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## **Epilepsy: structural or functional?**

J M Stevens

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# FORUM

## Epilepsy: Structural or Functional?

The case report by Patil et al (1) in the April 1995 issue of *AJNR* demonstrates very poignantly the confusion about whether epilepsy is mainly a functional or mainly a structural disease. If these authors had believed epilepsy was mainly a structural disease, all that would have been required in this case was magnetic resonance (MR) imaging and a surgeon prepared to do a lesionectomy, accepting a small risk of causing a hemiplegia. However, the functional approach led to the patient's being exposed to the surgical risks of subdural grid, multiple cortical transections, and, finally, the lesionectomy. This is notwithstanding the other expensive and entirely redundant tests also carried out more than once. In this particular case there was such clear clinical location that it could be argued that even a surface electrode electroencephalogram (EEG) was unnecessary.

Almost unbelievably, this case was presented as a success story for xenon-enhanced computed tomography (CT). In fact, this case illustrates very well that units that emphasize the functional aspect of epilepsy need to take a close look at what they are doing, because this approach is leading to a great deal of unnecessary and expensive investigation and may also occasion unnecessary surgical procedures. The implications are all too obvious.

I would urge epilepsy units to place their emphasis on structural imaging first and foremost and to reserve functional tests for last resort. This approach saves a great deal of time, costly investigation, and, more important, morbidity.

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## Reply

It would be very nice if intractable seizure surgery could be performed based on structural imaging alone. Unfortunately, this is not possible because (a) the seizure focus or foci may not be in the radiologically identified structural lesion and (b) there may be more than one seizure focus, which may or may not include the radiologically identified structural lesion. Specifically, in our patient, there was more than one seizure focus, one of which was in the radiologically identified structural lesion.

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*Editor's note.*—We solicited the following additional comments on Dr Stevens's letter.

## Comment

The view expressed by Dr Stevens reflects an unfortunately all-too-common misconception about epilepsy. Epilepsy is a *functional* disorder, although there *may be* a structural substrate, an epileptogenic lesion. The functional disturbance that characterizes epilepsy is recurrent epileptic seizures. Epileptic seizures exist in patients with no structural lesions, whereas many patients with structural lesions never have epileptic seizures. Furthermore, all patients who have epilepsy clearly caused by structural epileptogenic lesions do not have epileptic seizures *most of the time*. Consequently, epilepsy results from intermittent functional changes in neuronal activity, which may or may not be related to disturbances in neuronal structure.

Although I agree with Dr Stevens's contention that over-emphasis on the functional diagnostic approach to epilepsy can lead to unnecessary studies that are at times invasive as well as expensive, I emphatically disagree with his conclusion that presurgical evaluation should depend on structural imaging, reserving functional tests for "last resort." Patients with intractable epilepsy who are candidates for surgical treatment have compromised brain function and presumably need all the normal brain they have. Therefore, it is imperative to determine, with a high degree of confidence, that the resection will include epileptogenic tissue and spare normally functioning cortex. We do have an obligation to consider cost-effectiveness, as well as

risk-benefit ratio, when proposing invasive investigations such as chronic subdural grid recording, and it is true that many patients with neocortical epilepsy and obvious structural lesions can have the epileptogenic region adequately identified with ictal scalp EEG recording and intraoperative electrocorticography. It would, however, be extremely dangerous to promote the view that patients with intractable epilepsy and discrete structural lesions should automatically be treated by surgical removal of the structural lesion. In a significant number of such patients, some or all of the seizures will originate elsewhere, and an unnecessary expensive surgical intervention not only will fail to relieve the epileptic symptoms, but also could result in additional avoidable neurologic deficit.

Epilepsy surgery programs should be, and are, striving to reduce the cost of presurgical evaluation without compromising safety or efficacy. Advances in structural and functional neuroimaging have made it possible to eliminate long-term monitoring with intracranial electrodes for the majority of patients who undergo surgical treatment, and even scalp ictal recordings may soon be obviated for some. However, because epilepsy is a functional disorder, the epileptogenic region still needs to be identified primarily with functional studies, preferably of ictal events. Traditionally, this requires a multidisciplinary approach, with EEG recordings playing the central role and neuroimaging a confirmatory one, rather than the other way around as suggested by Dr Stevens.

To comment briefly on the interesting study by Dr Patil and his colleagues, the focality of the ictal imaging studies and the excellent result from a very limited resection are both somewhat unusual. I wonder whether these findings occurred because the patient had previously undergone multiple subpial transection to reduce cortical spread of ictal discharges.

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#### Comment

The role of neuroimaging in the evaluation of patients with epilepsy has increased significantly in the last several years. In fact, entire textbooks are now devoted to the subject (1, 2). As a result of the dramatically improved methods of imaging the brain, there has been a concomitant increase in interest in the neurosurgical treatment of epilepsy. The letter to the Editor from Stevens highlights a very important issue in this rapidly evolving area of neuroimaging and neurosurgery. Stevens states that there is "confusion about whether epilepsy is mainly a functional or mainly a structural disease." Let there be no confusion; epilepsy is a disorder of brain function! However, Stevens's point is well taken. There are certainly differing strategies

among various investigators involved in epilepsy evaluations that can be broadly divided along the lines of functional brain imaging versus structural brain imaging.

Stevens correctly points out that for the patient presented in this article, structural neuroimaging combined with clinical symptomatology would have been sufficient to locate the epileptic focus as proved by subsequent surgical resection. Stevens, however, fails to point out that accurate identification of the MR abnormality does not necessarily equal accurate identification of a seizure focus. As has clearly been demonstrated by other case examples, the obvious MR lesion may not be the appropriate location for surgical resection (3). Stevens's suggestion about performing a lesionectomy based solely on the clinical and MR findings while "accepting a small risk of causing a hemiplegia" should be regarded with caution. His approach to this case entirely misses the two most important aspects of the neurosurgical treatment of epilepsy. First, it is necessary to identify the location of the *seizure initiation zone*. Second, it is necessary to develop a neurosurgical approach that *minimizes inadvertent damage* to nearby healthy tissue involved in critical brain function, such as language and motor control.

Stevens's general suggestion for epilepsy units to "place their emphasis on structural imaging first and foremost and to reserve functional tests for last resort" is of great concern to us. The observation that the abnormal electrophysiology of epilepsy can at times be traced to a region of structurally compromised brain tissue is a valid point, but is often insufficient. The epileptic patient with normal CT and MR findings is not at all uncommon. Fever and a variety of drugs are also well known to induce epileptogenic activity in the absence of structural brain abnormalities. In addition, the majority of lesions identified with structural neuroimaging are in fact not associated with epileptogenic activity. When a gross lesion is identified in an epileptic patient, it may be a reasonable first assumption that it is causing nearby tissue to be epileptogenic, but this need not be the case. Functional location of a seizure focus, rather than mere identification of a lesion, *must* be the standard for clinical care.

In some instances, functional imaging may enable detailed structural evaluations that identify previously missed lesions. As structural imaging methods continue to improve, more-subtle abnormalities are being revealed. As a result, many patient examinations now demonstrate multiple regions of supposed structural disease, and only functional imaging will indicate the location of the critical seizure-onset zone. This is not to suggest that expensive functional neuroimaging techniques should be applied indiscriminately or that invasive location of a seizure focus with subdural grids and depth probes is always required. Indeed, the trend is toward developing appropriate noninvasive imaging modalities. MR certainly plays an important role, but the structural data must be supplemented.

Beyond structural MR data, there are two general types of functional data that can be of value in locating an epileptic focus. One class of techniques relies on examination of epilepsy-related alterations in cerebral metabo-

lism and hemodynamics. Example techniques are single-photon emission CT (SPECT), positron emission tomography (PET), and the xenon-enhanced CT methods described by Patil. The second class of techniques involves noninvasive assessment of electromagnetic signals generated by epileptic tissue. Scalp EEG has always been one of the primary diagnostic tools in the evaluation of patients with seizures. Although routine scalp EEG typically fails to provide adequate locating information for planning lesionectomies, the last decade has witnessed the development of powerful high-density (64+ electrodes) EEG source-modeling methods that can be used to locate brain regions responsible for seizures. By the same token, large-array magnetoencephalography has come of age and is being used at several centers to locate epileptic foci with high success, as evidenced by good surgical outcomes. Indeed, we feel that magnetoencephalography is particularly attractive in the evaluation of epilepsy because it provides direct insight into abnormal electrophysiology.

Functional and structural neuroimaging both play an important role in the evaluation of epilepsy patients. They are complementary, not competitive, strategies. Does an individual patient need MR, magnetoencephalography, EEG, PET, SPECT, and xenon CT? As a rule, No, but there needs to be a general agreement in seizure locus between two or three independent methods before resective surgery should be initiated.

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## Comment

The paper by Patil et al is a nice example of how functional neuroimaging complements the data yielded by neurophysiology and neuroradiology. I thought that the patient's presurgical evaluation was well thought out and followed a logical progression in location of seizure focus.

On the other hand, I must disagree with most of the points raised in the letter by J. M. Stevens. Dr Stevens appears to have conceptualized epilepsy as *either* a functional *or* structural disease (although he uses the word "mainly"), and he objects to the workup of this patient with both functional and radiologic neuroimaging studies. Stevens goes on to suggest that the patient's seizure focus location was so clear on the basis of clinical data that even "a surface electrode EEG was unnecessary." Yet, it is notable that the actual site was 1.5 cm below the surface of the motor cortex at a region too deep to have been reached by the previous subpial transection. Had a resection been tried without knowledge of the depth of the lesion, serious damage to the motor cortex would have ensued. The precentral gyrus is not a place in which an exploratory craniotomy is looked on favorably. The step-by-step manner in which Patil et al carried out their investigation does them credit and was certainly the safest way to proceed.

Dr Stevens's all-or-nothing dichotomy, functional versus structural, is, moreover, a considerable oversimplification. Although there is little question that epileptic tissue is most reliably identified with electrophysiological registration, that observation does not deny that the electrical abnormalities themselves are the result of structural changes at the cell or synaptic level (1, 2). In any event, it is clear that many MR lesions are not epileptogenic. Even in tumors, for example, the epileptogenic region does not coincide with the tumor, but extends for some distance into the surround and even distantly in synaptically related regions (3). Berger et al (4) have reported that excision of the epileptic surround results in substantially better seizure control than does resection of the tumor alone. Yeh et al (5) have made a similar observation with respect to arteriovenous malformations. Moreover, functional neuroimaging studies such as PET, SPECT and xenon-enhanced CT yield *complementary* data to those provided by neuro-radiologic examinations. For example, discordant functional and radiological neuroimaging data can alert the clinician to the possibility of dual pathology.

Although I agree with Dr Stevens's point on the need to avoid unnecessary and expensive studies, the paper of Patil et al is not an example of wasted expense.

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### Comment

First, it should be understood that the article by Dr Patil et al and the letter by Dr Stevens specifically refer to partial-onset epilepsy. (Although lesions may occur in the brains of patients with generalized-onset epilepsy, the relationship between a focal structural lesion and generalized-onset seizures is not clear). A cause-and-effect relationship between certain focal structural brain abnormalities and focal-onset seizures, however, has been recognized for more than a century. When partial epilepsy is viewed from the limited perspective of medical imaging, it seems quite reasonable to make a structure versus function argument as Dr Stevens does (ie, which imaging modality is more effective at locating the epileptogenic zone). From a broader perspective, however, abnormalities in the brain extend well beyond those found on either structural or functional medical imaging. Focal abnormalities can be seen in epileptic brain tissue with a wide variety of investigative techniques, including alterations in biochemistry, cell type and frequency distribution in tissue neuron receptor density, neuron morphology, intracellular messenger systems, and so forth.

Techniques commonly used clinically for seizure location before resective surgery also may reveal localized abnormalities. For example, MR and CT demonstrate structural lesions. Interictal PET, SPECT, and xenon CT may demonstrate regional hypoperfusion. Ictal SPECT and, when serendipitously acquired, ictal PET and ictal xenon CT demonstrate more localized hyperperfusion. Interictal scalp EEG and magnetoencephalography demonstrate localized sharp wave discharges. Ictal EEG demonstrates the actual onset and propagation of seizures, which can be recorded either by scalp electrodes or by invasive intracranial recording. The clinical examination in appropriate cases may reveal a functional deficit such as a

hemiparesis or usual field cut. Neuropsychological studies, including those associated with amobarbital testing, may reveal localized functional impairment.

A widely accepted concept in epilepsy in the 1980s was that the greatest probability of a seizure-free postoperative outcome would result when multiple independent tests converged on the same area of the brain, which was then targeted for resection. Although certainly true, this belief has led to a standard clinical practice in which many tests are performed in every epilepsy patient, in the search for multimodality convergence. More recently, however, it has become apparent that not only can society not pay for every test in every patient, but it is not necessary to do every test in every patient to achieve a high probability of a seizure-free surgical outcome. Dr Stevens's point is a very important one. That is, it has become apparent in the past couple of years that when an MR abnormality commonly associated with epilepsy (eg, cavernous angioma or mesial temporal sclerosis) is present, and the EEG findings are concordant, the probability of a seizure-free postoperative outcome is extremely high. Additional tests, particularly imaging studies, are probably unnecessary in these patients. However, there are patients with intractable partial-onset epilepsy in whom MR studies reveal no abnormality.

In my opinion, further imaging studies beyond diagnostic MR (ictal SPECT, PET, and MR spectroscopy) should be restricted to these patients in whom a diagnostic MR study does not demonstrate a resectable epileptogenic lesion. The key over the next few years in identifying the most cost-effective use of imaging in epilepsy patients will be to develop appropriate criteria, including clinical, neuropsychological, EEG, and imaging data, that define a logical flow of patients through a preoperative workup paradigm from simple to complex, with appropriate stopping points.

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