Ictal Localization by Invasive Recording of Infraslow Activity with DC-Coupled Amplifiers

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Abstract: Scalp recording of infraslow (<0.5 Hz) ictal activity is useful for localizing partial seizures (Vanhatalo et al., *Neurology* 2003*a*;60:1198–1104, Miller et al., *Neuroimage*. 2007;35:583–597). This study further characterizes these infraslow ictal shifts with invasive recordings. Invasive monitoring captured 82 seizures in 11 patients with a 64-channel direct-current amplifier coupled to arrays of subdural platinum electrodes with bandwidth of 0 to 100 Hz. Time of onset, location, amplitude, duration, and polarity of infraslow signals were determined. Infraslow ictal signals (800–10,000 μV), were seen in 10 patients, starting from 2 seconds before to 493 seconds after electrical ictal onset time on conventional recording. Seven patients had an infraslow ictal signal in at least one channel localizing ictal onset on conventional recordings. Nine patients had surgical resections, including five with infraslow localizations concordant with conventional EEG (five had Engel class IA outcome, 1 class IB, 1 class IIIA, and one with no follow-up). Seizure localization using infraslow ictal activity was concordant with conventional EEG for most patients and is useful for confirming localization. The high voltage of infraslow activity may explain why infraslow activity localizes seizures better than conventional EEG with scalp recordings.

Key Words: Partial seizure, Infraslow, Epilepsy surgery, Invasive EEG monitoring.

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Patients with localization related epilepsy may undergo surgical resection of epileptogenic tissue in an effort to control their seizures when medical treatment has been ineffective. Identification of the surgical target is achieved by correlating results of different diagnostic modalities, including EEG, MRI, positron emission tomography, single photon emission computed tomography, and neuropsychological testing (Engel, 1993). Patients typically undergo long-term videotelemetry monitoring (LTM) with EEG recording with scalp electrodes, and may sometimes undergo further LTM with invasive recording from an array of surgically placed subdural electrodes to help determine the precise target for resection (Foldvary et al., 2001; Risinger et al., 1989).

In current practice, clinical EEG recordings are restricted to a frequency bandwidth of approximately 0.5 to 100 Hz. However, it has long been known that cerebral electrical activity contains components (Caspers, 1993; O'Leary and Goldring, 1964; Speckman and Elger, 1999) substantially below the lower limit of conventional ("AC") EEG recording frequency bandwidth that are referred to as "infraslow activity" (defined as electrical activity of less than 0.5 Hz (Vanhatalo et al., 2004)). Of historical interest, infraslow activity was reported as early as 1875 by Caton from measurements of spontaneous electrical activity of the brain by a galvanometer (Caton, 1875), describing it as follows: "When any part of the gray matter is in a state of functional activity, its electric current usually exhibits negative variation." Infraslow ictal activity (sometimes referred to as "DC shifts") has been demonstrated with focal and generalized seizures in humans, and with experimental seizures in animals (Gumnit, 1974). Earlier human studies include intraoperative direct-current (DC) coupled electrocorticographic recordings with calomel half-cell electrodes (Goldring, 1963) and noninvasive DC-coupled EEG recording of generalized spike and wave discharges with scalp electrodes (Bates, 1963; Chatrian et al., 1968; Cohn, 1964). The recordings of that era used DC-coupled amplifiers with small dynamic range, that required rebalancing the circuit every few minutes to correct baseline drift (Chatrian, personal communication to JWM May 2003), precluding introduction of this technique into clinical practice.

A small number of recent articles have studied low frequency baseline shifts during invasive monitoring with polarizable intracranial electrodes and conventional EEG amplifiers with long time constant. One group (Gross et al., 1999), using stainless steel epidural electrodes and a 0.01 Hz high pass filter, did not find baseline shifts with most seizures. In contrast, Ikeda et al. (1996, 1999), using platinum subdural electrodes (which have somewhat better low frequency recording properties than steel (Tallgren et al., 2005) and a high pass filter of 0.0l6 to 0.03 Hz, found highly localized ictal shifts, congruent with, but more localized than the higher frequency ictal phenomena, and some ictal infraslow shifts with scalp recordings. The latter studies had some compelling results in demonstrating cortical infraslow ictal activity, but raise the question as to whether use of true DC-coupled amplifiers rather than conventional "AC" amplifiers would better demonstrate infraslow shifts and yield additional information of practical use for seizure localization.

In prior studies with patients undergoing LTM for medically intractable localization related epilepsy, it was shown (Vanhatalo et al., 2003*a*) that infraslow activity in DC-coupled scalp recordings may lateralize temporal lobe seizures better than the conventional EEG in some cases. A follow-up study (Miller et al., 2007) demonstrated that the DC-coupled scalp recording of infraslow ictal activity coupled with EEG source analysis methods could elucidate temporal and extratemporal seizure onset zone in certain surgical candidates better than conventional scalp recording alone. Both of these studies made use of a number of advancements toward the incorporation of DC-coupled scalp EEG recording at the bedside, namely nonpolarizable sintered Ag-AgCl electrodes and relatively

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inexpensive amplifiers having true DC-coupled amplification capability and wide dynamic range.

Our goal in the current study is to extend our findings from these scalp recordings by performing DC-coupled intracranial EEG recordings from polarizable subdural electrodes in patients undergoing invasive LTM and further clarify the basis of the scalp-recorded infraslow activity. Furthermore, we set out to explore the potential clinical value and limitations of this recording method. We hypothesize that the infraslow ictal signals arise from regions of ictal onset and spread and should therefore correlate well with the results of other diagnostic methods of localizing the seizure onset region, and ultimately, with surgical outcome.

METHODS

Direct-current-coupled intracranial EEG recording was performed at bedside simultaneously with LTM using the same set of intracranial electrodes, for periods of 24 hours to several days. This study was approved by the Human Subjects Committee of the University of Washington, with informed consent obtained from all subjects according to the Declaration of Helsinki. This study included 11 patients who had been surgically implanted with sets of polarizable platinum subdural arrays, or depth electrodes and were undergoing invasive monitoring for medically intractable epilepsy at the UW Regional Epilepsy Center from 2005 to 2006. Surgical outcomes were extracted from a Human Studies Committee approved database, and were classified after Engel (1993).

Recording Methods

The subdural electrodes were grid arrays (8 × 2, 8 × 4, or 8 × 8) or strips (1 × 4, 1 × 6, or 1 × 8) (Ad-Tech Medical Instrument, Racine, WI) with an interelectrode distance of 10 mm and exposed electrode surface diameter of 2.3 mm. The depth electrodes were Spencer (Ad-Tech Medical Instrument, Racine, WI) multicontact with 1-mm diameter. Pin-connector cables with a Y-configuration were used to link the array of electrodes to the DC amplifier headbox, in parallel with the conventional EEG recording device (BMSI 5000, Nicolet, Madison WI, or XLTEK, London, Ontario, CA) recording, thus allowing simultaneous recording without further restriction of patients' daily activities. The reference and ground channels were connected to their respective electrodes in the conventional recording device, with the reference usually corresponding to an intracranial source. The recording equipment comprised a commercial 64-channel headbox with amplifier having true DC-coupled capability (SynAmps^2 system, Compumedics Neuroscan, El Paso, TX), connected via high speed USB 2.0 interface to a laptop (HP Compaq nx9010i, Hewlett Packard Co., Palo Alto CA), running Windows 2000 Professional (Microsoft Corporation, Redmond, WA). The data acquisition software, Scan 4.3 (Compumedics Neuroscan, El Paso, TX), stored the EEG data directly on hard disk in continuous files in 32-bit.CNT format. The frequency range for each channel was 0 to 100 Hz with accuracy of 29.80 nV/(least significant bit) and dynamic range of ±200 mV at a sampling rate of 250/s.

Analysis Methods

Analysis of the conventional EEG and DC-coupled recordings was performed independently by different interpreters, who were blinded to each other's findings and conclusions. Ictal events for each patient were determined independently of this investigation by a board-certified electroencephalographer using the conventional LTM recording. The study recordings were then synchronized with the LTM recordings and 20 minute recorded segments containing each ictal event were extracted and exported into a MATLAB v6.1 (The Mathworks, Natick, MA) EEG analysis software package, EEGLab v4.515 (Delorme and Makeig, 2004), for visual inspection. The time of onset, channels, duration, and polarity of infraslow signals in the extracted ictal files up to 10 minutes before and 10 minutes after clinical onset of the seizure (defined as the earliest time either of the first report of seizure symptoms by the patient, or the time of the first seizure related behavioral change on video), or the electrical onset for subclinical seizures ("electrical onset" is defined as the onset of a visible electrographic discharge determined by the original interpreting electroencephalographer from the conventional recording with a frequency of 1–100 Hz), were catalogued by a nonepileptologist (WK) blinded to the conventional EEG analysis, and indexed with a code number to correlate analysis of DC-coupled EEG recording with the clinical data from the LTM.

A straightforward but systematic approach was developed to determine the location and time of onset of infraslow shifts, and to distinguish seizure related activity from other infraslow activity. When inspecting the DC-coupled recorded data, it was apparent that there existed other, nonseizure related infraslow activity, consisting of (1) slow baseline drift of tens to hundreds mV over minutes to hours (corresponding to activity under 0.01 Hz), part of which may possibly due to the use of polarizable electrodes, and (2) near continuous small variations under 5 seconds duration with voltage in a range of hundreds of μV (corresponding to activity on the order of 0.1 Hz and above). Ictal infraslow shifts were readily distinguished from these other slow activities by their time course, with characteristic large voltage shifts of several hundred μV to mV over a time course of 5 to over 30 seconds (approximately 0.01–0.1 Hz). Therefore, the optimal method to inspect the seizure recordings was with 60-second-wide windows (1 cm corresponding approximately to 2 seconds) with the vertical axis gain set approximately at 1 mV per 0.5 to 1 cm. In so doing, the frequent smaller amplitude transient infraslow activity was effectively "filtered" in visual comparison to the much higher amplitude and longer ictal infraslow activity. In this analysis, we required that shifts be at least 5 seconds in duration. In addition, the 60-second window length was sufficiently short that baseline drift was not a factor in analysis. We found this method could be applied to all patients, and correlated well with visual analysis of higher frequency activity. It should be easily reproducible by other laboratories.

Although the dynamic range of the amplifiers is quite substantial, ±200 mV, the baseline drift in some channels could cause them to saturate and clipped data to be recorded. If these channels happened to contain electrical ictal discharges in the conventional LTM recording, this would have contributed to the loss of potential useful information. Furthermore, as the number of implanted electrodes sometimes exceeded 64, the number of recordable channels, the choice of electrodes to be linked had to be carefully decided based on available clinical knowledge as to where ictal activity was most likely to originate and spread. As a consequence, in a small number of recordings in one case (patient 3), the electrodes corresponding to the onset of electrical activity were unfortunately not recorded.

RESULTS

Overall, a total of 82 ictal events were recorded in the 11 study patients. Table 1 displays a summary of the analysis for each of these seizures. The number of ictal events captured for each patient was highly variable, ranging from one (patients 1, 2, and 4) to 40 (patient 10). Eight patients (#2, #3, #4, #6, #7, #8, #10, and #11) had ictal events with clinical manifestations (simple partial, complex partial, or secondarily generalized tonic-clonic) for a total of 59 clinical seizures. Again, the number of clinical seizures per patient displayed wide variation. Four pa-

TABLE 1. Summary of the Analysis of the Intracranial DC-Coupled EEG Recordings for the 11 Study Patients

Patient #	1	2	3	4	5	6	7	8	9	10	11	Total
Number of ictal events	1	1	2	1	8	4	4	3	14	40	4	82
Number of clinical seizures	0	1	2	1	0	4	4	3	0	40	4	59
Infraslow ictal activity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	10/11
% of seizures with infraslow shifts	100% (1/1)	100% (1/1)	100% (2/2)	100% (1/1)	87.5% (7/8)	75% (3/4)	75% (3/4)	100% (3/3)	0% (0/14)	80% (32/40)	100% (4/4)	69.5% (57/82)
Number secondarily generalized tonic clonic seizures	0	1	2	0	0	0	0	3	0	0	4	10
% of secondarily generalized tonic clonic seizures with infraslow shifts	—	100% (1/1)	100% (2/2)	—	—	—	—	100% (3/3)	—	—	100% (4/4)	100% (10/10)
Infraslow activity agrees with conventional EEG onset	100% (1/1)	0% (0/1)	0% (0/2)[a]	100% (1/1)	100% (7/7)	66.7% (2/3)	66.7% (2/3)	100% (3/3)	—	90.6% (29/32)	0% (0/4)	78.9% (45/57)
Time to EO (sec)[b]	+49	+493	+54	+9	+8 to +328	+8 to +13	+32 to +45	+5	—	−2 to +80	+2 to +9	−2 to +493
Time to CO (sec)[b]	—	−29	+45	+2	—	−12 to +1	—	−15 to 0	—	−4 to +78	+1 to +8	−29 to +78
Amplitude range of infraslow ictal signals (μV)	−800	−1,500	+4,000	−1,700	−3,500 to −1,500	−1,000 to +1,400	−10,000 to +1,400	+800 to +1,000	—	−2,500 to +1,200	−3,400 to −1,500	−3,500 to +4,000

If the patient had any seizures with infraslow ictal activity, it was marked affirmatively. The number of secondarily generalized tonic clonic seizures per patient was tabulated—all displayed infraslow activity. The time to EO (onset of electrographic seizure on conventional EEG) and CO (time of onset of the clinical seizure signs or symptoms) were tabulated as ranges from the seizures with the smallest and the largest time offsets. The amplitude of infraslow ictal signal was also tabulated as a range from smallest to largest, and indicates whether the patient had either negative polarity or positive polarity infraslow signals, or both.

[a]Patient's DC-coupled recordings did not contain the EO from the conventional recording.

[b]Positive numbers refer to occurrences after time of onset in conventional EEG, negative before.

DC, direct-current; EO, electrical onset; CO, clinical onset.

tients (#2, #3, #8, and #11) had seizures that became generalized, consisting of a total of 10 secondarily generalized tonic clonic seizures. All these seizures were associated with obvious, high amplitude infraslow activity. Patients 1 (one seizure), 5 (nine seizures), and 9 (14 seizures) exhibited only subclinical seizures during recording.

Almost all infraslow ictal signals were seen following the electrical onset with a delay ranging from less than 1 second to 493 seconds. Three seizures (seizures 27, 28, and 30, patient 10) were associated with infraslow signals preceding electrical onset by 2 seconds or less. The accurate estimation of the shift duration was the most difficult due to overlying faster activity and the asymptotic tail of many of the infraslow signals.

Figure 1 shows the EEG tracing of subclinical seizure (patient 5, seizure 1) with conventional electrical onset in electrode AST2 (in a 1 × 6 strip placed in the left mesial temporal region). The top tracing is the DC-coupled EEG recording, demonstrating a negative polarity infraslow signal beginning about 8 seconds after electrical onset. The infraslow signal is well localized to 2 adjacent electrodes AST1 and 2, with maximum amplitude of approximately −2000 μV in AST2 occurring 10 to 15 seconds after the start of the shift. The bottom tracing displays the same seizure after processing through a digital 1 Hz low-pass filter (a zero-phase, two-pass Butterworth filter with 12 dB/octave drop-off), emulating the conventional EEG recording. In contrast to the DC-coupled EEG recording, infraslow ictal activity is not visible in the conventional EEG. This patient underwent a left temporal lobectomy.

Figure 2 shows the DC-coupled EEG tracing of a simple partial seizure (patient 10, seizure 18) with electrical onset on conventional recording in electrodes RIMP7–8 (in a 1 × 8 strip in the right mesial frontoparietal region). The infraslow ictal signal occurs a few seconds after the electrical onset and clinical onset of the seizure, indicated by the labels EO and CO, respectively, and appears as a sharp negative polarity drop followed by a positive polarity rise to the previous baseline. There is a significant infraslow activity in RMF14 (in the right mesial frontal grid), which happens to be an origin for electrical activity in several other seizures by this patient. The infraslow signal is not constrained only to these electrodes but appears in others as well, implying that the

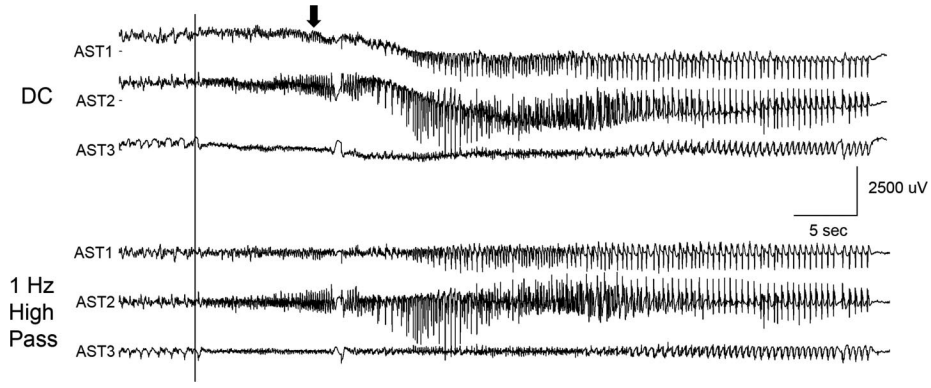

FIGURE 1. Comparison of direct-current (DC)-coupled recording (DC, Top) versus the same recording passed through a high-pass filter with 1 Hz, 12 dB cutoff (Bottom) for a subclinical seizure (seizure 1, patient 5). The vertical line represents the onset of electrical activity in the conventional EEG in AST2 in a 1 × 6 strip placed in the left mesial temporal region and the arrow is the onset of the infraslow signal, which is also largest in AST2. The amplitude of the signal is approximately 2000 μV. This patient underwent a left temporal lobectomy (Table 2).

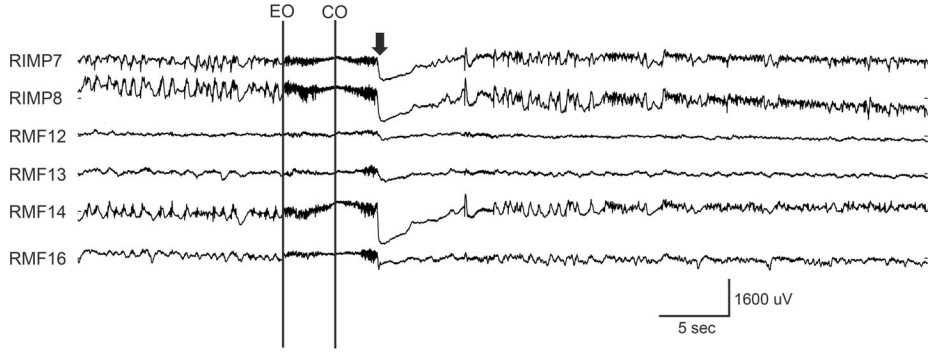

FIGURE 2. Seizure 18 in patient 10, a simple partial seizure, interpreted as having ictal onset in electrodes RIMP7–8 from the LTM recording. RIMP refers to a 1 × 8 strip in the right mesial frontoparietal region; RMF is an 8 × 2 grid in the right mesial frontal region. EO = conventional EEG ictal onset time, CO = onset time of clinical seizure signs or symptoms. The arrow refers to the onset of the infraslow ictal signal, which comprises a sharp negative shift followed by a steady rise to the previous baseline over the next 5 to 10 seconds. The infraslow signal occurs in several channels, not just RIMP7–8, including RMF12, 13, 14, and 16, and in fact has greatest amplitude in RMF14. Thus infraslow ictal activity in this recording, while coincident with the channels of electrical ictal onset, is actually more diffuse than the conventional ictal activity. This patient later had a resection of the right frontoparietal region.

infraslow ictal activity is even more diffuse than that of the conventional recording. This patient later underwent right mesial frontoparietal resection.

Figure 3 shows the DC-coupled EEG tracing of a secondarily generalized tonic clonic seizure (patient 11, seizure 2) with conventional electrical onset in electrodes RMT1 (in a 1 × 8 strip in the right mesial temporal region). The infraslow ictal signal occurs 2 seconds after the electrical onset and clinical onset of the seizure, which occur simultaneously. The infraslow activity is diffuse and appears as a strong negative polarity shift over 5 to 10 seconds in all channels, with highest amplitude in RMT2 (by a small percentage). This is followed by a slower predominantly positive polarity shift in all channels. This gives another example of a seizure with diffuse infraslow ictal activity that is not more localized than the conventional EEG. This patient had right temporal cortical dysplasia that was resected.

Table 1 summarizes the results of analysis by patient. Ten of 11 patients in the study had seizures with unequivocal infraslow signals (57 of 82 total seizures) that ranged in amplitude from approximately 800 to 10000 μV. One patient (#9, 14 seizures) did not have infraslow ictal signals with any seizure.

Seven of 10 (70%) patients displaying infraslow ictal activity had a seizure with a localized infraslow signal that coincided with one of the channels in the epileptogenic zone, as determined from the electrical onset of the seizure in the LTM recording (45 of 57 seizures). For two other patients (#2, and #11) the infraslow activity coincided with an area of spread of electrical ictal activity in the LTM recording. Patient 2 had one seizure in a channel adjacent to location of ictal onset, whereas patient 11 had 4 secondarily generalized tonic clonic seizures, in which all channels displayed simultaneous infraslow activity after electrical onset. Furthermore, in two of the seizures in patient 11 the largest signal coincided with a channel adjacent to that with the initial electrical onset. The recording of patient 3 failed to include the channels of electrical ictal onset from the LTM, therefore precluding a meaningful correlation of infraslow ictal activity for that patient.

Five patients (#1, #2, #4, #5, and #11) had negative polarity ictal shifts, 2 (#3 and #8) had positive shifts. The remaining three patients had seizures with both negative and positive polarity infraslow activity. However, for the seizures with correctly localizing infraslow ictal activity, the infraslow ictal signals all had negative polarity in patients 7 and 10, and positive polarity in patient 6.

Eight patients had multiple seizures recorded; those infraslow signals that localized to conventional EEG findings had similar time course and polarity across each patient. That is, the seizures for a given patient tended not only to have similar electrical onset and spread in conventional EEG bandwidth, but also similar infraslow onset and spread. Figure 4 demonstrates this with two seizures from patient 8 (seizure 1 and 2). In both seizures, the earliest infraslow signal occurs in the same channel, LD1 (from the depth electrode in an area of dysplasia in the left posterior temporal region), and spreads to the left mesial temporal area (to the strip electrode LMT1) before becoming secondarily generalized tonic clonic seizures. Note that although the times to clinical onset differ substantially between the two seizures, the shapes of their infraslow signals are quite similar.

Table 2 summarizes the clinical assessment and known outcomes of each patient in the study. In total, 9 of the 11 study patients had a surgical resection performed. Of these, 6 (#2, #4, #5, #6, #9, and #10) had a class I seizure outcome, and one (#3) was lost to follow-up. Two patients (#1 and #11) had seizure reduction but were not seizure free (class IIIA). Five of 6 patients with class I seizure outcome had seizures with infraslow signals that agreed with the overall findings of the conventional EEG (#4, #5, #6, #10) or were

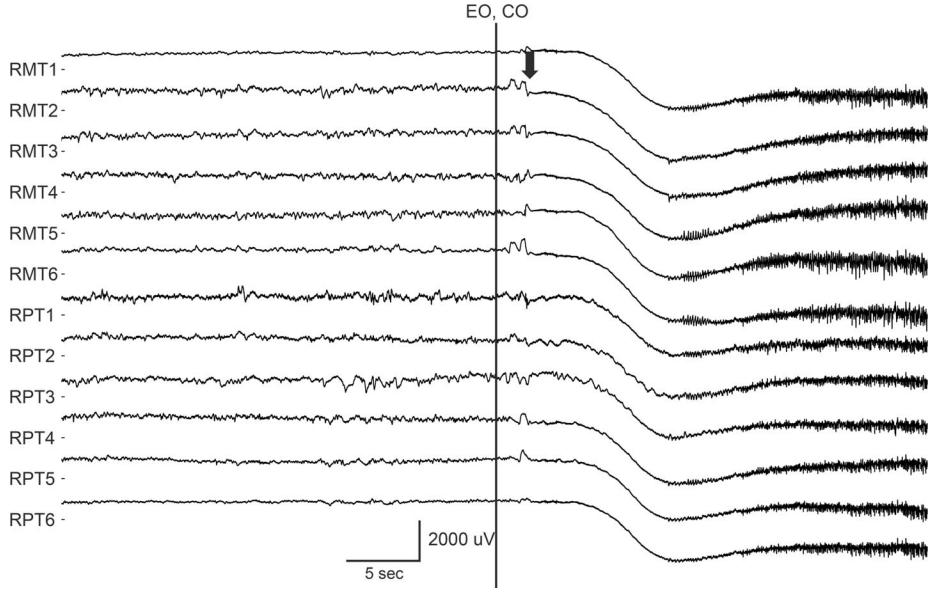

FIGURE 3. Seizure 2 in patient 11, a secondarily generalized tonic clonic seizure, interpreted on conventional EEG recording as having onset of electrical ictal activity in electrode RMT1 simultaneous with onset of the clinical seizure. RMT refers to a 1 × 6 strip in the right mesial temporal region; RPT is a 1 × 6 strip in the right mesial temporal region. EO = conventional EEG ictal onset, CO = onset of clinical seizure. The arrow refers to the onset of the infraslow ictal signal, which comprises a strong negative shift over 5 to 10 seconds in all channels followed by a slower, predominantly positive increase in most channels. The infraslow ictal signal is not localizing to RMT1, instead being diffuse with largest amplitude component in RMT2 by a small amount (approximately 10%). This patient had a right temporal lobectomy performed, finding cortical dysplasia.

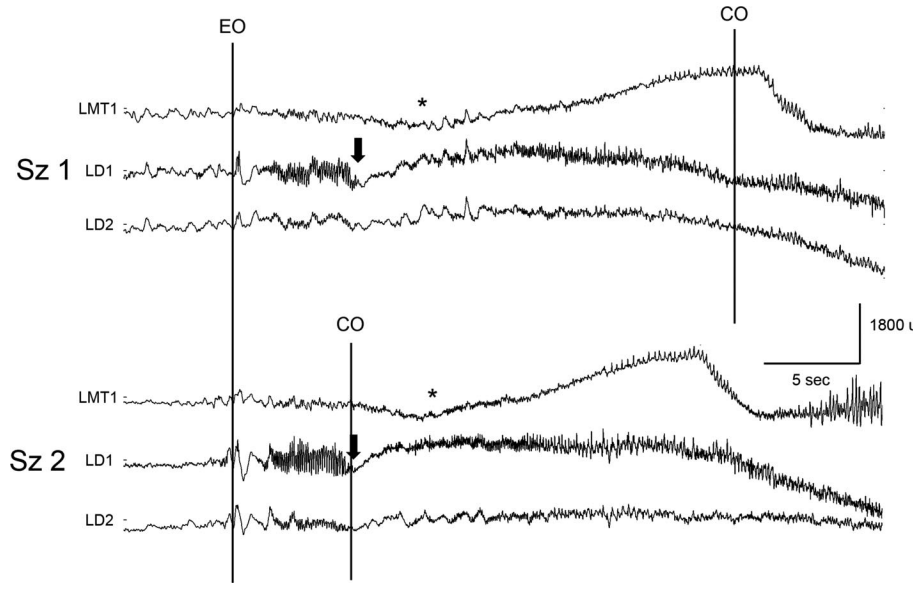

FIGURE 4. Comparison of DC-coupled recording for 2 seizures in the same patient (patient 8, seizures 1 and 2). EO = Onset of electrical ictal activity by conventional (LTM) EEG, in electrode LD1, depth electrode in the left posterior temporal region. CO = Onset of clinical signs or symptoms of seizure, determined by video monitoring. *Onset of infraslow signal in LMT1 (left mesial temporal), indicating spread of infraslow activity. Note that the CO of the 2 seizures differs by approximately 15 seconds, but the shapes of the infraslow signals in LD1 and LMT1 are similar. This patient declined surgical resection.

in an adjacent electrode to the conventional EEG localization (#2) (Table 3). The areas of identified infraslow onset and spread happened to be included in the area of resection in 8 of the 9 patients with surgical resections. One patient (#9) had no infraslow shifts recorded.

DISCUSSION

Although there have been previous reports of ictal infraslow activity during invasive monitoring in a smaller number of patients using conventional amplifiers with a long time constant (Gross et al., 1999; Ikeda et al., 1996, 1999), this is the first study using true DC-coupled amplification since the work of Goldring (1963). In the present study, ictal infraslow shifts were detected in a high proportion of seizures, and had a higher range of amplitudes than seen in these prior investigations. This is not surprising, since the recording characteristics of a true DC-coupled amplifier should be superior for recording of slow activity than those of conventional amplifiers, even with a low cutoff of 0.016 Hz. Although much of the infraslow ictal activity described is above the low frequency cutoff for the conventional amplifiers, the nonideal behavior of all frequency filters (lack of infinitely sharp cutoff) practically ensures some attenuation of any low frequency activity by the conventional amplifier. At the same time, the lack of a frequency cutoff introduces significant baseline drift and other infraslow artifact (both physiologic and nonphysiologic, such as "pops" because of the impedance change at the electrode-brain interface) that complicates the task of analysis and may obscure signals of interest.

Seizure localization using infraslow activity was concordant with that obtained from analysis of higher frequency activity in 7 of 11 patients with medically intractable localization related epilepsy. Both the present study and Ikeda et al. (1999) agree on the existence of localizing infraslow activity. All patients reported by Ikeda et al. had localizing infraslow ictal activity, with an incidence ranging from 42% to 100%. In our 7 patients, the incidence ranged from 66.7% to 100%. Ikeda et al. reported infraslow ictal shifts with negative polarity in five of six patients and both negative and positive polarity in one, while we found seven patients who had localization infraslow activity with negative polarity and three with positive shifts. Ikeda also found that all but one patient had infraslow ictal shifts that preceded or were simultaneous with electrographic onset, but only one of our patients had seizures with infraslow activity preceding conventional electrographic onset. This small difference could be due to chance, and possibly also to variation in electrode placement and conventional EEG interpretation between centers. Finally, the major difference between our studies is that all patients studied by Ikeda et al. had infraslow activity that was more localizing than conventional EEG, and constrained to at most two channels, whereas we found more diffuse infraslow activity in several patients. The diffuse activity was either associated with a more diffuse electrical onset as in patients 7 and 10 or with spread of electrical ictal activity as in patient 8. It must be stressed, however, that the Ikeda study gathered more seizures per patient (minimum of 5 seizures) while recording fewer patients (6 versus 11), and the differences between the findings of these 2 small studies may not be contradictory, but due to sampling, or to systematic differences in the analysis of infraslow activity. Also, the fact Ikeda et al. (1999) did not use DC-coupled amplifiers, means that the infraslow shifts were more attenuated, and smaller shifts may not have been always observable in that study.

Ikeda et al. (1999) did use their findings to help determine sites of resection. The requirements of our Human Studies Protocol precluded using these recordings for clinical decisions. The fact that infraslow localization most often correlated with conventional EEG localization (Tables 1 and 2) and that the majority of resected patients had a favorable outcome (Table 2) suggests that DC-coupled recording of the ictal signal can give additional confirmatory information for surgical decisions.

The extremely large amplitude—up to 10 mV—of the observed infraslow ictal shifts on electrocorticography may help explain our observations that DC-coupled EEG scalp recordings can sometimes localize seizures better than the conventional EEG (Miller et al., 2007; Vanhatalo et al., 2003a). It was not uncommon (e.g., Fig. 3), for the infraslow shifts to have amplitudes more than 10 times greater than that of the higher frequency ictal signal. Although the infraslow shift may not occur any earlier than higher frequency changes, its higher voltage may allow it be better detected and localized at the scalp. This could explain why it is possible to accurately localize some seizures by infraslow shifts on scalp recordings, even if they could not be localized with analysis of conventional EEG frequencies (Miller et al., 2007; Vanhatalo et al.,

TABLE 2. Clinical Assessment, Surgical Procedures, and Outcomes

Pt	Overall Invasive EEG	MRI	Surgery	Surgical Outcome
1	Left lateral temporal: G59,60, G50,51	Prior left temporal resection	Left lateral temporal resection	Class IIIA, 30 mo
2	Right frontal: RAF 2–3; G15,23; G32,24	Bifrontal encephalmacia, right worse	Right frontal lobectomy	Class IA, 21 mo
3	Right mesial temporal: RMS 4	Right perisylvian schizencephaly	Right temporal and insular resection	No follow-up
4	Right frontal: G5–6, G13–15, RF 4–7, RF 14–16	Right frontal focal cortical dysplasia	Partial right frontal lobectomy of Taylor-type dysplasia	Class IA, 22 mo
5	Left mesial temporal: AST 2, 3, 4	Hyperintensity of left hippocampus; old left cerebral peduncle and left internal capsule posterior limb infarction	Left temporal lobectomy	Class IA, 18 mo
6	Left mesial temporal: LAT1, LMT1	Normal	Left temporal lobectomy	Class IA, 18 mo
7	Independent right and left mesial temporal: LMT1, RMT1 and others	Midline cerebellar hemispheric cleft	No resection	—
8	Left posterior temporal: LD1	Left medial occipital dysplasia	No resection (declined)	—
9	Right occipitotemporal, mostly G36/44 and RIO 8	Prior right occipitoparietal resection	Right occipitotemporal resection	Class IB, 16 mo
10	Right mesial frontoparietal: RIMP 7–8	Normal	Right mesial frontoparietal resection	Class IA, 6 mo
11	Poorly localized right mesial temporal: RMT1/RPT1	Normal	Right temporal lobectomy with cortical dysplasia	Class IIIA, 15 mo

Abbreviations in second column (overall invasive EEG) are labels given to electrodes at the time of recording and are used so that findings can be compared with Table 3. Surgical outcomes are classified as per Engel et al., 1993.

2003a). The high amplitude of the very slow frequencies has also been used for functional characterization of the underlying cortex. For example, Schalk et al. (2007) could predict direction of movement from motor cortex using the amplitude of a 300 milliseconds window of electrocorticography with accuracy comparable to the information found at high gamma frequencies.

An unavoidable limitation of the current study is the use of polarizable platinum electrodes, which attenuates slow signals and may also produce slow artifact and baseline drifts. There are no nonpolarizing, reversible electrodes that are proven safe, and are Food and Drug Administration approved, for intracranial use. Not only are ictal infraslow shifts lower in amplitude because of the electrode properties, but also it may be more difficult to distinguish lower amplitude, slower signals from artifact. It is hoped that the current ongoing investigation into post processing tools such as digital filters to correct baseline drift and independent component analysis (Makeig et al., 2004; Stone, 2004) to help separate infraslow signals from artifact, will improve the sensitivity of intracranial DC EEG analysis and render it a more powerful clinical and investigational method.

The very high amplitude of the ictal infraslow shift suggests that it may have a different underlying physiological generator than the higher frequency electrographic changes during seizures. There is a wealth of evidence that ictal electrographic changes in this conventional 0.5 to 100 Hz range relate to spatiotemporal summation of neuronal EPSPs and IPSPs as well as changes in glial membrane potentials (Speckmann and Elger, 1999). However, there is now evidence that some infraslow cerebral potentials have a nonneural mechanism. The monotonic infraslow signals that can be recorded in the mV range at the scalp during a number of physiologic procedures, including hyperventilation, jugular vein compression, tilting of the body, and the Valsalva and Mueller maneuvers correlate closely with changes in cerebral blood volume (Vanhatalo et al., 2003*b*). This has been explained by the proposal that there is a large whole brain resting potential which is due to the standing blood brain barrier potential (Voipio et al., 2003). Any event that alters blood brain barrier permeability, or the size of intracranial vascular compartments, will alter the magnitude of this resting potential, and its associated leakage currents that will be recorded as an infraslow shift.

The nonneural mechanism of slow shifts during physiological maneuvers has been verified by Nita et al. (2004) who produced, in artificially ventilated animals, infraslow cerebral potential changes associated with change in systemic pCO_2 that were similar to the infraslow shifts seen with hyperventilation in humans. There was no correlation between these slow shifts and recordings of neuronal and glial activity. These infraslow potentials were greatly diminished or eliminated by opening the blood brain barrier with by intracarotid sodium dehydrocholate. Local changes in blood perfusion, pCO_2, pH, and blood brain barrier permeability occur during seizures, and could well substantially contribute to ictal infraslow potentials, but this needs to be directly tested experimentally.

This study demonstrates that DC-coupled intracranial recordings are practical, and that infraslow shifts are present with most focal seizures. Because ictal infraslow potentials are so large, and because they may have a different physiological mechanism than higher frequency changes during seizures, they are a useful part of the ictal signal which should not be overlooked when localizing and characterizing seizures in clinical practice.

TABLE 3. Summary of the Analysis of the Intracranial DC-Coupled EEG Recordings for All Patient Seizures (82 Total Recorded for 11 Patients)

Pt #	Overall Invasive Conventional EEG Localization	Sz #	Primary Infraslow Shift Location	Infraslow Localization Agrees With Conventional EEG?	Onset of Infraslow Signal Relative to Conventional EO (sec)[a]	Onset of Infraslow Signal Relative to Clinical Onset (sec)[b]	Amplitude of Infraslow Signal (μV)
1[c]	Left lateral temporal: G59,60, G50,51	1	G60, later G51	Yes	49	—	−800
2	Right frontal: RAF 2–3; G15,23; G32,24	1	G31	Adjacent electrode	493	−29	−1,500
3	Right mesial temporal: RMS 4	1	RPT 6 (right posterior temporal)	Indeterminate/channels not in DC-coupled recording	54	45	+4,000
		2	—	—	—	—	—
4[c]	Right frontal: G5–6, G13–15, RF 4–7, RF 14–16	1	G13, many others	Yes	9	2	−1,700
5	Left mesial temporal: AST 2–4	1	AST 2 and PST 5 (posterior superior temporal)	Yes	8	—	−2,000
		2	AST 1, then AST 2	Yes	48	—	−1,500
		3	AST 2	Yes	80	—	−3,000
		4	AST 2	Yes	36	—	−3,000
		5	—	—	—	—	—
		6	AST 2	Yes	328	—	−2,500
		7	AST 2	Yes	100	—	−3,500
		8	AST 2 and PST 5	Yes	35	—	−2,000
6	Left mesial temporal: LAT1, LMT1	1	LAT 5	No	8	1	−1,000
		2	LST 1, 2	Yes	12	−9	+1,300
		3	—	—	—	—	—
		4	LST 1, 2	Yes	13	−12	+1,400
7	Independent right and left mesial temporal: LMT1, RMT1 and others	1	LMT 1	Yes	45	—	−10,000
		2	LMT 4, 5	No	32	—	−1,500
		3	LMT1	Yes	38	—	−3,000
		4	—	—	—	—	—
8[c]	Left posterior temporal: LD1 (depth electrode)	1	LD 1	Yes	5	−15	+800
		2	LD 1	Yes	5	0	+1,000
		3	LD 1	Yes	5	−15	+1,000
9	Right occipitotemporal, mostly G36/44 and RIO 8	1	—	—	—	—	—
		2	—	—	—	—	—
		3	—	—	—	—	—
		4	—	—	—	—	—
		5	—	—	—	—	—
		6	—	—	—	—	—
		7	—	—	—	—	—
		8	—	—	—	—	—
		9	—	—	—	—	—
		10	—	—	—	—	—
		11	—	—	—	—	—
		12	—	—	—	—	—
		13	—	—	—	—	—
		14	—	—	—	—	—
10	Right mesial frontoparietal: RIMP 7–8	1	RIMP 7–8, RMF 14 others	Yes	23	18	−1,000
		2	RIMP 7–8, 14	Yes	19	16	−1,700
		3	RIMP 7, RMF 14, 16	Yes	80	78	−2,000
		4	—	—	—	—	—
		5	—	—	—	—	—

(*Continued*)

TABLE 3. (*Continued*)

Pt #	Overall Invasive Conventional EEG Localization	Sz #	Primary Infraslow Shift Location	Infraslow Localization Agrees With Conventional EEG?	Onset of Infraslow Signal Relative to Conventional EO (sec)[a]	Onset of Infraslow Signal Relative to Clinical Onset (sec)[b]	Amplitude of Infraslow Signal (μV)
		6	—	—	—	—	—
		7	RMF 11	No	7	4	+1,200
		8	—	—	—	—	—
		9	RMF 2	No	18	16	+900
		10	RG2–3	No	3	0	−2,400
		11	—	—	—	—	—
		12	—	—	—	—	—
		13	RIMP 8, RMF 14, others	Yes	21	19	−2,000
		14	RIMP 7–8, RMF 14, others	Yes	15	3	−2,000
		15	RIMP 7–8, RMF 14, others	Yes	6	3	−1,900
		16	RIMP 7–8, RMF 14, others	Yes	5	3	−1,500
		17	RIMP 7–8, RMF 14	Yes	6	3	−1,200
		18	RIMP 7–8, RMF 14	Yes	4	1	−1,700
		19	—	—	—	—	—
		20	—	—	—	—	—
		21	RIMP 7–8, RMF 14	Yes	3	0	−1,700
		22	RIMP 7–8, RMF 14, RG2	Yes	3	0	−2,500
		23	RIMP 7–8, RMF 14, RG2	Yes	1	−1	−2,500
		24	RIMP 7–8, RMF 14	Yes	0	−2	−1,500
		25	RIMP 7–8, RMF 14	Yes	7	−2	−1,600
		26	RIMP 7–8, RMF 14	Yes	−2	−3	−1,900
		27	RIMP 7–8, RMF 14	Yes	11	−1	−1,200
		28	RIMP 7–8, RMF 14	Yes	8	7	−600
		29	RIMP 7–8, RMF 14	Yes	−2	−4	−1,600
		30	RIMP 7–8, RMF 14	Yes	−2	−4	−1,600
		31	RIMP 7–8, RMF 14	Yes	0	−2	−1,800
		32	RIMP 7–8, RMF 7, 14, others	Yes	15	14	−1,500
		33	RIMP 7–8, RMF 7, 14, others	Yes	15	14	−1,500
		34	RIMP 7–8, RMF 7, 14	Yes	18	14	−1,500
		35	RIMP 7–8, RMF 7, 14	Yes	16	15	−2,000
		36	RIMP 7–8, RMF 7, 14, others	Yes	20	14	−1,800
		37	RIMP 7–8, RMF 7, 14, others	Yes	16	15	−1,800
		38	RIMP 7–8, RMF 7, 14, others	Yes	18	17	−1,500
		39	RIMP 7–8, RMF 7, 14, others	Yes	15	13	−1,700
		40	RIMP 7–8, RMF 7, 14, others	Yes	14	12	−1,800
11	Poorly localized right mesial temporal: RMT1/RPT1	1	All channels	No	8	8	−1,500
		2	All channels	No	3	3	−2,600
		3	All channels	No	9	2	−2,700
		4	All channels	No	2	1	−3,400

The locations of identifiable infraslow ictal signal were recorded, and compared to the location coincided with the location from the conventional EEG. The electrode names used at the time of intracranial recording are used in all tables and figures in order to aid comparisons between localization on DC-coupled and conventional EEG recordings. The offset between the onset of the infraslow ictal signal and the onset of electrical ictal activity on conventional EEG (EO) and clinical seizure signs or symptoms if present (CO) was calculated and the amplitude of the largest infraslow signal was estimated.

[a]Positive numbers refer to onset of infraslow shift after time of onset of electrographic discharge on conventional EEG onset, negative before.

[b]Positive numbers refer to onset of infraslow shift after time of onset of the clinical seizure, negative before.

[c]Patients where localization of all seizures with infraslow shifts agreed with conventional EEG.

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