2-11-2003

Use of SPECT Difference Imaging to Assess Subcortical Blood Flow Changes During Epileptic Seizures

Andrew Norden

Use of SPECT Difference Imaging to Assess Subcortical Blood Flow Changes During Epileptic Seizures

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Andrew D. Norden
2002

Abstract

USE OF SPECT DIFFERENCE IMAGING TO ASSES S SUBCORTICAL BLOOD FLOW CHANGES DURING EPILEPTIC SEIZURES. Andrew D. Norden and Hal Blumenfeld. Departments of Neurology and Neurobiology, Yale University School of Medicine, New Haven, CT.

Seizures are thought to arise primarily from the cerebral cortex. However, the propagation and behavioral manifestations of seizures involve a network of both cortical and subcortical structures. The medial thalamus and upper brainstem reticular formation are crucial areas for the maintenance of normal consciousness. Bilateral involvement of these structures may be responsible for loss of consciousness during partial seizures. Therefore, we sought to investigate the role of the medial thalamus and brainstem in seizures. We performed SPECT ictal-interictal difference imaging co-registered with high-resolution MRI scans to localize regions of cerebral blood flow changes in patients undergoing inpatient monitoring for epilepsy. Ictal-interictal SPECT scans from 43 seizures in 40 patients were analyzed. The medial thalami showed SPECT difference imaging changes of >20% in 18 patients. Of patients with medial thalamic changes, the majority (13 of 18) had seizure onset in the temporal lobe, while only 1 had confirmed onset in extratemporal structures, and the remainder were non-localized. In contrast, in the 22 patients without >20% SPECT changes in the medial thalami, 6 had extratemporal onset, 6 had temporal onset, and the remainder were non-localized. In patients with temporal lobe seizures, the side of greater medial thalamic and brainstem reticular formation involvement was strongly related to SPECT injection timing such that there was a sequential pattern of ipsilateral followed by contralateral changes. Brainstem structures showed >20% SPECT changes in 27 of 43 seizures with no clear relation to temporal or extratemporal onset. We conclude that the medial thalamus is preferentially involved in seizures arising from the temporal lobes, possibly reflecting the strong connections between limbic temporal structures and the medial thalamus. Sequential involvement of ipsilateral followed by contralateral structures in the medial thalamus and upper brainstem may explain how seizures produce peri-ictal loss of consciousness despite incomplete involvement of the cerebral cortex.

Acknowledgements

I am deeply grateful to my mentor, Dr. Hal Blumenfeld, for his tremendous enthusiasm, encouragement, support, time, and friendship. I also thank the Office of Student Research for financial support.

Table of Contents

Introduction

The word epilepsy comes from a Greek word that means "to be *seized* by forces from without." Interestingly, it is from this definition that the word seizure is derived as well. Apparently, early physicians and scientists believed that patients with epilepsy were infected with dangerous supernatural beings. Modern medical science is more comfortable with the assumption that epilepsy is caused by an organic brain defect. Indeed, a number of epileptic syndromes are caused by discrete cerebral lesions, often the result of developmental defects, trauma, cerebrovascular disease, tumors, tissue atrophy, or infection. There are also some forms of epilepsy (idiopathic epilepsies), most notably those which are characterized by absence (*petit mal*) seizures, for which no diseased portion of brain is currently identifiable.

Epilepsy is a disorder characterized by paroxysmal, excessive, and disorderly discharging of neurons that generally produces clinical manifestations in the form of recurrent seizures. In some cases, this hyperactive neuronal state can be detected by a physician with electroencephalographic (EEG) recording. The signs and symptoms of epileptic seizures are numerous, and they often depend on the type of seizure that one observes. Seizures are classified as partial or generalized, the former originating from a distinct focus in the brain and the latter appearing to occur everywhere at once. Partial seizures are further classified as simple partial (with no impairment of consciousness), complex partial (with impairment or loss of consciousness), or partial seizures that evolve to secondarily generalized seizures. Partial seizures are characterized by a wide variety of symptoms that may be predicted by the portion of brain from which the seizures originate. These may include motor, sensory, autonomic, or psychological components. Generalized seizures occur in many subtypes as well: absence (*petit mal*), myoclonic, tonic, atonic, clonic, and tonic-clonic (*grand mal*) seizures. Each of these involves very different manifestations, so they will not all be discussed here. However, it is worth mentioning that the initial, tonic phase of a tonic-clonic seizure often includes increased muscle tone with a rigid, flexed posture followed by a rigid, extended posture. During the next part of the seizure, the clonic phase, the patient experiences bilateral rhythmic jerks of the whole body. All of this occurs in the absence of consciousness, and it is typically followed by a confused, drowsy state or by a brief period of coma [1].

The prevalence of epilepsy is reported to be between 5 and 8 people per 1,000, or approximately 1.25 to 2 million people in the United States. Of these individuals, many have seizures that respond well to

therapy with anti-epileptic drugs [1]. However, there are between 50,000 and 300,000 people in the U.S. whose seizures are not adequately controlled by therapy with one drug or with any combination of drugs [2, 3]. These individuals are said to have medically intractable epilepsy. The primary treatment option available to these patients is epilepsy surgery in which the diseased portion of brain is removed after accurate localization of the seizure focus. As one might expect, surgery is only a possibility for epileptic syndromes that produce partial seizures; generalized seizures do not, by definition, have a discernible focus. Furthermore, many considerations must be taken into account by a patient who may be a candidate for epilepsy surgery. The degree to which seizures affect a patient's quality of life is obviously an extremely important factor, as is the likelihood that the diseased portion of brain can be resected without significant loss of function.

For patients who elect to have epilepsy surgery, accurate localization of the focus is absolutely crucial to success. A localized EEG abnormality at the beginning of a seizure is typically taken to indicate the location of the focus. However, scalp EEG recordings may be unreliable and inaccurate [4, 5]. When scalp EEG fails to localize the zone of seizure onset, depth electrodes are often implanted intracerebrally and subdurally so that chronic recordings with minimal interference from non-neuronal tissue are possible. Because depth electrode implantation carries with it substantial risk and expense, efforts have recently been directed toward developing noninvasive means of precise focus identification. Such techniques include ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), which is used to measure cerebral glucose uptake, and ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) single-photon emission computed tomography (SPECT), which measures regional cerebral blood flow (rCBF). These imaging modalities are logical choices for seizure focus localization because of the typical changes in blood flow and metabolism that accompany seizures.

Because neurons require a continuous source of ATP for electrical signaling, and because ATP synthesis requires a blood-delivered supply of glucose, rCBF is generally accepted as a measure of neuronal activity in brain tissue. As epileptic seizure activity involves excessive neuronal firing, it is not surprising that rCBF increases substantially during epileptic seizures. This finding was first reported in 1939 by Wilder Penfield and his colleagues [6]. Indeed, ictal SPECT studies of patients with partial seizures point to focal increases in CBF. Interictal SPECT scans (performed when seizures are not occurring) show

a *decrease* in rCBF often in the same regions that are ictally hyperperfused [7]. Parallel findings have been demonstrated using PET, that is, ictal PET scans show areas of hypermetabolism while interictal scans suggest hypometabolism [3, 8, 9]. PET studies in humans and radiographic studies in rats also point to a *global* increase in glucose metabolism in the ictal state followed by a global decrease when the seizure ends [10]. However, ictal PET studies are difficult to interpret because PET scanning has poor time resolution in comparison to SPECT scanning. Whereas a SPECT scan reflects blood flow during a 30 – 60 second window, the PET technique reflects metabolism during a 30 – 45 minute period. In addition, the situation as assessed with SPECT and PET may be more complicated than these findings suggest because of the recently detected uncoupling of metabolism and blood flow. Using a rat model of epilepsy in which seizures are induced with intracerebral penicillin injections, Bruehl and colleagues showed significant differences in the degree to which blood flow and glucose uptake are increased at the epileptic focus. They also found intriguing differences between blood flow and metabolism in cortical areas close to the focus, in remote portions of the ipsilateral cerebral hemisphere, and even in the ventrolateral and posterior thalamic nuclei on the same side as the seizure focus. Control rats that did not receive penicillin showed close coupling of blood flow and metabolism everywhere in the brain [11]. An additional complicating factor is that, for unknown reasons, interictal hypometabolism has been far easier to detect in humans when the seizure focus is in the temporal lobe than when seizures commence in the frontal lobe [12].

Though the interpretation of blood flow and metabolism data is not always straightforward, PET and SPECT have improved the ability of neurosurgeons to localize a seizure focus [13-15]. Since 1995, a team of Yale researchers headed by George Zubal and Susan Spencer has been using computer-aided processing of SPECT images to further improve the localizing ability of SPECT scans; this work may ultimately be extended to PET and other imaging modalities. SPECT measures blood flow by detection of an intravenously-injected tracer substance, typically, ^{99m}Tc-HMPAO. ^{99m}Tc-HMPAO SPECT scanning is a particularly versatile method because the tracer crosses the blood-brain barrier within 30 – 60 seconds after injection, binds tightly to brain tissue, and does not redistribute for 6 – 8 hours. Thus, tracer injection during a seizure with SPECT scanning an hour or more later allows for visualization of rCBF in the ictal state [16]. rCBF during a seizure is much more difficult to measure with PET or with other imaging

modalities than with SPECT. Zubal and Spencer's technique relies on computer software that co-registers an ictal and an interictal SPECT image. The software then subtracts the two SPECT images and generates a "difference image." This image highlights areas of increased and decreased blood flow during a seizure, and it also indicates the magnitude of changes in rCBF. The difference image may be superimposed onto a high-resolution structural magnetic resonance imaging (MRI) scan of the patient's brain; this allows one to determine which brain structures are preferentially hyper- and hypoperfused during a seizure as shown in Figure 1 [3]. By carefully applying this image processing technique, one may learn a great deal about which brain structures are important in seizure origination, propagation, and regulation.

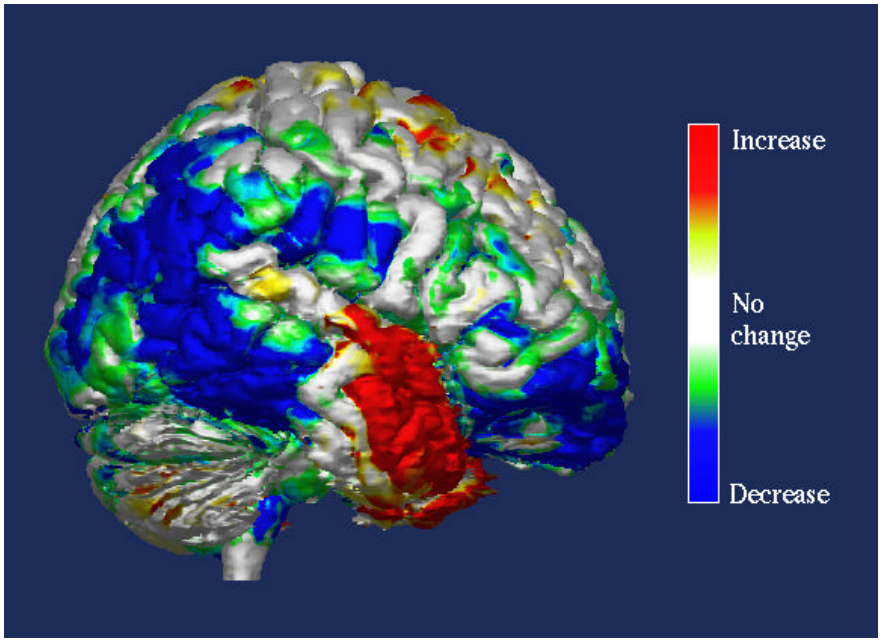

Figure 1. This image represents a three-dimensional MRI reconstruction of one patient's brain. The SPECT difference image is super-imposed on the MRI with red areas representing ictal hyperperfusion and blue areas ictal hypoperfusion. As is evidenced by strong temporal lobe hyperperfusion, the ictal SPECT scan used to prepare this image was acquired during a temporal lobe seizure. Note that large areas of frontal, parietal, and occipital cortex are hypoperfused at the same time.

Sometimes using techniques similar to Zubal and Spencer's, many research groups have conducted SPECT studies in recent years to analyze rCBF during seizures. The majority of these studies examine rCBF in cerebral cortex because epileptic seizures have long been thought to commence in neocortex and spread to brainstem and subcortical structures [8]. As explained previously, studies of cortical blood flow often show ictal hyperperfusion at the seizure focus with interictal hypoperfusion at the same site. However, there is no reason to believe that the clinical manifestations of seizures depend solely on cerebral cortex for their expression. Subcortical structures such as the basal ganglia and thalamus as well

as the cerebellum and brainstem may be important for some aspects of seizure development or expression. The basal ganglia are thought to play a role because of the complex motor manifestations of some seizures. The thalamus has been implicated in seizures because of its unique electrophysiological properties and massive connections with cerebral cortex; indeed, recent functional magnetic resonance imaging (fMRI) studies demonstrate a close coupling of cortical and thalamic metabolism during seizures [17]. The cerebellum is an area of interest because of the increased likelihood of cerebellar atrophy in patients with long-standing partial epilepsy (as compared to healthy individuals). This atrophy occurs for unknown reasons, but it may well yield clues to the pathophysiology of epilepsy [18].

Thus, in addition to cerebral cortex, scientists have used SPECT to study a number of subcortical structures and the cerebellum. In all of these structures, ictal changes in rCBF have been observed, although they have not always been consistent with respect to laterality or direction of change. Since more of these studies examined cerebellum than either basal ganglia or thalamus, cerebellar blood flow will be considered first. The most common finding of cerebellar SPECT studies is crossed cerebellar hyperperfusion (CCH) in which the cerebellar hemisphere contralateral to the epileptic focus shows increased blood flow during the ictal state. This has been reported in patients with various types of partial epilepsy [18, 19], with frontal lobe epilepsy [20], with epilepsy of the supplementary sensorimotor area (SSMA) [21], and with partial complex seizures related to herpes simplex encephalitis [22]. CCH was found in these studies to occur in as few as 33% of patients studied [19] or in as many as 100% [21]. Patients without CCH showed ipsilateral cerebellar hyperperfusion, bilateral cerebellar hyperperfusion, or no significant change in perfusion. Note that cerebellar hypoperfusion was never observed during seizures. However, as one might expect, there are reports of interictal hypoperfusion of cerebellum in children with partial epilepsy [23]. This study reports that interictal hypoperfusion may be ipsilateral or contralateral to the epileptogenic focus, and bilateral hypoperfusion was observed as well. Finally, there was one recent report of epileptic seizures that *originate* in the cerebellum [24]. Harvey and his colleagues at Miami Children's Hospital present a 6-month old female patient with a left cerebellar ganglioglioma. Using scalp and intracranial EEG, MRI, CT, and SPECT, they confirm that this patient's seizures, which consist of left hemifacial contraction, head and eye deviation to the right with nystagmus, and autonomic dysfunction,

have their origin in the diseased region of the cerebellum. After surgical removal of the tumor, this patient's seizures resolved completely.

Similar studies have been performed with attention paid to the basal ganglia. In their study of 8 patients with SSMA seizures, Laich *et al*. report that some patients showed ipsilateral hyperperfusion of the basal ganglia, some showed bilaterally symmetric or asymmetric hyperperfusion, and one patient exhibited no change in perfusion [21]. All of these patients had significantly more blood flow to the basal ganglia than did healthy controls. Another study demonstrates ictal hyperperfusion of the ipsilateral basal ganglia in 2 of 5 patients with complex partial seizures that originate in posterolateral cortex [25]. Similar findings have been reported in patients with temporal lobe epilepsy; one study of 42 patients with temporal lobe epilepsy reports a statistically significant mean increase in basal ganglia perfusion of 8% during seizures [26]. Individual cases are not reported in this study, so it is unclear whether the basal ganglia changes occur ipsilaterally, contralaterally, or bilaterally. Furthermore, the number of patients who actually show basal ganglia hyperperfusion is not apparent. An interesting additional result, however, is that basal ganglia perfusion in these patients correlates with upper limb dystonia such that increased asymmetry of basal ganglia perfusion during seizures occurred more often in patients with unilateral upper limb dystonia. In addition, the group of patients whose seizures involved unilateral dystonia showed a mean increase in basal ganglia perfusion of 9.5%, while the group of patients who did not have dystonia showed a mean increase of only 4.4%. Finally, interictal hypoperfusion has been shown for the basal ganglia as well. In 4 of 20 patients with medically refractory complex partial seizures, one study found basal ganglia hypoperfusion; 3 of these patients showed ipsilateral hypoperfusion, and the fourth patient showed hypoperfusion contralaterally [27].

The third subcortical structure that has been studied in some depth using SPECT is the thalamus. Reports concerning the thalamus are very similar to those discussed for cerebellum and basal ganglia. For example, one of the same studies that demonstrates CCH mentions ipsilateral increases in thalamic perfusion during seizures; unfortunately, the magnitude of increased thalamic perfusion is not mentioned, and this result pertains only to one patient [20]. One study also reports that 26% of 67 patients with temporal lobe epilepsy show ipsilateral thalamic hypoperfusion interictally. None of these patients showed

contralateral hypoperfusion, ipsilateral hyperperfusion, or bilateral changes in thalamic perfusion [28]. Note that these findings are in line with PET studies which show similar subcortical metabolic changes in patients with temporal lobe epilepsy.

Clearly, a substantial amount of research effort in this field has been devoted to subcortical structures. It is also clear that the results obtained to date are difficult to understand; though changes in perfusion have been observed, the significance of these changes remains to be determined. Additionally, the described changes are often reported to occur in only a small subset of patients. There has been little speculation as to why certain patients show these changes and why many do not. There may well be methodological issues that must be resolved before these studies will yield fruit. Also, many of these studies use small numbers of patients because of the technical difficulty of the experiments. Patient cohorts often comprise a wide range of ages and types of epilepsy, so the results are not as generalizable as they might otherwise be. That being said, these studies have revealed interesting and clinically relevant information. Though the results have not yet dramatically altered the face of epilepsy therapy, these studies provide one of the only tools that allows physicians to examine brain activity during seizures. Accordingly, it is surprising that there is no report in the literature of a SPECT study that examined rCBF in the brainstem and thalamus during seizures.

The brainstem reticular formation and related structures are thought to be involved in modulating the excitability of neurons in cerebral cortex; thus, researchers tend to think of the brainstem as a group of structures that have a primarily regulatory role on cortical seizure activity [8]. However, a small number of animal studies during the 1980's and early 1990's suggest a significant role for the brainstem in propagation and maintenance of various seizure types. For example, two independent groups of researchers determined that seizure activity requires a functional substantia nigra. One research team inhibited the pars reticulata of the rat substantia nigra (SN_R) with muscimol, a γ-aminobutyric acid (GABA) agonist, and found that seizure activity was substantially inhibited. These rats were highly prone to seizures because of "kindling," an experimental paradigm in which electrical stimulation is repeatedly applied to the amygdala. Initially, the electrical stimulus is insufficient to elicit a seizure, but after repeated stimulation, the stimulus causes a seizure every time it is applied. In these rats, muscimol treatment of the SN_R bilaterally eliminated seizures in 91% of attempts that were supra-threshold for seizure induction

before injection of the drug. Increased stimulation intensity, however, was able to elicit seizures with regularity. Note that kindling from sites other than the amygdala is also effective in producing seizures; muscimol treatment of the SN_R blocked seizures kindled from the entorhinal cortex and olfactory structures with similar potency. In all cases, muscimol injections were effective only when they were localized precisely to the SN_R. Surrounding structures were *not* equally or even similarly effective. As would be expected, these authors report the same results when an inhibitor of GABA breakdown was injected into the SN_R and also when the SN_R was bilaterally destroyed by N-methyl-D-aspartate, a neurotoxin [29].

A second group of researchers also determined that bilateral lesions of the SN_R have a protective effect against seizures [30]. In this study, seizures in rats were induced using one of two paradigms, intravenous bicuculline (a GABA antagonist) or maximal electroshock (MES) in which the head is electrically stimulated. They found that bilateral SN_R lesions significantly attenuated seizures activity induced by either paradigm; for seizures induced by bicuculline, higher doses of the drug were effective in eliciting seizures after SN_R lesioning, thus suggesting that SN_R lesions do not eliminate the potential for seizure generation. In MES seizures, SN_R lesions blocked specifically the tonic hindlimb extension (THE) component, a hallmark of MES seizures, thus supporting the notion that MES seizure regulatory sites are somehow involved with the extrapyramidal motor system. These findings are analogous to the result in the previously discussed study that increased stimulation intensities were required to produce seizures after SN_R lesions. Because previous studies demonstrated conclusively that electrical or chemical stimulation of the SN_R fails to initiate seizures, it seems most likely that the SN_R is involved in amplification or sustenance of seizure activity generated elsewhere in the brain [31]. These results are in line with an earlier study of generalized motor seizures induced by amygdala kindling in rats which showed increased glucose uptake bilaterally in the substantia nigra during seizures [32].

Besides the substantia nigra, the brainstem reticular formation (RF) has often been implicated as having an important regulatory role in seizures. An important set of experiments conducted in the 1950's demonstrated that stimulation of the RF in the medulla, pons, or midbrain of rats and cats could induce seizures [33]. These were characterized by tonic limb extension, much like MES seizures, and there was no evidence of hypersynchronized activity in the forebrain. Thus, it seemed that seizures, or at least the tonic components of seizures, required participation of the brainstem RF. These seizures were unchanged in cats

after precollicular transection, and they could not be induced by stimulation rostral to the midbrain. These findings clearly indicated that the forebrain was not required for behavioral expression of at least one type of seizure. Transection studies in rabbits around the same time suggested that the tonic components of MES seizures required an intact pons [34]. Again, precollicular transection failed to alter tonic seizure components.

During the 1980's, a series of experiments conducted by Ronald Browning and his colleagues at South Illinois University School of Medicine verified earlier findings. First, they lesioned the superior cerebellar peduncle (SCP) or midbrain RF in rats and attempted to induce seizures using the MES paradigm. They found that the THE response was substantially attenuated by mechanical lesions to either structure [35]. In a subsequent paper, they showed that these lesions had no effect on the clonic components of seizures induced by a number of methods [36]. The same group went on to show that they could eradicate the tonic components of seizures with a smaller lesion than they had previously used. They lesioned the nucleus reticularis pontis oralis (RPO), a part of the pontine and mesencephalic RF, along with the SCP and were able to effectively eliminate the tonic components of sound-induced seizures in genetically epilepsy-prone rats (GEPR) and MES seizures in normal rats [37]. However, the clonic component of audiogenic seizures (running and bouncing clonus) was also attenuated by the RPO/SCP lesions. This was an interesting finding because these lesions affected the tonic components of a variety of seizure types while sparing the clonic components (face and forelimb clonus). It quickly became clear that running and bouncing clonus is different from face and forelimb clonus in that it depends on the brainstem and not on the forebrain for expression. This realization occurred after rats with precollicular transections failed to display face and forelimb clonus when exposed to electroshock or pentylenetetrazol (PTZ) seizure-induction paradigms [38]. Both electroshock and PTZ-induced seizures typically contain a face and forelimb clonic component.

Using transection experiments and multi-unit recordings in cats, a group of scientists in Mexico during the early 1980's sought to further define the importance of the brainstem RF in the behavioral manifestations of seizures. This group had shown previously that PTZ-induced seizures begin in the brainstem RF and propagate to cortex and other structures [39]. However, the anatomical route by which

seizure activity spread from RF to the spinal cord was unclear, that is, activity may have propagated via cortex and the pyramidal tract or it may have used "extrapyramidal" pathways. By recording multi-unit activity from the pyramidal tract while monitoring musculature with electromyography (EMG), it was shown that there was no correlation in time between the increase of pyramidal tract activity and the onset of clinical and EMG seizures. In contrast, the change in firing rate of RF neurons was chronologically related to the seizure activity. Based on these results, the authors conclude that seizure activity in the RF propagates to the spinal cord via "extrapyramidal" pathways. Note that these results do not dismiss the pyramidal pathway as unimportant for seizure activity; rather, an increase in pyramidal tract multi-unit firing was associated with a further increase in EMG activity, thus suggesting some kind of facilitatory role for the cortex and pyramidal tract in PTZ-induced seizures [40]. Subsequent experiments sought to better define the region of the RF that was most important in PTZ-induced seizure generation and concluded, based on "pretrigeminal" transections, that the mesencephalic RF was activated first and drove other areas [41]. This finding was verified using transections within the midbrain [42].

This view, that PTZ-induced seizures begin in the mesencephalic RF, is by no means uncontested. Magistris *et al*. performed a thorough study in 1988 to characterize the roles of the forebrain, brainstem, and spinal cord in PTZ-induced seizures [43]. They studied intact cats as well as cats with precollicular transections, spinal cord transections, or both transections. These animals were monitored with EEG and EMG, and they received PTZ injections of various doses. In animals with precollicular transections, cortical EEG showed seizure activity that was very similar to that observed in intact cats. However, functional disconnection of the forebrain did inhibit the clonic motor components of these seizures. These results bolster the argument that the forebrain is critical for clonic seizure activity and that such activity is initiated in the forebrain. Magistris' group therefore concludes that the mesencephalic RF is *not* necessary for cortical seizure activity to occur. They point out that the multi-unit recordings of Velasco *et al*. are highly filtered and may actually represent activity in pathways descending from the forebrain to the spinal cord.

In humans, some recent compelling evidence for a key brainstem function in epileptic seizures comes from vagus nerve stimulation therapy. One study showed that left cervical vagus nerve stimulation could reduce the frequency of partial seizures in patients with medically refractory epilepsy by 28% [2].

Vagus nerve stimulation directly activates neurons in brainstem nuclei that give rise to vagus nerve efferents and receive vagal afferents. These include the dorsal motor nucleus of the vagus and the nucleus tractus solitarius, respectively. It is not yet known why vagus nerve stimulation reduces the frequency of epileptic seizures, but brainstem structures are quite likely to be involved.

Though the precise role of the brainstem in epilepsy remains to be clarified, then, ample evidence suggests that the propagation and behavioral manifestations of seizures involve a network of cortical and subcortical structures. This fact may be exploited by scientists who are interested in the neural mechanisms that underlie consciousness. In a generalized seizure, consciousness is lost due to bilateral, diffuse involvement of cerebral cortex with synchronized electrical activity. Partial seizures involve much smaller regions of cortex, yet patients are often observed to have impaired consciousness during the ictus. Animal studies in 1949 showed conclusively that the thalamus and pontomesencephalic reticular formation are crucial areas for the maintenance of normal consciousness [44, 45]. More recently, rCBF in the medial thalamus and brainstem reticular formation has been shown to correlate with level of consciousness in healthy human volunteers [46]. Furthermore, it is known that the medial temporal structures have strong reciprocal connections with structures in the medial thalamus such as the mediodorsal nucleus and midline thalamic nuclei [47]. There are also connections between the medial temporal lobes and brainstem. Therefore, it may be hypothesized that bilateral involvement of the medial thalamus and pontomesencephalic reticular formation is responsible for loss of consciousness during seizures despite only partial involvement of the cortex. Theoretically, increased activity in the medial thalamus and brainstem reticular formation might produce widespread cortical inhibition sufficient to cause impairment of consciousness.

Statement of Purpose

We hope to determine, using SPECT, whether there are changes in rCBF in the medial thalamus and brainstem reticular formation during seizures. Our goals are to fully characterize any observed changes with respect to laterality, magnitude, and timing; to determine where these changes occur with reasonable anatomical accuracy; and to determine whether these changes have any behavioral correlates. By answering these questions, we hope to achieve a deeper understanding of the thalamus' and brainstem's role in the pathophysiology of impaired consciousness in epilepsy. This work will shed light on the neural substrate that underlies consciousness in general as well. Ultimately, an understanding of the mechanisms that modulate arousal states may lead to novel therapies for epilepsy, sleep disorders, and coma. Furthermore, the neural machinery that is responsible for the normal maintenance of consciousness may be organized very similarly to that which controls other sophisticated human functions such as thought. If indeed there are brainstem and thalamic structures that impact consciousness by widespread cortical connections, it is reasonable to hypothesize that thought and memory are encoded in a similar fashion.

Methods

Patient selection: 40 subjects with intractable seizure disorders were chosen from the cohort of patients referred to the Yale Epilepsy Program between 1993 and 2001. Subjects were chosen for study if they had MRI, ictal SPECT, and interictal SPECT scans of suitable quality. Though many of these subjects went on to have intracranial electrodes placed for improved seizure localization, data obtained during the preliminary non-invasive evaluation was used for the purposes of this study. Patients were excluded if they had previous brain surgery or gross abnormalities of the brain. Additionally, patients whose seizures were likely to be nonepileptic in nature were excluded.

Patient evaluation: As part of the standard pre-surgical evaluation, each patient gave a detailed history and underwent a general and neurological examination. Diagnostic testing included a high-resolution MRI scan, PET scan, ictal SPECT scan, interictal SPECT scan, continuous scalp EEG with audio-video monitoring, detailed neuropsychiatric testing, and Wada testing. PET scans were obtained following the intravenous (IV) injection of 10 mCi of 18F-FDG. Transverse image reconstruction was performed with reoriented tomograms displayed in the axial, coronal, and saggital planes. Many patients whose seizures remained poorly localized after this battery of non-invasive tests had intracranial depth electrodes placed and additional in-patient monitoring. A variety of clinical information was collected for each patient, including seizure localization, seizure type and duration, injection time, and surgical outcome and pathology when applicable. Seizure type and duration were determined by video review of the seizure during which the SPECT agent was injected. All videotapes were reviewed by the same epileptologist along with a medical student. Seizure duration and SPECT injection time were determined with

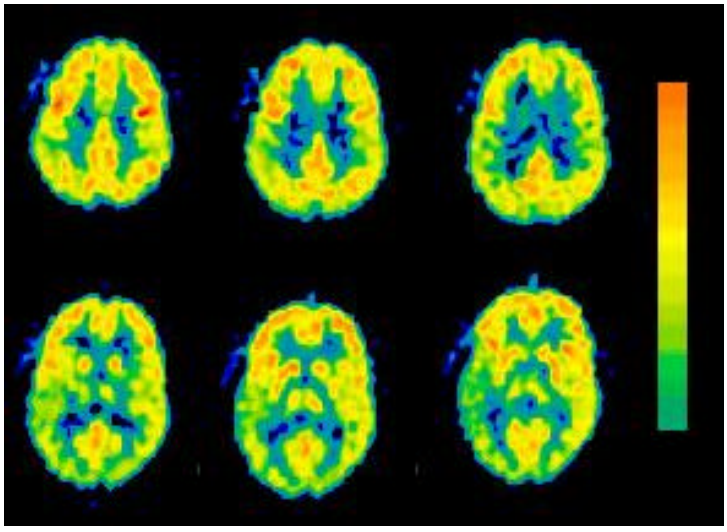

Figure 2. Raw SPECT images have this appearance prior to normalization. The scale on the right indicates magnitude of perfusion; red areas are highly perfused, whereas blue areas receive minimal blood flow.

respect to the beginning and end of the electrographic and behavioral seizure. Concordance of findings on EEG, MRI, PET, SPECT, neuropsychiatric testing, Wada testing, and surgical outcome were used to classify seizures as temporal, extratemporal, or of uncertain onset.

Ictal-Interictal SPECT Study: ^{99m}Tc-HMPAO was injected for SPECT studies. As discussed earlier, this radiopharmaceutical agent rapidly enters the brain in proportion to cerebral blood flow and becomes trapped within cells. Cerebral uptake is more than 90% complete within 60 seconds following the IV injection[48], and since the tracer tightly binds to brain tissue, accurate scans may be obtained hours after the seizure ends. Ictal injections of 20mCi ^{99m}Tc-HMPAO were made during seizure activity or as soon as possible after seizure cessation. The patients were continuously monitored with video and EEG during this

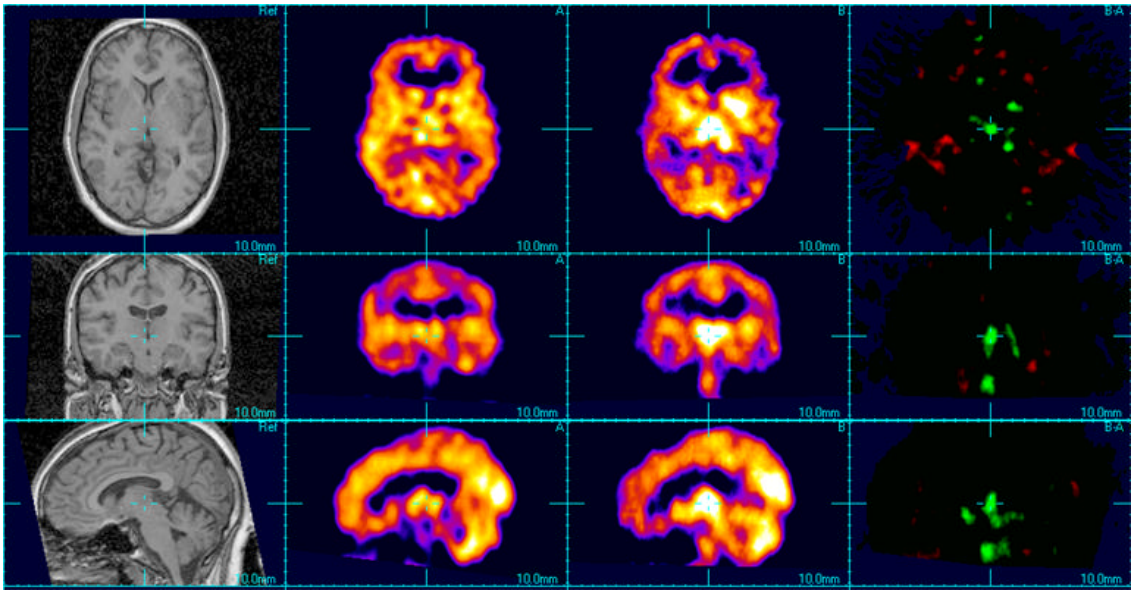

Figure 3. Typical Rview layout with an MRI scan, interictal SPECT scan, ictal SPECT scan, and SPECT difference image (from left to right). The two SPECT scans are normalized to account for global differences in tracer uptake, and the MRI and SPECT scans are aligned in three-dimensional space.

phase. As soon as seizure activity was witnessed, an epilepsy fellow or EEG technician quickly injected the ^{99m}Tc-HMPAO intravenously. Interictal injections were performed in patients who were free of seizure activity for 24 hours or more. SPECT images were typically acquired within 90 minutes after injection using a three-headed Picker PRISM 3000 camera (Picker International, Cleveland Heights, OH). Projection data were acquired over 40 minutes on the PRISM 3000 mounted with ultra-high-resolution, parallel-hole collimators. A 128 x 128 matrix resolution was used with a 1.6 magnification factor. Transverse slices were reconstructed using a routine clinical filtered back projection algorithm with Chang

attenuation correction; the attenuation coefficient was 0.11/cm. The available reconstruction package allows prefiltering of the projection data using a selectable Butterworth filter whose cut-off frequency can be set to the position at which the image power spectrum is equal to the noise level in the projection images. Approximately 30-40 transverse slices covering the whole brain were reconstructed using the ramp filter.

Image manipulation: Rview, proprietary software designed by Colin Studholme, PhD[15], was used to analyze SPECT images (Figure 2). The software runs on a Microsoft Windows platform. For each patient, an ictal and an interictal SPECT image were acquired as described above. A high-resolution MRI scan was obtained as well. Both SPECT images and the MRI scan were aligned in three-dimensional space using a sophisticated mathematical algorithm that ensured optimal alignment. The software then normalized the two SPECT images according to total pixel counts in the brain to account for any global differences in tracer uptake between the scans. The SPECT images were subsequently subtracted, pixel-by-pixel, to yield a SPECT difference image, as shown in Figure 3. The difference image was then superimposed on the MRI scan so that areas of hyper- and hypoperfusion during the ictus could be readily identified. Positive differences represent increases in perfusion and are displayed in green, while negative differences represent decreased perfusion and are displayed in red. The magnitude of blood flow changes is indicated by the intensity of the green or red color and can be measured in Rview quite easily.

Regions of interest (ROIs): ROIs were drawn to identify SPECT CBF changes in the thalamus and brainstem. The anatomical locations of CBF changes in the thalamus were based on high-resolution MRI images using anatomical criteria defined by Potts *et al* (Figure 4) [49]. The borders of the thalamus were defined medially as the third and lateral ventricles, and laterally as the internal capsule. The medial thalamus was defined as the middle third of the thalamus in the anterior to posterior axis and the medial half in the

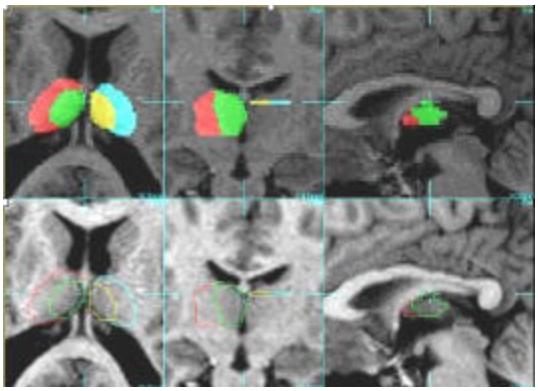

Figure 4. Example anatomical boundaries used to define the thalamus and to subdivide the thalamus into lateral and medial regions, based on each individual's MRI scan. Red=right lateral thalamus, green=right medial thalamus, blue=left lateral thalamus, yellow=left medial thalamus. In the top panels, the regions are filled in with color; in the bottom panels the same regions are outlined with thin colored lines.

medial to lateral axis, running parallel to the lateral border. The medial thalamic region thus defined includes the mediodorsal nucleus and is also likely to include the midline and intralaminar thalamic nuclei. Similar anatomic criteria were used to define the tegmentum of the upper pons and midbrain.

Data acquisition: SPECT ictal-interictal difference images were superimposed on MRI scans for review. Using visual inspection, one could now readily identify perfusion changes within the thalamus or brainstem RF. Scans were systematically reviewed, and all perfusion changes within these areas were measured with Rview and recorded. Changes of greater than 20% were accepted as significant. All scans were reviewed by two observers who were blinded to the patients' clinical information at the time of review, and the locations and percent changes of all foci were indentified by consensus and recorded.

Results

Patient	Seizure Localization	Localization Category	Seizure Type	Seizure Duration (seconds)	Injection Time (Relative to seizure end, seconds)	Medial thalamic changes >20%	Brainstem reticular formation changes >20%
1	left hippocampus	T	complex partial (CPS)	120	(+) 30	yes	yes
2	right temporo-occipital or right anterior temporal	T	CPS	240	(-) 180	yes	yes
3	right or left temporal neocortex	T	CPS with secondarily generalized tonic-clonic seizure (sGTCS)	94 (+55, sGTCS)	(+) 44	yes	no
4	left entorhinal cortex	T	CPS	53	(+) 23	yes	no
5	left entorhinal cortex or left inferior temporo-occipital lesion	T	CPS	76	(+) 45	yes	yes
6	left temporal neocortex	T	simple partial (SPS)	74	(+) 8	yes	yes
7	right temporal	T	CPS, SGTCS	95	(+) 7	yes	yes
8	right temporal	T	CPS	114	(-) 3	yes	no
9	right temporal	T	CPS	168	(-) 149	yes	yes
10	right medial temporal lesion	T	SPS	36	(+) 31	yes	yes
11	left hippocampus	T	CPS, SGTCS	96	(+) 40	yes	yes
12	left inferior temporal neocortex	T	CPS	59	(+) 14	yes	yes
13	right temporal	T	?	?	?	yes	no
14	right entorhinal cortex	T	CPS (with marked left arm tonic extension)	95	(+) 44	no	no
15	right hippocampus	T	CPS	46	(+) 35	no	no
16	right anterior temporal neocortex	T	CPS (with leg marching movements)	75	(+) 45	no	yes
17	right temporal	T	CPS	95	(-) 23	no	no
18	right temporal lesion	T	SPS	34	(+) 39	no	yes
19	left entorhinal cortex	T	CPS with crying	64	(-) 6	no	yes
20	right paracentral lobule (foot sensorimotor cortex)	ET	?	?	?	yes	yes
21	bilateral occipital (right>left)	ET	CPS	26	(+) 11	no	no
22	right parietal	ET	CPS, SGTCS	200	(-) 150	no	no
23	right temporo-parietal	ET	CPS, SGTCS	64	(+) 69	no	yes
	right temporo-	ET	CPS,	59	(+) 35	no	yes

	parietal		SGTCS				
24	right foot sensorimotor cortex	ET	SPS	5	(+) 20	no	yes
	right foot sensorimotor cortex	ET	SPS	5	(+) 19	no	no
25	poor localization	U	CPS	65	(+) 10	yes	no
26	right hemisphere	U	CPS	95	(+) 10	yes	yes
27	poor localization	U	CPS with bilateral thrashing automatisms and grunting	24	(+) 52	yes	yes
28	poor localization	U	CPS with left arm dystonia, alert and oriented but amnestic	119	(-) 22	yes	no
	poor localization	U	CPS	70	(-) 31	no	yes
29	left temporo-occipital neocortex (?)	U	CPS	100	(+) 60	no	no
30	left parieto-occipital (?)	U	CPS, sGTCS	188	(+) 40	no	yes
31	left frontal (?)	U	CPS	35	(+) 15	no	no
32	poor localization	U	tonic	25	(+) 87	no	yes
33	hypothalamic hamartoma (?)	U	CPS	36	0	no	yes
34	poor localization	U	CPS with right-sided clonic movements and tonic rightward head deviation	94	(-) 9	no	yes
35	poor localization	U	?	?	?	no	yes
36	left hemisphere	U	CPS	62	(+) 131	no	yes
37	left frontal (?)	U	SPS or CPS	9	(+) 25	no	no
38	left temporal (?)	U	CPS w/screaming and upper extremity thrashing automatisms	40	(+) 107	no	yes
39	left temporal (?)	U	CPS	244	(-) 146	no	no
40	left temporal (?)	U	CPS	110	(-) 41	no	yes

Table 1. Relevant clinical information for the 40 study subjects. Localization category refers to location of seizure onset; all seizures were categorized as arising in the temporal lobe (T), extratemporal regions (ET), or uncertain localization (U).

Clinical features: Clinical information for each subject is presented in Table 1. 19/40 (48%) patients had temporal lobe seizures, 5/40 (13%) had extra-temporal seizures, and the remaining 16/40 (40%) had uncertain seizure onset. The majority of patients (33/40; 83%) were injected for ictal SPECT scanning during a complex partial seizure (CPS). In 7 patients, a CPS evolved into a secondarily generalized tonic-clonic seizure (sGTCS). The remaining patients had simple partial seizures (SPS; 5/40; 13%), tonic

seizures (1/40; 3%), or seizures that were difficult to classify (3/40; 8%). Seizures lasted between 5 and 244 seconds with a mean duration of 84.1±59.1 seconds. In 29/43 (67%) seizures, the injection occurred after the end of the electrographic seizure. Late injections were made between 7 and 131 seconds after seizure cessation with a mean delay of 39.1±29.9 seconds. In 11/43 (26%) seizures, the injection occurred prior to seizure cessation or at the moment the seizure ended. Injections were made as early as 180 seconds before seizure cessation. On average, early injections took place 57.3±71.8 seconds prior to the termination of ictal activity.

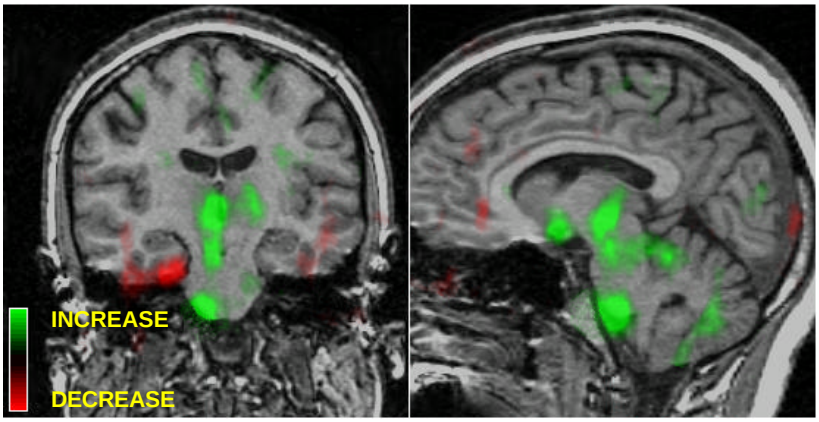

Figure 5. Example of a SPECT difference image super-imposed on an MRI. This patient had left temporal lobe seizures with marked hyperperfusion in the right medial thalamus, as seen in the coronal section above. These images were taken from patient 5 in Table 1. Note that the late SPECT injection (45 seconds post-ictal) is associated with activation of the contralateral medial thalamus.

SPECT findings: Previous studies at Yale have shown that the epileptogenic area can often be identified by excess post-ictal hypoperfusion >20% that lasts as long as 100 seconds after the end of the seizure [16]. Because it is known that changes of at least this magnitude are clinically important, changes in SPECT signal of more than 20% were accepted as significant blood flow changes.

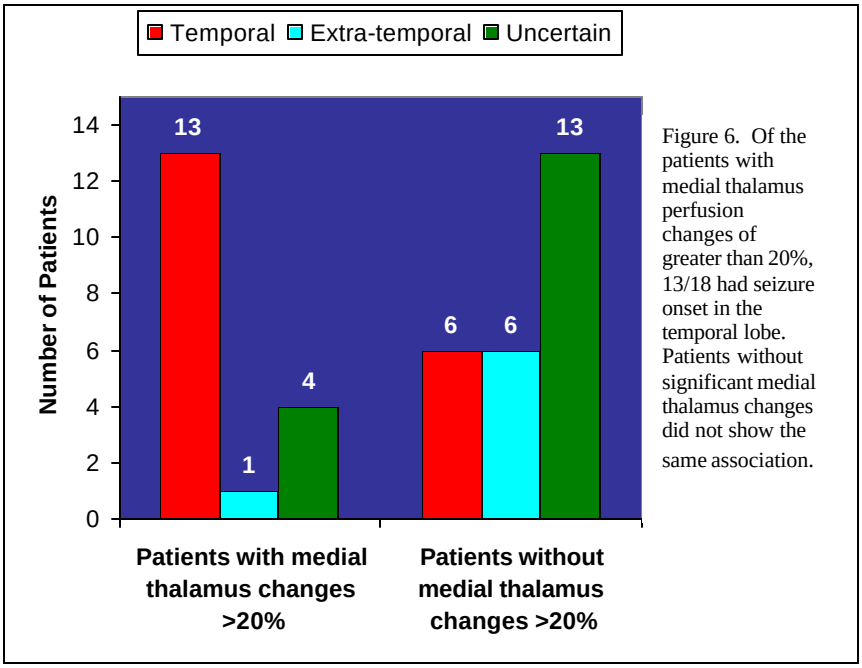

Figure 6. Of the patients with medial thalamus perfusion changes of greater than 20%, 13/18 had seizure onset in the temporal lobe. Patients without significant medial thalamus changes did not show the same association.

As shown in Table 1, medial thalamic changes of greater than 20% (and as large as 116%) were seen unilaterally or bilaterally in 18 of 43 (42%) seizures. Pontomesencephalic reticular formation changes of greater than 20% (and as large as 77%) were seen unilaterally or bilaterally in 27 of 43 (63%) seizures. Interestingly, perfusion changes in these regions were observed to correlate with seizure localization (Figures 5 and 6). Of patients with medial thalamus changes of more than 20%, 13 of 18 (72%) had seizure onset in the temporal lobe. Only 1 of 18 (6%) had confirmed extra-temporal seizure onset. The remaining 4 patients had poorly localized seizures. In patients without significant medial thalamus changes, seizure onset was more likely to occur in extra-temporal regions or to be unknown. Of the 25 seizures in which significant medial temporal changes were absent, 6 had temporal onset, 6 extra-temporal onset, and the remaining 13 were poorly localized (Figure 6). Thus, medial thalamic perfusion changes greater than 20% may be strongly predictive of temporal lobe epilepsy, although not all patients with temporal lobe epilepsy show these changes. The sensitivity, specificity, and positive predictive value (PPV) of these changes for the diagnosis of temporal lobe epilepsy are 68%, 79%, and 72%, respectively.

Perfusion changes in the medial thalamus

	Ipsilateral	**Contralateral**
Injection prior to 30 seconds post-ictal	7	1
Injection after 30 seconds post-ictal	0	4

Perfusion changes in the brainstem reticular formation

	Ipsilateral	**Contralateral**
Injection prior to 30 seconds post-ictal	6	1
Injection after 30 seconds post-ictal	1 (bilateral)	4

Table 2. Association of laterality and injection timing. In patients with temporal lobe seizures, injection timing was strongly associated with the side of perfusion changes such that early injections showed ipsilateral changes while later injections showed contralateral changes. This was true for changes in the medial thalamus and brainstem reticular formation.

Timing and Laterality: In patients with temporal lobe seizures, the side of greater medial thalamic involvement was strongly related to SPECT injection timing (Table 2). Thus, 7 of 8 patients (patients 1, 2, 4, 6, 7, 8, 9, and 12) injected ictally or within 30 seconds of electrographic seizure termination showed greater medial thalamic changes ipsilateral to the side of seizure onset. Only patient 2 had contralateral perfusion changes. Patient 13 would have been included in this analysis as well, but the videotaped seizure

represented by the ictal SPECT scan could not be located. In contrast, 4 of 4 patients (patients 3, 5, 10, and 11) injected more than 30 seconds after seizure termination showed greater medial thalamic changes contralateral to the seizure focus. The midbrain and pontine reticular formation also showed a sequential pattern of ipsilateral followed by contralateral changes (Table 2). 6 of 7 patients (patients 1, 2, 6, 7, 9, 12, and 19) injected ictally or within 30 seconds of seizure termination had greater brainstem tegmentum changes ipsilateral to the side of seizure onset. Again, only patient 2 had contralateral perfusion changes. 4 of 5 patients (patients 5, 10, 11, 16, and 18) injected more than 30 seconds after seizure termination had greater brainstem tegmentum changes contralateral to the side of seizure onset. Only patient 11 showed bilateral changes. Thus, sequential activation of ipsilateral followed by contralateral thalamus and brainstem reticular formation was observed in the vast majority of patients. This phenomenon may reflect the pathophysiology of impaired consciousness during partial seizures.

Discussion

Though epilepsy has long been considered a disorder of cerebral cortical dysfunction, a variety of animal and human studies have demonstrated the importance of thalamic and brainstem structures in seizures. The recent success of vagus nerve stimulation in controlling seizures and even preventing them after an aura has begun is particularly strong evidence in support of a role for these subcortical structures [2]. Some of these regions, particularly medial thalamus and pontomesencephalic reticular formation, are also known to play a role in regulation of consciousness. Early studies demonstrate that destruction of these areas render cats somnolent and inhibit low-voltage fast EEG activity typically seen in the waking state [45, 50]. Furthermore, blood flow changes in these areas in humans correlate with level of consciousness [46]. Because of the extensive connections known to exist between these structures and cortex, an interesting hypothesis suggests that medial thalamus and brainstem reticular formation are important for changes in consciousness during epileptic seizures. Since much of cortex is spared of electrical involvement during partial seizures, it is difficult to account for the impairment of consciousness that often occurs. If, however, deep brainstem and thalamic structures are electrically activated during seizures, they may depress cortical activity through their widespread anatomical connections and thereby affect consciousness as one typically observes during generalized seizures.

To investigate this hypothesis, we utilized SPECT ictal-interictal difference imaging in 40 patients with intractable epilepsy. We demonstrated that 42% and 63% of the 43 seizures analyzed exhibited perfusion changes in the medial thalamus and pontomesencephalic reticular formation, respectively. Interestingly, of the patients with significant medial thalamus changes, 72% had temporal lobe seizure onset, whereas only 24% of patients without these changes had temporal lobe onset. Finally, we showed that SPECT injection timing was strongly associated with laterality of changes in the medial thalamus. Seizures with true ictal or early post-ictal injections were much more likely to show medial thalamus involvement ipsilateral to the seizure focus. Late injections, however, were much more likely to show contralateral involvement.

A number of conclusions may be drawn from this data. First, focal perfusion changes in thalamic and brainstem regions support involvement of these structures in human epilepsy. Additionally, the preferential involvement of medial thalamus in temporal lobe seizures likely reflects the strong connections

between limbic temporal structures and medial thalamus. Finally, sequential involvement of ipsilateral followed by contralateral structures in the medial thalamus and upper brainstem may explain how seizures produce peri-ictal loss of consciousness despite incomplete involvement of the cerebral cortex.

Several important questions pertaining to each of these conclusions remain to be answered by future investigations. Though this data supports involvement of thalamic and brainstem structures in epilepsy, significant perfusion changes in these regions were not observed in every patient. Rather, medial thalamus changes were observed in 42% of patients, and brainstem reticular formation changes occurred in 63%. It is likely that these low numbers result from the heterogeneity of this patient group. Because a variety of seizure types are represented and because there are relatively few patients with each of these seizure types, one may fail to notice an important trend that occurs in one subset of patients. This explains why it was critical to conduct a subgroup analysis in which changes in the medial thalamus and brainstem were examined based on seizure localization. Indeed, when patients with significant medial thalamus changes were analyzed separately, it became clear that the majority of them (72%) had temporal lobe seizure onset. This leaves 28% of patients with significant medial thalamus changes and extra-temporal or unknown seizure onset. The mechanism by which medial thalamus becomes activated in these patients is unclear, and the impact this activation has on consciousness is not known.

The finding of sequential involvement of ipsilateral followed by contralateral thalamus and brainstem activation is unexpected and intriguing. There is no published data to suggest that the two sides of the thalamus or brainstem have unique functions with respect to seizure propagation or loss of consciousness. Of course, it is logical to assume that the side ipsilateral to the seizure focus would become involved first. This side is physically closest to the seizure focus and has the strongest anatomical connectivity. However, it is not clear why the ipsilateral side returns to normal levels of perfusion when the contralateral side becomes activated. Furthermore, the path of propagation of electrical activation from one side of the thalamus or brainstem to the other is unknown.

Ideally, in future studies one would have a large cohort of patients with proven temporal lobe epilepsy and an equally large cohort of patients with extra-temporal epilepsy. To be certain that the seizure localization is correct, one should select patients who have undergone epilepsy surgery and achieved excellent results, that is, the patients should be free of seizures after the operation. In the current study, it is

difficult to generalize the results because of the relatively small number of patients and also because a wide variety of epilepsy and seizure subtypes are represented. By creating "pure" patient groups, one could better understand in which patients thalamic and brainstem perfusion changes are important. In addition, it would be helpful to choose patients with both simple and complex partial seizures. Considering that a chief aim of this study was to evaluate the role of thalamic and brainstem structures in consciousness, one should directly compare seizures in which consciousness is maintained with seizures in which consciousness is impaired or lost. There were too few patients with simple partial seizures in our study to draw definitive conclusions. In an ideal study, one could use rigorous statistical techniques to compare groups of patients with surgery-proven temporal lobe epilepsy and simple partial or complex partial seizures only. There is a statistical software package, Statistical Parametric Mapping (SPM), that allows users to average SPECT scans across several patients and then analyze these averaged scans to assess statistical significance of group differences. However, such a system requires that each patient's MRI be modified so as to be super-imposed on a standard reference MRI. It also requires that each group of patients be as homogeneous as possible. Because of time constraints, the SPM system was not a viable option for data analysis in this study.

This study has one additional shortcoming that must be mentioned. Because the measurement of perfusion relies on SPECT imaging, the anatomical resolution is limited. Typical SPECT scanning used in clinical situations allows one to discriminate between points that are approximately 7 mm apart [51]. Therefore, although it is realistic to determine that changes occur in the medial thalamus or in the brainstem reticular formation, it would not be scientifically sound to assess changes in small subdivisions of these regions. Although we believe, for example, that the mediodorsal and intralaminar nuclei are included in ROIs around the medial thalamus, the medial thalamus measures approximately 1 cm in diameter, so it is impossible to determine which of these substructures are responsible for the measured perfusion changes. However, SPECT remains an extremely powerful imaging technique for this type of study because it is the only modality that allows for routine measurement of *ictal* blood flow. Only under rare circumstances can one capture an ictal image with PET or fMRI scanning.

Though important questions remain to be answered, this study sheds light on the impact of thalamus and brainstem structures on consciousness in epileptic patients. Future studies will determine

which seizure types preferentially activate these structures and how electrical activity propagates to them. As the anatomic resolution of SPECT and other imaging techniques improve, researchers will be able to examine subcortical structures more closely and perhaps identify critical subregions of thalamus and reticular formation that are important in maintenance of consciousness. Perhaps most exciting, functional studies of this sort may ultimately reveal the true neural substrate of consciousness. With this information in hand, neurologists will be in a position to better understand disorders of consciousness such as epilepsy, sleep disorders, and coma.

References

1. Browne TR, Holmes GL. Handbook of Epilepsy. Philadephia: Lippincott-Raven, 1997.

2. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998; 51:48-55.

3. Zubal IG, Spencer SS, Imam K, et al. Difference images calculated from ictal and interictal technetium-99m-HMPAO SPECT scans of epilepsy. J Nucl Med 1995; 36:684-9.

4. Walczak TS, Radtke RA, Lewis DV. Accuracy and interobserver reliability of scalp ictal EEG. Neurology 1992; 42:2279-2285.

5. Spencer SS, Williamson PD, Bridgers SL, Mattson RH, Cicchetti DV, Spencer DD. Reliability and accuracy of localization by scalp ictal EEG. Neurology 1985; 35:1567-1575.

6. Penfield W, Von Santha K, Cipriani A. Cerebral blood flow during induced epileptiform seizures in animal and man. Neurophysiol 1939; 2:257-67.

7. Markand ON, Andersen AR, Spencer SS. SPECT in epilepsy. J Neuroimaging 1995; 5:S23-S34.

8. Engel J, Jr. Seizures and Epilepsy. Philadelphia: F.A. Davis, 1989.

9. Chugani HT, Rintahaka PJ, Shewmon DA. Ictal patterns of cerebral glucose utilization in children with epilepsy. Epilepsia 1994; 35:813-22.

10. Ackermann RF, Engel J, Jr., Baxter L. Positron emission tomography and autoradiographic studies of glucose utilization following electroconvulsive seizures in humans and rats. Ann N Y Acad Sci 1986; 462:263-9.

11. Bruehl C, Hagemann G, Witte OW. Uncoupling of blood flow and metabolism in focal epilepsy. Epilepsia 1998; 39:1235-42.

12. Theodore WH, Fishbein D, Dubinsky R. Patterns of cerebral glucose metabolism in patients with partial seizures. Neurology 1998; 38:1201-6.

13. Hogan RE, Cook MJ, Binns DW, et al. Perfusion patterns in postictal ^{99m}Tc-HMPAO SPECT after coregistration with MRI in patients with mesial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 1997; 63:235-9.

14. O'Brien TJ, So EL, Mullan BP, et al. Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. Neurology 1998; 40:445-54.

15. Zubal IG, Spanaki MV, MacMullan J, Corsi M, Seibyl JP, Spencer SS. Influence of technetium-99m-hexamethylpropylene amine oxime injection time on single-photon emission tomography perfusion changes in epilepsy. Eur J Nucl Med 1999; 26:12-17.

16. Spanaki MV, Spencer SS, Wisniewski G, MacMullan J, Seibyl J, Zubal IG. Evolution and localization of postictal blood flow changes in partial seizures demonstrated by SPECT: use of quantitative difference images. J Epilepsy 1998; 11:25-33.

17. Detre JA, Alsop DC, Aguirre GK, Sperling MR. Coupling of cortical and thalamic ictal activity in human partial epilepsy: demonstration by functional magnetic resonance imaging. Epilepsia 1996; 37:657-61.

18. Bohnen NI, O'Brien TJ, Mullan BP, So EL. Cerebellar changes in partial seizures: clinical correlations of quantitative SPECT and MRI analysis. Epilepsia 1998; 39:640-50.

19. Won JH, Lee JD, Chung TS, Park CY, Lee BI. Increased contralateral cerebellar uptake of technetium-99m-HMPAO on ictal brain SPECT. J Nucl Med 1996; 37:426-9.

20. Seto H, Shimizu M, Watanabe N, et al. Contralateral cerebellar activation in frontal lobe epilepsy detected by ictal Tc-99m HMPAO brain SPECT. Clin Nucl Med 1997; 22:194-5.

21. Laich E, Kuzniecky R, Mountz J, et al. Supplementary sensorimotor area epilepsy: seizure localization, cortical propagation and subcortical activation pathways using ictal SPECT. Brain 1997; 120:855-64.

22. Park CH, Kim SM, Streletz LJ, Zhang J, Intenzo C. Reverse crossed cerebellar diaschisis in partial complex seizures related to herpes simplex encephalitis. Clin Nucl Med 1992; 17:732-5.

23. Sozuer DT, Onsel C, Altiok E, Uslu I, Yalcin E. Cerebellar and subcortical blood flow abnormalities in children with partial epilepsy. Brain Dev 1996; 18:95-8.

24. Harvey AS, Jayakar P, Duchowny M, et al. Hemifacial seizures and cerebellar ganglioglioma: an epilepsy syndrome of infancy with seizures of cerebellar origin. Ann Neurol 1996; 40:91-8.

25. Duncan R, Rahi S, Bernard AM, et al. Ictal cerebral blood flow in seizures originating in the posterolateral cortex. J Nucl Med 1996; 37:1946-51.

26. Newton MR, Berkovic SF, Austin MC, Reutens DC, McKay WJ, Bladin PF. Dystonia, clinical lateralization, and regional blood flow changes in temporal lobe seizures. Neurology 1992; 42:371-7.

27. Rodrigues M, Botelho MM, Fonseca AT, Peter JP, Pimentel T, Vieira MR. Combined study of ^{99m}Tc-HMPAO SPECT and computerized electroencephalographic topography (CET) in patients with medically refractory complex partial epilepsy. Ann Nucl Med 1996; 10:113-8.

28. Yune MJ, Lee JD, Ryu YH, Kim DI, Lee BI, Kim SJ. Ipsilateral thalamic hypoperfusion on interictal SPECT in temporal lobe epilepsy. J Nucl Med 1998; 39:281-5.

29. McNamara JO, Galloway MT, Rigsbee LC, Shin C. Evidence implicating substantia nigra in regulation of kindled seizure threshold. J Neurosci 1984; 4:2410-7.

30. Miller JW. The role of mesencephalic and thalamic arousal systems in experimental seizures. Prog Neurobiol 1992; 39:155-78.

31. Garant DS, Gale K. Lesions of substantia nigra protect against experimentally induced seizures. Brain Res 1983; 273:156-61.

32. Engel J, Jr., Wolfson L, Brown L. Anatomical correlates of electrical and behavioral events related to amygdaloid kindling. Ann Neurol 1978; 3:538-44.

33. Kreindler A, Zuckermann E, Steriade M, Chimion D. Electroclinical features of convulsions induced by stimulation of brain stem. J Neurophysiol 1958; 21:430-6.

34. Tanaka K, Mishima O. The localization of the center dealing with the tonic extensor seizure of electroshock. Jpn J Pharmacol 1953; 3:6-9.

35. Browning RA, Turner FJ, Simonton RL, Bundman MC. Effect of midbrain and pontine tegmental lesions on the maximal electroshock seizure pattern in rats. Epilepsia 1981; 22:583-94.

36. Browning RA, Simonton RL, Turner FJ. Antagonism of experimentally induced tonic seizures following a lesion in the midbrain tegmentum. Epilepsia 1981; 22:595-601.

37. Browning RA, Nelson DK, Moghareban N, Jobe PC, Laird HEn. Effect of midbrain and pontine tegmental lesions on audiogenic seizures in genetically epilepsy-prone rats. Epilepsia 1985; 26:175-83.

38. Browning RA, Nelson DK. Modification of electroshock and pentylenetetrazol seizure patterns in rats after precollicular transections. Exp Neurol 1986; 93:546-56.

39. Velasco F, Velasco M, Estrada-Villaneuva F, Machado JP. Specific and nonspecific multiple unit activities during the onset of pentylenetetrazol seizures. I. Intact animals. Epilepsia 1975; 16:207-14.

40. Velasco F, Velasco M, Romo R. Specific and non-specific multiple unit activities during pentylenetetrazol seizures in animals with 'encephale isolé'. Electroencephalogr Clin Neurophysiol 1980; 49:600-7.

41. Velasco F, Velasco M, Romo R. Specific and nonspecific multiple-unit activities during pentylenetetrazol seizures in animals with pretrigeminal brain stem transection. Exp Neurol 1981; 74:1-10.

42. Velasco F, Velasco M, Romo R. Specific and non-specific multiple unit activities during pentylenetetrazol seizures in animals with mesencephalic transections. Electroencephalogr Clin Neurophysiol 1982; 53:289-97.

43. Magistris MR, Mouradian MS, Gloor P. Generalized convulsions induced by pentylenetetrazol in the cat: participation of forebrain, brainstem, and spinal cord. Epilepsia 1988; 29:379-88.

44. Jasper H. Diffuse projection systems: the integrative action of the thalamic reticular system. Electroencephgr Clin Neurophysiol 1949; 1:405-419.

45. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949; 1:455-73.

46. Fiset P, Paus T, Daloze T, et al. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci 1999; 19:5506-13.

47. Aggleton JP, Desimone R, Mishkin M. The origin, course, and termination of the hippocampothalamic projections in the macaque. J Comp Neurol 1986; 243:409-421.

48. Andersen AR. ^{99m}Tc-D,L-Hexamethylene-propyleneamine oxime (^{99m}Tc-HMPAO): basic kinetic studies of a tracer of cerebral blood flow. Cerebrovasc Brain Metab Rev 1989; 1:288-318.

49. Potts NL, Davidson JR, Krishnan KR, Doraiswamy PM. Magnetic resonance imaging in social phobia. Psychiatry Res 1994; 52:35-42.

50. Lindsley DB, Bowden JW, Magoun HW. Effect upon the EEG of acute injury to the brain stem activating system. Electroencephalogr Clin Neurophysiol 1949; 1:475-486.

51. Marks DA, Katz A, Hoffer P, Spencer SS. Localization of extratemporal epileptic foci during ictal single photon emission computed tomography. Ann Neurol 1992; 31:250-5.