 unpredictability of AD occurrence - is unclear. Early observations in humans (Jasper, 1954) established that ADs adopt certain stereotypic waveforms, confirmed and re-classified 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 synaptic 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 frontotemporal 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 bi-phasic, 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 ~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.

Clinical details on the patient group are summarised in Table 1. Fig. 1 shows grid positions on reconstructed surfaces of the patients' own cranial MRI, electrodes stimulated and electrodes exhibiting ADs in a single example patient. Such data were available for all 15 patients.

2.3. Analysis

Downloaded digital ECoG data were imported into and processed in MATLAB (The Mathworks, Natick, MA, USA). Single-channel power spectra of length-matched AD epochs, baseline epochs, and epochs following sub-threshold stimulation were computed by the periodogram method (Karl, 1989) and visually compared. The sampling frequencies employed (200 and 1000 Hz, depending on the subject studied) implied that ECoG data in the respective passbands of 0.3–70 Hz and 0.3–300 Hz were represented without aliasing. The use of a minimum data length of 7 s indicated a spectral resolution of at least $1/7 \approx 0.14$ Hz for all epochs analysed. A fixed-step fourth-order Runge-Kutta method (Press et al., 1992) was implemented in MATLAB for the numerical solution of the illustrative mathematical model proposed (see Section 4).

The study was approved by the Institutional Review Board of the University of Texas Health Science Center.

3. Results

3.1. Afterdischarge occurrence

Two hundred and twenty-seven ADs were observed following a total of 5318 separate stimuli applied to the patient group. Numbers of stimuli applied to individual patients ranged from 34 to 700 (median 335); numbers of ADs elicited per patient varied from 2 to 48 (0.47–17.64% of stimuli; mean 4.27%). Thresholds for eliciting ADs varied widely between patients and electrode contacts, and on repeat testing of the same contact in the same patient (Lesser et al., 2008; Pouratian et al., 2004). However, there was an unequivocal tendency for ADs on the whole to occur at high, rather than low, stimulus strengths (Pinsky and Delisle Burns, 1962). One hundred and twenty-nine ADs were judged ≥ 7 s in length and were chosen for further analysis.

All four of the distinct AD morphologies classified by Blume (2004) - rhythmic waves, spike-waves, polyspikes, and sequential spikes (henceforth denoted Blume type I, II, III and IV, respectively) - were observed (Fig. 2A–D). Most ADs however exhibited features of more than one Blume type. Relevant to analysis below, we also classified all ADs as *regular*, as in having near-metronomic periodicity as assessed visually, and *irregular*, where the rhythm's basic period was indeterminate or drifted significantly. Fig. 2E–F show two examples of irregular ADs. ADs switching between regularity and irregularity were classified on the basis of their predominant character. Overall, 81/129 $\approx 62\%$ of ADs were judged regular; the remainder were labelled irregular.

Summary data regarding all 129 ADs of duration ≥ 7 s appears as Table 2: shown are patient data, electrode contact numbers, stimulation strengths, Blume type, and regularity.

3.2. Comparison of AD spectra before and after stimulation

Comparison of power spectra of ADs with those derived from length-matched non-AD ECoG epochs from the same channel revealed three types of relationship between the spectra, not obvious on visual review of the raw time-series.

3.2.1. 'Condensation'—The major power peak in the baseline epoch was also present in the AD spectrum, but with less of a distribution around the mean, minor variable shift of the mean itself, and relatively reduced power in frequencies away from the mean. In other words, the AD power spectrum appeared as a narrowed and subtly translated version of the baseline spectrum, as though the spectrum of the baseline had 'condensed' or 'clumped' together to yield the AD spectrum. We quantified the latter effect by computing σ/μ , the coefficient of variation of the spectrum, confirming that the visual impression of 'condensation' of the afterdischarge spectra was indeed associated with a smaller σ/μ . Fig. 3 illustrates an example.

3.2.2. Condensation-plus-harmonics—In addition to the condensate corresponding to the baseline spectrum's major peak, the AD spectrum showed significant harmonic content: additional peaks centred around integral multiples and/or submultiples of the fundamental peak. Fig. 4 shows an example.

3.2.3. Harmonic-dominant—The AD spectrum was predominantly composed of harmonics of the fundamental peak that was itself barely visible in comparison. Fig. 5 shows an example.

Overall, 26/129 ($\approx 20.1\%$) of ADs showed condensation only, 46/129 ($\approx 35.6\%$) showed condensation-plus-harmonics behaviour, and 17/129 ($\approx 13.2\%$) showed a harmonic-dominant pattern. In the remainder ($40/129 = 31\%$), these relationships were less evident due to a variably broadband nature to the AD spectrum. All ADs with broadband spectra were irregular (as defined above) in the time domain. Conversely, all regular ADs had non-broadband spectra; there were also eight instances of ADs classified as irregular that nevertheless had non-broadband spectra. ADs with broadband spectra were not analysed further (see Section 4).

3.3. Multiple AD morphologies

The presence of three fundamental patterns to the baseline ECoG-AD power spectral relationship suggested the following: when ADs of more than a single Blume type occurred at the same location (say, following separate stimulations of the same electrode pair), their power spectra would only differ in the extent to which they belonged to one of the three classes. In other words, that different Blume classes at the same location, though visually different when viewed as time-series, would differ in the frequency domain only in the relative proportion of power accorded to the fundamental peak and its harmonics. This expectation was confirmed in the observations below.

Across subjects, there were 28 instances of more than one AD at the same location following different stimulations of the same electrode pair. In the majority, these ADs were of the same Blume type (and so possessed identical power spectra). However, we observed five instances of ADs at the same location clearly differing in Blume type; Fig. 6 illustrates two examples from different patients. Fig. 6A (top trace; blue) shows a Blume Type III, and the bottom trace (black) a Blume Type II AD, seen following a different stimulus at the same electrode. There is some similarity in the visual character of the two ADs, but their real relationship is appreciated on comparing power spectra: the Type III discharge has less relative power in the slower frequency cluster, but possesses several higher harmonics of the subsidiary peaks that are also seen in the Type II discharge. Fig. 6B shows the change from a Type II discharge (top trace) to a Type I–II discharge (bottom trace). Similar correspondence was seen in all five instances of multiple Blume Types at a single electrode. Fig. 7 illustrates a different situation: a single prolonged AD flips spontaneously from Blume Type II to Type IV. The Type IV sequential spike pattern naturally possesses more power at higher frequencies than spike-wave, but comparison of the power spectra between the two AD segments reveals that their relationship is *quantitative*: the Type IV pattern is essentially composed of second, 4th, 8th and 12th harmonics of the fundamental major peak of the slower Type II pattern (≈ 2 Hz). There were five instances of spontaneous Blume Type change in our dataset, and findings similar to those described were seen in every case. Fig. 8 illustrates a different situation still. Here an ongoing Blume Type IV AD is ‘hit’ after ≈ 12 s with a second stimulus (at the same strength and at the same electrode pair) in an effort to abort it. The AD is not extinguished but instead changes to a Blume Type II, which finally

self-extinguishes after a further ≈ 16 s. Again, the frequency domain reveals the quantitative relationship between the ADs as an adjustment of power distribution between fundamental and harmonic clusters. There was one further instance of such a ‘double hit’ AD in our dataset, which also revealed similar phenomenology.

Table 3 summarises all the instances of multiple AD types in our dataset.

3.4. Sub-threshold stimuli

The three defining relationships between baseline and AD power spectra could themselves be considered variations on a single theme. That is, an AD spectrum ‘arose’ from the baseline by condensation of one or more of the baseline spectrum’s fundamental peaks, with added harmonics at varying strength. Considering condensation and harmonic generation as continuous processes, we predicted that sub-threshold stimuli would induce the same changes to the baseline ECoG spectrum - but to an extent insufficient to induce visible AD-like change in the time domain. For this, we selected three paired epochs (immediately before and after a sub-threshold stimulus) at random from each of the 15 patients and compared members of the 45 power spectral pairs against each other. In comparison with the pre-stimulus spectrum, condensation and variable harmonic generation in the post-stimulus spectrum was seen in every case. Fig. 9 shows an example. There is little visual difference between the baseline ECoG time series (Fig. 9A, bottom panel) and the response to even large (10 mA) stimulation (middle panel). However, on another occasion, the same stimulus strength elicits a robust Blume Type IV AD. Despite the obvious visual difference in the time-domain outcomes of the two stimuli, examination of the spectra reveals a systematic effect at work: the subthreshold stimulus causes frequency condensation with respect to the baseline and the appearance of a harmonic (Fig. 9B, bottom and middle panels). The effect is evidently insufficient to yield a full-blown AD - which occurs with the same stimulation at another time, accompanying a spectrum with a fully-developed condensation-plus-harmonics structure.

3.5. A quantitative framework for ADs

Our observations suggest that, in a phenomenological sense, AD arise from the baseline ECoG by: (i) sufficient condensing of disparate oscillations into one or more spectral ‘clumps’, and (ii) the addition of harmonics of the clumps. Intuitively, condensation of a multi-oscillator mixture has the effect of grouping them closer in frequency; the resultant rhythm is more narrowly centred around an average, and so less polymorphic in the time domain (in the extreme case, the rhythms may be imagined to collapse into a single frequency, yielding a pure sinusoid). Conversely, when the effect of the stimulation wears off, the condensed cluster of frequencies spreads out and the mixed-frequency baseline rhythm reasserts itself. The addition of harmonics alters the profile of the sinusoid; when harmonic content increases relative to the fundamental, the faster components of the discharge dominate.

Part (i) of our hypothesis for AD generation recalls a celebrated mechanism for the coalescence of multi-oscillator systems originally proposed by the mathematician Norbert

Weiner in the 1950s and developed further by Winfree and Kuramoto (Strogatz, 2003). Consider an additive cohort of N oscillators, all modelled as sine waves

$$a_1 \sin \theta_1 + a_2 \sin \theta_2 + a_3 \sin \theta_3 + \dots a_N \sin \theta_N \quad (1)$$

representing the various different spectral components composing the baseline ECoG. Assume the phases to be linear functions of time parameterised by constants ω_i , that is,

$$\theta_1 = \omega_1 t, \theta_2 = \omega_2 t, \theta_3 = \omega_3 t, \dots \theta_N = \omega_N t.$$

The system of N oscillators may succinctly be written as

$$\dot{\theta}_i = \omega_i, i = 1, 2, 3, \dots N \quad (2)$$

where the dot represents the time derivative. In this scheme none of the oscillators influences another (i.e., the system of differential equations is uncoupled); each oscillates independently at its own prescribed frequency; the sum total of the oscillators is the mixed-frequency rhythm

$$a_1 \sin \omega_1 t + a_2 \sin \omega_2 t + a_3 \sin \omega_3 t + \dots a_N \sin \omega_N t. \quad (3)$$

Now assume the oscillators begin to influence each other reciprocally, such that the faster ones accelerate the slower ones, and the slower ones retard the faster ones. The system (2) then becomes coupled and each oscillator's phase equation includes appropriate terms arising from other oscillators. We argue later (see Section 4) that electrical stimulation induces intra-cortical coupling of a similar nature, so that the formerly independent spectral modes of the baseline ECoG begin to interact with one another. One explicit formulation of coupling studied by Kuramoto (Kuramoto, 1984) leads to the system

$$\dot{\theta} = \omega_i + \frac{k}{N} \sum_{j=1}^N \sin(\theta_j - \theta_i), i = 1, 2, 3, \dots N. \quad (4)$$

Here the coupling parameter k determines the degree of 'binding' of an oscillator to the rest of the population; for $k = 0$ there is no coupling, and the system is just (2). As k is increased from zero, the oscillators begin to increasingly influence each other, though they still maintain some independent behaviour. As k crosses a critical value, individual independence is lost and the population 'snaps' into synchrony, which is maintained as k is increased further (Strogatz, 1994, 2003). Fig. 10A–C show computer simulations of these phenomena for a system of 250 (i.e., $N = 250$) oscillators. Fig. 10A (i) shows an uncoupled ($k = 0$) polyfrequency rhythm: the amplitudes of the spectral components were chosen to mimic the 'spread' of frequencies in a real ECoG (Fig. 10B (i) is its power spectrum). Fig. 10A (ii), shows the effect of k increased to a moderate nonzero value; this has little noticeable change on the time series, but frequency clumping is evident in the spectrum (Fig. 10B (ii)). Complete synchronisation is achieved with larger k (Fig. 10A–B (iii)), yielding a

monomorphic and fast sinusoidal rhythm: this serves as a model for the Blume Type IV AD (or a Blume Type I AD using a slower time scale).

Part (ii) of our hypothesis is that the differing Blume AD types arise from varying harmonic mixtures added to a central ('fundamental') cluster of frequencies. Generation of harmonics in dynamical systems commonly occurs from nonlinear feedback (Jordan and Smith, 2007); one may envision the fundamental frequencies being 'multiplied' or 'demultiplied' in a feedback loop that yields their higher or lower harmonics. We propose (see Section 4) that such feedback arises from the recurrent contribution of synchronous action potentials to the ongoing AD (Grenier et al., 2003). The net result is of an AD rhythm incorporating both the 'fundamental' and 'harmonic' elements; depending on their relative proportion, ADs of varying morphologies (i.e., Blume types) appear in the time domain. Fig. 10A–B (iv) is a simple illustration of the idea: the Blume Type IV model AD's spectrum is altered by the addition of a subharmonic. The effect in the time domain is dramatic - the rapidly spiking discharge accrues a prominent slow component at half the parent frequency and morphs into a model of a Blume Type II spike-wave AD. Such a transition (Type II $\rightarrow$ IV or vice versa) was in fact the most common type of transition observed in the real data (Table 3).

4. Discussion

For the epileptologist trained to diagnose EEG patterns based on their visual appearance (Kellaway, 2003), afterdischarges are a compelling demonstration of the brain's capacity to reversibly generate dramatically different rhythms on short time scales. ADs are also unarguably 'epileptiform', fulfilling one or more of the orthodox criteria of rhythmicity, possession of a sharp contour, and clear distinction from the baseline (Pedley et al., 2003).

We addressed the *phenomenological* - rather than the mechanistic - question of the process(es) underlying transformation of a multi-frequency polymorphic baseline ECoG into a repetitive, regular rhythm. We surmised that insight into neurophysiological mechanisms would secondarily follow. The central fact guiding our specific hypotheses was that ADs occur almost exclusively following stimulation and not during them (Pinsky and Delisle Burns, 1962). Thus, rather than representing cortical behaviour 'driven' directly by external electrical stimulation, ADs are a response to a perturbation: a dynamical consequence of change in the system parameter (Glass and Mackey, 1987). This led us to hypothesising AD emergence from the baseline as a continuous transition: incipient following minimal stimuli, increasingly observable following stronger stimulation, and fully developed following a supra-threshold stimulus. Our choice of frequency (Fourier) domain (as opposed to working with the ECoG and AD time series) confirmed our hypotheses in an intuitive manner. The consistency between the known neurophysiology of stimulation-excited cortex and our macroscopic ECoG-level results allowed us to propose below mechanisms for how and why ADs arise at all.

Notwithstanding the complexities of computing the vector field distribution due to focal galvanic stimulation of the cortex (Schuele et al., 2008), the effects of electrical stimulation can be understood as either local (arising from depolarisation of neural elements in immediate proximity to the stimulating contact) or remote (by the excitation of white matter

fibres of passage synapsing on distant targets). Local effects are evidently maximal in the neighbourhood of stimulation and drop off rapidly beyond short distances; we consider only these. Single pulses of stimulating current, if sufficiently strong, cause depolarisation of single units; high frequency currents cause repetitive depolarisation that is ratelimited only by the neurons' absolute refractory period (Koester and Seigelbaum, 2013). If carried out for a sufficient length of time, high-frequency (>15 Hz) stimulation leads to a state of synaptic depression that suppresses further action potentials (Seigelbaum et al., 2013): it is from this state of local cortical neural 'exhaustion' that an AD emerges (Pinsky and Delisle Burns, 1962). Though the latter observations of 50 years ago provide undisputed evidence for the substrate responsible for ADs, the mechanism for AD emergence has itself remained unclear.

We suggest the following: It has been known since the earliest ECoG studies (Grey Walter, 1950) that the brain's local field potentials (LFPs) have complex spatiotemporal structure: the classic alpha rhythm, for instance, arises from virtually the entire neocortex as a family of alpha 'rhythms' of overlapping frequencies and differing spatial extents (Nunez and Srinivasan, 2006). The macro-columnar architecture of the cortex naturally supports such a dynamic 'tensegrity' (Buzsaki, 2006) structure, with inhibitory and excitatory connections between columns determining the moment-to-moment degree of inter-columnar LFP coalescence. If inhibitory interaction amongst a group of cortical columnar domains were selectively weakened, synchronisation between spatially adjacent LFPs would more readily ensue. Sustained high-frequency stimulation does so: action potential thresholds are lower in inhibitory interneurons than cortical principal cells (Csicsvari et al., 1998), so that prolonged repetitive stimulation exhausts interneurons more than other neuronal populations. Related evidence comes from studies of cortical excitability performed with repetitive transcranial magnetic stimulation (rTMS) when the inter-stimulus interval (ISI) is varied. Very short ISIs (<5 ms) produce an inhibitory influence on cortical excitability (short intra-cortical inhibition); ISIs in the 6–20 ms range produce a facilitatory effect (short intra-cortical facilitation; SICF); long ISIs (50–200 ms) again produce inhibition (long intra-cortical inhibition) (Hallett, 2007; Ziemann et al., 1996). The precise mechanisms for all three effects remain to be fully elucidated but are likely mediated through interneurons (Hallett, 2007). The frequency range for eliciting SICF is the reciprocal of the ISI, i.e. 50–166 Hz - the lower limit of which is the commonly used frequency parameter for CSM studies in epilepsy patients (as it was in ours). A direct analogy between the excitatory effects of electrical stimulation and rTMS therefore suggests itself. High-frequency (≈ 50 Hz) electrical stimulation 'homogenises' the cortical volume around the stimulating contact by weakening inhibitory interactions more than excitatory ones. Adjacent LFPs, no longer walled off from one other by inhibitory influence, readily phase-lock into a common rhythm. The constructive effect of phase-locking causes neighbouring LFP amplitudes to add up on average, producing a large-amplitude ensemble rhythm that stands out from the background ECoG, leading to the visually-diagnosable electroencephalographer's AD. As the exhausted principal units recover, they are progressively recruited into the AD, firing synchronously with the phase of the AD that takes them over threshold. We therefore see why the beginning of an AD is virtually exclusively an LFP phenomenon, with single-unit firing prominent only in the later stages of a discharge (Gerin, 1960). The later recovery of interneurons re-

establishes the inhibitory interactions between adjacent cortical domains; inter-LFP coupling weakens and the AD desynchronises to the baseline ECoG.

The above-hypothesised scenario led to an explanation of our ECoG-level results as follows. Due to the provenance of an AD from pre-existing LFPs, the period of the AD - otherwise, its dominant frequency content - would necessarily arise from within the pre-existing frequencies. That is, the 'common' rhythm that the baseline frequencies lock onto would necessarily belong to the original set. Also, if the baseline spectrum moved towards a common frequency, its variance would decrease; i.e., the AD spectrum in comparison to baseline would appear more 'bunched up'. Both these features were exactly those observed (Fig. 3). We termed the process of bunching up 'condensation'. As a corollary, we presume that condensation more readily occurs over cortex that is deficient in interneuron-mediated inhibition, i.e., epileptic foci (Powell, 2013). Thus, we may understand why ADs are in general more easily elicited over, or near, the epileptogenic zone than distant from it.

Not all AD spectra were mere condensed versions of baseline spectra. Several ADs had spectra with secondary peaks at higher frequencies, often well outside the range of the baseline spectrum. However, all such secondary peaks were harmonics of the fundamental. Though periodic phenomena must necessarily possess power spectral patterns of 'fundamental-plus-harmonics' (Karl 1989) we observed that the 'fundamental' was the *same* condensate that appeared in the harmonic-free cases, arguing for a unitary generative mechanism for ADs of all Blume types. As an elementary example of how harmonics arise from nonlinear feedback (Jordan and Smith, 2007), consider the signal $S = \cos \omega t$. Assume S is run through a feedback system F so that it becomes the composite signal $S + F(S)$. If F is a nonlinear operator (say a pure quadratic), the feedback signal has the form $S + S^2$, which, using the trigonometric identity for exponents, is simply of the form $\cos \omega t + \cos 2\omega t$, i.e., the original signal plus its second harmonic. We propose the same concept here. Remembering that LFPs ultimately derive from single unit activity (Speckman et al., 2013), it is seen that when single unit discharges become sufficiently wide-spread and synchronous the LFP itself becomes susceptible to their effects. That is, the AD spectrum accrues harmonics through feedback contributions made to the LFP (Grenier et al., 2003) by discharging single units phase-locked to the ongoing AD. Consequently, the AD's time-domain appearance changes. Coupled systems of this type have been studied in physical systems for decades; a wide variety of oscillatory behaviour incorporating multiple harmonic components may occur, depending on the exact value of the parameters (Jordan and Smith, 2007).

The above considerations explained two further observations. First, that *all* regular ADs possessed the same basic structure of 'fundamental plus harmonics', with the fundamental being the condensate of the baseline spectrum. Second (and consequently), that the various AD types (Blume classes) differed only in the details of that structure - less or more of the fundamental versus particular harmonics. In particular, when more than one Blume class occurred at the same electrode - whether following different stimulations, in the course of evolution of a single AD, or whether arising from a stimulation 'double hit' - they differed only in the details of that particular spectral make-up (Figs. 6-8).

Prompted by the unifying nature of our observations, we pursued quantitative modelling of ADs. Doing so offered insight into the effect of sub-threshold stimuli, as well as a defining and dramatic aspect of ADs – their abrupt emergence at threshold stimuli, and once elicited, their sudden spontaneous termination. We worked with the Weiner-Winfree-Kuramoto (WKK) formalism (Strogatz, 1994) as an idealisation, but one that captured the key qualitative feature of our vision of ADs: the locking together of a disparate group of oscillators of varying natural frequencies. In the WKK model, the coupling constant k may take any positive value; the system of oscillators responds by developing some coupling (equivalently, loss of independence) for even sub-threshold values of k (Figs. 10A–B (i)–(ii)), though it is only at and beyond threshold that complete synchronisation occurs. This was remarkably reminiscent of our observations of the real data (Fig. 9A–B), attesting to AD generation being a continuous transition. In a sense – and in contradiction to the ‘all-or-none’ dictum – even subthreshold electrical stimulation produces AD-like change in the resting ECoG, though only with stimulation beyond threshold is this effect sufficient to tip the cortex into an AD. Further, the abruptness of the latter change is exactly how WKK behaves: synchrony ‘pops out’ as the coupling constant k crosses a critical value (Strogatz, 1994). Abrupt transitive behaviour of this type, though striking when visualised in the setting of human ECoG, is common-place in a variety of natural and man-made nonlinear systems (Jordan and Smith, 2007; Pikovsky et al., 2003).

We extended our modelling to indicate the effect of harmonics on the appearance of ADs and Blume classes. Fig. 10A–B (iii)–(iv) demonstrate an example – the switch of a modelled Blume Type IV AD into a Type II, by the simple expedient of adding a sub-harmonic to the fundamental. Harmonics and sub-harmonics may arise through relatively modest changes in the parameters of a nonlinear system (Jordan and Smith, 2007). Thus, small changes in the milieu of an AD- generating brain region – say, following double-hit stimulation, or spontaneous drift in cortical micro-physiology – may lead to significant changes in the feedback mix of harmonics, giving rise to differing Blume morphologies in time domain.

We comment on a few data processing issues. First, our use of ADs of a minimum length (7 s) was purely to obtain an adequate data length. Power spectra of time series of inadequate length suffer from spectral ‘leakage’ (Karl, 1989): spreading out of the power spectrum even for purely monomorphic patterns. The exact threshold of 7 s was a natural watershed between the shorter and longer ADs in our dataset. Second, for reasons of convenience, we presented and analysed all our data with the baseline ECoG and AD time series – or equivalently, power spectra – scaled for amplitude equivalence. In practice, ADs were often of much higher amplitude than the background ECoG (which was in fact one of their diagnostic criteria). However, we do not believe any important features were lost by scaling; EEG amplitudes largely reflect the volume of cortex involved in that particular waveform (Tao et al., 2005), and our interest was in the frequency locations of the power peaks, not their size. All our results were described in reference to ADs with ‘clean’ (i.e., non-broadband) power spectra. Such ADs were the majority (~70%) encountered, the majority (81/89 = 91%; see Section 2) of which were also regular in the time domain. It is unlikely that the exclusion of irregular ADs affect our conclusions. Irregular ADs likely reflect parameter drift that cause variable excitation of harmonics and/or formation of the fundamental spectral condensate. Moreover, we observed both regular and irregular ADs

arising from the same location and with similar stimulations, precluding radically different mechanisms for their causation. Finally, all comparison of baseline and AD spectra comprised just visual analysis aided by simple summary statistics (i.e., coefficient of variation to confirm spectral condensation). We believe any detailed statistics on the spectra themselves (i.e., formal comparison of baseline and AD spectra to show ‘statistically significant’ differences) would be redundant, given that the spectra were no more than mathematical representations of signals that, in their native form (segments of baseline and AD ECoG time series), were ‘significantly different’ at the outset.

Some questions remain open. Our observations do not directly explain the short term variations in the brain state predisposing to ADs (Lesser et al., 2008). Evidently, the propensity for an electrical stimulus to elicit an AD ultimately depends on a cortical location’s intrinsic excitatory- inhibitory balance, which can be highly dynamic (Badawy et al., 2012). What our work does demonstrate is that there is a stereotypic ECoG response to *every* stimulation, whether threshold or not: the process of frequency condensation and harmonic generation. We can therefore explain one of Lesser et. al.’s other observations: higher low-frequency content of the baseline predisposing to AD. As evident in Figs. 2 and 8, frequency condensation involves a shift of power to the lower frequencies. Partially clumped frequencies are naturally easier to excite into an AD than those that are spread further apart; such a baseline is therefore more readily morphed into an AD with electrical stimulation.

A significant caveat to our work is that it is based entirely on data gathered from a conventional clinical macro-electrode system. Thus, our work describes and abstracts the spectral changes that distinguish normal ECoG from AD ECoG, and so offers a window into possible physiological mechanisms, but cannot conclusively demonstrate a causative chain of events from normal ECoG to AD ECoG. To do the latter would require a hybrid approach that simultaneously samples single units, extracellular potentials, and the macroscopic ECoG under a graded CSM protocol that maximally stimulates every contact over multiple brain areas – a scenario only feasible in an experimental model. Though several groups (Csicsvari et al., 2010; Van Gompel et al., 2008; Waziri et al., 2009) have reported on simultaneous single units (micro) and LFP (macro) recordings in humans, the area of overlap of micro- and macro- recordings are small (typically $<1\text{ cm}^2$); ethical consideration will also always prevent electrical stimulation from being used for more than minimal clinical necessity.

To conclude, we believe that our large observation-driven macro-electrode human study provides substantially novel perspectives on afterdischarge provoked by cortical electrical stimulation. We highlight the natural link that emerges between the behaviour of electrically-excited cortex and the physics of nonlinearly-coupled multioscillator systems. It is of immediate interest to apply these ideas to the investigation of neuronal synchrony in spontaneous epileptic foci, an important goal in current epilepsy research (Noebels et al., 2012).

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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.

Fig. 1.

A. Graphic reconstruction of the left hemispheric grey-white interface (A1: lateral view, A2: inferior view) of the subject's preoperative MRI with superimposed electrode contacts, as identified on a co-registered postoperative cranial CT scan (not shown; see text for brief details). B1, B2. Schema of grid positioning over the lateral and inferior left hemisphere. All contacts on every grid and strip were stimulated in this patient, with the exception of orange shaded contacts. Contacts yielding afterdischarges with supra-threshold stimulation are shaded grey. Abbreviations: LF – lateral frontal, LT – lateral temporal, LP – lateral parietal, OF – orbitofrontal, AST – anterior subtemporal, MST – middle subtemporal, PST – posterior subtemporal.

Fig. 2.

A-D: Examples from our dataset of the four canonical afterdischarge (AD) morphologies described by Blume et. al. (2004). *x*-axis: time (seconds); *y*-axis: waveform amplitudes referenced to a common average (μ volts). A – rhythmic waves, B – spike-waves, C – polyspikes, D – sequential spikes. All four examples (Blume types I-IV respectively) are also sufficiently repetitive and organised to be classified as ‘regular’ afterdischarges (see text). E-F: Examples of ‘irregular’ afterdischarges. Individual waveforms are less stereotyped, and the entire pattern is less periodic.

Fig. 3.

Example of the ‘condensation’ relationship between the baseline electrocorticogram and the ensuing AD following supra-threshold stimulation. A: an 8-s epoch from a single channel of a lateral temporal electrode contact in Patient #3, prior to any stimulation. *x*-axis: time (seconds); *y*-axis: waveform amplitudes referenced to a common average (μ volts). B: the power spectrum of the baseline epoch is an irregular mix of components that is biased towards the lower frequencies. *x*-axis: frequency (Hz); *y*-axis: power spectral density (μ volts²/Hz). C: an 8-s afterdischarge elicited by a 6 mA stimulus at the same electrode, of mixed Blume II-III morphology. D: The AD’s power spectrum is a ‘condensed’ version of the baseline spectrum: less spread out, more sharply peaked, and of much greater amplitude at the maximum, as if the spectral modes comprising the baseline had coalesced towards a common average. This phenomenon possibly represents selective weakening of inhibitory interactions between adjacent local field potentials (see text), allowing the latter to phase lock and yield an ensemble rhythm around the common average. Calculations yield the baseline spectrum’s mean frequency $\mu_B \approx 3.82$ Hz and standard deviation $\sigma_B \approx 3.49$ Hz, with coefficient of variation $\sigma_B/\mu_B = 3.49/3.82 \approx 0.91$. Corresponding figures for the afterdischarge spectrum are $\mu_{AD} \approx 3.18$ Hz and $\sigma_{AD} \approx 2.27$ Hz, with $\sigma_{AD}/\mu_{AD} \approx 0.71$. The latter is less than σ_B , objectively confirming the visual impression of ‘condensation’.

Fig. 4.

Example of the ‘condensation-plus-harmonics’ relationship between the baseline electrocortical and the ensuing AD. A: a single-channel 10-s baseline epoch from a lateral temporal contact in Patient #1, and B: its power spectrum. C: ensuing AD at the same electrode, of Blume Type IV. D: the AD’s power spectrum. The latter’s fundamental (leftmost) peak is situated at ≈ 6.5 Hz, and represents a ‘condensed’ version of the baseline’s broad maximum at 7–9 Hz. Using the notation of Fig. 2, $\mu_B \approx 6.78$ Hz, $\sigma_B \approx 2.33$ Hz, $\sigma_B \approx 0.34$; $\mu_{AD} \approx 6.47$ Hz, $\sigma_{AD} \approx 1.57$ Hz, $\sigma_{AD} \approx 0.24 < \sigma_B$. Subsequent peaks of the AD spectrum are seen at twice (≈ 13 Hz) and three times (≈ 19.5 Hz) the fundamental. Harmonics of this type may arise by recurrent nonlinear feedback to the ongoing AD from entrained single units (see text). Axes units as in Fig. 2.

Fig. 5.

Example of the ‘harmonic-dominant’ relationship between the baseline electrocorticogram and the ensuing AD. A: a single-channel 8-s baseline epoch from a lateral frontal contact in Patient #9, and B: its power spectrum, which shows a single dominant peak (arrow) just <2 Hz (confirmed ≈ 1.8 Hz; see inset). C: A Blume Type IV AD is elicited by 7 mA stimulation. D: The AD’s spectrum still possesses a peak at ≈ 1.8 Hz (arrow) that is the condensate of the baseline spectrum, but large amplitude 5th, 10th, 15th and 20th harmonics dominate (at ≈ 9 , 18, 27 and 36 Hz, respectively).

Fig. 6.

ADs of multiple Blume types at the same electrode. Only the x -axis (Hz) is labelled in these figures; y -axes dimensions were rescaled and vertically offset for clarity of visual comparison. A: (bottom trace; black) an 8-s AD of Blume Type II following stimulation at 6 mA from a lateral temporal contact of Patient #3. Stimulation at 7 mA at the same contact also elicits an AD (top trace; blue), but of somewhat different morphology (mixed Type II-III). B: Comparison of the power spectra reveals a relationship between the two ADs. The three marked peaks of the first AD are localised at ≈ 1.85 Hz (arrow), ≈ 2.4 Hz (circle) and ≈ 3.7 Hz (arrow), respectively. The third peak (3.7 Hz) is merely the 2nd harmonic of the first (1.85 Hz). The subsequent (7 mA) AD's spectrum is different only in its harmonic mix. Arrows mark the fundamental and 2nd, 3rd and 7th harmonics of the corresponding arrowed peaks of the earlier AD (≈ 1.85 , ≈ 3.7 , ≈ 5.55 , ≈ 12.95 Hz). Circles mark the 3rd and 5th harmonics of the corresponding ≈ 2.4 Hz peak of the initial AD (≈ 7.2 , ≈ 12 Hz). C: Another example, from an occipito-parietal contact of Patient #8. Stimulation at 4 mA elicits an 8-s AD of Blume Type I (bottom trace, black); increasing current strength to 5 mA yields an AD of Blume Type II (top trace, blue). D: The cluster of mixed frequencies comprising the spectrum of the first (4 mA, black) AD condenses further to yield a stronger, leftward translated peak at ≈ 2 Hz in the second (5 mA, blue) AD. The latter also accrues a solitary 8th harmonic at ≈ 16 Hz (arrow).

Fig. 7.

Spontaneous evolution of one Blume Type AD to another, following a 7 mA stimulation of a lateral temporal contact in Patient #9. A: A 21-s AD of Blume Type II for the first ≈ 14 s that evolves to Blume Type IV before resolving. The initial segment includes a ~ 4 s burst of faster activity. B: The two AD data segments displayed separately. C: The power spectrum of the initial 14-s segment is somewhat broadband, but is dominated by a peak (arrow) just < 2 Hz (confirmed ≈ 1.8 Hz; see inset). The following 7-s AD segment has a spectrum with three widely separated peaks at ≈ 7.3 , 14.6 and 22 Hz, which are the 4th, 8th and 12th harmonics of 1.83 Hz.

Fig. 8.

Change of Blume Type following a second ('double-hit') stimulation. A: A 12-s Type IV AD from a lateral frontal contact of Patient #9 following a 5 mA stimulation, over which a further stimulation of the same strength is applied (arrow). B: The AD is not extinguished but emerges after the second stimulation (arrow) as a Type II AD that continues for another ≈ 16 s before spontaneously resolving. C: The relationship between the respective spectra. Top panel: The first AD's main spectral peaks are at ≈ 8.5 Hz (arrow) and ≈ 17 Hz (circle), which are the 2nd and 4th harmonics of the small fundamental at ≈ 4.25 Hz (square). The 'double-hit' AD has more of a broadband character, but its main peak is now at the slightly leftward-translated fundamental at ≈ 3.8 Hz (square), and its second harmonic at ≈ 7.6 Hz. Third and 4th harmonics are also just seen.

Fig. 9.

The continuous effect of stimulation on the ECoG spectrum. A: Bottom trace (black): a 9-s epoch from a lateral temporal contact of patient #1. Middle trace (grey): Apart from some new faster frequency components, there is little visible organised change in the ECoG following a stimulation of 10 mA. Top trace (blue): Another 10 mA stimulation at a later time (now effectively ‘supra-threshold’) elicits a Blume Type IV afterdischarge. B: Bottom trace (black): baseline power spectrum shows an irregular mix of frequencies with scattered maxima. Middle trace (grey): The spectrum following subthreshold 10 mA stimulation shows some condensing of the baseline low frequency mix around 2 Hz (arrow); a discrete cluster of frequencies at the 4th harmonic (≈ 8 Hz) also appears (circle). Top trace (blue): a typical multipeak profile emerges, related to the subthreshold and baseline spectra: the fundamental is small, but is in the same location as before (≈ 2 Hz); the 4th harmonic (circle; ≈ 8 Hz) dominates, and the 8th (≈ 12 Hz) and 12th harmonics (≈ 24 Hz) make an appearance (squares).

Fig. 10.

Numerical results from simulation of the Kuramoto model. $N=250$ oscillators with k variable between runs. A: Time series for 10 s of simulated time. x -axis: seconds, y -axis: voltage amplitude (arbitrary units). (i) $k=0$. The time series (simulated ECoG) appears random and irregular. (ii) Increase to $k=8$. There is no visually appreciable organised change. (iii) $k=38$. The time series is highly synchronous as a single dominant rapid frequency, modelling a Blume Type IV AD. (iv) Addition of a subharmonic at half the frequency alters the Blume Type IV AD to a Blume Type II morphology. B: The corresponding changes in the frequency domain. (i) The spectrum corresponding to $k=0$ is an irregular mix in the range $\approx 3 - 12$ Hz with scattered maxima. (ii) With $k=8$ the spectrum condenses around ≈ 5 Hz and ≈ 8 Hz, a change not visually obvious in the time series. The weak coupling in this case models the effect of a subthreshold stimulation in the real data: there is no significant change in the time domain (i.e., no afterdischarge), but condensation of the power spectrum is already under way. (iii) A single dominant peak at ≈ 8 Hz appears, consistent with the highly monomorphic rhythm seen in the time domain. This situation models the appearance of afterdischarge in the real data – the power spectrum is sufficiently condensed by coalescence of adjacent local field potentials to result in a visible afterdischarge in the time domain. (iv) Addition of the subharmonic (4 Hz). Compare A-B (i)-(iii) with the real data of Fig. 9, and A-B (iv) with Fig. 8.

Table 1

Clinical details of patient group.

PT #	Age/s ex	Interictal EEG (scalp)	Seizure semiology	Ictal EEG (scalp)	Brain MRI	PET	Neuropsych deficit	Epilepsy classification	Ictal onset (invasive)	Surgery
1.	25/M	CS, L temporal; spike, L temporal	Complex motor → GTC	L hemispheric	Normal	Nonlateralising	Dominant F-T; memory intact	L neocortical temporal	L AMT	L ATL
2.	24/M	Spike, L temporal	Automotor	L temporal	L STG encephalomalacia; L hippocampal sclerosis	L temporal hypometabolism	Executive dysfunction; subtle figural memory impairment	L mixed neocortical/ mesial temporal	L AMT	L ATL
3.	48/F	IS, L temporal	Automotor → complex motor → GTC	L temporal	Normal	L temporal hypometabolism	Executive dysfunction; memory intact	L neocortical temporal	L AMT	L ATL
4.	42/F	IS, L temporal	Automotor → GTC	L hemispheric	L hippocampal sclerosis	Nonlateralising	Dominant F-T; impaired verbal memory	L mixed neocortical/ mesial temporal	L AMT	L ATL
5.	33/F	Breach rhythm, L temporal; spike, L > R temporal	R somatosensory aura → GTC	Nonlateralising	L temporal pole encephalomalacia	ND	Dominant F-T; memory intact	L neocortical temporal	L NCT	L neocortical temporal rxn
6.	32/F	CS, L temp; spike, L > R temporal	Automotor → face clonic → GTC	L temporal	Normal	L temporal hypometabolism	Bilateral F-T; memory intact	L neocortical temporal	L NCT	L neocortical temporal rxn
7.	30/F	IS, L temporal	Automotor or NCS	L temporal	Normal	Nonlateralising	Dominant F-T; impaired verbal and figural memory	L mixed neocortical/ mesial temporal	L AMT	L ATL
8.	30/F	IS, generalised; spike, L F-P	Experiential aura → dialeptic → GTC	L hemispheric or non-lateralising	Normal	L temporal hypometabolism	Bilateral F-T; memory intact	L neocortical temporal	L AMT	L ATL
9.	31/F	IS, L > R temporal; spikes, L > R temporal	Automotor	L temporal or R temporal or non-lateralising	Normal	L temporal hypometabolism	Non-dominant F-T Poor figural memory	Bilateral mixed neocortical/ mesial temporal, L > R	L AMT > R NCT	L ATL
10.	45/F	IS, L temporal; spike, L temporal	Psychic aura → GTC	L hemispheric or nonlateralising	Normal	L temporal hypometabolism	Dominant F-T; memory intact	L neocortical temporal	L AMT	L ATL
11.	39/F	IS, L temporal; spike, L temporal	Automotor	L temporal or nonlateralising	L hippocampal sclerosis	L temporal hypometabolism	Dominant F-T; memory intact	Bilateral mixed neocortical/ mesial temporal, L > R	L AMT > L NCT	L ATL

P.T #	Age/s ex	Interictal EEG (scalp)	Seizure semiology	Ictal EEG (scalp)	Brain MRI	PET	Neuropsych deficit	Epilepsy classification	Ictal onset (invasive)	Surgery
12.	23/F	IS, L temporal; spike, L temporal	Experiential aura → automotor	L temporal	Dysplastic L temporal pole; L hippocampal sclerosis	ND	Dominant F-T; impaired verbal memory	L mixed neocortical/ mesial temporal	L AMT	L ATL
13.	67/M	IS, L hemisphere	Multimodal sensory aura → R versive	L temporal	L hippocampal sclerosis	ND	Dominant F-T; impaired verbal memory	L mixed neocortical/ mesial temporal	L T-P + independent L AMT	L parietal topectomy + L ATL
14.	53/F	Spike, R > L temporal	Dialectic → R somatosensory aura	L temporal	L middle fossa encephalocle	L temporal hypometabolism	Dominant F-T; impaired verbal and figural memory	Bilateral mixed neocortical/ mesial temporal, L > R	L NCT + L OF	L neocortical temporal rxn + L OF rxn
15.	21/F	Spike, L temporal	Automotor → complex motor	L temporal	L hippocampal sclerosis	ND	Dominant F-T; impaired verbal memory	L mixed neocortical/ mesial temporal	L AMT	L ATL

Demographics, video-EEG monitoring results, imaging findings, neuropsychological deficits, epilepsy classification, ictal onset localisation on invasive monitoring, and surgical resection performed.

Seizure semiologies follow nomenclature outlined by Lueders and coworkers (1998): individual seizures comprise one or more phases indexed by a single defining quality, with the '→' symbol indicating continuity. Abbreviations/clarifications: EEG: scalp electroencephalogram; MRI: magnetic resonance imaging; PET: positron emission tomography. Complex motor: aimless or confused movements of both proximal and distal musculature and/or moderate vocalizations; automotor: chewing or swallowing movements and/or semipurposeful distal hand movements; NCS: no clinical signs; GTC: generalised tonic-clonic; dialectic: staring and unresponsiveness. L: left; R: right; STG: superior temporal gyrus; F-T: frontotemporal; F-P: frontopolar; T-P: temporoparietal; OF: orbitofrontal; IS: intermittent slowing; CS: continuous slowing; ATL: anterior temporal lobectomy with amygdala-hippocampectomy; rxn: resection; AMT: anteromesial temporal; NCT: neocortical temporal; ND: not done.

Table 2

Grid placements and afterdischarge occurrence summary.

Patient#	Invasive implantation scheme	Contacts exhibiting ADs	Total #STIMS	Total #ADs	#ADs ≥ 7s	Current Strength S	Blume type breakdown	Regular/irregular ADs
1.	HD (1 × 8); TP (1 × 6); AST (1 × 6); MST (1 × 5); PST (1 × 8); OF (4 × 4); LT (4 × 8); LF (4 × 8); LO (4 × 4); LP (1 × 6)	LT	110	2 (1.82%)	1 (50%)	9–10	II: 1 (100%)	1 (50%); 1 (50%)
2.	LT (4 × 10); LF (2 × 10); TP (1 × 6); AST (1 × 5); MST (1 × 5); PST (1 × 8); SO (1 × 8); OP (1 × 4); OF (4 × 4)	LT	322	4 (1.24%)	4 (100%)	6–8	III: 2 (50%) IV: 1 (25%) I-II: 1 (50%)	3 (75%); 1 (25%)
3.	TP (1 × 4); AST (1 × 6); MST (1 × 6); PST (1 × 7); LO (1 × 8); LT (4 × 8); LF (4 × 8); OF (4 × 4); LP (4 × 4)	LT, MST, PST	335	25 (7.46%)	20 (80%)	4.5–10	I: 9 (45%) II: 2 (10%) III: 4 (20%) I-II: 3 (15%) I-III: 1 (5%) II-IV: 1 (5%)	10 (50%); 10 (50%)
4.	TP (1 × 4); AST (1 × 5); MST (1 × 5); PST (1 × 8); LT (4 × 8); LF (2 × 10); OF (4 × 4); PO (1 × 4)	LT	350	11 (3.14%)	7 (63%)	5–8	I: 1 (14%) I-II: 3 (43%) II-IV: 3 (43%)	3 (43%); 4 (57%)
5.	AST (1 × 4); MST (1 × 5); PST (1 × 6); LT (4 × 8); LF (4 × 6); OF (4 × 4); LP (4 × 4)	LT	470	13 (2.76%)	9 (69%)	6–10	I: 6 (67%) II: 1 (11%) I-II: 2 (22%)	3 (33%); 6 (67%)
6.	TP (1 × 4); AST (1 × 4); STG(2 × 4); MST (1 × 5); PST (1 × 6); SO (1 × 8); LT (4 × 8); LF (4 × 8); OF (4 × 4); LO (4 × 4)	LT, PST, STG	655	6 (0.92%)	1 (17%)	10	I: 1 (100%)	1 (17%); 5 (83%)
7.	TP (1 × 4); AST (1 × 6); MST (1 × 5); PST (1 × 8); SO (1 × 6); LT (4 × 8); LF (2 × 10); OF (4 × 4); LP (4 × 4); LO (1 × 4)	LT, MST	455	4 (0.88%)	1 (25%)	8.5–10	I-II: 1 (100%)	1 (25%); 3 (75%)
8.	TP (1 × 6); AST (1 × 5); MST (1 × 5); PST (1 × 8); LT (4 × 8); LF (4 × 8); OF (4 × 4); LP (1 × 6); LO (1 × 6); FP (1 × 4)	LT, PST	275	14 (5.1%)	8 (57%)	3–6	I: 1 (12%) II: 3 (38%) I-II: 3 (38%) I-IV: 1 (12%)	7 (88%); 1 (12%)
9.	Left: TP (1 × 4); AST (1 × 6); MST (1 × 5); PST (1 × 8); SO (1 × 6); LT (4 × 8); LF (4 × 8); OF (4 × 4); Right: AST (1 × 6); PST (1 × 8); LT (1 × 8); LF (1 × 8); TO (1 × 8);	(Left) LT, LF	489	45 (9.2%)	24 (53%)	3–8	I: 7 (29%) II: 9 (38%) I-II: 2 (8%) II-III: 3 (13%) II-IV: 2 (8%) I-II-III: 1 (4%)	18 (75%); 6 (25%)
10.	TP (1 × 4); AST (1 × 6); MST (1 × 6); PST (1 × 6); SO (1 × 8); LT (4 × 8); LF (4 × 10); OF (4 × 4); LO (4 × 4)	LT, MST	426	2 (0.47%)	1 (50%)	3–10	I-II: 1 (100%)	1 (50%); 1 (50%)
11.	Left: TP (1 × 8); AST (1 × 6); PST (1 × 6); LT (4 × 6); LF (4 × 6); OF (4 × 4); PO (1 × 6) Right: OF (4 × 4); TP (1 × 6); AST (1 × 4); PST (1 × 4); LT (1 × 6)	(Left) LT	34	6 (17.6%)	3 (50%)	8–10	II: 1 (33%) III: 2 (67%)	1 (33%); 2 (67%)
12.	TP (1 × 6); AST (1 × 4); MST (1 × 4); PST (1 × 5); SO (1 × 8); LT (4 × 8); LF (4 × 8); OF (4 × 4); LO (1 × 4); LP (1 × 4)	MST, PST, SO	155	5 (3.2%)	3 (60%)	4–10	II: 1 (33%) III: 1 (33%) I-II: 1 (33%)	3 (100%)

Patient#	Invasive implantation scheme	Contacts exhibiting ADs	Total #STIMS	Total #ADs	#ADs $\geq 7s$	Current Strength S	Blume type breakdown	Regular/irregular ADs
13.	AST (1 $\times$ 6); MST (1 $\times$ 6); PST (1 $\times$ 8); LT (4 $\times$ 8); LF (4 $\times$ 8); OF (3 $\times$ 4); LP (1 $\times$ 4)	LT, LF, PST	700	48 (6.86%)	23 (48%)	2–10	I: 3 (13%) II: 4 (18%) III: 3 (13%) I-II: 6 (26%) I-III: 2 (9%) I-IV: 1 (4%) II-III: 2 (9%) II-IV: 1 (4%) I-II-III: 1 (4%)	11 (48%); 12 (52%)
14.	TP (1 $\times$ 4); AST (1 $\times$ 6); MST (1 $\times$ 4); PST (1 $\times$ 6); LT (4 $\times$ 6); LF (4 $\times$ 8); OF (4 $\times$ 4); LO (2 $\times$ 4)	LT, MST	251	34 (13.5%)	22 (65%)	3–10	I: 1 (4%) II: 2 (9%) III: 6 (27%) I-III: 4 (18%) II-III: 3 (15%) III:IV: 6 (27%)	15 (68%); 7 (32%)
15.	TP (1 $\times$ 6); AST (1 $\times$ 5); MST (1 $\times$ 4); PST (1 $\times$ 6); SO (1 $\times$ 8); LT (4 $\times$ 8); LF (4 $\times$ 8); OF (4 $\times$ 4)	LT, MST	291	9 (3.1%)	2 (22%)	4–10	II: 1 (50%) I-II-III-IV: 1 (50%)	2 (100%)

Left-to-right: Subject number, overall scheme of intracranial electrode placement with grids and strips (numbers of contacts per grid or strip); grids and/or strips exhibiting ADs during cortical stimulation mapping; total number of stimuli delivered; total numbers of ADs elicited (percent of total stimuli number); number of ADs $\geq 7s$; current strength range associated with ADs; Blume classes (see text) by number and percentages for ADs $\geq 7s$, as judged by visual analysis (most ADs had features of more than one Blume class, denoted by 'I-II', 'II-III-IV', etc.); numbers and percentages of 'regular' and 'irregular' ADs as defined in the text, also judged visually. Abbreviations: HD: hippocampal depth electrode; TP: temporopolar; LT: lateral temporal; LF: lateral frontal; OF: orbitofrontal; AST: anterior subtemporal; MST: mid subtemporal; PST: posterior subtemporal; LP: lateral parietal; SO: suboccipital; PO: parieto-occipital; LO: lateral occipital; TO: temporo-occipital; STG: subtemporal grid, FP: frontopolar.

Table 3

Multiple blume types at the same electrode.

Discrete occurrences following separate stimulations			
#3	LT 20–21	6 mA	II
		6.5 mA	IV
		7 mA	III
#4	LT 23–24	8 mA	II
		8 mA	IV
#8	OP 5–6	4 mA	I
		5 mA	II
#9	LT 26–27	4 mA, 5 mA	II
	LF 9–10	6 mA	IV
		5 mA	II
		5 mA	IV
<i>Spontaneous evolution</i>			
#3	LT 20–21	6.5 mA	IV → II
#4	LT 23–24	8 mA	II → IV
#5	LT 26–27	10 mA	II → IV
#8	PST 5–6	4 mA	I → I (at twice frequency)
#9	LF 3–4	7 mA	II → IV
<i>Double (or multiple) hits</i>			
#4	LT 25–26	7 mA	III → IV
#9	LF 9–10	5 mA	IV → II

Left-to-right: Patient number, contacts stimulated, strength of stimulus, and Blume Type AD(s). Top panel: Different Blume Type ADs seen at the same electrode following separate stimulations of the same electrode pair. Middle panel: Instances of spontaneous evolution of an AD from one Blume Type to another. Four such transitions were between Types II and IV; Patient #8 exhibited a transition of doubling of the frequency though the morphology remained that of a Type I AD. Bottom panel: Instances of change of Blume Type following stimulation over an ongoing AD. Abbreviations: LT: lateral temporal; LF: lateral frontal; OP: occipito-parietal; PST: posterior subtemporal.