Epilepsia, **43**(3):219–227, 2002
Blackwell Publishing, Inc.

Clinical Research

Neural Networks in Human Epilepsy: Evidence of and Implications for Treatment

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A considerable amount of compelling evidence exists, predominantly from animal models and experimental paradigms, for the existence of specific cortical and subcortical networks in the genesis and expression of partial- and generalized-onset seizures (1–13). My goal is to present the concept of human epilepsy as a disorder of large neural networks and to support through several lines of reasoning how applicable the observations from experimental models are to localization-related seizures in the human disorder. I do not attempt to define specifically every possible operational human network or even all the limits or components of those that I do address, but I hope to show in a compelling way that the evidence we already have is not consistent with any other explanation. This is a new way of understanding, diagnosing, and potentially treating the various forms of human epilepsy.

In this context, I consider a network to be a functionally and anatomically connected, bilaterally represented, set of cortical and subcortical brain structures and regions in which activity in any one part affects activity in all the others. The essential operational component of this definition is the observation that vulnerability to seizure activity in any one part of the network is influenced by activity everywhere else in the network, and that the network as a whole is responsible for the clinical and electrographic phenomena that we associate with human seizures. Implicit in this idea is that the seizures may entrain this large neural network from any given part, such that it becomes irrelevant to discuss the "onset" of seizures in any specific part of the network. In other words, the electrical hyperexcitability associated with seizure activity reverberates within the neural structures of the network, which operate together and inextricably to culminate in the eventual expression of seizures.

A singular concept is the distinction between the anatomic structures involved in seizure propagation, and those belonging to the neural network that underlies a specific patient's epilepsy. The network structures are connected functionally and structurally; they are essential to the development of the seizure and thus the existence and maintenance of the epileptic disorder. Independently, seizures propagate in a variably extensive way that might involve any region or neural structure with anatomic connections to the primary seizure network; seizures can propagate to many more regions than those that are involved in the network.

Important corollaries that derive from these ideas are that interruption of the network, in a structural sense, or modification of network activity by electrical, biochemical, or metabolic influences in any part of the network *will* alter seizure expression or its occurrence. The corollaries have the greatest implications for treatment, as we will see later.

Based on extensive experience with a great number and diversity of human epilepsy patients with intractable seizures, I describe and support the evidence for three specific large human epilepsy networks. Many others are likely, but the data are not so extensive. The first is the network associated with the most common human intractable epilepsy, and the one about which we have the most information: the medial temporal/limbic network. The medial temporal/limbic network is bilateral, cortical, and subcortical, and includes the hippocampi, the amygdalae, the entorhinal cortices, lateral temporal neocortices, and extratemporal components of the medial thalamus and the inferior frontal lobes. The other two networks are less commonly identified, even in their component parts: the medial occipital/lateral temporal network and the superior parietal/medial frontal network. Two additional networks, for which evidence is highly suggestive, but which I do not discuss in detail, include the bifrontal/pontine/subthalamic network and the parietal/medial temporal network. The lines of evidence that support the existence and importance of these networks in the genesis of human epilepsy are clinical observations, intracranial EEG, functional neuroimaging, anatomic observations, and the response of seizures to specific invasive treatments.

Accepted December 7, 2001.
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Intracranial EEG is the most significant of the observations that support the network hypothesis. Because the entire network participates in the expression of the seizure activity and can be entrained from any of its various parts, initial electrical events (at "seizure onset") may vary in their specific location of expression and occurrence within the network. The initial area of apparent seizure involvement is not really an onset area, because "onset" could be expressed any place in the network, and might even *vary* from seizure to seizure in a given patient. This locational variability may produce different morphologies of "seizure onset" when EEG recording is performed in only one part of the network (14–19). Figures 1–4 are examples of several seizures from each of three patients who show this locational variability of initial EEG change in different network components of the medial temporal lobe/limbic network, the occipital/temporal network, and the superior parietal/medial frontal network, visualized only because we were able to record with electrodes implanted into multiple network sites. Four consecutive 10-s intervals of two spontaneous seizures with identical clinical expression in a patient with the medial temporal limbic network are shown in Figs. 1 and 2. The patient had febrile seizures and then onset of uncontrolled complex partial seizures characterized by staring and right-hand dystonia at age 3 years. Magnetic resonance imaging (MRI) showed left hippocampal atrophy. In the first seizure, the hallmark of the medial temporal lobe/limbic network seizure onset, the periodic discharge recorded from the hippocampal depth electrode is seen. Shortly after, low-voltage fast activity and sharp theta/alpha activity are superimposed, and then low-voltage fast activity is seen in the contacts recording from the entorhinal cortex. In the second seizure from the same patient *with clinically stereotyped manifestations,* the hippocampal periodic spike discharge begins, but the seizure "starts" with low-voltage fast activity *first* in the *entorhinal cortex,* and *then* in the hippocampal contacts.

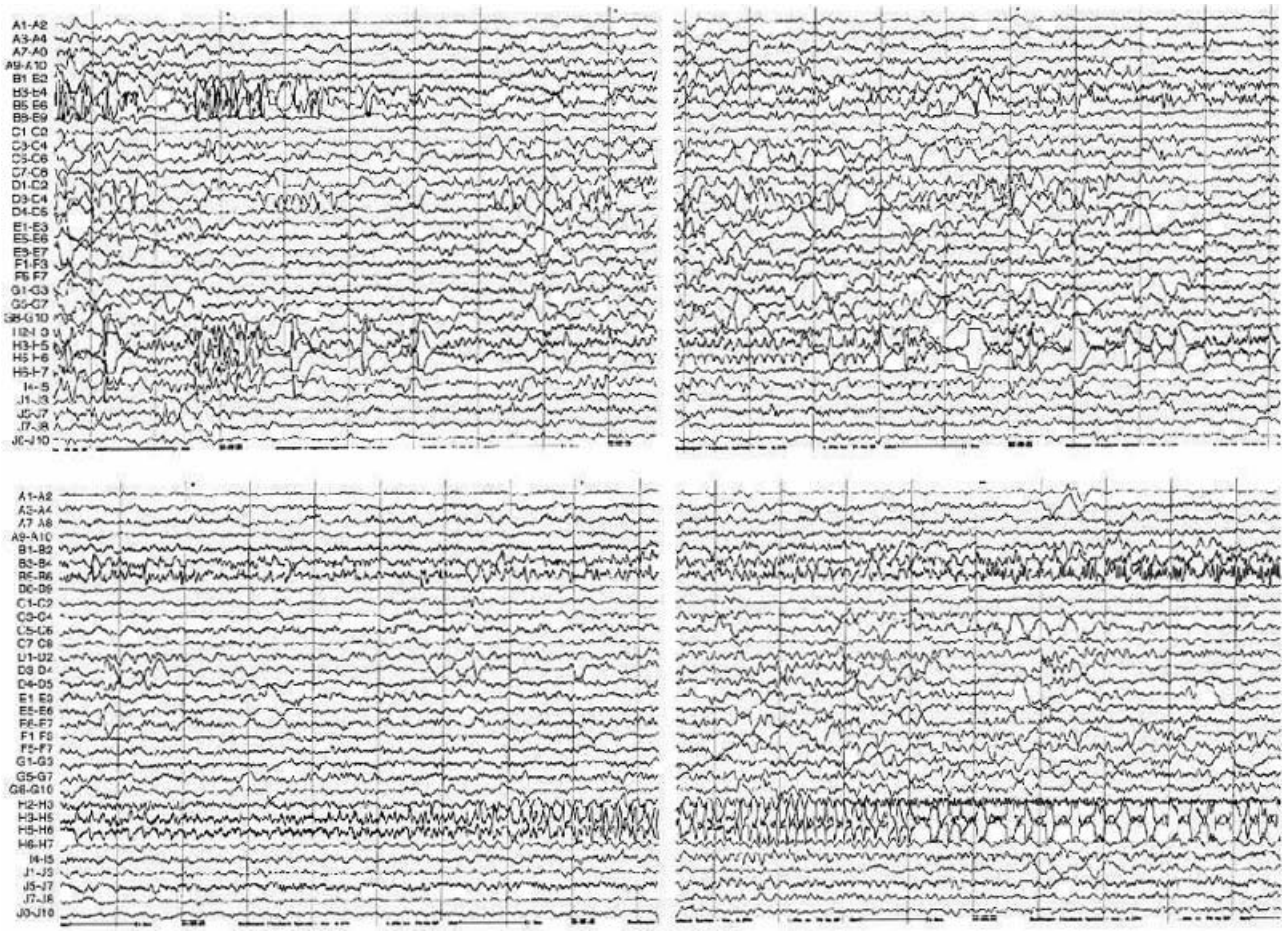

FIG. 1. Consecutive 10-s intervals of a spontaneous and typical complex partial seizure in a patient with epilepsy in the medial temporal/limbic network. A–J represent multicontact implanted subdural and depth electrodes with position 1 most distal; contacts are spaced 8–10 mm apart. The seizure is heralded by the classical 1- to 2-Hz periodic spike discharge in the hippocampal depth electrode (H3–H6), on which low-voltage fast discharge at 12–20 Hz is superimposed. Within 5 s, similar low-voltage fast discharge is seen in B3–6, a subdural strip electrode recording from entorhinal cortex. Subsequently, these two nearby locations show asynchronous development of the high-frequency ictal discharge. Clinical seizure activity follows the electrical changes by nearly 30 s.

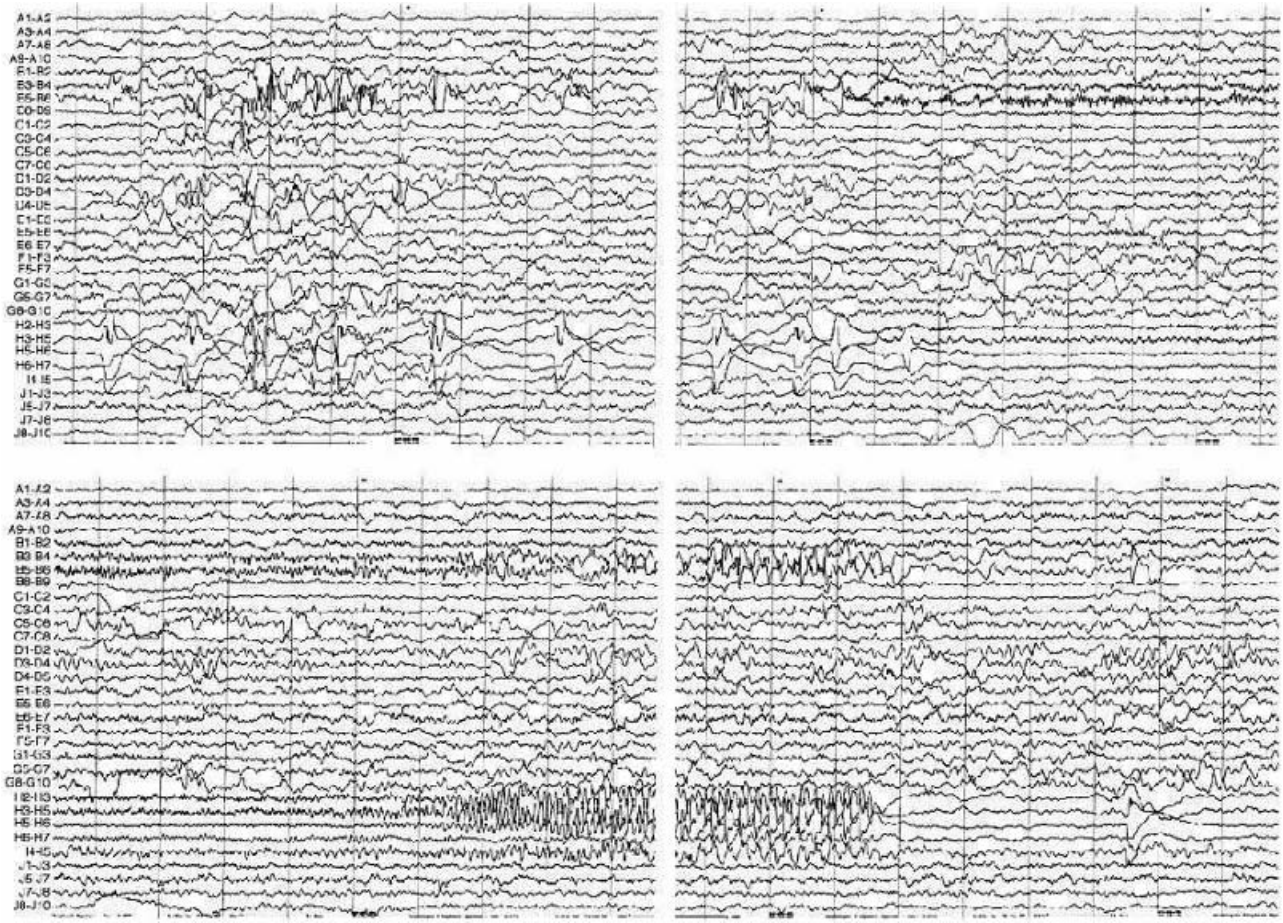

FIG. 2. Consecutive 10-s intervals of a spontaneous and typical complex partial seizure, from same patient as illustrated in Fig. 1. A–J represent multicontact implanted depth and subdural electrodes; contact 1 is most distal. Each division equals 1 s. The seizure is again heralded by 1-Hz periodic spikes seen best in hippocampal depth electrode (H3–6) but also in entorhinal cortex (B3–6). In contrast to prior illustrated seizure, low-voltage fast activity is next seen in entorhinal cortex, and only subsequently in hippocampus; both sites then continue to show fast seizure buildup before sudden cessation 30 s later.

This kind of locational and morphologic variability in the initial manifestations of the electrical seizure is extremely typical of the medial temporal/limbic network. Without the entorhinal contacts as part of the display, one would see only minor morphologic variability in the hippocampal depth electrode (or conversely, without the depth electrode recording, just in the entorhinal electrode) and have the sense of a stereotyped electrical pattern at the onset of the seizure.

Figure 3 shows two spontaneous seizures, each recorded from intracranial electrodes, that demonstrate the variable participatory order of the superior parietal and medial frontal regions in these two seizures with similar clinical manifestations. This patient began having seizures at age 8 years and was medically intractable immediately. Seizures were characterized by right foot and leg heaviness followed by tingling and rigidity. The positron emission tomography (PET) scan demonstrated reduction in metabolism in the left parietal lobe, and the ictal single-photon emission computed tomography (SPECT) study showed perfusion changes in both the left parietal and left frontal regions. MRI was negative. In the top illustrated seizure, the initial change is a low-voltage spike discharge, with low-voltage fast activity rapidly superimposed in the superior parietal region. About 4 s later, similar low-voltage fast activity is seen in the medial frontal recording contacts. In the bottom seizure, the initial low-voltage fast activity is clearly demonstrated in the medial frontal contacts, and only 3 s later is it seen in the superior parietal region. With intracranial electrodes in only the medial hemispheric or superior parietal area, these seizures would appear electrically identical, but there is clear locational variability of the participatory order of involvement within structures of the specific network. Figure 4 shows two spontaneous seizures with similar clinical manifestations in a patient with seizures characterized by flashing lights and complex behavior with falls. The PET scan demonstrated hypometabolism in the right temporal and occipital regions, and an ictal SPECT study showed hypoperfusion in both the right occipital and right temporal regions. In the setting of an extremely abnormal background with multifocal spike-

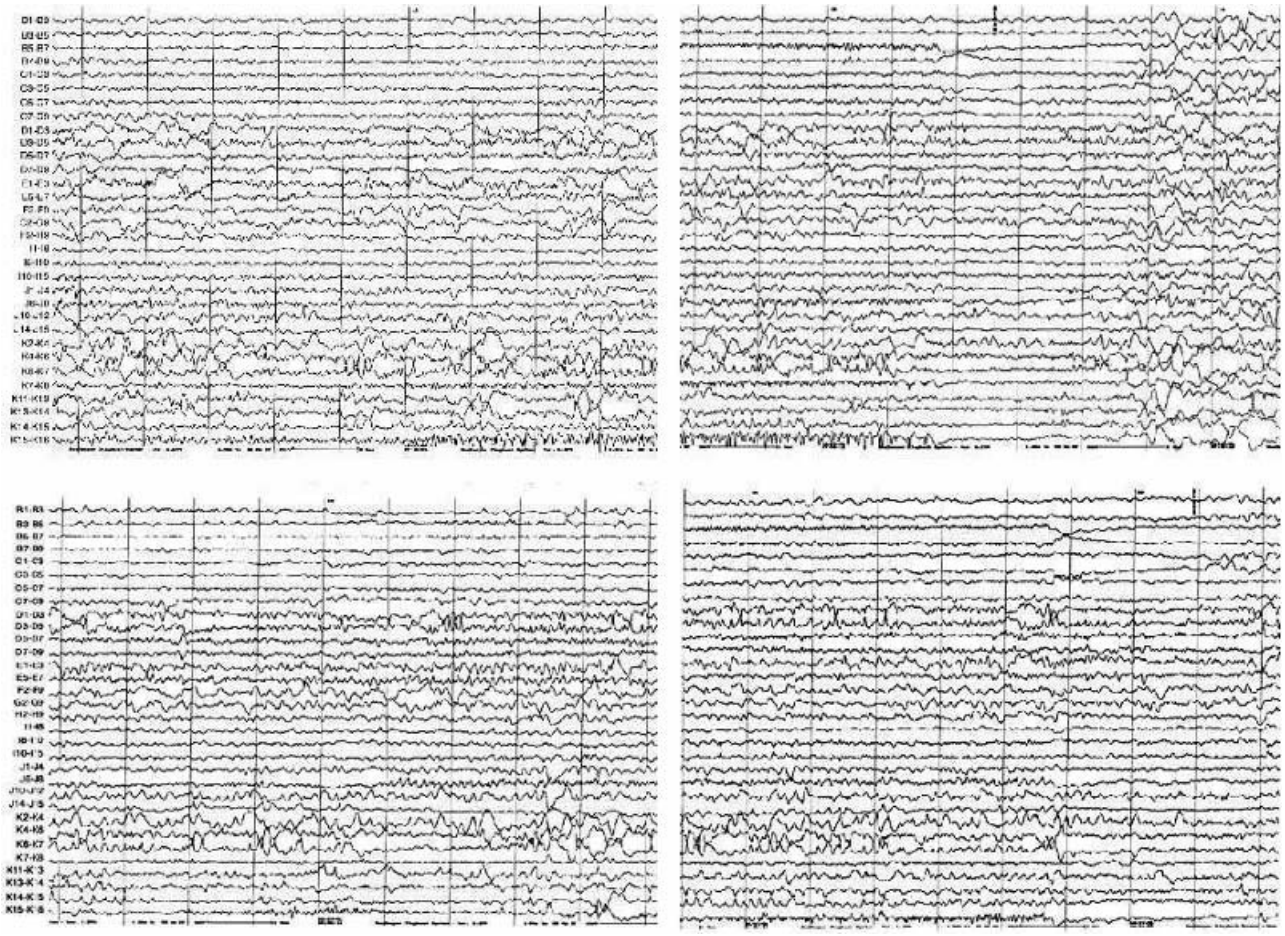

FIG. 3. Two consecutive 10-s intervals of two spontaneous typical and clinically identical seizures (top and bottom) in a patient with epilepsy of the superior parietal/medial frontal network. B–H represent implanted, multicontact subdural electrodes; contact 1 is most distal; electrode contacts are spaced 8 mm apart. I–K represent portions of an implanted, 64-contact subdural grid over left frontotemporoparietal cortex; the grid is composed of an 8 × 8 arrangement of contacts with 10-mm intercontact spacing. In the top seizure, initial seizure manifestation is with low-voltage fast discharge recorded from superior parietal area (last channel) followed in 3 s by low-voltage fast activity in medial frontal contacts (B7). In the second (bottom) seizure, the initial low-voltage fast activity preceding the clinical seizure is seen in medial frontal cortex contacts (B5, 7) followed in 4 s by similar discharge in superior parietal contact K16 (last channel).

and-wave activity, we see low-voltage fast activity first develop in the medial temporal lobe contacts in one seizure. In the other seizure, there is simultaneous activity in the temporal and occipital recording contacts.

Clinical observations also support the large neural network concept of human epilepsy. Despite variability in the early electrical patterns, clinical seizures are stereotyped, a key observation that truly reflects the operation of the epilepsy network. The best examples come from the medial temporal/limbic network, where a variable, specific, medial temporal location of manifest onset is often recorded (for example, in entorhinal cortex or hippocampus or lateral temporal neocortex), but the seizures are the same clinically, because the network as a whole is responsible for the manifestations of the seizures. Another example is found in patients with the medial temporal/limbic syndrome who have bilateral, independent temporal lobe seizure onset, although seizures appear clinically indistinguishable from one another (20–22). Patients who have variable occipital and temporal or frontal and parietal onset also reflect specific networks and the variability of ictal electrical expression, and also express clinical seizures in a stereotyped way. These are all examples of entrainment from different network sites, and the whole network acting to produce the clinically stereotyped events.

Variability in clinical seizures is likely to reflect *propagation* of seizure activity. As noted earlier, seizures can propagate variably to any and all areas unilaterally, bilaterally, cortically, or subcortically to which anatomic connections exist, but those are not necessarily part of the network that participates in the genesis and maintenance of the seizure disorder per se. An example of this difficult distinction is found in seizures that appear to originate in occipital structures and yet have variable propagation to the frontal lobes with variable frontal

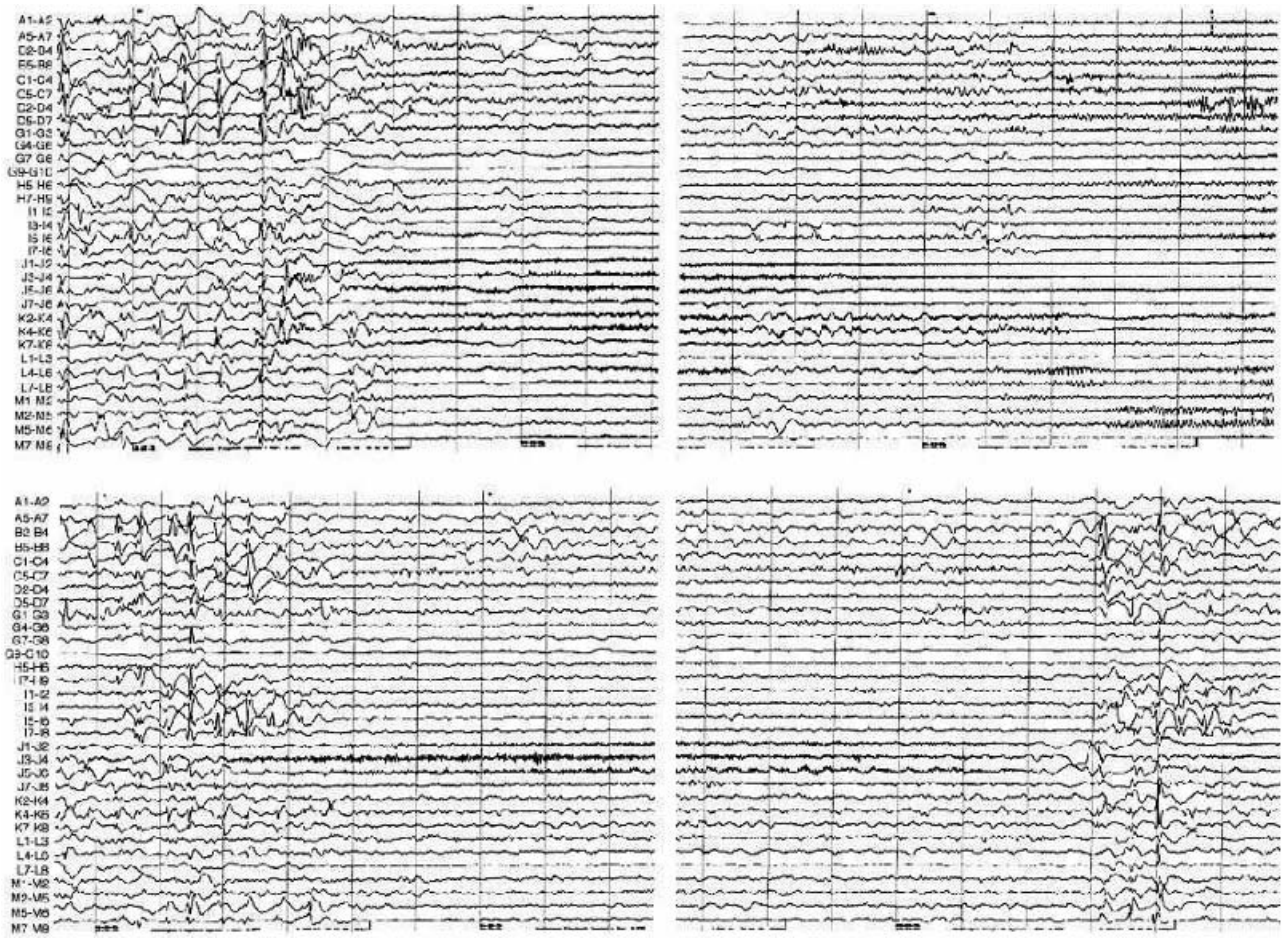

FIG. 4. Two consecutive 10-s intervals of two spontaneous, typical, and clinically identical seizures in a patient with epilepsy in the occipitotemporal network. A–I represent multiple implanted multicontact subdural electrodes with 8- to 10-mm intercontact spacing; contact 1 on each electrode is most distal; each division equals 1 s. J–M are parts of an 8 × 8 implanted subdural grid over parietooccipital cortex with uniform 10-mm intercontact spacing. The top seizure shows simultaneous low-voltage fast activity developing in temporal (electrodes B, D) and occipital regions (J), whereas the second seizure (bottom) shows similar ictal discharge restricted to the occipital region (J).

clinical manifestations (23–25). The frontal regions are not part of the occipital/temporal network.

Functional neuroimaging, specifically PET, has been very influential in development of the network hypothesis of human epilepsy. Although propagation of seizures is distinct from the network that generates them, the *question* of propagation frequently arises when we are dealing with evidence that involves spontaneous seizure activity and its evolution. Observations with functional neuroimaging (specifically PET) are so important in the concept of the epileptic network because they can avoid the confounding influence of possible propagation. PET demonstrates, especially in the medial temporal/limbic network syndrome, variably extensive, often multilobar, reduced interictal metabolism involving a variety of structures. Various authors have confirmed interictal hypometabolism in ipsilateral temporal neocortex, ipsilateral hippocampus, contralateral hippocampus, inferior frontal lobe, ipsilateral dorsomedial thalamus, and amygdala (26–32). Quantitatively, the most significant hypometabolism is in the lateral temporal and medial temporal regions, followed by the medial thalamus, basal ganglia, and frontal lobe. We usually do not have the opportunity to record electrical changes in the human seizure in all of these areas, particularly the subcortical ones, which makes this kind of information particularly valuable. It is likely that the areas involved in the interictal hypometabolism in the medial temporal lobe epilepsy syndrome define the components of the medial temporal/limbic network. There has been no other satisfactory explanation for this widespread hypometabolism, aside from the network concept. The interictal hypometabolism in these areas has been such a consistent finding in this syndrome, with a sensitivity 90%, that its absence actually questions the medial temporal/limbic diagnosis. After successful (i.e., curative) surgery for medial temporal lobe epilepsy, PET scans show *improvement* in the hypometabolism observed preoperatively in the ipsilat-

eral inferior frontal lobe, the ipsilateral temporal neocortex, and both thalami (32–34). Thus structural interruption of the medial temporal/limbic network results in cessation of seizures and cessation of the reverberating electrical activity that accompanied them.

Anatomic data confirm the importance of the medial thalamus in medial temporal/limbic epilepsy. Volume loss is present in ipsilateral thalamus, caudate, and amygdala in medial temporal lobe epilepsy (35,36), and thalamic cell loss is present in epilepsy patients (37,38). Furthermore, hippocampal cell density is significantly correlated with the amount of reduction in metabolism in bilateral thalamus and basal ganglia (39). Functionally, also, the evidence is consistent, in that synchronous activity is seen between thalamus and hippocampus, and thalamic stimulation gives a monosynaptic excitatory response in hippocampus.

Extratemporal epilepsy also is associated with multifocal, sometimes extensive, reductions in metabolism demonstrated on interictal PET studies, but this has not been as reproducible or as well documented as that in the medial temporal/limbic syndrome (29). Interestingly, despite high sensitivity to extratemporal regions of epileptogenicity, which show hypometabolism on interictal studies, PET scans are *not* sensitive to initial areas of seizure propagation in extratemporal epilepsy, another demonstration of the nonequivalence of network and propagation areas (29).

Figures 5 and 6 are examples of interictal hypometabolism in a patient with medial temporal/limbic network epilepsy (left medial and lateral temporal, and right medial temporal hypometabolism) and a patient with occipital/temporal network epilepsy (occipital and temporal hypometabolism).

SPECT functional neuroimaging also has helped to formulate the concepts of epileptic networks. Interictal hypoperfusion on SPECT, although present in some cases, is less sensitive than PET (40–42). The main use of SPECT is its unique ability to capture the status of blood flow at the time of seizure activity because of the lack of redistribution of the radioisotope, which is bound in the brain on its first pass. Ictal SPECT studies of patients with medial temporal lobe epilepsy, when obtained with early injections, show consistent blood-flow increases in the ipsilateral medial thalamic region as well as in the temporal structures (41–44). This is another way of demonstrating the participation of the medial thalamic region in the medial temporal lobe limbic network, and one that cannot be confirmed with usual electrode placement. Figure 7 is an image of increased blood flow in a right temporal lobe seizure obtained by subtracting interictal from ictal perfusion images and superimposing the differences onto MRI. The medial temporal/limbic network regions with increased flow include the medial temporal/hippocampal region, bilateral medial thalamus, lateral temporal neocortex, and midbrain structures. In a group of 18 patients at our center who were analyzed in this manner, we found a statistically significant increase in the perfusion measured in the medial thalamus ipsilateral to the medial temporal lobe of seizure activity. Ictal hyperperfusion has been demonstrated in multiple structures consistent with other epilepsy networks: the occipital/temporal and parietal/frontal networks. In Figure 8, another ictal SPECT difference image demonstrates occipital and temporal regions of increased perfusion. Figure 9 is a similar depiction of the regions of ictal hyperperfusion in the superior parietal/medial frontal network.

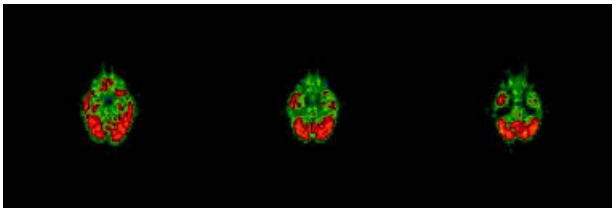

FIG. 5. ^{18}Fluorodeoxyglucose–positron emission tomography (^{18}FDG-PET) study demonstrates interictal hypometabolism in multiple areas (medial and lateral left temporal, medial right temporal) in a patient with epilepsy in the medial temporal/limbic network.

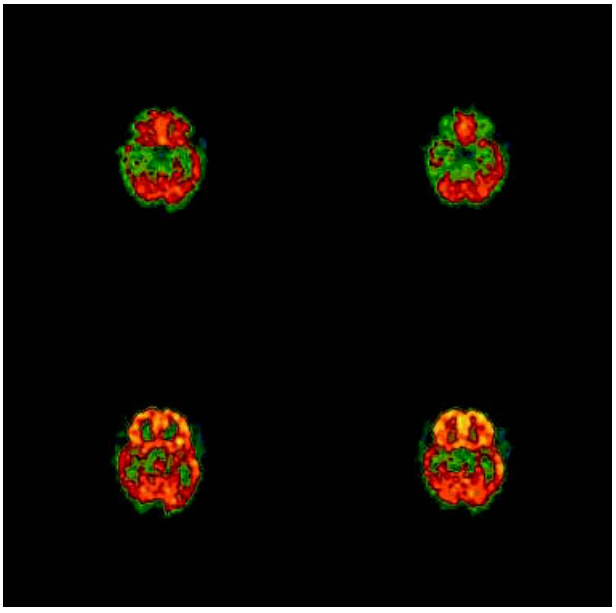

FIG. 6. ^{18}Fluorodeoxyglucose–positron emission tomography (^{18}FDG-PET) study demonstrates interictal hypometabolism in the right occipital and temporal lobes in a patient with epilepsy in the occipitotemporal network.

The response of uncontrolled seizures to invasive therapy is a final line of evidence that supports the existence of human epilepsy networks, and that also leads to novel approaches to diagnosis, treatment, and even prediction of seizures. If human epilepsy is the expression of specific, abnormally active, intrinsically defined

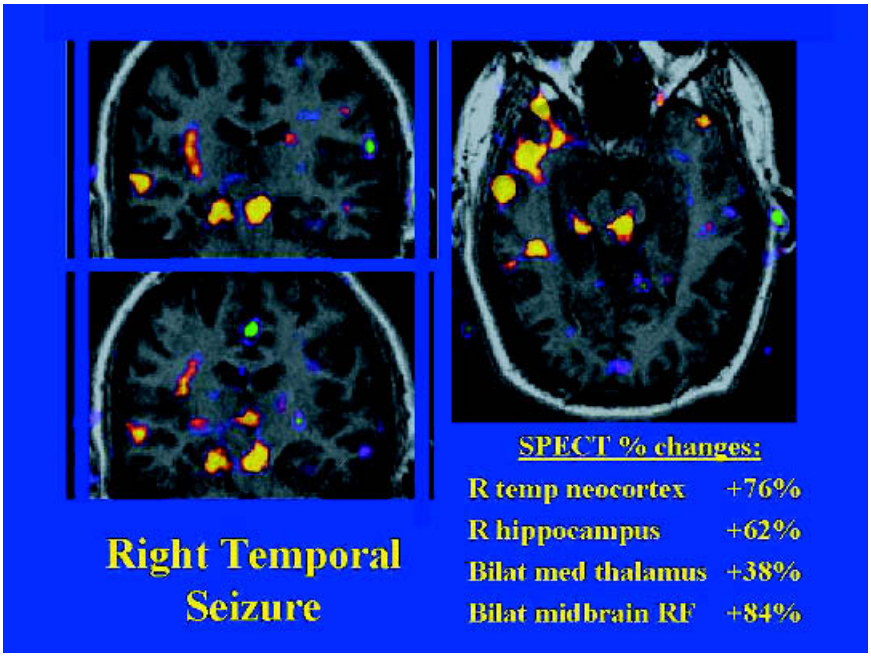

FIG. 7. Ictal [^{99}Tc]-HMPAO-SPECT subtraction image obtained by injection of HMPAO early during a right temporal seizure. A normalized interictal study was digitally subtracted from the ictal study, and differences were coregistered to magnetic resonance imaging for anatomic detail. Percentage increase in perfusion was calculated in those areas identified as showing significant perfusion changes, in this case, in the right temporal neocortex and hippocampus, both thalami, and bilateral midbrain reticular formation.

and connected cortical/subcortical/bilateral networks, then one could theoretically alter seizure expression by intervening in any part of the specific network. This reasoning grows from the corollaries presented earlier, indicating that any structural, metabolic, electrical, or chemical modification of the network, in any region, would alter the expression or frequency of seizure activity. Consider observations on the outcome of surgical treatment of uncontrolled medial temporal lobe epilepsy. Published reports document 60–90% excellent response, meaning cessation of seizures, after *any kind* or *extent* of temporal lobe resection in patients identified as having medial temporal lobe epilepsy. Operations involving anterior temporal lobe, medial structures only, lateral structures only, or more or less extensive lateral temporal resection can cure this disorder. Procedures with no ana-

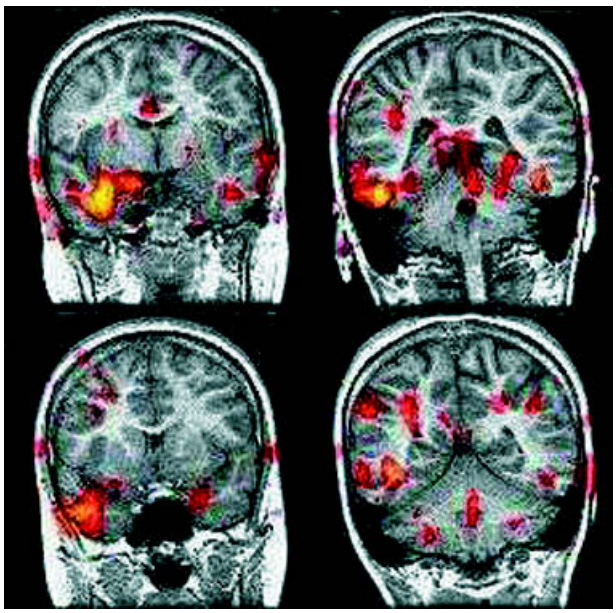

FIG. 8. Ictal single-photon emission computed tomography subtraction images, obtained by subtraction, normalization, and coregistration (see earlier figures), show temporal and occipital areas of increased perfusion in a patient with epilepsy in the occipitotemporal network.

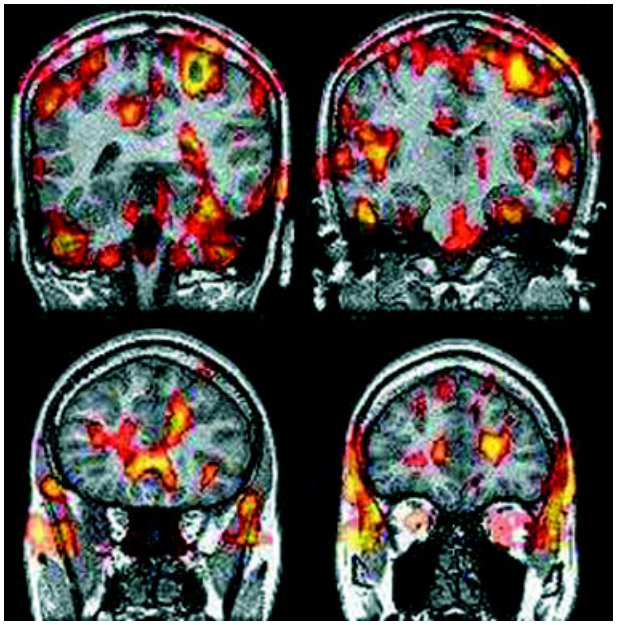

FIG. 9. Ictal single-photon emission computed tomography subtraction image, obtained by subtraction, normalization, and coregistration, shows multiple areas of perfusion increase in parietal and frontal lobes in a patient with epilepsy in the superior parietal/medial frontal network.

tomic overlap are similarly successful (45–47). This cannot be explained unless the multiple areas are all critical in the production of the intractable seizures of this disorder. Then interruption of the network in any one of those areas would be (and apparently is) sufficient to alter the seizures. The similarly excellent response with cessation of seizures after temporal lobe resection in well-selected patients who have bilateral independent medial temporal lobe origin of seizures is another example of the existence of a network, interference with which at any site alters the expression of the intractable seizures (20,21).

Disconnection can be considered an intervention that targets an epilepsy network, for example, corpus callosum section or multiple subpial transection. Both of these procedures reduce frequency and intensity of generalized and partial seizures in many, but not all, patients, and either procedure can (rarely) stop seizures entirely (48–52). This suggests that the surgery interferes with the mode of seizure generation, although the procedure is not targeted specifically to one area from which seizures "arise." The result is explainable only by the existence of intrinsic networks, which are structurally disrupted.

So far, electrical stimulation as a treatment for epilepsy has been used in a nontargeted way. The stimulation has been (presumably) directed at subcortical structures in common regions, independent of our knowledge of which cortical areas are involved. Prolonged stimulation of the centromedian nucleus reduces or controls generalized seizures, and prolonged intermittent vagal nerve stimulation (VNS) reduces seizure frequency by up to 50% in about half the patients to whom it is applied (53–55). VNS-induced reduction in thalamic blood flow (bilaterally) is correlated with the degree of seizure reduction (56). These results imply that subcortical structures are key to the manifestation of partial seizures, supporting the contention that specific subcortical regions are part of specific epilepsy networks. The targeted subcortical structures affected by stimulation may be part of the network in those individuals who respond the best to these various, "nontargeted," stimulation therapies.

What are the implications of these observations? These ideas question the very concepts of epileptogenic zone, irritative zone, symptomatogenic zone, and ictal-onset zone. Our evaluation of refractory epilepsy patients should use studies that define the epilepsy network (specifically PET, functional MRI) rather than (or at least in addition to) studies that are targeted at the region of "seizure onset" like EEG. It may be pertinent to consider study of other kinds of phenomena in individual patients, which may define the network in better terms than we have sought in the past because of our single-minded attention to defining regions of so-called seizure onset. For example, quantitative intracranial EEG analysis, background patterns, sleep effects on interictal and ictal activity, and other types of functional assessments may contribute considerably to our understanding of the role of networks in the expression of the epilepsies. Studying broad regions of brain structures related by the presence of such networks, using quantitative EEG analyses and sophisticated approaches, may detect alterations in the behavior of the network before the more traditional "seizure discharge" is seen, and allow prediction of seizures before manifestation clinically or on traditional EEG.

These kinds of data may have significant applicability to development of further therapy, in epilepsy and in other neurologic diseases as well. Broadly applied treatment (directed at any region of the network) should theoretically be just as effective as treatments directed at a specific "focus" of seizure activity. We have seen that this may be true in the application of VNS, thalamic stimulation, and other relatively nontargeted interventions for the treatment of uncontrolled localization-related epilepsy. This approach opens the door to directing surgical therapy to a region with the least likely functional consequences, as long as it is in the network. It also means that our patient-evaluation procedures could be revamped entirely. Cost and risk of this kind of evaluation might be considerably less than what we currently use. It also should be possible to develop new approaches to treatment and/or select pharmacologic approaches based on our knowledge of network components and properties. The specific neurotransmitters involved, for example, in regions of the network might allow us to choose truly synergistic therapy or to optimize or enhance alternative routes of function while we try to disable others because of their participation in an epileptic network. Based on knowledge we already have, derived from decades of intensive patient evaluation and studies, we need to think about human localization-related epilepsy and seizures in a different way, and use that new framework to chart the future.

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