

Comment Letters

Carbonic Anhydrase Inhibitors and Amobarbital Resistance

To the Editor:

We read with interest the report by Bookheimer et al. on amobarbital resistance during the intracarotid amobarbital (Wada) procedure, in patients treated with carbonic anhydrase inhibitors including topiramate (TPM) or zonisamide (ZNS) (1). We also were surprised by a high incidence of inadequate drug effect during Wada procedures over the past few years, and similarly speculated that a problem might have existed with amobarbital quality.

We reviewed our database of 40 patients who underwent the Wada procedure at UCI Medical Center between February 2000 and July 2003. The incidence of failure to achieve an amobarbital effect adequate to perform valid memory and language testing was higher in patients treated with TPM (44%, four of nine patients) than in patients not taking TPM (13%, four of 31 patients; two-sided Fisher's Exact test; $p = 0.059$). The effect was stronger when we included in the analysis three patients taking ZNS, which also has carbonic anhydrase inhibiting activity. Six (50%) of 12 subjects taking either TPM or ZNS had an inadequate amobarbital response, compared with only two (7%) of 29 not taking one of these two drugs. (Fisher's Exact test, $p = 0.005$).

The mean daily TPM dose was higher in the four patients with an inadequate amobarbital response (450 mg), than in the five patients with a successful procedure (280 mg), although this difference was not statistically significant ($p = 0.158$). Because relative metabolic acidosis was proposed as a possible mechanism for amobarbital resistance (1), we retrospectively examined bicarbonate levels in our patients. No significant difference in bicarbonate level was found between patients who did and did not respond to amobarbital, but in only three patients was the level obtained within 1 week of the Wada procedure.

Our results independently confirm the observation of Bookheimer et al. that patients taking TPM or ZNS are at significant risk for reduced sensitivity to the effects of amobarbital. Our results also suggest that, at least with TPM, the risk of amobarbital resistance may be related to dose. We agree with Bookheimer et al. that this effect is strong enough to warrant decreasing or discontinuing medications with carbonic anhydrase-inhibiting activity before the Wada procedure. The risk of discontinuing these medications (whether prescribed for epilepsy or other indications) must be weighed against the risk of an uninterpretable Wada test, and the possibility of requiring a second procedure.

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Epilepsy and Seizure Disorder

To the Editor:

Carl Stafstrom's letter to the editor (*Epilepsia* 2005; 46:456) makes an excellent case for semantic precision when dealing with seizures and epilepsy. We have reached a stage of understanding that permits us to describe precisely ictal events, epilepsy syndromes, and relevant features of individual patients for clinical and research purposes. A task force of the International League Against Epilepsy is working to develop a system that will permit continuing improvements in classification and terminology as scientific developments in our field progress. But why on earth would Dr. Stafstrom wish to eliminate the term *seizure disorder* from our lexicon? The term *seizure disorder* is not synonymous with epilepsy and should not be used in this manner; however, this nonspecific term has an essential application in describing the broad range of conditions that constitutes our area of expertise as epileptologists. The term *seizure disorder* and more specific terminology are by no means mutually exclusive. Should the field of movement disorders give up its name, or, indeed, should we no longer refer to neurological or psychiatric disorders? Would Dr. Stafstrom recommend that we rename the UCLA Seizure Disorder Center the UCLA Epilepsy and Related Conditions Including Provoked, Isolated, and Nonepileptic Seizures Center? Precise use of words and terminology is an admirable goal for clinicians and scientists, but this involves using words and terms correctly, not expunging them from our vocabulary.

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Response: Epilepsy and Seizure Disorder

To the Editor:

I greatly appreciate Dr. Engel's comments on my letter to *Epilepsia*, "It's time to eliminate the term *seizure disorder* from our lexicon." My purpose was to stimulate careful thought about the use and misuse of terms among epileptologists, and to this extent, the letter has achieved its goal. Dr. Engel agrees that semantic precision is necessary but opines that the term seizure disorder retains usefulness in our collective vocabulary.

Dr. Engel states, "... seizure disorder is not synonymous with epilepsy." That is exactly my point! Because the terms are not synonymous, they should not be used interchangeably. But in medical practice, they often *are* used synonymously. Patients, conversely, may be confused by the different terms. Since the publication of the letter, I have received several communications from patients, relating that their physicians used the term seizure disorder for years before the patients realized that they had epilepsy! These experiences speak to our need as epilepsy professionals to use terms accurately, not assume that patients know the difference between similar terms, and to insist on the use of proper terminology by our students and colleagues.

I do not propose elimination the word "disorder" in general. Indeed, the terms *movement disorders* and *psychiatric disorders* form a useful framework for the various diseases in those fields. But we have an alternative, and the more the term *epilepsy* is specified, the better I believe that our patients will be served.

As for Dr. Engel's query as to whether I would suggest an alternative name for the UCLA Seizure Disorder Center I would not touch that one with a 10-foot depth electrode!

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Comorbidity of Epilepsy

To the Editor:

The study of the comorbidities of epilepsy, reported in December 2004, is important for what it reports of the health problems of people with epilepsy, but it also raises the issue of the use of the term "comorbidity." In this study of adults with epilepsy, it is used as an epidemiologic description of conditions that have an increased prevalence in the specific disease that is being studied. No necessary causal relation is implied by such an association, and both CNS- and non-CNS-based impairments are included. However, the causes of these associations may

already be understood or be at the hypothesis stage. From the pediatric perspective, these associations are many, and subsume much of what makes pediatric epileptology so complex.

The term comorbidity is perhaps tending to be used to describe any associated condition.

Examples:

1. One caused by the primary pathogenesis of the epilepsy (e.g., hemiplegia caused by hemimegalencephaly).
2. One caused by epilepsy (i.e., secondary brain damage, which is permanent; e.g. mesial temporal sclerosis, after febrile status epilepticus).
3. Brain dysfunction, caused by epilepsy (epileptic encephalopathy), which may be treatable (e.g., selective, or global, or cognitive). Deterioration in Landau-Kleffner syndrome and West syndrome, respectively.
3. Problems caused by treatment, particularly antiepileptic drugs.
4. Problems caused by social disadvantage associated with epilepsy.
5. Problems in which the connection is uncertain.

Thus for specific problems/conditions/syndromes, an increasing trend is to describe as many features of the phenotype as possible and, where possible, the pathogenesis of each aspect. To take two examples, Landau-Kleffner syndrome is identified by its seizure, cognitive, and (we would suggest) behavioral characteristics, with the implication that the latter features are caused by epileptic activity and constitute an epileptic encephalopathy. West syndrome would similarly be defined by seizures, EEG, and the cognitive and social impairments, with the latter also being at least in part an epileptic encephalopathy. However, in West syndrome, fixed primary cognitive and motor impairments may well be consequent on the initial cerebral defect that also subsequently caused the epilepsy.

In these contexts, the term comorbidity does not help us. Comorbidity may be a useful term in the epidemiology of epilepsy, in helping to define the support services required, and raising research questions and hypotheses about why—for example—overall a high rate of autism-spectrum disorder is found in a range of early-onset epilepsies and why psychoses are overrepresented, as is illustrated in the study in question.

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Response: Comorbidity of Epilepsy

To the Editor:

We are grateful to Neville and Gillberg for pointing out the semantic problems in using the word “comorbidity” in the context of a heterogeneous condition like epilepsy, and we would like to comment. In our understanding, comorbidity in epilepsy refers to associated conditions and not to symptoms, medication side effects, or specific pathologies, such as hemiplegia, dizziness, or hippocampal sclerosis. In this respect, brain dysfunction associated with a syndromic diagnosis (e.g., Landau–Kleffner and West syndrome) would not count as comorbid, as it is usually part and parcel of the same condition. Strictly speaking, comorbidity in epilepsy should refer only to conditions that are not known causal factors for epilepsy. They may or may not share a common mechanism predisposing to the development of both disorders. It is not, however, always possible to differentiate between cause and effect in epidemiologic studies (1,2). Neville and Gillberg close by saying,

Comorbidity may be a useful term in the epidemiology of epilepsy, in helping to define the support services required and raising research questions and hypotheses about why—for example—there is overall a high rate of autism spectrum disorder in a range of early onset epilepsies and why psychoses are overrepresented, as is illustrated in the study in question.

This is an important statement and further emphasizes the importance of the study of the comorbidity of epilepsy.

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Seizure Anticipation: Do Mathematical Measures Correlate with Video-EEG Evaluation?

To the Editor:

We read with great interest the manuscript by Navarro and colleagues (1) who investigated correlations between

clinical EEG changes and a nonlinear EEG measure for dynamic similarity that has been used in previous studies on seizure anticipation. This study aims to bridge the gap between nonlinear EEG analysis and visual changes with respect to seizure anticipation by analyzing unselected continuous EEG recordings (which are generally assumed to pose a greater challenge to any seizure-prediction algorithm than highly selected data). Although the goal of this study is a highly deserving one, important shortcomings limit its conclusiveness.

For the detection of a pre-seizure state, sensitivity and specificity play an equally important role, because any measure or algorithm can easily be tuned to yield a high sensitivity if specificity is neglected. In previous seizure-anticipation studies using this measure, the issue of specificity has mostly been ignored (2–4). Only one study provided a selected example of interictal control data (5); a systematic investigation is missing. Moreover, a substantial debate exists concerning the reproducibility of results (6). The only published study that includes a systematic investigation of sensitivity and specificity for the similarity measure was carried out by another group by using selected intracranial EEG recordings from patients with medial temporal lobe epilepsy (7). In this study, the similarity measure was found to perform only slightly better than a random predictor. For a sensitivity as low as 42%, the false-positive rate was so high (0.15 per hour) that 50% of alarms were false alarms.

An evaluation including both sensitivity and specificity would have been particularly important for the present study, because the authors used unselected data in their study and analyzed all possible combinations of three of 27–64 channels of EEG. This poses important problems to a proper statistical evaluation of the sensitivity, as a high chance exists that changes in the dynamics occur in three of 64 channels within a time window of 20 min, independent of the fact that a seizure will occur. This point should have been addressed by a proper statistical validation (8), including data on the rate of false positives.

Over the past years, a lot of controversy has taken place in the field of seizure prediction. Most of the promising results reported in early studies could not be confirmed in reevaluation studies on larger data bases using a complete statistical evaluation [see, e.g. (9) and references therein]. If this field is to retain its credibility, then certain basic standards have to be met. A retrospective analysis on seizure prediction must comprise an evaluation of both sensitivity and specificity, as well as a proper statistical evaluation to prove that a predictor performs better than random. The mere reference to other studies is not sufficient if different data are analyzed. The conclusion that can be drawn from this study is that changes in the similarity measure show a certain association with clinical and EEG changes. Unfortunately, it remains an open question

whether any of these changes is specifically related to the occurrence of seizures.

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Response: Seizure Anticipation: Do Mathematical Measures Correlate with Video-EEG Evaluation?

To the Editor:

We recently reported that preictal changes detected by a nonlinear mathematical analysis of the EEG could be associated with various visually detectable EEG changes and/or changes of vigilance or behavior (1). These findings suggest that the preictal period may correspond to different dynamic states: *physiologic* changes of the brain activity that may increase the probability of a seizure, or *pathologic* changes of the brain activity due to the progressive building of a seizure.

We fully agree with the comments of Mormann et al., underlining that each method of seizure anticipation must be evaluated with respect to its sensitivity (capacity to detect preictal changes) and its specificity (rate of false-positive detection). The properties of the similarity method we used have been largely studied in previous reports, showing a good sensitivity [in specific and selected populations of partial epilepsies (2–4), as well in unselected patients (1)] and a specificity that depends mainly on fluctuations of the patient's vigilance level (1,4).

In the field of seizure anticipation, several periods existed. The first period consisted of the identification of preictal changes in specific populations of partial epilepsies, mostly in medial temporal lobe epilepsies (MTLEs).

The second period consisted of an evaluation of the methods through their sensitivity and specificity. The first International Collaborative Workshop on Seizure Detection, organized in Bonn in 2002, was dedicated to the comparison of numerous methods on the same data set (five patients with MTLE). Results obtained by each group were not easily comparable, but one major conclusion was that no available method has a high level of both sensitivity and specificity when used for periods of several days (5,6).

In addition, an independent group did an extensive evaluation of several methods (7–9). They showed that the similarity method behaves slightly better than the others, but they also stated that most current methods developed with the aim of seizure anticipation have sensitivity and specificity that are not sufficient for clinical applications.

Instead of remaining with this pessimistic view, we are now in a third period; the improvement of anticipation methods based on a better knowledge of pathophysiology of the preictal period. The goal of our recent study was a better understanding of the nature of the preictal changes that we and others have observed by using complex mathematical measures of EEG dynamics. We think this sheds an interesting light on many of the earlier publications that often neglected an assessment of behavioral changes and visually observed EEG changes. We used the similarity method for its ability to describe faithfully the EEG dynamic for several hours and to track possible preictal changes. Our findings showed various types of EEG and behavioral changes, suggesting the existence of pathologic and physiologic preictal changes. Therefore future strategies of seizure anticipation should be insensitive to circadian physiologic changes. The analysis of phase synchrony of the EEG signals in narrow frequency bands may have this potential (6).

The field of seizure anticipation is still highly interesting, and numerous questions are now debated: What are the cellular mechanisms associated with the preictal periods? Is the EEG signal informative enough to contain highly specific and sensitive markers of the preictal period?

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Interhemispheric Preponderance of Noninvasive Source Algorithms: Commentary on Two Recently Published Articles

To the Editor:

We read with great interest the articles of Kobayashi et al. (1), reporting on the accuracy and pitfalls of dipole source modeling of epileptic spikes by using simulated spike generators of different cortical extents, and Holmes et al. (2), reporting on localized mesial frontal and frontopolar discharges in patients with absence seizures.

During the last two decades, source modeling techniques such as single equivalent dipole estimations or three-dimensional current density distributions have been increasingly used for noninvasive localization of epileptiform and event-related activity. Irrespective of the method used, the scalp-recorded EEG or magnetoencephalogram (MEG) signals do not provide conclusive information about the localization and distribution of putative sources, and a priori assumptions must be implemented into these methods to overcome the nonuniqueness of the inverse solution. With dipole models, the source of the voltage field recorded from the scalp is considered to be a theoretical pointlike dipole, equivalent in location and orientation to the generating cortical area. The intracerebral field of epileptiform activity, however, is often complex

and might involve extended areas of active cortex rather than pointlike dipoles, perhaps most evident in the case of primary generalized spike-wave epilepsy. In their study, Kobayashi et al. (1) show perfectly how the locations of estimated dipoles can be very misleading when the source area of a spike is extended over a large area of cortex, despite (or because of) a small residual variance. This problem was particularly conspicuous with very large bilateral sources covering the convexities and mesial surfaces of the frontal lobes. Dipole modeling of this widespread cortical activity resulted in consistent dipoles with minimal residual variance situated in the cingulate gyri, 3 cm away from the cortical generating surface, irrespective of inclusion or exclusion of mesial frontal areas in the source simulation.

We too have been bothered by the propensity for noninvasive source models to localize widespread frontally predominant generalized activity into the bilateral anterior cingulate gyri. This interhemispheric preponderance is not restricted to dipole models but occurs also with distributed source models. Holmes et al. (2) present interhemispheric solutions for spike-wave complexes of absence seizures by using both a dipole model (BESA) and a distributed linear source model (low-resolution electromagnetic tomography, LORETA). With both methods, they found similar source solutions for the spike-wave complexes within bilateral frontal interhemispheric cortical areas, including the anterior cingulate gyri and supplementary sensorimotor areas (Figs. 5, 9, and 10 in their study). These findings were interpreted as evidence that absence seizures are not truly “generalized” but rather involve selective cortical networks within mesial frontal and orbital frontal regions. Although these speculations are supported by other lines of evidence, we do not have much confidence in this interpretation of the source modeling data, in that the findings may simply reflect the limitations of the source models.

In Fig. 1, we demonstrate the interhemispheric preponderance of noninvasive source models by modeling four different frontally predominant symmetrical EEG patterns: two real, physiologic signals (3-Hz spike-wave, eye blink) and two artificial signals (10-Hz sine wave, random noise). LORETA clearly offers similar interhemispheric solutions for all four symmetrical EEG patterns, irrespective of the underlying signal. In the case of the eye blink, LORETA offers an interhemispheric solution although the two sources are a priori known to be separate and bilateral (the eyeballs act as dipoles, with the negative poles oriented toward the retinas). The interhemispheric solutions for the generalized sine wave activity and random noise exemplify the problem of modeling sources for widespread bilateral signals. Although the noncerebral examples in the figure obviously violate the basic assumptions of LORETA by computing the inverse solutions of extracortical sources, they were chosen here to illustrate a point. Source models, irrespective of their basic assumptions, just offer the putative source(s) that best

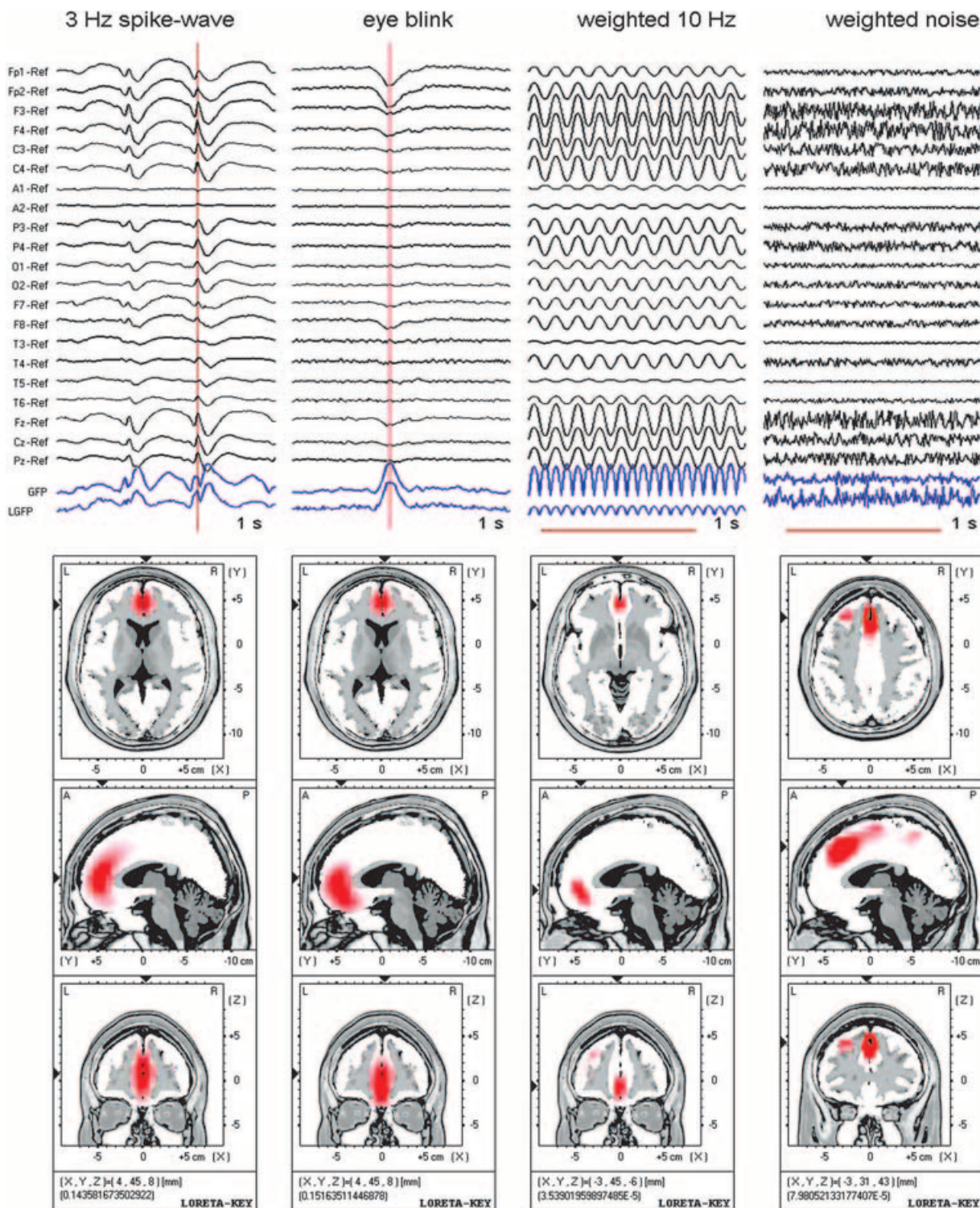


FIG. 1. Low-resolution electromagnetic tomography (LORETA) provides virtually identical interhemispheric solutions for four different symmetrical EEG patterns (calculated during individual time sample points (red vertical lines) or epochs (red horizontal lines); “weighted” denotes adjustment of each electrode in the 10-Hz sine wave and random noise signals to accord with the magnitude of a typical 3-Hz spike-wave discharge, as shown on the left).

explain(s) a given scalp voltage field. Given that a symmetrical EEG voltage field can be explained by either (a) a single interhemispheric source, or (b) by two or more symmetric and bilaterally synchronous hemispheric sources,

the source models provide us with the simpler solution, which is explanation (a).

This preponderance for simple interhemispheric solutions becomes problematic when examining the many

EEG phenomena that reflect synergistic subcortical activity, such as generalized epileptiform activity or sleep patterns, which show symmetrical EEG voltage fields that are most likely related to widespread bilateral hemispheric cortical activity and not the result of a distinct, well-defined, midline near generator. In this regard, we are increasingly being confronted with source modeling studies that present bilateral sources in and around the anterior cingulate gyri for a multitude of diseases and conditions. Indeed, it is beginning to seem that activity in the anterior cingulate gyrus may be responsible not only for most psychiatric disturbances such as obsessive-compulsive disorder, depression, and schizophrenia, but also for generalized epilepsy syndromes as well as physiologic sleep patterns.

As emphasized by Kobayashi et al. (1), the neurophysiologic principles underlying generation of the recorded EEG signals must always be taken into consideration when interpreting the results provided by these source-modeling methods. It also is important, however, to avoid self-fulfilling prophecies whereby potentially meaningless source-localization data are justified by a priori neurophysiologic constructs. In the case of 3-Hz spike-wave activity, prevailing neurophysiologic concepts implicating a mesial frontal predominance within the thalamocortical circuitry underlying primary generalized epilepsy are not actually further supported (or discredited) by deep midline source solutions for the widespread cortical activity: the findings are simply not helpful one way or the other. We suggest that all interhemispheric solutions of noninvasive source models should be regarded with suspicion whenever widespread and symmetrical EEG voltage fields are analyzed.

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Response: Interhemispheric Preponderance of Noninvasive Source Algorithms: A reply to Zumsteg and Wennberg

To the Editor:

It has long been recognized that the equivalent dipole for a coherently active patch of cortex will be localized at a depth below the patch, toward the center of the head (1). The study by Kobayashi et al. (2), cited by Zumsteg

and Wennberg, nicely illustrates this error with specific geometries of cortical regions. However, the simulations of Kobayashi et al. were limited to the spatial sampling of conventional (sparse array), 25-channel, EEG. It would be instructive to see a careful study of the behavior of distributed linear inverse solutions, such as LORETA-KEY, with similar synchronous patches. Zumsteg and Wennberg make a reasonable case that linear inverse solutions will have a similar problem as the equivalent dipole method, when applied to sparse-array EEG data.

Unfortunately, the commentary and data presented by Zumsteg and Wennberg also betray a significant misunderstanding of some critical factors that are important in affecting the solutions to EEG source analysis. Specifically, Zumsteg and Wennberg do not consider the effects of undersampled EEG signals, and they apply the same spatial weights to multiple waveforms in their analyses. The results are meaningless with this approach: because EEG spatial resolution and weighting determine the source model, undersampled signals will always have the same source solutions, when given the same weights!

All the data in the Zumsteg and Wennberg commentary, both recorded and simulated, use a standard 21-channel EEG array. Poor spatial sampling limits the precision of the interpretations of these data. It is difficult to relate, for example, the spike-wave seizure in the commentary figure to that from the 256-channel recordings in our original study (3). When a scalp potential field is undersampled (as during standard recordings), the spatial aliasing has the same effect as temporal aliasing caused by inadequate digitization (4). This effect, in turn, results in the apparent potential distribution to appear to be lower in frequency (smoother in space) than it actually is, because no higher spatial frequency (variation in space) can be characterized by the sparse sensor array. The artifactually smooth distribution, particularly when sampling is restricted to the top half of the head, as is the situation in recordings that use the International 10-20 system, inevitably leads to inaccurate source modeling. This includes the modeling of deeper sources that would be required for the more-complex source pattern to fit the actual potential distribution. Spatial undersampling thus confounds the problem of modeling synchronous activation of widespread cortical regions.

Furthermore, the simulations presented by Zumsteg and Wennberg are not useful in discriminating between synchronous superficial sources and deep single sources. The 10-Hz and noise distributions are irrelevant time courses that are weighted by the scalp distribution that would produce a deep medial frontal source. The logic of these simulations escapes us. We could digitize the first four notes of Beethoven's Ninth Symphony, and then weight the waveforms to create this same scalp distribution, but we should not be surprised when all four notes localize to the medial frontal lobe.

The effect of poor sampling of the data can be seen in the eye-blink recording and LORETA-KEY localization in the Zumsteg and Wennberg commentary. In a 256-channel recording, the accurate characterization of the potential distribution around the eye sockets (Fig. 1, ref. 3) causes eye-blinks to be modeled by sources in the eye socket, not by a source deep in the frontal lobe.

This error of spatial undersampling, of course, does not cancel the potential error of (deep) mislocalization of a synchronous patch. It simply means that sparse-array data, or sparse simulations, are of limited use in determining the actual localization of sources. We agree that an alternative explanation for the medial frontal localizations presented for the waves (of the absence seizures) in our article could be synchronous activation of widespread, and more superficial, regions of the medial frontal lobe. Perhaps we should have emphasized more clearly that the source models, whether linear inverse or equivalent dipoles, are models for the data, and must be accompanied by careful inspection of the actual scalp potential distributions. The clinical utility of source modeling will depend on future research that leads to considerable improvement in the accuracy of physical modeling, including exact specification of sensor positions, accurate conductivity models of head tissues, and using the patient's individual magnetic resonance imaging to capture the actual geometry of the cortex.

Conversely, as we thought would be clear in the figures in our article, the importance of noninvasive dense-array EEG recordings for understanding the neurophysiology of absence seizures is not dependent on source modeling. The scalp potential distributions, such as shown for one spike-wave complex in Fig. 3 of our article, and for an-

other in Fig. 7, reveal focal patterns of activity that are not consistent with the common notion that these seizures show a "generalized" appearance across cortical regions simultaneously (3). Rather, the dense-array recordings show that, for all absence seizures in these patients, the surface-negative wave builds across the dorsolateral frontal scalp and then is terminated by a positive spike with a focal onset over the frontopolar scalp (e.g., as shown by the topographic maps in Fig. 8, ref. 3). The localized nature and differential distributions of these features of the seizure are apparent to inspection of the dense-array data and may be important in understanding the role of frontal cortex in the thalamocortical interactions in absence epilepsy.

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