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Going beyond hippocampocentricity in the concept of mesial temporal lobe epilepsy

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The emergence of electroencephalography (EEG) as a diagnostic tool in epilepsy, not only for distinguishing among different types of epilepsy (Gibbs et al., 1938), but also for localizing epileptic brain tissue (Jasper & Kershman, 1941), spawned a tremendous interest in epilepsy surgery worldwide (Engel, 2005). Bailey and Gibbs (1951) are credited as the first to report a series of surgical procedures (all temporal lobe resections) based on EEG evidence alone, whereas Jasper et al. (1951) clearly described the EEG characteristics of what subsequently became known as temporal lobe epilepsy (TLE). Of interest, however, these early workers did not remove the hippocampus for fear it might cause irreversible behavioral disturbances, accounting for the relatively meager outcomes compared to today's results. Indeed, it has been speculated that these early results were largely placebo effects, and that had it not been for the placebo effect of aggressive intervention such as surgery, temporal lobe resection may not have been pursued.

Morris (1950) may have been the first to remove a presumably epileptogenic hippocampus, but when this practice became widespread, results with respect to epileptic seizures greatly improved. Falconer's subsequent observation (1953)—made possible by his en bloc resective procedure—that removal of a sclerotic hippocampus predicted an excellent surgical outcome (1974), lifted the hippocampus, and particularly hippocampal sclerosis (HS), to center stage among basic scientists as well as clinicians who were interested in epilepsy. This hippocampocentricity has persisted, rightly or wrongly, until today. Not only does presurgical evaluation for mesial temporal lobe epilepsy (MTLE) tend to concentrate on hippocampal epileptogenic abnormalities, but also the most common chronic animal models of MTLE are created by inducing chemical or electrical damage to the hippocampus. In this issue of *Epilepsia*, Bonilha et al. (2012) correctly point out that there is much more to the story, and that modern diagnostic technologies might reveal broader epileptogenic networks

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that would better predict surgical outcome and perhaps inform the extent of surgical resections.

The important involvement of extrahippocampal structures in MTLE is not a new concept. Over 20 years ago, Siegel et al. (1990) measured postoperative magnetic resonance imaging(MRI) studies to determine the extent of selective amygdalohippocampal resections and discovered that seizure outcome depended more on the amount of parahippocampal tissue than on the amount of hippocampus and amygdala removed. A popular experimental animal model at the time was kindling (Goddard et al., 1969), where daily, brief, initially ineffective, electrical stimulation of amygdala or hippocampus gradually results in behavioral effects that culminate in a tonic–clonic seizure reflecting an enduring epileptogenic process. Almost 30 years ago, Kairiss et al. (1984) demonstrated that the generator of the epileptic activity in this model might actually be the piriform cortex, and Piredda and Gale (1985) identified an area of the prepiriform cortex, subsequently referred to as area tempestas, to have the lowest threshold for chemically induced seizures. In fact, a recent EEG-functional MRI (fMRI) study found this area to be preferentially involved across a wide variety of acquired focal epilepsies (Laufs et al., 2011).

A modern view of acquired focal epilepsy, including MTLE with HS, eschews the concept of a discrete epileptogenic region in favor of a widely distributed network. The location of principal structures involved in this network have been relatively well-defined to lie within the standard anteromesial temporal resection for most patients with MTLE, as evidenced by the fact that two thirds of patients with this condition do become seizure free following this surgical procedure. It is unlikely, however, that the entire epileptogenic region is removed, even in patients who become seizure free, but, rather, that results depend on a critical mass effect. Retained epileptogenic tissue may cause interictal EEG spikes, or auras, but be incapable of generating spontaneous disabling seizures, whereas, in some cases, spontaneous disabling seizures that persist after surgery run down and eventually disappear. Consequently, the task of the epilepsy surgery team is not necessarily to identify the extent of the entire epileptogenic region, but to determine what would constitute removal of a sufficient amount to yield a seizure-free result.

In this issue Bonilha et al. suggest that there might be several different types of MTLE with HS that could be diagnosed presurgically, some with better surgical prognoses than others. Ten years ago, the International League Against Epilepsy (ILAE) convened a workshop that involved leaders in the field of research on MTLE with HS to determine whether this condition was a syndrome or a disease (Wieser et al., 2004). The conclusion was that it was neither, but that rather it was perhaps several different diseases. Attempts to define different types of HS based on structural pathology are weakened because only the surgically removed specimens can usually be evaluated (Thom et al., 2010). Similarly, characterization based on different types of depth-recorded ictal EEG onsets (Velasco et al., 2000) and high-frequency oscillations (HFOs) (Staba et al., 2002) are subject to sampling error. Whereas MRI manual morphometry introduces investigator bias, automated whole brain voxel-based morphometry (VBM) offers an opportunity to identify structural disturbances throughout the entire brain (Keller et al., 2002). When VBM is used, three-dimensional (3D) maps of gray matter distribution are created for a group of subjects—which may include patients and

controls—and aligned to a common stereotaxic space. Statistical maps are then compiled to highlight regions where anatomic differences predict patient outcomes, or where they relate to clinical measures, such as treatment parameters or duration of illness. A recent meta-analysis of VBM studies shows widespread gray matter volume reductions in patients with unilateral refractory temporal lobe epilepsy (Li et al., 2011); asymmetries in gray matter volumes extended well beyond the mesial temporal structures. An earlier study of patients with unilateral MTLE by Bonilha et al. (2010) noted widespread deficits in gray matter volume involving the putamen, pallidum, middle and inferior temporal areas, amygdala, and even the cerebellar hemispheres. In the same report, diffusion tensor imaging (DTI) studies were also analyzed to assess perihippocampal white matter. The resulting voxel-based maps, from both standard anatomic MRI and diffusion imaging of white matter, strongly suggest that hippocampal deafferentation contributes to extrahippocampal brain damage in MTLE, and that the extent of such deficits is widespread.

It is not surprising, therefore, that categorization of HS based on VBM, especially when the contralateral hippocampus can also be evaluated (Ogren et al., 2009a), differs from that identified by pathologists (Thom et al., 2010). Not only does VBM demonstrate thinning in wide areas of neocortex distant from mesial temporal structures in patients with classical MTLE with HS (Lin et al., 2007), but also the hippocampal atrophy is not homogeneously distributed. Patches of atrophy appear to correlate with the location of neuronal clusters that generate epileptogenic pathologic HFOs (pHFOs) (Ogren et al., 2009b). Although multiple variations of HS have been described based on electrophysiologic and structural criteria, it remains unclear whether these represent truly unique independent disturbances, or progression of a single or perhaps a few discrete pathophysiologic conditions.

The problem with current VBM methodology, however, as pointed out by Bonilha et al., is that clinically relevant patterns have so far only been demonstrated by averaging of groups of patients. To be useful for presurgical evaluation, characteristic abnormalities must be clearly defined as applicable to individual patients. Some research groups have attempted to assess whether VBM is sufficiently sensitive to detect subtle pathologic changes in single subjects, or preoperative differences that might predict patient outcomes. Eriksson et al. (2009), for example, used VBM to compare individual patients with hippocampal and laminar cortical neuronal loss to a reference group of matched controls. When applied to individuals, VBM did not detect any abnormalities attributable to laminar cortical neuronal loss or hippocampal sclerosis. The poor power of VBM to pick up known abnormalities in individuals results from its lack of sensitivity in anatomic areas with large cross-subject differences in structure (Keller & Roberts, 2008). To mitigate this, some have proposed a form of VBM that uses heavy smoothing of the images, in an effort to compare a patient to a reference group without flagging as abnormal the normal variations in gyral/sulcal patterns. Bruggemann et al. (2009), for example, found that VBM analysis of gray matter can detect focal cortical dysplasia and neoplasia relatively well, in individual children with epilepsy, but that its sensitivity may be inadequate for routine clinical application.

A variety of different diagnostic approaches may be needed to approximate the location and extent of the epileptogenic region (Lüders et al., 1993); similarly, VBM alone is not likely to be sufficient to characterize network abnormalities associated with different types of MTLE

with HS. Other approaches will continue to be necessary. These likely will include DTI tractography, positron emission tomography (PET) with MRI fusion, EEG fMRI, and resting connectivity fMRI. The latter has only recently been applied to characterize functional connectivity of the whole brain, without prior assumptions, in patients with focal epilepsy (Meador, 2011). Finally, susceptibility genes undoubtedly determine, to some extent, the development of MTLE with HS in individual patients, and genetic screening could eventually play an important role in determining what specific disease exists in individual patients, what presurgical diagnostic tests need to be done to determine prognosis, and perhaps even delineation of the extent of the resection.

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