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Periodic focal epileptiform discharges

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HIGHLIGHTS

- Periodic Focal Epileptiform Discharges (PFEDs) are a novel epileptiform pattern identified using HD-ECoG.
- PFEDs have a temporospatial scale distinct from other epileptiform discharges on ECoG.
- No relationship to seizures was identifiable in our cohort with brain tumor and seizures.

ABSTRACT

Objective: To report intraoperative periodic focal epileptiform discharges (PFEDs) during awake craniotomy using high-density electrocorticography (HD-ECoG).
Methods: We retrospectively analyzed 81 patients undergoing awake craniotomy between 9/29/2016 and 7/5/2018. Intraoperative HD-ECoG was performed with direct electrocortical stimulation (DECS) for functional brain mapping. Real-time interpretation was performed and compared to scalp EEG when performed. Perioperative seizures, surgical complications, and characteristics of PFEDs were assessed.
Results: 69/81 patients (mean age 48.5 years) underwent awake surgery; 55 operated for brain tumor, 11 for epilepsy and 3 for cavernomas. A focal abnormality on brain MRI was present in 63/69 (91.3%) patients. 43/69 (62.3%) patients had seizures preoperatively, 4/69 (5.7%) had seizures during DECS. PFEDs were identified in 11 patients (15.9%); 2 on depth recording and 9 during intraoperative HD-ECoG. 32 patients (46.3%) had preoperative EEG. HD-ECoG detected more epileptiform discharges (EDs) than standard EEG (32/43; 74.4% vs 9/32; 28.1%) (***p = <0.001***). Of 9/43 patients with PFEDs on HD-ECoG, 7 patients also had scalp EEG but only one case had EDs ***(p = 0.02)***, and 0/32 had periodic EDs.
Conclusions: Intraoperative PFEDs are novel, highly focal EDs approximating a single gyrus. In patients with brain tumors, PFEDs did not demonstrate a relationship to pre-operative seizures though has similarities to other common waveforms in patients with epilepsy.
Significance: PFEDs expand our understanding of the interictal-ictal continuum and highlight improved temporo-spatial information obtained from increasing sensor density during intracranial EEG recording.

1. Introduction

Periodic lateralized epileptiform discharges (PLEDs) are a familiar pattern to neurologists on standard EEG (Afra et al., 2008). They were initially described more than 6 decades ago (Chatrian et al., 1964) though were recently renamed lateralized periodic discharges (LPDs) by the American Clinical Neurophysiology Society to de-emphasize *epileptiform* properties that were felt to be non-essential for clinical importance. PLEDs have been typically associated with critically ill patients sustaining an acute destructive structural brain lesion such as stroke (Herlopian et al., 2018; Afra et al., 2008; Gurer et al., 2004; Chatrian et al., 1964;

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Garcia-Morales et al., 2002) characteristically associated with impaired consciousness and seizures acting as a harbinger of poor neurological outcome (Herlopian et al., 2018). Distinguishing PLEDs as an interictal or ictal phenomenon is a common treatment challenge for clinicians (Kalamangalam and Slater, 2015; Chong and Hirsch, 2005). PLEDs may have a similar electrophysiological pattern on EEG that strongly correlates with seizures (Chatrian et al., 1964; Reiher et al., 1991, Garcia-Morales et al., 2002; Gurer et al., 2004) and have been accurately identified on different methods of EEG recordings (Johnson et al., 2018; Asano et al., 2004). Periodic discharges may be an ictal phenomenon, yet the frequency of PLEDs is lower than the higher frequency anticipated with non-convulsive status epilepticus (Leitinger et al., 2015).

Standard ECoG tailoring surgical resections in epilepsy has targeted interictal spikes and sharp waves (Gavaret et al., 2015; Stead et al., 2010). However, intraoperative ECoG has been inconsistently useful for guiding resective surgery because of incongruent targets, biomarker targeted variability, and challenging time and space requirements in the OR for recording (Asano et al., 2004). Limited clinically useful information has been derived from ECoG focused upon resecting spike discharges (Jiruska et al., 2017). However, ECoG in combination with direct electrical cortical stimulation (DECS) and functional brain mapping has practical use to identify functional cortical regions during awake brain surgery (Berger et al., 1989; Eseonu et al., 2017; Berger et al., 1991; Berger and Ojemann, 1992; Berger et al., 1990; Nelson et al., 2002). Intraoperative functional brain mapping during awake craniotomy is an accepted practice that allows for dynamic clinical examination during neurosurgery (Eseonu et al., 2017; Gavaret et al., 2015; Stefan et al., 2008) and localizes epileptiform activity to provide neurosurgeons with real-time monitoring for immediate feedback. Still, limited validity to define a relationship between the epileptogenic zone and eloquent cortex has been shown beyond DECS (Sugano et al., 2007; Lachaux et al., 2012). Prior clinical investigations in epilepsy using high-density EEG scalp recording provides greater sampling rates and improved source localization (Hirsch et al., 2004; Michel et al., 2004). Recently, greater spatiotemporal resolution of ECoG has been acquired in epilepsy patients undergoing intracranial EEG hybridized with flexible microwires to identify micro-discharges (Hirsch et al., 2004; Michel et al., 2004; Staba et al., 2002; Schevon et al., 2008; Worrell et al., 2004). Therefore, we hypothesized that similar to other waveforms occupying an atypical spatiotemporal domain such as high-frequency oscillations that usage of high-density recording with ECoG in patients with brain tumor and epilepsy would lead to additional neurophysiological information.

An inherent gap in knowledge exists using standard ECoG grids to identify epileptogenic networks when they arise from spatially restricted local field potentials (Stead et al., 2010). In this study, we aimed to report our serendipitous findings of periodic focal epileptiform discharges (PFEDs) using HD-ECoG. We defined PFEDs as a continuous run of spatially restricted, periodic spike or sharp wave discharges with a reproducible waveform frequency and focal distribution. Morphological subtypes such as PLEDs plus are associated with a higher risk of status epilepticus using scalp EEG (Reiher et al., 1991; Chong and Hirsch, 2005). In addition, several epileptiform patterns have been observed on ECoG (Ferrier et al., 2006; Brunner et al., 2009). We now report and describe PFEDs in awake patients identified in the operating room (OR) using HD-ECoG to expand the concept of periodic discharges and the relationship to seizures along the interictal-ictal continuum.

2. Methods

2.1. Patient selection

The present study complied with the institutional review board-approved ethical guidelines of Mayo Clinic. Written informed consent was obtained for the procedures. Patients were selected between September 2016 and July 2018 based on the following inclusion criteria; age $\geq$18 years old, patient submitted for brain tumor or epilepsy surgery, elective procedure, a solitary lesion, and no comorbidities that would interfere with surgery during an awake craniotomy. Two authors (W.O.T. and A.M.F.) visually interpreted real-time intraoperative ECoG recordings during functional brain mapping.

Clinical variables analyzed included age, gender, presenting symptoms, history of epilepsy and neurological deficits at the time of ECoG and functional outcome. Outcome was evaluated at the end of surgery and at the first post-operative follow-up visit. Complications were recorded in the OR including any subjective or objective abnormality in the neurological examination and perioperative and seizure freedom was assessed by an epileptologist (W.O.T. or A.M.F.) at follow-up visit when the patient had a history of seizures. Lesion size and location was identified preoperatively by the neuroradiology.

2.2. Definitions

The frequency of periodic discharges and definition of electrographic seizures were defined and implemented according to current standardized EEG terminology set forth by the American Clinical Neurophysiology Society (Hirsch et al., 2013). We defined PFEDs as a continuous run of focal periodic epileptiform discharges with a reproducible waveform frequency and distribution during real-time intraoperative ECoG with a uniform distribution, morphology, duration and quantifiable inter-discharge intervals that varied <50% from one cycle to the next between consecutive waveforms and morphology based upon standard descriptive terminology obtained through published reports (Herlopian et al., 2018; Gurer et al., 2004; Reiher et al., 1991; Kalamangalam and Slater, 2015; Johnson et al., 2018; Michel et al., 2004; Hirsch et al., 2013). PFEDs "proper" consisted of a waveform that crossed the baseline no more than twice (Herlopian et al., 2018; Gurer et al., 2004; Reiher et al., 1991; Kalamangalam and Slater, 2015; Johnson et al., 2018). PFEDs "Plus" consisted of PFEDs associated with a polyspike waveform that crossed the baseline in at least 3 phases (Reiher et al., 1991; Hirsch et al., 2013). We chose to retain "epileptiform" in PFEDs despite their occurrence in non-epilepsy patients due to the consistent relationship with a spike or sharp wave (unlike LPDs). In addition, benign patterns exist that incorporate "epileptiform" and epileptiform morphology (i.e., wicket "spikes", benign "epileptiform" transients of sleep, 6-Hz "spike-and-waves") yet are unassociated with seizures or epilepsy. Spatial distribution was classified as superficial or deep for each channel involving EDs and PFEDs based upon electrode recording using either subdural high-density grid or stereotactic depth recording, in addition to the mean area of involvement in millimeters (mms) judged based upon inter-electrode distance and the number of contacts involved.

2.3. Electrocorticography (ECoG)

All patients undergoing ECoG utilized neuroanesthesia according to standard technique involved during awake craniotomy.

One unblinded interpreter during the operation and a second interpreter assessed uninterrupted artifact-free HD-ECoG following acquisition. ECoG and hand-held DECS (Eseonu et al., 2017) led by a single surgeon (A.Q-H), was performed according to a pre-established institutional protocol using pre-excision ECoG, depth, functional brain mapping, and post-excision ECoG (Fig. 1). ECoG was recorded using a digital, 128-channel XLTEK video-EEG system (Natus Biomedical, San Carlos, CA) for post-processing analysis. Referential recording used band-pass filters from 0.1 to 100 Hz, a sampling rate of 512 Hz, and 16 bit analogue-digital conversion. Monopolar recording and bipolar montage reformatting was used to clarify potentially epileptiform activity. Attempts to optimize electrode impedance during surgery were made in real-time to minimize mechanical artifacts due to non-adherence to the brain (e.g., grid repositioning, filtering, "hiding" a channel without success) during real-time HD-ECoG interpretation. A digital 60 Hz notch filter was used when line noise interfered with interpretation. Customized high-density subdural grids (Ad-Tech, Racine, WI) (W.O.T) were used for ECoG recording and identification of after-discharges (AD) during DECS. High-density subdural grid arrays used 64 platinum sensors separated by 0.5 cm with 0.3 cm contact surface area embedded in silastic®. Stereotactic depth ECoG using eight contact 2 mm platinum sensors with 3.5 mm center-to-center electrode separation was performed using sampling tailored to operative conditions in selected patients.

2.4. Statistical analysis

Data were expressed as a mean, range for continuous variables and counts (percentages) for categorical variables. Chi-square or Fisher's exact test were used for categorical variables while t-test or Wilcoxon rank-sum test were used for continuous variables. All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. Analysis was performed using GraphPad Prism7.00 for Windows (GraphPad Software, La Jolla California USA).

3. Results

3.1. Study population

The cohort consisted of 81 patients and 69 eligible patients (37 females; mean age: 48.5 yrs.) undergoing awake brain surgery. 12 patients did not meet inclusion criteria and were excluded from analysis. 55 patients were operated for brain tumor, 11 for epilepsy, and 3 for cavernous malformations. Patient characteristics are summarized in Table 1. All patients underwent awake craniotomy during functional brain mapping using intraoperative ECoG.

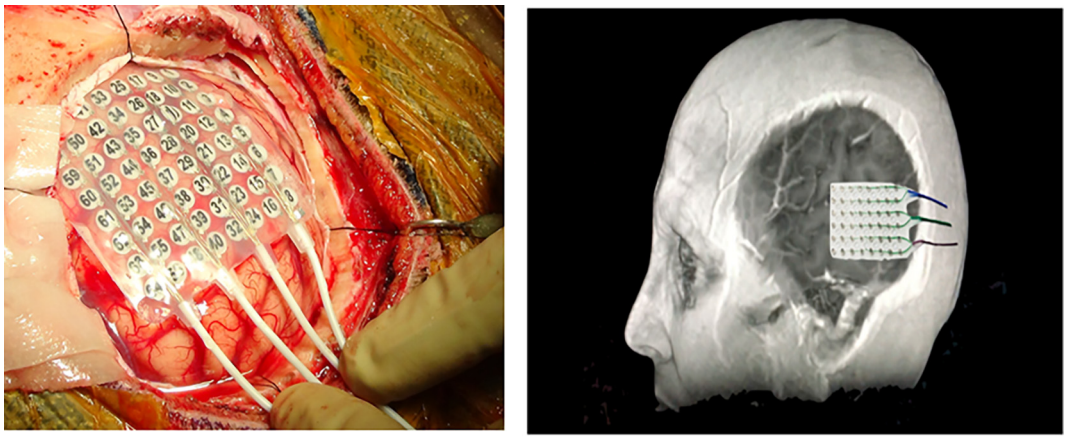
3.2. Seizures

Forty-three patients (61%) had seizures before surgery. Among patients with seizures, 74.4% (n = 32) were associated with a brain tumor; this constituted 58.1% of patients with brain tumors in the cohort (n = 55). Focal aware and focal impaired awareness seizures were the most frequent semiology and present in every patient with seizures. Four out of 69 patients (5.7%) experienced intraoperative seizures (1 focal motor, 1 focal aware and 2 had electrographic seizures) and 2/4 seizures occurred in patients with PFEDs. All resolved with a second stimulation and/or application of cold saline irrigation and anti-seizure medication. Nearly 75% of patients with epilepsy were uncontrolled by anti-seizure drugs before surgery. Overall, 77.8% of all patients were seizure-free at a mean follow-up of 6 months (range = 0.5–11.5 months). The rate of perioperative seizures was not found to be associated with presence of PFEDs (8/11; 72.7% vs 35/53; 61.4%) ($p = 0.52$).

Among patients with intra-operative seizures (n = 4), 1 patient had PFED (9% of all PFEDs) and 3 had no epileptiform discharges (6.25% of all patients with no epileptiform discharges). None of the patients with non-periodic epileptiform discharges were found to have an intra-operative seizure ($p = 0.6$). At 3 months follow up, 59 patients (85.5%) were reported to be seizure-free; of these, 10 had PFEDs (91% of all patients with PFEDs) and 6 patients had

Table 1
Demographics of the study cohort.

Number of patients	69
Age (mean in years; range)	48.5 (range 18–79)
Gender (females)	37
Pre-operative brain MRI (number and percent)	69 (100%)
Pre-operative scalp EEG (number and percent)	38/69 (55.1%)
Craniotomy site (Left hemisphere)	48
Brain Tumor patients (total number/percent)	55/69 (80.0%)
Seizure patients (total number/percent)	42 (61%)
Patients with focal neurological deficits (total number/percent)	38/69 (55.1%)
Intraoperative seizures during FBM (number/percent)	4 (5.7%)
Complications	14 (20.2%)
Hospital duration of stay (mean in days)	4.8



A B

Fig. 1. Image of a HD-ECoG grid placed over the language neocortex in the operating room (A) and illustration showing the 3-T brain MRI and head model with superficial grid approximation (B).

non-periodic epileptiform discharges (60% of all patients with non-periodic epileptiform discharges) (p = 0.04). 43 had no other epileptiform discharges (89.6% of all patients with no epileptiform discharges).

3.3. Brain lesion

High-resolution brain MRI brain revealed a single structural lesion in 63/69 (91.3%) cases, including suspected brain tumor, post-operative encephalomalacia following epilepsy surgery, non-specific gliosis, and cavernous vascular malformation. Varying distance from the cortex was present from immediately subcortical to periventricular undercutting the cortex. No other structural lesions were present involving cerebellum or brainstem. Lesion type included suspected primary brain tumor/glioma in 52/69 (75.3%) in addition to 16 other focal lesions. All patients with PFEDs had a structural lesion identified on brain MRI. The mean change in size of a lesion on preoperative MRI was similar before and after surgery for patients evaluated with HD-ECoG (29.5 cm^3 and 8.2 cm^3) and those without HD-ECoG (33.7 cm^3 and 13.7 cm^3). PFEDs were co-localized over the site of the brain lesion in all but one patient. Among patients who underwent scalp EEG (n = 32), those with epileptiform discharges were less likely to achieve seizure freedom compared to those with no epileptiform discharges (69.9%, n = 9 vs 92%, n = 23).

3.4. Epileptiform activity

Pre-operative scalp EEG was obtained in 32/69 (49.2%) patients who underwent awake craniotomy. 44 patients had HD-ECoG and 72.7% (32/44) patients had epileptiform discharges. Ten out of 32 patients (30.3%) had EDs in the scalp EEG. One patient with epileptiform discharges was in the contralateral hemisphere remote from the site of operation and HD-ECoG (patient# 7) (Table 2). When both scalp EEG and HD-ECoG were obtained (n = 23; 35.4%) EDs were identified in 10/23 (43.5%) patients. Of the 11 patients with PFEDs, 7/9 HD-ECoG had a preoperative scalp EEG and only 1/7 (14.29%) had EDs (p = 0.02); none were periodic.

3.5. Periodic focal epileptiform discharges

We identified 11/69 (16%) patients undergoing awake craniotomy (7 females; mean age 60.3) with PFEDs on ECoG. The location of PFEDs was identified in the right temporal region in two patients, left temporal region in seven patients, right perirolandic in two patients, and right parietal in one patient. Out of this subgroup, nine patients had brain tumor as the primary reason for operation and epilepsy was the main reason in three patients (patients# 5, 7, 11). HD-ECoG was better than standard scalp recording to detect PFEDs (Fig. 2) with none of the standard scalp EEG demonstrating them (Fig. 3). PFEDs occurred in awake asymptomatic patients relative to the EEG finding in each patient. The most common pattern seen with PFEDs was a continuous run of periodic spiking without appreciable evolution. The spatial distribution of PFEDs was focal on HD-ECoG localizing to a mean of 4.25 contacts (range: 2–16) approximating a diameter of 2 cm (Table 2). The typical frequency for PFEDs was 1 Hz in 10/11patients (Fig. 3). One patient demonstrated 0.33 Hz PFEDs Plus on depth recording (Fig. 4). The morphology of PFEDs consisted of periodic spikes in 10 patients and one patient had periodic sharply-contoured theta on depth ECoG (Fig. 4). Overall, PFEDs did not predict a significant difference in outcome compared with those without PFEDs present relative to seizure frequency, surgical complications, or neurological outcome.

3.6. Outcome

No perioperative deficits were found in any of the patients. The mean post-operative hospitalization lasted 3.75 days. Among patients with PFEDs, 2 patients (18.1%) had complications which included transient aphasia in 1 case and mild facial weakness in the other. Among patients without PFEDs, 22.4% (n = 13) patients

Table 2
Characteristics of 11 patients with PFEDs recorded during awake craniotomy.

PFED patients	Frequency of PFEDs and HD-ECoG	No. of Contacts involved	Post-op Persisted	Depth ECOG	DECS Results at site of surgery	Pathology	Outcome
1	1 Hz HD-ECoG	3	No	n/a	n/a	Cavernous Vascular malformation	Aphasia improved after surgery No seizures
2	0.5–1 HzHD-ECoG	2	No	No EDs	Non-eloquent	Glioblastoma multiforme IV IDH-wild	Seizure-free Chemotherapy radiation therapy
3	1 Hz HD-ECoG	3	No	PFEDS and EEG seizure with DECS	Eloquent	Glioblastoma multiforme IV IDH-wild	Seizure-free
4	1–1.25 Hz HD-ECoG	7	No	n/a	Non-eloquent	Glioblastoma multiforme IV IDH-mutant	Chemotherapy and radiation therapy. Seizures improved (Engel class 2)
5	1–2 Hz PFEDs HD-ECoG	4	No	No EDs	Non-eloquent	Anaplastic Astrocytoma Grade III IDH-wild	Seizure-free, Improved memory
6	0.75 Hz HD-ECoG	4	No	n/a	Eloquent for sensory function	Glioblastoma multiforme IV IDH-wild	Left hemiparesis improved following in-patient rehabilitation. Seizure-free
7	1–2 Hz PFEDs HD-ECog	4	PFEDs resolved	Deep spikes without periodicity	Eloquent	Glioblastoma multiforme IV IDH-wild	Seizure-free
8	1 Hz PFEDs HD-ECoG	16	PFEDs resolved	PFEDs in superficial anterior depth electrode	Eloquent	Anaplastic astrocytoma III IDH-wild	Seizure-free
9	1 Hz HD-ECoG	3 with fast activity	No	n/a	Eloquent	Glioblastoma multiforme IV IDH-wild	Seizure-free
10	Minimal spiking	3	No	PFEDs Plus 0.25–0.33 Hz	Eloquent for language and access avoided	Post-operative encephalomalacia after failed temporal lobectomy	Seizures improved (Engel class 3)
11	None	4	No	PFEDs 1 Hz	Eloquent for language	Anaplastic Astrocytoma III IDH-mutant	Aphasia improved after surgery. Seizure-free

ADs = after-discharges, DECS = direct cortical stimulation, n/a = not applicable.

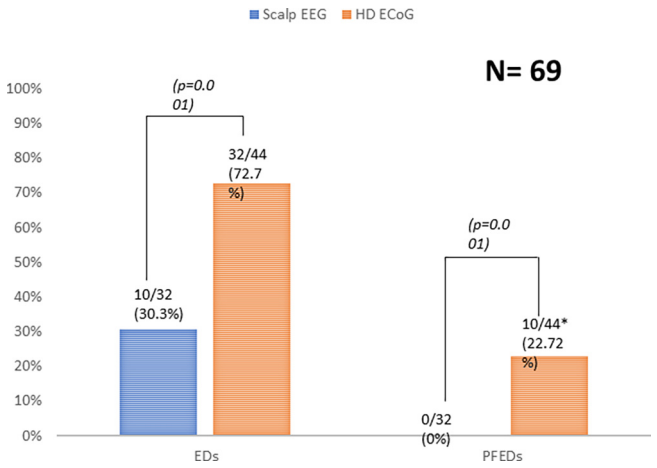


Fig. 2. Bar graph demonstrating Epileptiform Discharges (EDs) and PFEDs with scalp EEG (n = 32) and HD-ECoG (n = 10). *Only patients with PFEDs recorded on HD-ECoG are included.

had complications which included new transient aphasia in 2, brief anomia in 1, worsened hemiparesis in 4 patients, post-operative hemorrhage in 1, new onset facial weakness in 1, extension of visual field deficits in 1, perioperative respiratory failure requiring intubation in 1 patient and pneumocephalus in 1. Unexpected "complications" of surgery included two patients with PFEDs (one with PFEDs Plus), who reported immediate post-operative resolution of chronic memory difficulties (one validated with formal neuropsychological testing).

Pathology included oligodendroglioma (n = 10), anaplastic astrocytoma (15), glioblastoma multiforme (19), meningioma (2), cavernous vascular malformation (n = 3), diffuse astrocytoma (3), pilocytic astrocytoma (1), mesial temporal sclerosis (1), gangli-oglioma (3), and non-specific gliosis (12). High-grade gliomas were the primary pathology in 21/69 (30.43%) in the entire cohort but 9/11 (75%) of patients with PFEDs and 7/9 (77.8%) were IDH-wild type. None of the pathologies were found to be associated with presence or absence of PFEDs (Tumors: 81.82%, n = 9 in PFED group vs 79.3%, n = 46 in no PFEDs group; Epilepsy: 9%, n = 1 vs 17.2, n = 10; cavernous malformation: 9%, n = 1 vs 3.4%, n = 2).

4. Discussion

By usage of a high-density grid that recorded ECoG we found PFEDs with a cross-sectional prevalence of 20.9% in 44 cases. Similar to scalp-recorded PLEDs we suggest that PFEDs may be due to synchronization of pre-existing field potentials favoring cellular excitation (Kalamangalam and Slater, 2015; Hirsch et al., 2004). In contrast, PFEDs are focal as opposed to lateralized with a spatial distribution approximating a single gyrus. Some suggest that they occur when a cortical region is disconnected from subcortical structures, though variability in subcortical lesion location has challenged that theory (Gurer et al., 2004).

In our study, most patients with PFEDs were associated with seizures and high-grade gliomas (IDH-wild type). Their chronicity, presence during the awake state, spatially-restricted distribution and the lack of clinical signs seen with PFEDs suggest they are unique periodic epileptiform discharge. (Table 3) Due to the high incidence of pre-operative seizures and complete resection in our patients, we were unable to establish a link between PFEDs and seizures following surgery (Table 3). Like patients with PLEDs, those with PFEDs had clinical seizures, but unlike patients with PLEDs they were infrequently associated with a focal neurological deficit.

Most abnormal epileptiform morphological patterns on ECoG have been observed in epilepsy patients with cortical dysplasia (Guerreiro et al., 2003). In a previous retrospective study, ECoG more often showed continuous spiking in patients with focal cortical dysplasia (55%) as opposed to those with glioneuronal tumors (12%) suggesting high neuronal density when continuous spiking was found (Ferrier et al., 2006). In contrast, our population with glioneuronal tumors demonstrated focal periodic spiking typically at 1 Hz in approximately 20% of patients on HD-ECoG. In a prior study involving 11 cases of gliosis and cortical dysplasia, continuous spiking was more likely to be lobar, bilobar, or multifocal

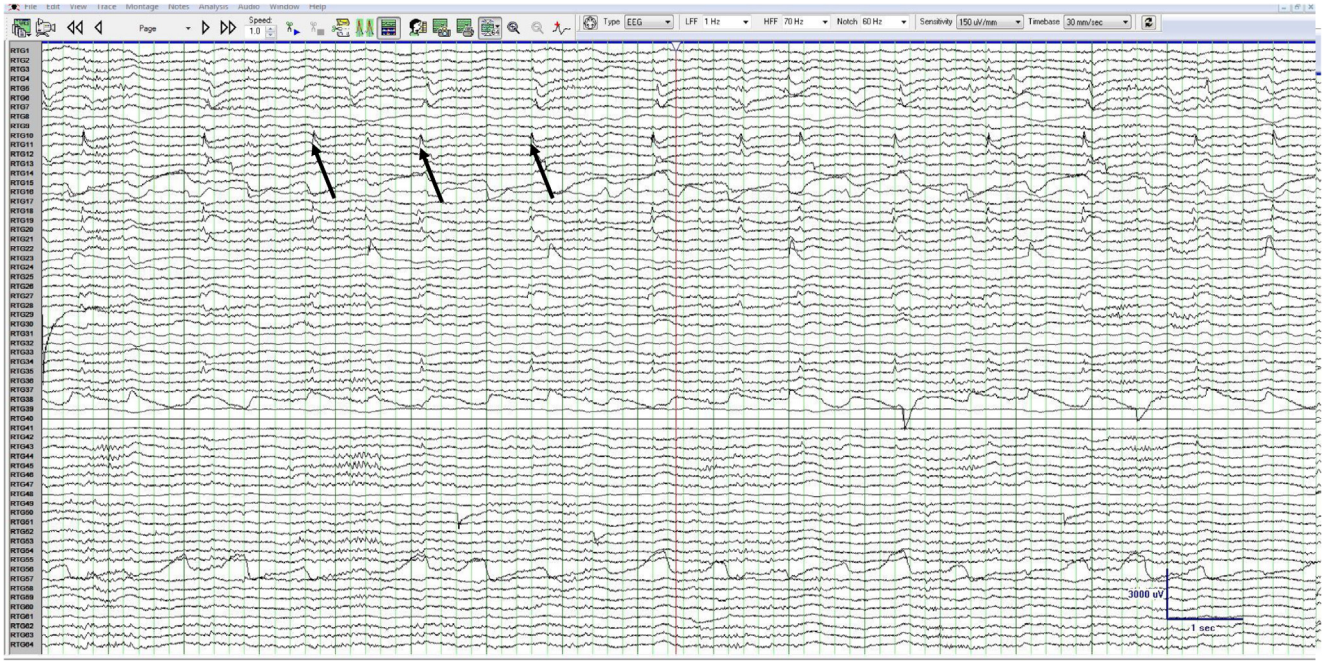


Fig. 3. Representative HD-ECoG demonstrating PFEDs (arrows) in a 68-year-old man with a glioblastoma multiforme.

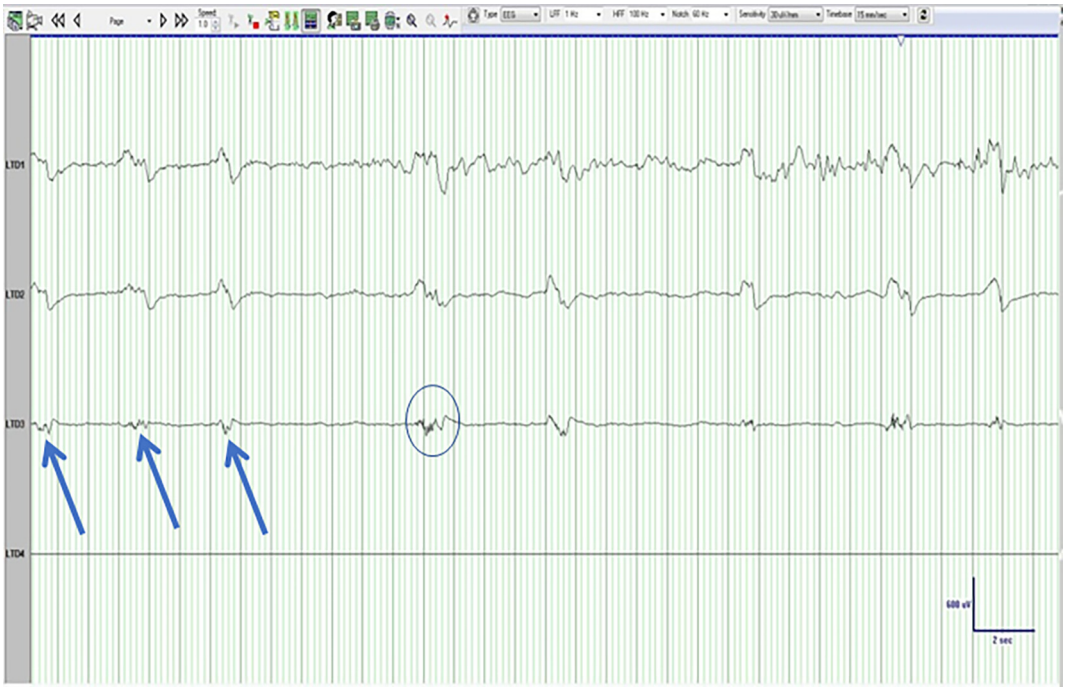


Fig. 4. PFEDs with fast activity (PFEDs Plus) in LT03 recorded in the OR from a stereo-EEG depth electrode placed in the region of encephalomalacia involving the left posterior hippocampus re-operated for failed temporal lobectomy (patient 10). Post-operatively, following resection of PFEDs she reported immediate and significant subjective memory improvement. Note the semi-periodic sharp waves (arrows) associated with a rhythmic high-frequency oscillation (blue circle) every 3 to 4 seconds. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Electroclinical features distinguishing PFEDs from HFOs and PLEDs.

Feature	PFEDs	HFOs	LPDs
Acuity	Chronic	Chronic	Acute
Structural lesion	Yes	Yes/No	Yes in 2/3rds to 3/4ths of patients
Brain structures involved	Cortical-subcortical gray matter	Cortical –subcortical gray matter	Cortical-subcortical gray +/– white matter
Mental Status	Awake	Awake	Altered mental status/coma
Clinical signs	Focal neurological deficit/ Seizures	Chronic epilepsy	Focal neurological deficit
Pathological	Yes; commonly brain tumor/ Seizures	Variable (may be normal)	Yes; commonly ischemic stroke
Seizures Common	Yes	Yes/No	Yes
Typical Site for Recording	OR (ECoG)	iEEG in the EMU/OR	ICU (scalp EEG)
Standard EEG feature	Absent	Absent	Present
Morphology	Focal, periodic, epileptiform discharges (typically 1 Hz or slower)	Fast ripples. Can be physiologic (80–250 Hz) or pathologic (>250 Hz)	Hemispheric or regional sharp theta/delta or epileptiform discharges (typically 1 Hz though may be slower or faster)
Optimal medical-surgical management	Lesionectomy	Resection	Medical

(Brunner et al., 2009). We found 3–6 contacts (1.5–3 cm) involved by PFEDs to approximate a "focal" (confined to 1 gyrus) or "regional" (2 gyri) spatial distribution similar to the taxonomy used in other series (Brunner et al., 2009; Schevon et al., 2009). Another study reported 3 cases of "focal PLED-suppression" following epilepsy surgery (Schevon et al., 2009). The finding of "focal PLEDs" is similar to our findings involving PFEDs though the morphology, spatial field and conditions of recording differed (Stead et al., 2010). Recruiting EDs and electrographic seizures were rare in this series and did not predict postoperative outcome similar to other reports (Alarcon et al., 1997). Like other investigators, we were unable to show PFEDs predicted a favorable prognosis following resection of "ictaform" discharges on ECoG (Hosain et al., 1995).

To our knowledge PFEDs has not been fully described in the OR though we observed some examples in the literature with continuous EDs during standard ECoG that appeared to have similar periodicity (Jasper, 1949; Chatrian et al., 1964; Ferrier et al., 2006). In our cohort, only 14.28% of the cases even demonstrated *non-periodic* EDs on pre-operative scalp EEG using the standard 10–20 International system of electrode placement when HD-ECoG detected PFEDs. Furthermore, we did not find focal intermittent rhythmic activity in the scalp EEG as reported in patients with focal cortical dysplasia (Gross et al., 1999). Detecting EDs with a spatial distribution of <2–3 cm is not possible on scalp EEG until 6–10 cm^2 are involved and even using standard ECoG with 1 cm interspaced electrodes may not have made PFEDs readily apparent. Electroencephalographers are strongly influenced by discharge frequency and their perception of periodicity, and uniformity of discharge morphology is a reliable feature of the EEG (Asano et al., 2004). Prior reports in children demonstrated a close correlation of EDs

on scalp EEG with ECoG when a 1 Hz frequency was encountered (Hashiguchi et al., 2007). This lies in stark contrast to our adult population monitored with HD-ECoG where PFEDs repeating at 1 Hz never correlated with interictal spiking present on standard scalp EEG. Given the restricted spatial distribution, it is not surprising that scalp EEG did not reveal PFEDs in our patients due to limited volume conduction from the brain to the surface of the scalp (Hashiguchi et al., 2007). Newer sensor technology and computational models involved in EEG acquisition continue to provide more information about the spatial-temporal extent of epileptogenic tissue (Zijlmans et al., 2017). Prior results have estimated the spatial Nyquist rate of EEG and concluded that inter-electrode distances of 20–30 mm provide the maximum resolution from EEG signals (Zijlmans et al., 2017). However recent theoretical work establishes that these rates underestimate the required number of sensors under low signal-to-noise ratio conditions (Ryynänen et al., 2004).

We found PFEDs on both HD-ECoG and depth EEG recording and propose they represent an intermediate waveform between PLEDs seen with standard EEG disc electrodes and "micro-PLEDs" recorded with research intraparenchymal microwires sampling a cortical surface area of 0.2 to 4 mm^2 (Bragin et al., 2002, Kuruvilla and Flink, 2003, Schevon et al., 2008, Stead et al., 2010). In situ epileptiform activity has previously been identified on smaller scales of 1 mm^3 in humans (confined to cortical regions as small as 200 μm^2) (Stead et al., 2010, Schevon et al., 2008). Hybrid grids studies in humans with focal seizures combining standard inter-electrodes distances (1.0 cm) together with cortical penetrating microwire recordings have yielded micro-periodic epileptiform discharges and microseizures (Lachaux et al., 2012). Still, little is known about the spatiotemporal dynamics of EDs recorded from small dimensions (Stead et al., 2010; Hashiguchi et al., 2007). High frequency oscillations (HFOs) were recently found to be a significant biomarker in patient with focal seizures (Jiruska et al., 2017). The potential to use HD-ECoG to identify new local field potentials without specialized recording equipment could become a useful and readily detectable target for resection and predict better surgical and seizure-related outcomes (Feyissa et al., 2018; Grover and Venkatesh, 2017). In our pragmatic series using HD-ECoG, PFEDs occurred with a morphology characteristic of PLEDs but on a smaller spatial scale similar to HFOs (Worrell et al., 2008). It is interesting that all patients with PFEDs had a structural lesion identified on brain MRI. In these cases, PFEDs were co-localized over the site of the brain lesion in all but one patient. The clinical significance of this pattern may therefore reflect that ability of PFEDs to localize a lesion in cases that are uncertain on the MRI and define surgical strategies.

No difference in postoperative surgical complications was encountered in patients with resected PFEDs though unexpectedly 2/11 patients with PFEDs provided unsolicited improvement in a baseline neurocognitive deficit immediately after surgery. It is remarkable to note because dramatic improvement immediately following surgery is not expected (Holmes, 2013). Studies in adults suggest that clinical behavioral changes can coexist with EDs lasting as brief as two seconds in duration (Van't Klooster et al., 2015; Aldenkamp and Arends, 2004). Nevertheless, impaired cognition may have a cumulative individual "threshold" to manifest a clinical effect, when EDs persist to impair consolidation of neural assemblies (Aldenkamp and Arends, 2004; Buzsaki, 2015). In the absence of interruption in brain function due to seizures, what is referred to as "interictal" epileptiform discharges in patients with PFEDs may instead reflect subtle undetected ictal activity (Hill et al., 2012) with clinical effects on cognition due to brain injury over time interfering with long-term potentiation and working memory (Leitinger et al., 2015). It is possible that use of another metric in our analysis might have identified a non-ictal significance to PFEDs such as cognition (Kucewicz et al., 2014). We are unable to exclude pre-clinical ictogenesis and clinically unidentified seizures in our patients with a structural lesion without seizures. Also, like focal cortical dysplasia, PFEDs could remain "silent" due to restricted spatial involvement. Other waveforms (i.e., triphasic waves) and biomarkers (i.e., HFOs) have been identified in patients without seizures but include other disorders (i.e., encephalopathy and chronic pain). PFEDs adds to our knowledge on periodic discharges that may affect patient management.

Our retrospective research study is associated with the usual limitations of bias. Nonetheless, this study contains a relatively large cohort and acknowledges the descriptive role and retrospective observational method used to clarify its place along the interictal-ictal continuum. We were unable to compare simultaneous standard ECoG with HD-ECoG to make definite statements about superiority yet, differences between them could potentially be clinically relevant to individual patients and impact ECoG reliability. Additionally, our focus on brain tumor and epilepsy patients likely reflects a referral bias and prevents generalization to other disease states where differences may occur such as neurodegenerative diseases (Morales Chacón et al., 2009; Palmini, 2006). The high sensitivity and specificity in identifying PFEDs using HD-ECoG in our study suggests that PFEDs are probably under-recognized and under-reported. Furthermore, the relationship with brain tumor and specifically high-grade IDH-1 wild-type gliomas merits future study as an electrophysiological biomarker since 75% involved this tissue type (San Juan Orta et al., 2009). We also recognize that prior classification systems (Chatrian et al., 1964) and terminology (Hosain et al., 1995) may have been recognized but not specifically referred to as PFEDs by other investigators. However, the highly restricted spatial fields and precise periodicity present on HD-ECoG in our patients with PFEDs differs from prior reports because patients were awake and the waveforms were not confounded by the effect of anesthesia nor limited by widely-spaced, commercially-available grids used in recording. Advances in technology for direct brain recording are needed to confirm the epilepsy network hypothesis and improve surgical outcomes by providing individualized therapies based on specific network contributions (Spencer et al., 2018). By using newer methods of electrophysiological recording such as HD-ECoG we expand our knowledge on the optimal surgical approach to patient management of brain tumor and seizures and extend our knowledge of the interictal-ictal continuum. Future directions may address understanding the neurobiology involved in PFEDs which could provide insight into subclinical excitatory networks for patients with a structural lesion. Larger prospective studies using HD-ECoG in patients with and without structural lesions and/or epilepsy are needed to expand upon our initial findings.

5. Conclusions

We propose PFEDs as a new term and describe them as a novel periodic epileptiform abnormality identified using HD-ECoG in the OR. The highly focal spatial distribution present in awake patients using HD-ECoG grid adds to our knowledge of periodic discharges with electrophysiological activity approximating a single gyrus in most cases by scalp EEG.

With our report of PFEDs on commercially-available HD-ECoG, we expand the spectrum of periodic patterns within the interictal-ictal continuum and extend the spectrum from the hospital and ICU to the OR. Increasing sensor density provides high resolution neural information and is superior to standard scalp EEG in detecting small scale domains of epileptiform abnormalities. PFEDs are microphysiological discharges that reflect disordered neural networks involving potentially epileptogenic cortex

that may play a role in important brain function and have neurological implications beyond standard outcome metrics assessing seizure freedom.

Disclosures

None of the authors have any financial interests to disclose.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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