Publication VI

Vanhatalo S, Holmes MD, Tallgren P, Voipio J, Kaila K, Miller JW. Very slow EEG responses lateralize temporal lobe seizures: an evaluation of non-invasive DC-EEG. Neurology, 2003, 60:1098-1104.

"The average Ph.D thesis is nothing but the transference of bones from one graveyard to another."

Frank J. Dobie

Very slow EEG responses lateralize temporal lobe seizures

An evaluation of non-invasive DC-EEG

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Abstract—*Background:* This study tested the idea that very slow EEG responses (direct current [DC] potential shifts) could be detected noninvasively during temporal lobe (TL) seizures, and that these shifts give lateralizing information consistent with that obtained by other methods. *Methods:* Seven patients with TL epilepsy (TLE) were recorded with scalp DC-EEG technique at bedside. All recordings were performed simultaneously with conventional EEG (scalp in five, and intracranially in two; two patients with scalp recordings were recorded intracranially later). Seizures in five patients originated in the mesial TL. Ictal DC shifts were evaluated by comparing them to the temporal evolution of ictal discharges, and by comparing the laterality of these shifts to the side of seizure onset defined by routine EEG and other presurgical diagnostic tests. *Results:* All seizures (35/35) were associated with negative DC shifts at temporal derivations (30 to 150 μV relative to vertex), beginning at the electrical seizure onset, and lasting for the whole seizure. In eight seizures (five patients) with documented mesial TL onset, the polarity of the DC shift was initially positive followed by a negative one after lateral spread of seizure activity. In all cases, the side of the EEG shift agreed with other diagnostic tests, and, at times, was more clearly lateralized than the conventional scalp EEG. *Conclusions:* DC-EEG recordings are practical and achievable at the bedside. Ictal DC shifts are consistently observed in scalp recordings in TL seizures, and reliably lateralize them. This method may hold promise in reducing the need for invasive monitoring in patients with TLE where other noninvasive tests are equivocal.

NEUROLOGY 2003;60:1098–1104

Neurosurgical treatment of medically intractable seizures requires determination of the site of origin (epileptogenic zone)—this is initially attempted by ictal video EEG recordings with scalp electrodes, correlated with other noninvasive studies, particularly neuroimaging.[1] However, ictal EEG often gives equivocal information about the localization or laterality of seizure origin,[2-5] or it is incongruent with other tests, leading to the requirement for further, invasive ictal recordings with intracranial electrodes. A potentially straightforward way to enhance the utility of scalp recorded EEG in seizure localization, and to reduce the need for invasive recordings, would be to detect electric signals that are associated with seizures but reflect mechanisms that differ from those giving rise to the fast ictal activity detected by conventional EEG techniques. It is well established by a large number of animal experiments,[6-8] and by early invasive recordings on humans,[9,10] that seizures are associated with very slow EEG responses called direct current (DC) potential shifts. They are, however, not detected by conventional clinical EEG techniques owing to high pass (i.e., low cut) filtering. Recording of these low frequencies requires a genuine DC-EEG amplifier and nonpolarizable (i.e., Ag/AgCl) electrodes.[11]

There are no published noninvasive DC-EEG recordings of human focal epilepsy. Some articles from the last 10 years have studied low-frequency fluctuations with conventional EEG amplifiers and arrays of polarizable subdural electrodes. One study[12] used stainless steel electrodes and found baseline shifts in only some seizures, whereas another group[13,14] used platinum electrodes (which have somewhat better low frequency recording properties[15]) and observed highly localized ictal shifts that were congruent with but more localized than the AC-EEG. The latter study[14] also re-

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Supported by grants from The Academy of Finland; Finnish Cultural Foundation; Arvo and Lea Ylppö Foundation; and the Regional Epilepsy Center, University of Washington.

Received May 15, 2002. Accepted in final form December 2, 2002.

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Table 1 *Summary of the patient data including the other clinical findings used for lateralization of the seizure focus*

Patient no./sex/ age, y/handedness	Seizure type	Data for lateralization			
		Ictal semiology	Neuropsychological deficits	Neuroradiology	Histology
1/M/36/R	SPS (also GTC)	Mostly subclinical	L > R	MRI normal	NO
2/F/41/R	CPS, B	Loss of speech, chewing	NL	MRI normal	Mild gliosis, no MTS
3/F/32/R	CPS, B	Unresponsiveness, chewing	NL	MRI normal	NO
4/F/35/R	CPS	Staring, unresponsiveness, moaning	L > R	MRI focal signal enhancement on R temp	Ganglioglioma in lateral cortex
5/M/35/R	CPS and GTC (post-traumatic)	Unresponsiveness, chewing, shifting in bed	L > R	MRI cystic encephalomalacia in L temp	Mild gliosis, no MTS
6/M/21/R	CPS (some B)	Staring, confusion	L > R	MRI normal, FDG-PET L temp hypometabolism	Mild gliosis, no MTS
7/F/45/R	CPS	Staring, chewing, eye blinking	L > R	MRI L MTS, interictal SPECT normal, ictal SPECT L temp hyperperfusion	MTS

SPS = simple partial seizure; GTC = generalized tonic-clonic; NO = not operated; CPS = complex partial seizure; B = bilateral spread; NL = not lateralizing; MTS = mesial temporal sclerosis; temp = temporal.

ported occasional slow baseline fluctuations in scalp recordings with Ag/AgCl electrodes in three patients with frontal and parietal lobe seizures.

We recently developed DC-EEG techniques capable of stable, long-term bedside recordings from human scalp[16] (see also reference [17]). This is a relatively easy and inexpensive method, which makes it an ideal candidate as a clinical tool. In this study we examined a series of patients with temporal lobe epilepsy (TLE) undergoing presurgical evaluation. The main objective of this study was to find out whether ictal DC shifts are measurable from human scalp, and, if so, whether these DC shifts could be used to determine the side of seizure origin in TLE.

Methods. Seven patients (table 1) with TLE were studied. DC-EEG was performed at bedside in the epilepsy monitoring unit, simultaneously with long-term EEG-videotelemetry monitoring (LTM) for presurgical evaluation.[1] No restrictions of patients' daily activities were needed other than those required by the LTM. This study was approved by the Human Subjects Committee of the University of Washington. Informed consent was obtained from all subjects according to the Declaration of Helsinki.

DC-EEG method. Scalp DC-EEG was recorded using a custom-designed 16-channel DC-EEG amplifier (bandwidth DC, 160 Hz; high input impedance differential preamplifiers equipped with circuits for automatic electrode offset voltage compensation and testing of electrode-skin contact impedance) and sintered Ag/AgCl electrodes with 12 mm^2 of active area (type E220N-LP; In Vivo Metric, Ukiah, CA). We used custom-made electrode holders to lift the electrodes 6 mm above the skin, and thereby to form a closed space that was filled with electrode gel (Signa Gel, Parker Laboratories, NJ). The relatively large volume of the gel together with the airtight contact between the holder and the skin minimized drying of gel, which would cause marked baseline drifts due to changes in electrode potentials.[18] The electrode holders were attached to the skin with collodion, and the skin beneath was scratched with a tiny needle through the basal lamina in order to short-circuit skin-generated potentials.[19,20] After allowing 10 to 15 minutes for stabilization, baseline drift was always unidirectional and less than 500 μV per hour. DC-EEG electrodes were always placed symmetrically and their locations conformed to the international 10:10 system.[21] Most of the electrodes were placed around the temporal lobes, two to three electrodes were in the midline, and in some cases frontal, central, and parietal locations were added. Reference electrode was at vertex. In addition, one or two channels for recording eye movement (disposable Ag/AgCl disk electrodes; Nicolet, WI) were included to confirm that the DC shifts during seizures were not due to electric fields caused by eye movements. EEG signals were sampled at 500 Hz by a 12-bit data acquisition board with an amplitude resolution of 2.4 μV. The software for data recording and analysis was programmed under Labview (National Instruments, Austin, TX).

Analysis. Exact timing of electrical seizure onset, electrical generalization of the seizure, and clinical seizure onset (for seizure semiology, see table 1) were determined from the LTM recording by two board certified, experienced electroencephalographers (J.W.M. and M.D.H.). The occurrence and possible temporal difference of DC shifts between left and right side were analyzed by reformatting the derivations to midline references, either to Pz alone or to calculated average of midline electrodes (e.g., AFz + Cz + Pz). Average reference was used to mitigate the effect of midline signal on the trace. For all our analyses, DC shifts were defined as a clear baseline deviation with duration of longer than 5 seconds, and in close temporal proximity to ictal electrographic discharge. Both board certified electroencephalographers (J.W.M. and M.D.H.) independently agreed upon the timing and location of the DC shifts for each seizure.

Results. We recorded 35 seizures, all of which had a focal origin. In one patient (no. 1) the seizures were all subclinical (all over 4 seconds, mean duration 20 seconds) and confined to one side only, but he had normal results on MRI scan and did not undergo subsequent surgery. In the other patients the seizures (n = 9) spread bilaterally and they showed clear clinical manifestations. Owing to equivocal laterality of seizure onset, arrays of intracranial subdural electrodes were utilized in four patients. Two (nos. 5 and 6) had intracranial electrodes during the DC-EEG recording, and two (nos. 2 and 4) had intracranial recording done at a later session. Intracranial recording of all these four patients demonstrated that the onset of the seizures took place in the mesial TL (table 2). In addition, one more patient (no. 7) with bilateral seizure onset at scalp recording was considered to have probable

Table 2 *Summary of the electrophysiologic findings from conventional EEG (intracranial and scalp) and DC-EEG recordings*

	Scalp EEG		Intracranial EEG		DC-EEG recording		
Patient no.	Interictal spikes	Ictal onset	Electrode location	Ictal onset	Duration, h	No. sz	Ictal findings (DC shifts)
1	L anterior temporal	L temporal (subclinical events)	—	—	3	26	Prominent unilateral (throughout) negative DC shifts (see figure 1)
2	L anterior temporal	L temporal	L grid and L temporal strips	L mesial temporal	4	2	First positive, then negative shift
3	L and R anterior temporal	R temporal	—	—	21.5	1	R side negative shift
4	L and R anterior temporal	R temporal	R grid and R temporal and OF strips	R mesial temporal	16	1	First positive, then negative shift (see figure 2)
5	L and R anterior temporal	L frontotemporal	R and L temporal, parietal, and OF strips	L mesial temporal	11	1	First positive, then negative shift
6	L and R anterior temporal	L temporal	Temporal strips	L mesial temporal	24	3	In all seizures first positive shift, then either positive or negative (see figure 3)
7	L anterior temporal	Bilateral temporal (see ictal SPECT)	—	—	1.5	1	L positive DC shift at the beginning (then lots of movement artifacts)

All grids were placed over fronto-temporo-parietal convexity.

DC = direct current; SZ = seizures; OF = orbitofrontal.

mesial TL origin of seizures, because of her MRI (left mesial temporal sclerosis) and ictal SPECT (left mesial temporal hyperperfusion) findings (see table 1). As to potential problems caused by artifacts, gross movements after generalization of the seizures did not obscure the onset of DC shifts in the beginning of seizures. Some problems were, however, caused by chewing, persistent ictal gaze shifts (not by blinking), and possible gross movements before seizure onset. Although we were able to distinguish DC shifts during every seizure, we recognize the possibility that DC shifts may be missed occasionally because of these types of artifacts.

General observations of DC shifts during seizures. All 35 seizures were associated with DC shifts of considerable amplitude (30 to 150 μV) in temporal derivations relative to midline reference. Polarity of the shift in the temporal derivations was either positive or negative (relative to vertex) in the beginning of the seizure, whereas it was always negative during the later, bilateral seizure activity. The overall pattern (polarity and form) of DC shift was the same for each seizure of a given patient. DC shift was consistently observed first on the side of seizure onset, and it commenced within few seconds after the beginning of the high voltage spiking. Every unilaterally persisting seizure was associated with a clear unilateral DC shift (figure 1), which lasted until the end of electrographic discharge. During seizures with bilateral spread the DC shifts were always confined to the area with high voltage fast spiking discharge (figure 2); i.e., DC shift became bilateral only after the spread of seizure activity. In seizures with a very rapid (within seconds) bilateral spread, lateralization was possible by an initially more pronounced DC shift on the side of onset.

Comparison of DC-EEG and invasive recordings: Mesial vs lateral temporal lobe. Four patients underwent intracranial recording, which enabled comparing of DC shifts during seizure activity in mesial temporal regions (usually recorded from electrodes over the parahippocampal gyrus) vs lateral temporal regions (electrodes over neocortical regions). Activity from mesial TL is typically not seen at scalp with conventional EEG techniques, or it may even be detected bilaterally. Interestingly, we observed an initial positive DC shift in all seizures (n = 7) with mesial TL onset (figures 2 and 3). The DC shift in these cases was seen in the temporal and mastoid derivations. When the seizures spread to the lateral temporal subdural electrodes, negative DC shifts developed (see figures 2 and 3). Likewise, in some seizures the highest amplitude of spiking fluctuated between mesial and lateral TL derivations, and was also reflected in the polarity of the

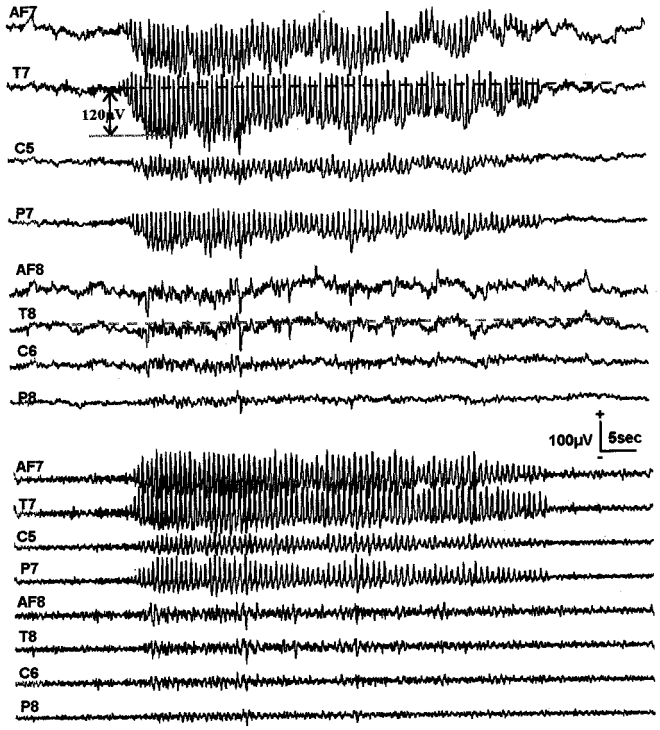

Figure 1. Unilateral direct current (DC) shift during a subclinical partial seizure on the left side (Patient 1). Traces above show the seizure with DC-EEG recording (no high pass filter), and the traces below show the same EEG with a conventional high pass filter (0.5 Hz). Note the rapid and prominent DC shift on the side of seizure. The amplitude of the DC shift is seemingly higher in the derivations with higher spiking activity (e.g., T7 vs C5). All derivations are referred to a linked Cz + Oz. Positivity is upwards in all figures.

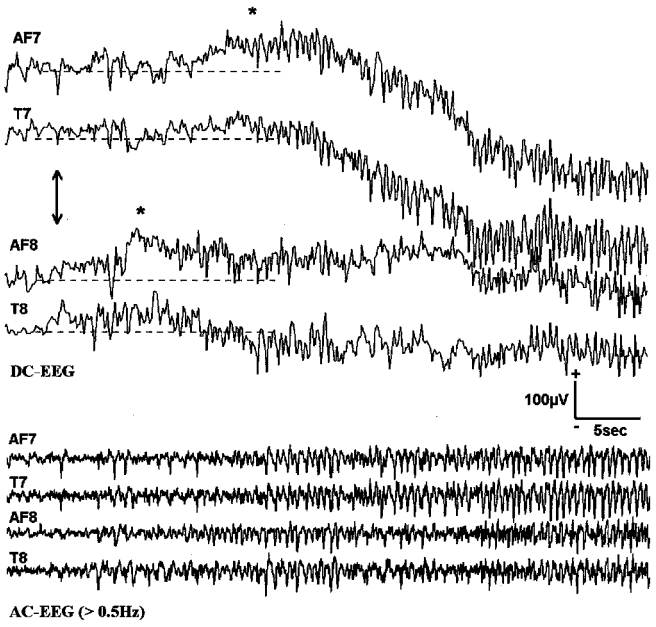

Figure 2. Complex partial seizure with subsequent bilateral spread after right side seizure onset (Patient 4). Traces above show the seizure with direct current (DC)–EEG recording (no high pass filter), and the traces below show the same EEG with a conventional high pass filter (0.5 Hz). Seizure onset at scalp EEG is shown with an arrow. Note a positive DC shift (asterisk) first at right side, followed by a positive DC shift on the left side. Negative DC shift is observed only much later. Intracranial recording of this patient at a later time (not shown; see table 2) demonstrated a right mesial temporal lobe onset. Hence positive DC shifts likely reflect sequential (right followed by left) mesial temporal lobe activation. All derivations are referred to Pz.

DC shift (see figure 3). In addition, the fifth patient (no. 7) with likely mesial TL onset seizures (see above) showed bilateral onset at conventional scalp recording, whereas there was a clear positive DC shift on left without any DC shift on right. This initial positive shift on the left side was considered to reflect mesial TL origin of her seizure.

Discussion. In current clinical practice lateralization of seizures is based on pieces of evidence gathered from multiple diagnostic techniques. Often an intracranial recording is required because of equivocal information obtained by other methods. Any additional noninvasive method of lateralization, such as the DC-EEG technique used in the current study, might reduce the need of invasive monitoring. In our study, lateralization of the DC shifts agrees with that obtained from conventional presurgical evaluation. Hence this approach holds promise to provide additional clinically useful information on the side of origin of TL seizures.

There have been a number of prior studies of slow potential shifts during focal seizures in humans.[10,12-14] However, except for the early intraoperative recordings,[10] true DC recording techniques were not used, unlike the current study. Recordings of focal seizures using arrays of polarizable subdural electrodes demonstrated localized shifts in some patients.[12-14] Recordings with scalp Ag/AgCl electrodes have been reported in three patients with extratemporal lobe seizures with conventional amplifiers with a long time constant,[14] revealing baseline fluctuation with some seizures. Because of the technical differences and because these patients did not have TL seizures, the results cannot be meaningfully compared to the current study.

Previous animal studies[6-8] and some invasive recordings on humans[9,10] have established the idea that seizure activity is always associated with a negative DC shift at the cortical surface. The current study demonstrates DC shifts at human scalp. We also show that the distribution of ictal DC shifts is limited to seizure activity; i.e., the DC shifts are unilateral until the electrographic discharge spreads bilaterally. Compared to conventional EEG, DC-EEG may thus give more information about the laterality of ictal discharge. It is notable that in the current study all DC shifts were evaluated retrospectively when the time of seizure onset was known. Validation of the clinical accuracy of our findings will require a prospective, blind analysis of DC shifts without knowledge of exact electrical seizure onset times. Also, all our patients had TLE, and hence further studies are needed to test the value of DC-EEG in seizure localization in patients whose seizures originate in other cortical (e.g., frontal or parietal) areas.

We did not observe DC shifts earlier than the ictal electrographic discharges, which is in line with the idea that ictal DC shifts reflect the ictal recruitment of cortical surface,[8,10] and hence arise only after ictal discharges have begun. Many currently used functional imaging techniques (e.g., SPECT and PET) are based on the same rationale; i.e., detecting the volume of brain tissue primarily involved in seizure activity. Although lacking the spatial information of these imaging techniques, DC-EEG is able to show the changes in cortical seizure recruitment with a high temporal resolution, which is critical in cases with rapid bilateral spread.

Intracranial recordings are often required primarily because of the mesial TL origin of seizure activity, which may spread bilaterally before appearing in scalp electrodes.[22-25] In this context it is intriguing that the ictal DC shifts in all five patients with mesial TL origin seizures suggested a side of seizure origin that was consistent with other clinical information (see tables 1 and 2). This observation raises the prospect that noninvasive DC-EEG could reduce the need for intracranial EEG in such cases. One may wonder why, in these cases, we saw initial positive DC shifts (relative to midline), which were followed by clear negative DC shifts only after the seizure activity spread to lateral TL or other areas in the neocortex (see figure 3). Previous studies have demonstrated that (epicortically) negative DC shifts are consistently seen with invasive foramen ovale electrodes in patients,[9] whereas DC shifts with either positive or negative polarity may be observed

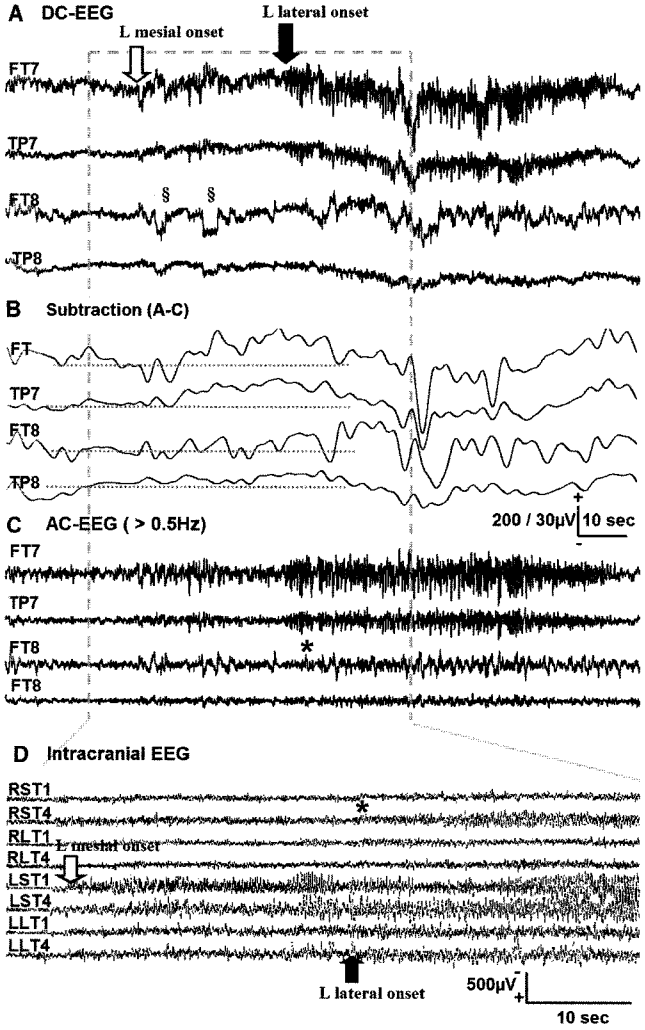

Figure 3. Comparison of direct current (DC)–EEG recordings (A–C) to an intracranial recording with subdural strip electrodes (D) during a complex partial seizure with left mesial temporal lobe (TL) onset (Patient 6). A through C are all in the same time scale (amplitude bar 200 μV for A and C, 30 μV for B). Traces in A show the seizure with DC-EEG recording. Traces in B show the slow component (subtraction of a high pass [as in C] signal from the DC-EEG) of the same EEG signal. Traces in C demonstrate the same EEG with conventional settings (i.e., high pass filtered at 0.5 Hz). Traces in the bottom (D) are selected channels from an intracranial recording, which has been stretched slightly to better illustrate the changes in fast activity. Seizure onset (mesial) and spread (to lateral) in the intracranial EEG are shown with respective arrows, and seizure spread to right mesial TL is shown with an asterisk. Note the prominent positive DC shift in the left temporal derivations after mesial TL activation, and the negative DC shift later after neocortical spread. All derivations in DC-EEG are referred to a linked Cz + Pz, whereas traces in the intracranial recording are referred to a scalp electrode at vertex. Lateral eye movement artifacts before the seizure (marked with § in trace A) have been removed offline in trace B before A − C subtraction in order to improve the visual clarity of the later occurring DC shift. RST = right mesial TL; RLT = right lateral temporal lobe; LST = left mesial TL; LLT = left lateral temporal lobe.

using intracranial electrodes over lateral side of the TL during seizures with mesial TL or hippocampal origin in monkeys.[6] Although the mechanisms that generate the characteristic shape of the DC responses seen in the current work during seizure onset remain to be worked out in future studies, the determination of the side of seizure origin with DC shifts can be based on observation of unilaterally pronounced DC shifts irrespective of their polarity.

Mechanisms of generation of slow EEG responses differ markedly from those giving rise to high frequency oscillations.[11] Substantial evidence suggests that an important mechanism of slow EEG signals may be related to spatial potassium buffering by glial cells,[26-30] especially during the slow unipolar DC shifts associated with seizure activity. Further, later in vitro studies with epileptic human hippocampal tissue have demonstrated that even gliotic brain tissue (with Ammon horn sclerosis) is able to produce DC shifts (i.e., slow field potentials), which are to a large extent mediated by potassium ions.[28] It is notable, however, that several studies have also provided evidence supporting the presence of intracranial, nonneural (i.e., other than neurons or glia) generation of slow DC shifts.[31-34] The slowest EEG potentials may thus have marked non-neuronal components, especially epithelial potentials modified by pH or blood flow (the "blood brain barrier potential"[32-34]). Although the question of the generator mechanisms is of considerable interest, the clinical utility of DC-EEG must be based on the empirical observations of the close correlation between DC shifts and seizure localization, such as was shown in the current study.

In pioneering work done in the 1960s, scalp DC-EEG recordings of generalized spike and wave discharges were consistently shown to be linked with negative DC shifts.[35-37] These early DC-EEG recordings were performed with amplifiers that required frequent rebalancing to correct for baseline drift (Chatrian, personal communication). This technical shortcoming precluded the introduction of this technique into clinical practice, which explains why scalp recordings of focal seizures have not been previously performed. In our experience, DC-EEG is a reliable method that is readily applicable to bedside recordings once basic[15-17] technical requirements are met. In short, one must use a genuine DC-EEG amplifier with sufficiently high input impedance and sufficient stability as well as a wide enough dynamic range combined with automatic offset compensation to avoid amplifier saturation due to possible artifactual changes or drift of the baseline. The electrodes must be reversible, because all polarizable electrode materials (such as gold, tin, platinum, or steel) are coupled in a mainly capacitative manner to their external environment, which leads to high-pass filtering at the electrode-gel interface.[38] Among the currently available electrodes only those based on Ag/AgCl are adequate, and the sintered contact elements used in our study proved to be both maintenance-free and very stable. Our experience

with recordings lasting up to 24 hours indicates that it is possible to extend the duration to even several days as needed. An additional issue to be considered is the electrode-skin contact, where drying of electrode gel must be prevented, and scratching of skin must be performed to short-circuit skin potentials, such as galvanic skin responses (sweat artifacts).[19,20,39] In practical terms, implementation of DC-EEG recording into routine clinical practice would be remarkably easy. DC-EEG amplifiers are not significantly more expensive than the current clinical amplifiers; suitable electrode material (Ag/AgCl) is sterilizable and has been in clinical use for decades; the specific holders used in our study can be integrated with the electrodes to make them easier to use; attachment of the electrodes on skin is practically as quick as with the conventional electrode types; and finally, sufficient scratching of the skin is so painless that we have successfully done that even with sleeping neonates.[16]

The limitations of the DC-EEG technique are mostly similar to those of conventional EEG. Proper interpretation requires use of appropriate montages and familiarity with various sources of artifacts. When comparing DC-EEG and conventional EEG, the visual appearance of slow artifacts (e.g., eye and tongue movements; see online figure e1 at www.neurology.org) is somewhat different due to the lack of high-pass filtering in the former, and hence some experience is needed for their proper identification. Distinguishing between artifacts and seizure-related DC shifts, however, is easy because artifacts have their characteristic waveforms with a typically faster time course (only up to a few seconds) and usually a global distribution. Unlike in conventional EEG, skin potentials do not cause problems in DC-EEG recordings of the present kind because they have been excluded by puncturing the skin (see Methods). Movement artifacts just before and during seizure onset might occasionally make evaluation of DC shifts impossible. However, most of the movement artifacts can be avoided by firm attachment of the electrodes to the skin (e.g., with collodion), and by using appropriate placing of the reference electrode (e.g., vertex).

Our study shows that DC-EEG may be recorded bedside with easily achievable modifications of routine EEG techniques. Ictal DC shifts are consistently seen in scalp recordings, and the DC shifts give information that agrees with seizure lateralization as defined by the other established criteria. Our observation of DC shifts with mesial TL seizures also suggests that scalp-recorded DC-EEG might provide an invaluable tool in noninvasive determination of the side of seizure origin in these patients. Although in our study the number of patients was limited, and there is as yet no postsurgical follow-up to correlate the localizations of DC shift with a postoperative seizure-free outcome, our results are robust and consistent, and suggest a clinically useful role for DC-EEG. Further prospective studies are warranted, particularly in the subgroup of patients with TL seizures where ictal scalp EEG gives unclear lateralization.

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