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Temporal Lobe Epilepsy: Where Do the Seizures Really Begin?

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Abstract

Defining precisely the site of seizure onset has important implication for our understanding of the pathophysiology of temporal lobe epilepsy as well as for the surgical treatment of the disorder. Removal of the limbic areas of the medial temporal lobe has led to a high rate of seizure control, but the relatively large number of patients for whom seizure control is incomplete as well as the low rate of surgical cure suggest that the focus extends beyond the usual limits of surgical resection. A reevaluation of the extent of the pathology as well as new data from animal models suggest that the seizure focus extends, at least in some cases, beyond the hippocampus and amygdala that are usually removed at the time of surgery. In this review we will examine current information about the pathology and physiology of the mesial temporal lobe epilepsy syndrome, with a special emphasis on the distribution of the changes and the patterns of seizure onset. We will then propose a hypothesis for the nature of the seizure focus in this disorder and discuss its clinical implications, with the ultimate goal of improving surgical outcomes and developing nonsurgical therapies that may improve seizure control.

Keywords

epilepsy; temporal lobe; limbic system; seizure focus

Introduction

The question of where seizures start in temporal lobe epilepsy is a seemingly simple one, but, as one begins to examine the issue, it becomes progressively complex. The immediate answer is, of course, the temporal lobe, and, for some, the hippocampus. This commonly accepted notion is based on the experience that removal of the temporal lobe, and specifically the mesial temporal structures, stops the seizures and that there are pathological changes in the hippocampus (hippocampal sclerosis) that are strongly tied to this syndrome. Does this association of removal of a particular brain structure or region and seizure control imply causality? It is often presumed so, and there are good data to support the hypothesis. But there are a growing number of observations that suggest that this assumption may not be completely true. In this review we will examine the nature of the circuits that may be involved in temporal lobe or limbic epilepsy and the possible patterns of seizure onset. We will often refer to mesial temporal lobe epilepsy as limbic epilepsy to emphasize the likelihood that the seizures arise within a more distributed limbic system. Understanding how and where seizures start are critical for, defining the focus for surgery, identifying the

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regions where proepileptic changes may lie, designing more effective surgeries and targeting pharmacotherapy to the right areas.

Functional anatomy of epilepsy

Functional anatomy is the term we use for the physical and physiological substrate in which seizures arise and spread. It implies that there may be more complex networks that are involved in the initiation of seizures and suggests as well that different parts play particular roles in a seizure's evolution. Although we speak of a seizure focus as the place a seizure starts and the target for surgical intervention, there are likely, in view of seizure functional anatomy, a number of areas which play a critical role in the initial stages of seizures. The seizure focus is always present, but does not always seize. For this reason we have to consider neuromodulatory input to the focus that permits or pushes the focus to seize. These inputs to the focus are key to that process and are every bit a part of the functional anatomy, even if they do not directly participate in the electrographic seizure activity. At the moment these inputs are not well known and may be difficult to identify.

The focus is identified as the cortical region (included in this concept, though perhaps a little inappropriately from the purist's perspective are the hippocampus and amygdala) in which seizure activity can first be identified. As will be described below in the circuits section, the focus probably has a subcortical connection that is key to the development of the ictal discharge, and without which the potential seizure will make attempts to start, but will never cross over the seizure threshold. These subcortical structures, such as the thalamus are also under the influence of neuromodulators which control these area's propensity to support seizure activity. These neuromodulatory subcortical zones are largely conjectured but can be studied as we move toward a better understanding of the functional anatomy of seizures (Figure 1). We will, for the moment, focus on the focus.

Temporal Lobe Epilepsy

Temporal lobe epilepsy covers a variety of disorders that have the common feature of seizures that arise in the temporal lobe. The underlying pathologies include tumors, vascular malformations, cortical dysplasias, tubers, trauma as well as hippocampal sclerosis. Presumably each pathology has a unique pathophysiology that is tied to the nature of the abnormality, and the functional anatomy of the seizure generated by the pathology will vary according to the location of the abnormality. In this article we will restrict ourselves to a discussion of seizures associated with hippocampal sclerosis, the mesial temporal or limbic epilepsy. For many reasons, as we will see below, the latter term is preferred because it implies that the seizures arise in a brain system, not a single structure.

Limbic epilepsy is one of the most common forms of focal epilepsy and is also one of the syndromes most frequently operated on. Unlike other types of epilepsy which vary in pathology and location, limbic epilepsy has an advantage for understanding its pathophysiology in that this syndrome is strictly limited to a set of abnormalities that have similar appearance across individuals [1]. In addition, with some variability from one patient to the next, there is a common set of regions that are involved pathologically [1]. Because there is a certain uniformity in limbic seizures we may be able to determine which structures are critical for seizure initiation, and the role they play in the seizure circuitry.

The Circuitry of Epilepsy

Seizures do not occur in isolated neurons, rather in an assemblage of neurons, local and remote. This issue was made particularly clear by Pierre Gloor who with a number of colleagues demonstrated that without circuit interactions between the cortex and the

thalamus, the spike wave discharges of absence seizures would not arise [2]. In a series of simple but elegant studies they revealed that not only did the spike wave seizures depend on an intact thalamocortical circuit, but also that each component had a distinct and separate role in the discharge: the cortex supplied the excitatory drive and the thalamic nuclei organized this drive into an ictal discharge (Figure 2). Both components had to be present, and if one were inactivated or missing, seizures would not occur. Just as in any electrical circuit, if there is a break somewhere, the circuit won't work, even if the primary components are present and functioning normally. These relationships have been reviewed more extensively elsewhere [3] and also demonstrated in animal models of spontaneous spike and wave [4].

Such a cortical-subcortical relationship in the focal epilepsies has not been examined to the same extent, and this group of epilepsies has been considered primarily a cortical disorder, but recent evidence suggests that the thalamus may play a critical role here as well [5,6]. In limbic epilepsy there were several lines of raising the possibility of thalamic involvement. In a number of mammalian tract tracing studies there were significant connections between the limbic sites associated with limbic epilepsy and the midline thalamic nuclei [7,8,9], and a number of physiology studies have shown that these connections are largely excitatory between the limbic cortical regions and the midline nuclei [10,11] (Figure 3). In addition, imaging studies have demonstrated parallel atrophy and hypometabolism in the ipsilateral thalamus, with some specificity for the midline nuclei [12,13]. As a result there is at least a physical substrate for a potential seizure circuit between particular thalamic nuclei and selected parts of the limbic cortex.

Experiments over the last several decades have supported the concept that the thalamus, particularly the midline nuclei, is part of the limbic seizure circuit. The earliest studies showed that modulating inhibitory or excitatory function in the region of the medial dorsal nucleus had a profound effect on the behavioral expression of seizures, an observation that suggested that these nuclei had a role in seizure spread to other regions [14,15]. More recent studies have shown that either inactivating the midline nuclei pharmacologically or manipulating the excitability of this region has a profound effect on the seizure activity in the hippocampus as well [6,16] (Figure 4). Although this finding does not define a particular role for the thalamus, it does suggest that this region has a significant influence on limbic seizure activity. Further, although kindling of limbic seizures can occur with stimulation of the midline nuclei (and only the midline nuclei), the threshold for electrical current to induce the seizure is significantly higher than the threshold in the limbic sites [16]. This observation draws a potential parallel between Gloor's model of spike wave seizures and limbic seizures in which the cortex provides the excitatory drive and the thalamus serves to organize and support the seizure. In both seizure types, seizures do not happen unless both sites are involved. Thus, as we consider where seizures begin in temporal lobe epilepsy we have to keep in mind the connectivity of the limbic system as it relates to circuits and the roles that the various components of the circuits may play in seizure initiation and spread.

The Anatomy of Limbic Epilepsy

The temporal lobe, especially the medial structures of the temporal lobe, have been of interest in epilepsy since the first descriptions of hippocampal abnormalities in the 19th century. A potential role of these structures in seizures was supported when surgical removal led to seizure control, with the implication that the mesial temporal regions were important for generating seizures. Kindling studies that have shown that it is easy to initiate seizures in these structures in animals by direct low intensity electrical stimulation have further strengthened the concept that this region is important for seizure initiation [17].

Unfortunately, although these observations have strongly suggested that this region plays an important role in epilepsy, the exact role is not clear.

What has become clear since the first descriptions of anatomic changes in the temporal lobe is the broad distribution of the changes as well as the variability of these changes among individuals [1]. The quintessential pathology of limbic epilepsy has been hippocampal sclerosis, a combination of neuronal loss, atrophy and gliosis. The pattern of loss is usually in the hilus of the dentate gyrus and the CA1 region, but there are some variants. This pattern has been seen in specimens from surgical resections as well as in post mortem studies of patients with temporal lobe epilepsy, although it is also found from time to time in patients with no history of epilepsy. However there are other limbic sites that also have changes, typically neuronal loss, atrophy and gliosis, in patients with mesial temporal lobe epilepsy. These areas include the amygdala and the entorhinal cortex as well as specific nuclei in the thalamus [12,13,18,19]. Animal studies in rats with post-status epilepticus limbic epilepsy have also revealed changes in the olfactory cortex, a region that is not regularly available in surgical specimens or examined in post mortem tissue [20]. Because the availability of these regions varies considerably in surgical specimens, the frequency with which these abnormalities occur in relation to hippocampal sclerosis is uncertain, as the criteria are not well established and the nature of the specimens also varies. At the moment we can say that the pathology associated with limbic epilepsy extends beyond the hippocampus to other limbic regions, and, at least in a few cases, the pathology in these other regions can occur in the absence of hippocampal sclerosis (Table 1). These observations suggest that the substrate for the seizures of limbic epilepsy is broader than just the hippocampus. The question is often raised whether some or all of these changes are the consequence of repeated seizures. Although the answer is not completely resolved and is still debated, much of the evidence suggests that the majority of the pathology preceded the onset of the seizures [21,22]. These observations raise the possibility that the seizure generating zone extends beyond the hippocampus, but at the moment it is only a speculation. This anatomic potential needs confirmation through physiology.

The Physiology of Temporal Lobe Epilepsy

The ultimate measure of where seizures begin is actually recording where they start. The reality is that, in people, we can only sample a limited number of sites and extrapolate, based in part on our concept of the functional anatomy of the seizures, where they actually begin. Animal studies could resolve some of these issues, but the results would always be open to the criticism that the models are not a perfect replica of human limbic epilepsy. On the other hand, animal studies allow us to explore sites and the relationships among the sites in a way that is not possible with people. Although these results from animals will always be open to question with regard to the relevance for the human condition, valuable information can still be obtained as long as we keep the potential limitations in mind. Another measure, also imperfect, is the examination of changes in the regional and cellular physiology to determine if the neurons are hyperexcitable and, thus, prone to support a seizure more readily. In this section we will discuss the pattern and regions of seizure onset first and touch what is known about alterations of neuronal physiology second. One thing that we will not discuss is the issue of a second pathology that sometimes accompanies hippocampal sclerosis. This dual pathology can be a second source of independent seizures, and would be inappropriate to consider under the issue of where do seizures start in limbic epilepsy, as these other seizures often start far away from the mesial temporal lobe.

In human intracranial monitoring, there have been several technical approaches for recording seizure onset, but the primary goal has been to define the seizure generating zone sufficiently accurately so that seizure freedom is likely if that zone is removed. Although the

implication of the studies has been that the recordings locate the site of seizure onset, the data have only occasionally be evaluated with that goal. One of the problems with human recordings is variability in the location of the electrodes so that consistent placement in the same region of one structure as well as in placement consistently in multiple structures. Some areas, such as the olfactory cortex, a region regularly shown to be involved in limbic seizures in animals, is rarely recorded in humans, in part because of its hard to reach location. However, overall, with some variability across the patients, there is a consistent finding of a broad regional seizure onset involving multiple limbic sites at seizure onset [23,24]. This observation raises the possibility of a multifocal seizure focus or of a more centrally synchronized seizure initiation.

Data from animal studies raise the same possibility of a seizure focus that involves multiple limbic sites. Kindling studies have shown that it is quite possible to induce the same type of behavioral seizure through stimulation of a number of different limbic sites [17]. Although the ease with which the seizures can be induced and the rapidity with which they spread depends on which site is stimulated, all of the limbic sites can induce the same seizure type. In recording multiple limbic sites in rats with limbic epilepsy, there is some variability from seizure to seizure with regard to where the seizure is first recorded, but, just as in people, the overall the pattern of onset that is most commonly recorded is broadly synchronized over multiple areas [25]. Within the limits of temporal resolution this observation suggests that either there is a multifocal seizure generator, or there is another site that synchronizes the activity broadly over multiple areas. These concepts may not be mutually exclusive, but it would be helpful to study the neuronal characteristics to determine if there are intrinsic changes in neuronal physiology that may predispose one region over another as a potential generator of seizures.

One of the advantages of the animal models, especially those of limbic epilepsy, is that we can examine neuronal physiology in multiple ways and from multiple regions in ways that would never be possible in people. The first question to answer is where changes occur that might predispose a region to generating seizures. In tissue taken from epileptic animals, multiple sites have neurons with clearly epileptogenic changes: hippocampus, amygdala, entorhinal cortex and olfactory cortex [5,26]. Similar changes have also been found in neurons in some nuclei of the thalamus [6]. When synaptically stimulated these neurons have prolonged depolarizations, sometimes longer than 250 milliseconds with multiple superimposed action potentials, very similar to the prolonged depolarization shifts demonstrated in some experimental seizure models [27]. These observations suggest that there is a broad change in the limbic system with multiple areas that will have greater propensity to support seizure activity. Together with the kindling data which demonstrate that all of these sites (with the exception of the thalamus) support stimulated seizures readily the observations of hyperexcitable neurons throughout the limbic system suggest that it might be possible to initiate spontaneous seizures from multiple sites.

Ideally determining the site where seizures begin is the preferred means for defining the site of seizure onset. However, this approach has not led us to the goal of a precise point of onset. This unfortunate result may be the consequence of the technical limitations of the intracerebral recordings as well as the real possibility that there may not be that sought after point of onset. The technical issues are several: the placement is not consistent across all patients and, for this reason results from all of these patients are not comparable. In addition, although we can generally point to where a seizure begins with regard to which channels are involved, saying when a seizure begins with perhaps a millisecond or tens of milliseconds precision is not so easy. For this latter reason, when multiple electrodes are involved with seizure onset it is not possible to identify a single point where the seizures begin. As a result, one of the most common patterns of onset in human limbic epilepsy has been described as

regional, involving multiple sites within the mesial temporal lobe region [23,24]. It was hoped that animals with limbic epilepsy could provide a more precise localization of seizure onset, as the pathology of the limbic system was similar to what we find in people, and we are able to place electrodes in the designated regions more consistently. However, the data to date suggest that, although focal onset can occur, the regional pattern described in humans is also true in the rat models of limbic epilepsy [25]. If a more broadly distributed onset is, in fact, the reality, we will have to rethink our concept of the functional anatomy of limbic epilepsy.

So, where do seizures begin in temporal lobe epilepsy?

The real answer at the moment is that we don't really know. However, we can speculate based on a set of observations and known connections on a hypothetical functional anatomy for limbic epilepsy onset. The facts known with some certainty as outlined above include a pathological substrate that is distributed, with some variation, among the hippocampus, the amygdala, the entorhinal and possibly olfactory/piriform cortices, as well as the midline thalamic nuclei. All of these sites have been associated with an increased excitability in the neurons, and these regions are the same ones that are relatively easy to elicit limbic seizures in the kindling models. These observations can be combined with the multifocal and regional patterns of seizure onset in this syndrome, to create a functional anatomy of limbic epilepsy that can be described as multiple independent generators of seizures. The implication of this hypothesis is that each of the sites could act independently to initiate a seizure or, potentially, to drive another site into a seizure. In other words, one seizure could be driven by the hippocampus, another by the amygdala (Figure 5). This potential functional anatomy could explain the observation that surgical success for limbic epilepsy is correlated with the amount of tissue removed, and likely, the number of the seizure generating areas resected. If multiple sites can generate seizures, the seizures won't be controlled until those sites are gone.

It must be emphasized that this hypothesis is just that, and something that remains to be proved. Proving the hypothesis will require a number of steps, not the least of which will be altering the limits of seizure resection (expanding or tailoring them) to increase the rate of control and cure. But that approach requires some degree of organization and logic to answer specific questions. On the practical clinical side there is the goal of improving seizure control and cure through surgery, which will require a more precise knowledge of the extent of all of the seizure generating tissue. Better preoperative imaging with the aim of defining the extent of abnormality in the limbic structures would be one step, but that approach presupposes that any abnormality is part of a seizure generating region. Defining areas of pathology can direct the placement of electrodes into the regions that may be prone to initiate seizures, but it will likely be necessary to record all of the potential limbic sites as seizures start. Alternatively, defining those regions may be facilitated by other physiological markers, perhaps by evoked potentials that show clear epileptiform changes. This approach will not likely help in that presumed small number of patients with a second, extralimbic pathology and focus, but it may define the focus better and improve surgical outcomes in those patients with pure limbic epilepsy.

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References

1. Margerison JH, Corsellis JAN. Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain* 1966;89:499–530. [PubMed: 5922048]
2. Avoli M, Gloor P. Interaction of cortex and thalamus in spike and wave discharges of feline generalized penicillin epilepsy. *Exp Neurol* 1982;76:196–217. [PubMed: 7084360]
3. Steriade M. Sleep, epilepsy and thalamic reticular inhibitory neurons. *Trends Neurosci* 2005;28:317–324. [PubMed: 15927688]
4. Meeren HK, Pijn JP, Van Luijckelaar EL, Coenen AM, Lopes da Silva FH. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *J Neurosci* 2002;22:1480–1495. [PubMed: 11850474]
5. Bertram EH, Zhang DX, Mangan P, Fountain N, Rempe D. Functional anatomy of limbic epilepsy: a proposal for central synchronization of a diffusely hyperexcitable network. *Epilepsy Res* 1998;32:194–205. [PubMed: 9761320]
6. Bertram EH, Williamson JM, Scott C, Mangan PS, Zhang DX. The midline thalamus: alterations and a potential role in limbic epilepsy. *Epilepsia* 2001;42:967–978. [PubMed: 11554881]
7. Herkenham M. The connections of the nucleus reuniens thalami: evidence for a direct thalamo-hippocampal pathway in the rat. *J Comp Neurol* 1978;177:589–610. [PubMed: 624792]
8. Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Rev* 2002;39:107–140. [PubMed: 12423763]
9. Su H-S, Bentivoglio M. Thalamic midline cell populations projecting to the nucleus accumbens, amygdala, and hippocampus in the rat. *J Comp Neurol* 1990;297:582–593. [PubMed: 1696591]
10. Zhang DX, Bertram EH. Midline thalamic region has widespread excitatory input to the entorhinal cortex and amygdala. *J Neurosci* 2002;22:3277–3284.
11. Bertram EH, Zhang DX. Thalamic excitation of hippocampal CA1 neurons: a comparison with the effects of CA3 stimulation. *Neurosci* 1999;92:15–26.
12. Juhász C, Nagy F, Watson C, da Silva EA, Muzik O, Chugani DC, Shah J, Chugani HT. Glucose and [C-11]flumazenil positron emission tomography abnormalities thalamic nuclei in temporal lobe epilepsy. *Neurology* 1999;53:2037–2045. [PubMed: 10599778]
13. Natsume J, Bernasconi N, Andermann F, Bernasconi A. MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. *Neurology* 2003;60:1296–300. [PubMed: 12707432]
14. Cassidy RM, Gale K. Mediodorsal thalamus plays a critical role in the development of limbic motor seizures. *J Neurosci* 1998;18:9002–9009. [PubMed: 9787005]
15. Miller JW, Hall CM, Holland KD, Ferrendelli JA. Identification of a median thalamic system regulating seizures and arousal. *Epilepsia* 1989;30:493–500. [PubMed: 2753001]
16. Bertram EH, Zhang DX, Williamson JM. Multiple roles of midline dorsal thalamic nuclei in induction and spread of limbic seizures. *Epilepsia* 2008;49:256–268. [PubMed: 18028408]
17. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol* 1969;25:295–330. [PubMed: 4981856]
18. Hudson LP, Munoz DG, Miller L, McLachlan RS, Girvin JP, Blume WT. Amygdaloid sclerosis in temporal lobe epilepsy. *Ann Neurol* 1993;33:622–631. [PubMed: 8498843]
19. Du F, Whetsell WO, Abou-Khalil B, Blumenkopf B, Lothman EW, Schwarcz R. Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy. *Epilepsy Res* 1993;16:223–233. [PubMed: 8119273]
20. Bertram EH, Scott C. Pathological substrate for limbic epilepsy: is the medial dorsal thalamic nucleus the unifying abnormality. *Epilepsia* 2000;41:S3–S9. [PubMed: 10999511]
21. Mathern GW, Bertram EH, Babb TL, Pretorius JK, Kuhlmann PA, Spradlin S, Mendoza D. In contrast to kindled seizures, the frequency of spontaneous epilepsy in the limbic status model correlates with greater fascia dentata excitatory and inhibitory axon sprouting and increased staining for NMDA, AMPA and GABA-A receptors. *Neuroscience* 1997;77:1003–1019. [PubMed: 9130782]

22. Mathern GW, Adelson PD, Cahan LD, Leite JP. Hippocampal neuron damage in human epilepsy: Meyer's hypothesis revisited. *ProgBrain Res* 2002;135:237–51.
23. So, NK. Depth electrode studie in meial temporal epilepy. In: Lüders, H., editor. *Epilepsy Surgery*. New York: Raven Press; 1991. p. 371-384.
24. Spencer SS, Spencer DD. Entorhinal-hippocampal interaction in medial temporal epilepsy. *Epilepsia* 1994;35:721–727. [PubMed: 8082614]
25. Bertram EH. The functional anatomy of spontaneous seizures in a rat model of chronic limbic epilepsy. *Epilepsia* 1997;38:95–105. [PubMed: 9024190]
26. Mangan, PS.; Scott, C.; Williamson, JM.; Bertram, EH. *Neurosci*. Vol. 101. 2000. Aberrant neuronal physiology in the basal nucleus of the amygdala in a model of chronic limbic epilepsy; p. 377-391.
27. Fountain NB, Bear J, Bertram EH, Lothman EW. Responses of deep entorhinal cortex are epileptiform in an electrogenic model of chronic temporal lobe epilepsy. *J Neurophysiol* 1998;80:230–240. [PubMed: 9658044]

Figure 1. Basic circuitry of a neocortical seizure focus with a cortical excitatory driver, a subcortical seizure synchronizer and a number of neuromodulatory inputs (NM) that regulate excitability of synchronizer, driver or both.

Figure 2.

Summary of Gloor's absence circuitry experiments. A. Regular spike wave activity occurs in intact thalamocortical circuit. B. Separating cortex from the thalamus prevents regular spike and wave activity. C. Removal of cortex prevents abnormal activity from developing in the thalamus.

Figure 3. Connections between limbic structures and medial dorsal and midline thalamic nuclei. Simplified outline of significant known pathways between limbic sites that are strongly associated with seizure activity and the medial dorsal (MD) and midline thalamic nuclei. Direction of arrows indicates efferent and afferent pathways.

Figure 4.

Modulation of limbic seizure activity through manipulation of the midline region of the thalamus. Seizure induced in anesthetized rat by stimulation of contralateral CA 3 in the hippocampus, with simultaneous seizure activity in CA 1 of the hippocampus and the medial dorsal thalamic nucleus (MD) before and after infusion of the GABA-A antagonist bicuculline. Seizure duration is significantly lengthened by bicuculline (arrows). First 10 seconds of each recording is stimulation artifact.

Figure 5.

Variable pattern of limbic seizure onset according to the multiple independent generator hypothesis of limbic epilepsy. A. shows the situation in which all three sites contribute equally to seizure onset. B. displays a theoretical amygdala dominant seizure onset, whereas C. depicts a seizure in which the amygdala would play a minor role in relation to the other sites.

Table 1

Regional Pathology Associated with Limbic Epilepsy

<u>Human</u>	<u>Animal Models</u>
Hippocampus	Hippocampus
Amygdala	Amygdala
Entorhinal Cortex	Entorhinal Cortex
Thalamus	Piriform Cortex
Mammillary Bodies	Midline thalamic nuclei
Basal Ganglia	Lateral Septal Nucleus
	Substantia Nigra