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Pathophysiology and functional consequences of human partial epilepsy: lessons from positron emission tomography studies

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Positron emission tomography (PET) is a powerful clinical and research tool that, in the past two decades, has provided a great amount of novel data on the pathophysiology and functional consequences of human epilepsy. PET studies revealed cortical and subcortical brain dysfunction of a widespread brain circuitry, providing an unprecedented insight in the complex functional abnormalities of the epileptic brain. Correlation of metabolic and neuroreceptor PET abnormalities with electro-clinical variables helped identify parts of this circuitry, some of which are directly related to primary epileptogenesis, while others, adjacent to or remote from the primary epileptic focus, may be secondary to longstanding epilepsy. PET studies have also provided detailed data on the functional anatomy of cognitive and behavioral abnormalities associated with epilepsy. PET, along with other neuroimaging modalities, can measure longitudinal changes in brain function attributed to chronic seizures as well as therapeutic interventions. This review demonstrates how development of more specific PET tracers and application of multimodality imaging by combining structural and functional neuroimaging with electrophysiological data can further improve our understanding of human partial epilepsy, and helps more effective application of PET in presurgical evaluation of patients with intractable seizures.

Keywords: positron emission tomography, epilepsy, cortical and subcortical brain dysfunction, cognitive and behavioral abnormalities, neuroimaging

Epilepsy is one of the most common neurological disorders. It affects approximately 0.5%–1.0% of the population, and in 15%–20% of cases the seizures are intractable, i.e., refractory to medical treatment with anticonvulsants. When chronic seizures cannot be controlled with medication, surgical treatment (resection of the epileptic focus) may

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be considered. The most important aspect of presurgical evaluation is the identification of the *epileptogenic region* (i.e. the area of brain necessary and sufficient for generation of habitual spontaneous seizures (28), which can be surgically resected without causing an unacceptable loss of neurological function, and which will lead to complete and long-term seizure control. The epileptogenic region, however, is a theoretical entity, and its boundaries can be only assumed, but not directly defined, from complementary structural (epileptogenic lesion(s) delineated by structural neuroimaging) and functional information (obtained from seizure semiology, electrophysiological and functional neuroimaging data) derived from the epileptic brain. It has been increasingly recognized, however, that the epileptogenic brain tissue is not well circumscribed. In fact, the brain of patients with medically refractory partial epilepsy can be abnormal in many different areas. Therefore, some discourage the use of the term "epileptic focus", since the electrophysiological, neurological and behavioral phenomena associated with seizures are related to abnormal function of a widespread cortico-subcortical epileptic circuitry, rather than purely the consequence of epileptic discharges arising from a discrete epileptic focus (28). Obviously, surgical treatment of seizures cannot target the entire circuit, but complete resection of the primary epileptogenic region is usually enough to alleviate seizures provided that no secondary independent epileptogenesis has developed in remote parts of the epileptic circuitry.

1. Imaging techniques in the investigation of the epileptic brain

The advent and clinical utilization of high-resolution tomographic neuroimaging techniques in the past two decades had a significant impact on the management of epilepsy, and has lead to an unprecedented accuracy in non-invasive delineation of the epileptogenic region and also better characterization of the entire epileptic circuitry. Both *structural neuroimaging*, especially magnetic resonance imaging (MRI), and *functional neuroimaging* modalities, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), functional MRI (fMRI), magnetic resonance spectroscopy (MRS) and optical imaging (35, 89) are potentially useful methods for investigating various aspects of focal and generalized abnormalities in the epileptic brain.

MRI studies are particularly useful to identify epileptogenic structural brain lesions. With the application of fluid attenuated recovery (FLAIR) sequences, hippocampal volumetry, and proton magnetic resonance spectroscopic imaging (7, 8), MRI became a very reliable non-invasive imaging method for detection of hippocampal sclerosis, the most common pathological substrate of temporal lobe epilepsy. In partial epilepsies of neocortical origin, recent advances in MRI techniques (e.g., high resolution MRI imaging with thin slices, multiplanar reconstruction etc.) have greatly improved the sensitivity of MRI for detecting subtle *cortical dysgenesis* (3, 9), which has been reported in up to 30% of epilepsy surgery specimens and is believed to represent the central pathologic substrate responsible for seizures of neocortical origin (21).

Table I

PET tracers applied to imaging the epileptic brain

Isotope	Half-life	Tracer	Target function	Change in epileptic focus
^{18}F	109 min	2-deoxy-2[^{18}F]fluoro-D-glucose (FDG)	Glucose metabolism	Interictal decrease* Ictal increase
		^{18}F-cyclofoxy	Mu- and kappa opiate receptors	Increase
^{11}C	20 min	[^{11}C]-flumazenil	$GABA_A$-receptors	Decrease
		a[^{11}C]-methyl-L-tryptophan quinolinic acid	Brain serotonin synthesis or tryptophan metabolism to	Increase
		[^{11}C]FCWAY	$5\text{-}HT_{1A}$ receptors	Decrease
		(S)-[N-methyl-		
		[^{11}C]ketamine	NMDA-receptors	Decrease
		[^{11}C]doxepin	Histamine H_1 receptors	Increase
		[^{11}C]carfentanil	Mu-opiate receptors	Increase
		[^{11}C]methyl-naltrindole	Delta-opiate receptors	Increase
^{15}O	2 min	^{15}O-water	Cerebral blood flow	Ictal increase* Brain activation studies

* Can be increased interictally if cortex is actively spiking during uptake.

Nevertheless, structural imaging studies do not provide information on *functional* brain abnormalities, which almost invariably extend beyond visible structural lesions or brain malformations generating seizures.

Functional neuroimaging techniques have provided a new insight into various aspects of functional abnormalities of the epileptic brain. Among several available modalities, PET scanning has a prominent role in the investigation of the epileptic brain. PET has been used for more than two decades in presurgical evaluation of patients with medically intractable epilepsy, and it has several advantages when compared to other imaging or electrophysiological modalities. For example: 1. PET can utilize a large variety of tracers designed to target specific brain metabolic and neuroreceptor functions; some of them show decreased while others increased uptake in epileptic brain regions (Table I). 2. PET has superior spatial resolution (mm range), much better than that of SPECT or MRS (cm range). 3. PET has the ability of absolute quantification of the measured functions (such as glucose metabolism); this is not possible with SPECT or functional MRI, which can only measure percent changes compared to a baseline value (activation/subtraction studies). 4. PET provides functional information about the entire brain. In contrast, although EEG remains the gold standard in diagnosis and presurgical workup of epilepsy, electrophysiological studies usually provide functional information from a limited portion of the brain (mostly from the cortex) only. On the contrary, PET studies give comprehensive information about various aspects of functional abnormalities of both cortical and subcortical structures.

Application of PET in epilepsy can go far beyond presurgical localization of epileptic foci. The present review summarizes some of the clinical PET findings to demonstrate the capability of PET to help better understanding of functional organization of epileptic circuitries, their anatomical substrates, as well as functional consequences of chronic seizures.

2. Mapping the epileptic circuitry by PET

2.1. Functional abnormalities of perifocal and remote cortical regions on PET

Initial PET studies in epilepsy were performed using 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG; the most commonly used PET tracer) in patients with intractable seizures of temporal lobe origin, and showed localized glucose metabolic changes (interictal hypometabolism) that apparently coincided with the general location of the EEG-defined epileptic focus (26, 27, 60). Subsequent studies also demonstrated that interictal hypometabolic regions are not confined to the presumed epileptogenic zone or to the brain tissue showing pathologic changes, but they commonly extend beyond the temporal lobe (30, 39, 87, 95). Brain regions most commonly demonstrating interictal hypometabolism in temporal lobe epilepsy include ipsilateral parietal and frontal cortex as well as thalamus (Fig. 1); these remote cortical regions, however, rarely show epileptiform activity on EEG, typically do not show structural abnormalities on high-resolution MRI, and their resection is usually not necessary to alleviate seizures.

These extratemporal cortical and subcortical areas are known to have synaptic connections with temporal structures. Progressive involvement of these stuctures during status epilepticus has been demonstrated by autoradiography studies in animals (37). Our studies in patients with intractable *neocortical epilepsy* have shown that cortical regions remote from the primary epileptic focus, that show decreased [^{11}C]flumazenil (a PET tracer for the inhibitory $GABA_A$ receptors) binding on PET, are involved in rapid seizure propagation in approximately 2/3 of the cases during intracranial EEG monitoring with subdural electrodes (45). The involved cortical areas are commonly directly connected with the primary epileptic focus and they are potential sites of developing secondary epileptic foci (68). This notion is further supported by findings showing that, in patients with lesional epilepsy, presence of decreased $GABA_A$ receptor binding remote from the primary epileptogenic region is associated with early age of seizure onset and long duration of epilepsy (46). This suggests that such remote regions (or at least some of them) may be the result of chronic, repeated involvement in long-standing epilepsy causing local structural and/or receptor changes. On the other hand, interictal metabolic abnormalities remote from the primary epileptic focus can be clearly functional and reversible, most likely due to remote effects ("diaschisis") resulted from massive loss of synaptic input from the connected and pathologically damaged epileptic regions (e.g., the sclerotic hippocampus). This is supported by post-resection FDG PET studies demonstrating recovery of some of the remote metabolic abnormalities following successful removal of the primary epileptic focus (36, 85).

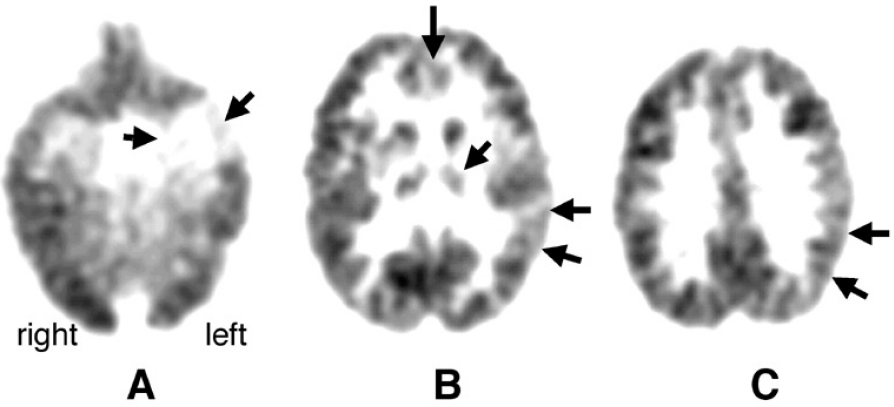

Fig. 1. Involvement of extratemporal areas in unilateral (left) temporal lobe epilepsy on FDG PET. Note the severe hypometabolism of the epileptogenic left medial temporal structures and lateral temporal cortex (**A**; arrows). This is accompanied by a less severe hypometabolism of the ipsilateral prefrontal cortex and thalamus (**B**) as well as a mild hypometabolism in the ipsilateral parietal cortex (**C**; also see arrows). The seizures originated from the left hippocampus

Another interesting aspect of cortical metabolic abnormalities in neocortical epilepsy is their spatial localization and extent in and around the EEG-defined seizure onset zone or cortical epileptogenic lesions. Three-dimensional surface rendering of co-registered PET, MRI and intracranial EEG datasets has recently allowed us to analyze spatial relationships between structural, metabolic, receptor, and electrophysiological abnormalities with an unprecedented spatial accuracy (Fig. 2). In patients with focal cortical brain lesion (such as benign tumors, cysts, or focal cortical dysplasia visible on MRI), these studies demonstrated that perilesional hypometabolism and decreased $GABA_A$ receptor binding are often located in an eccentric position around the lesion (46) (Fig. 2). Average size of perilesional glucose metabolic abnormalities was almost two times larger than the extent of the corresponding $GABA_A$ receptor decrease (reflected by decreased [^{11}C]flumazenil binding on PET). Furthermore, while location of decreased [^{11}C]flumazenil binding corresponds well with frequent spiking detected by electrocorticography, perilesional metabolic abnormalities often extend beyond this area. A similar relationship was found in patients with extratemporal, non-lesional epilepsy, where focal cortical areas with decreased FMZ binding detected more accurately the area of seizure onset than more extensive areas of glucose hypometabolism (72) (Fig. 3). These findings strongly suggest that areas with decreased $GABA_A$ receptor binding in and around epileptogenic regions have a close relationship with epileptogenicity, while surrounding cortex with interictal hypometabolism may represent a non-epileptogenic functional deficit zone.

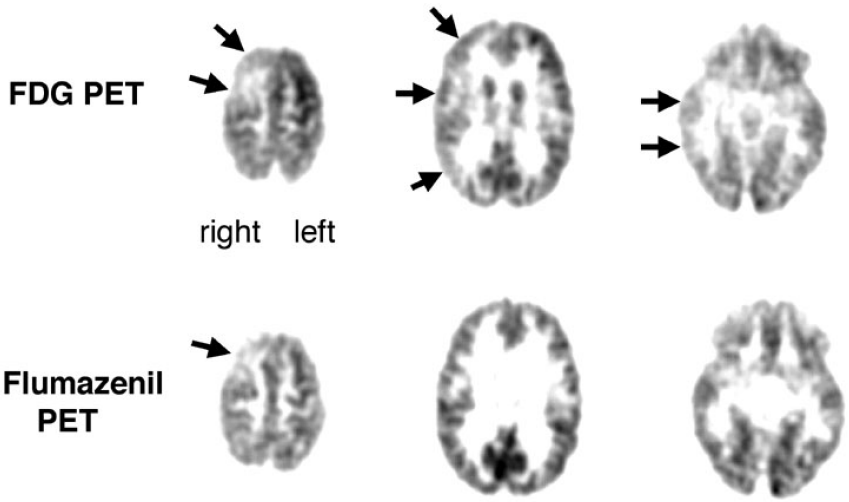

Fig. 3. Comparison of FDG and [^{11}C]flumazenil PET (mapping $GABA_A$ receptor binding) in extratemporal (neocortical) epilepsy. The FDG PET images show widespread hypometabolism in the right hemisphere, including multiple lobes. FMZ PET shows a focal area of decreased FMZ binding confined to the frontal cortex. Seizures originated from this frontal region

Fig. 2. Eccentric location of cortical glucose hypometabolism and decreased [^{11}C]flumazenil binding around an epileptogenic lesion. The black/gray area indicates the surface extent of the left parietal lesion, a histologically verified focal cortical dysplasia (FCD), which was visualized as an area of increased signal intensity on FLAIR MRI. The red areas show the location and extent of perilesional PET abnormalities on the 3D reconstructed brain surface. Note that the area of perilesional decreased [^{11}C]flumazenil binding is smaller than the hypometabolism, and it matched well with the subdural EEG-defined seizure onset that was confined to the cortex superior-posterior to the lesion

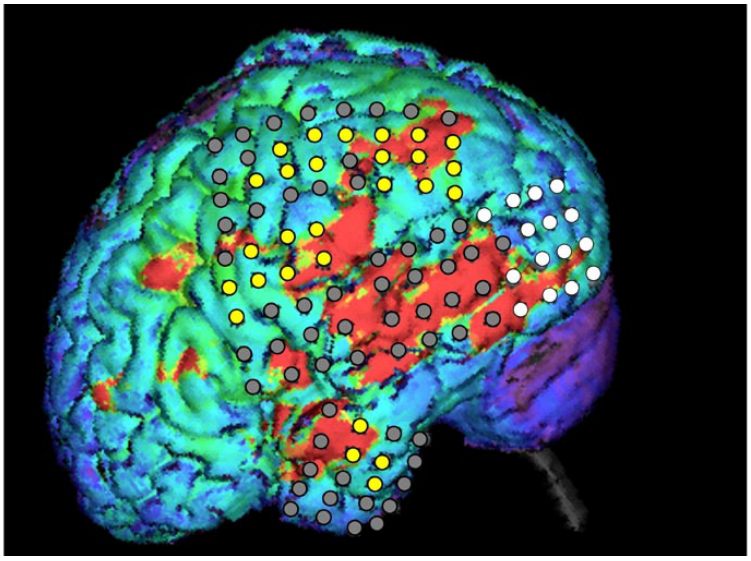

Fig. 4

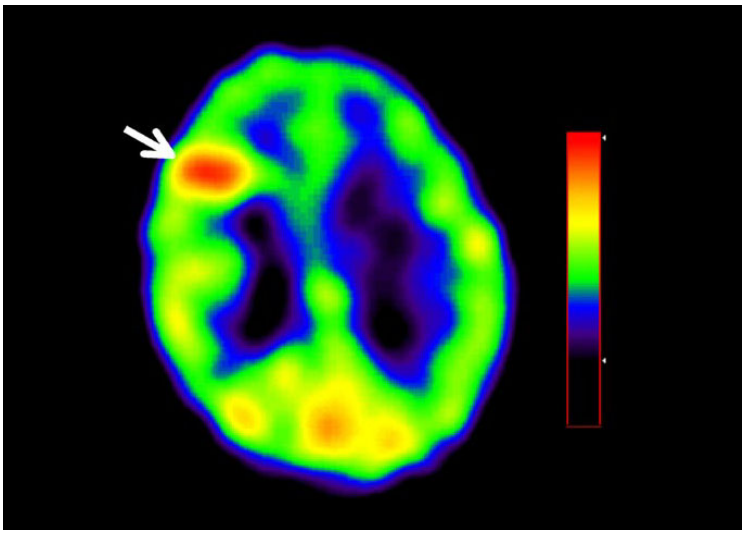

Fig. 8

2.2. Are cortical epileptic foci truly hypometabolic interictally?

As discussed above, clinical use of FDG PET in localization of epileptic foci is based on the fundamental observation that epileptic foci are located within the general area of interictal hypometabolism. This correlation, however, was challenged by the poor performance of FDG PET in detecting epileptogenic zones (as defined by intracranial EEG) and its inability to predict surgical outcome in extratemporal epilepsy (48, 72). A further piece in this puzzle was found by detailed analysis of the locations of seizure onset zones in and around metabolic abnormalities detected by PET (47). In this study of young patients with intractable neocortical epilepsy, ictal onsets on subdural grid electrodes occurred most commonly in cortex bordering objectively identified hypometabolic areas, while non-lesional cortex within the hypometabolism was generally less epileptogenic (Fig. 4). This finding seemed to be at odds with the traditional and apparently oversimplified concept that focal areas of hypometabolism represent epileptic cortex. In fact, our study demonstrated that ictal electrophysiological changes often skip or "flow" around hypometabolic areas, which appear to be often protected against seizure involvement. The pathophysiological basis of this phenomenon is not completely clear. Possible explanations may emerge from animal studies of experimental epilepsy. It has been demonstrated that artificially induced cortical epileptic foci and surrounding cortical zones display different, occasionally opposite electrophysiological, metabolic and neurochemical properties (20, 62, 63, 78, 81, 98). Actively spiking epileptic foci show increased glucose metabolism (4) and are surrounded by widespread hypometabolic cortex, which can extend in a dynamic fashion during transition from interictal to ictal activity (98). In a model of acutely induced focal seizure activity, [^{14}C]2-deoxyglucose uptake was related to the overall strength of synaptic activity, and reduced metabolism was found to be associated with decreased synaptic activity and tonic hyperpolarization of the neurons (5). Such electrophysiological characteristics may protect these cortical areas from ictal involvement, and can result in a functional disconnection of the focus from surrounding synaptically connected areas.

← Fig. 4. Spatial relationship between interictal glucose hypometabolism (displayed in red) vs. ictal onset (white electrodes) and interictal spiking (yellow electrodes) cortex (defined by recordings from subdural grid electrodes), displayed on the 3D brain surface reconstructed from the high-resolution MRI co-registered with the PET scan. Silent electrodes are gray. The Figure demonstrates that neocortical seizures typically do not originate from the center of hypometabolic areas, but often from normometabolic cortex directly bordering these hypometabolic regions. Thus, cortical areas, that are normal structurally but show significant hypometabolism, appear to be protected from seizure onset while their surrounding cortex can be highly epileptogenic

← Fig. 8. Focal cortical increase of AMT uptake (arrow) in the epileptogenic right frontal cortex of a 3 year old boy

Functional isolation of epileptic foci from their surrounding neuronal connections may influence the excitability of this neuronal population and may prevent self-sustaining synchronized neuronal activity (40), as shown by successful suppression of focal epileptic activity by subpial transections both in animal models and in human epilepsy surgery of eloquent (e.g. primary motor) cortex (38, 69, 83). Based on these observations, one can hypothesize that significant parts of the hypometabolic cortex (without ictal electrophysiological involvement) represent regions that are actually protected against participation in seizure activity. Still, the findings demonstrate a firm relationship between the general location of the EEG-defined epileptogenic zone and interictal hypometabolism, but also demonstrate that metabolic abnormalities themselves fail to accurately localize such zones and cannot be used to accurately tailor surgical resection.

2.3. Functional involvement of subcortical structures in epilepsy – imaging correlates

2.3.1. Thalamic involvement in temporal lobe epilepsy. Subcortical structures are strongly implicated in the process of generalization and intercortical seizure spread. In animal seizure models, for example, the thalamus, especially the *dorsomedial nucleus*, an important relay station between limbic structures, plays a central role in limbic seizure propagation (33). Early PET studies in human temporal lobe epilepsy demonstrated a high prevalence of interictal metabolic abnormalities of the thalamus ipsilateral to the seizure focus (39, 86). FDG PET studies performed during seizures also often show increased thalamic (and also striatal, see below) metabolism ipsilateral to the focus, or bilaterally, in addition to cortical increases (17, 18). Intrathalamic localization of the interictal PET abnormalities has become possible by applying MRI-based partial volume correction of the PET images (44). These studies demonstrated that decreased glucose metabolism and $GABA_A$ receptor binding ipsilateral to the seizure focus affects specifically the dorsomedial nucleus in patients with temporal lobe epilepsy (Fig. 5). A strong correlation between the severity of decreased FMZ binding of the amygdala and the ipsilateral dorsomedial nucleus has also suggested that propagation pathways may utilize the abundant reciprocal connections between these two structures. The concomitant ipsilateral volume loss of the thalamus (22, 44) also suggests a neuronal cell loss. This volume loss seems to be specific for temporal lobe epilepsy, since a recent study including patients with extratemporal epilepsy and idiopathic generalized epilepsy did not find thalamic volume loss in these forms of epilepsy (73). PET studies in patients who underwent temporal lobectomy also showed postoperative increase of thalamic metabolism after elimination of seizures, indicating that at least some of the interictal thalamic metabolic abnormalities are functional (not due to neuronal loss), probably related to chronic seizure activity (85). From a clinical point of view, the most important advantage of thalamic PET abnormalities is that the presence of thalamic involvement has a strong lateralization value for the seizure focus and can support the lateralization when cortical abnormalities are subtle. In fact, temporal lobectomy contralateral to a hypometabolic thalamus likely results in poor seizure outcome (74).

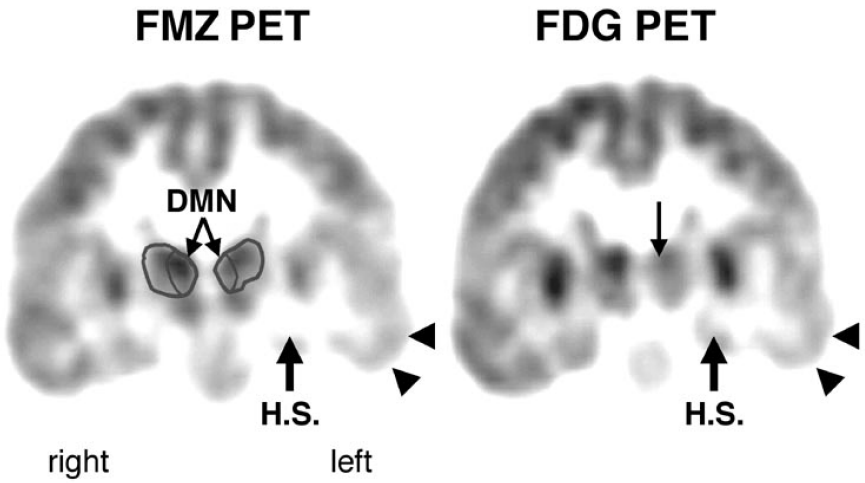

Fig. 5. Coronal glucose (FDG) and [^{11}C]flumazenil (FMZ) PET images of a patient with temporal lobe epilepsy and left hippocampal sclerosis (H.S.). The PET scans show decreased metabolism and FMZ binding in the left hippocampus, temporal neocortex (arrowheads) and in the ipsilateral dorsomedial nucleus (DMN) of the thalamus. DMN has abundant reciprocal connections with the medial temporal structures and plays a central role in limbic seizure propagation

2.3.2. Functional abnormalities of the basal ganglia. In addition to thalamic abnormalities, functional involvement of the basal ganglia in human epilepsy is also common. Ictal hypermetabolism of the striatum was described first in children with epilepsy (17, 18). An ictal SPECT study linked ictal activation of the lenticular nuclei to rotational seizures (96), while interictal striatal hypometabolism was found to be more common in patients whose seizure semiology included dystonia (25).

A peculiar pattern of subcortical involvement has been observed in children with *West syndrome*. West syndrome is an age-specific epilepsy syndrome typically beginning in early infancy, and characterized by symmetric ("infantile") spasms, hypsarrhythmia on the EEG, and developmental delay. Infantile spasms are often very difficult to control. West syndrome has been classified as a generalized epilepsy syndrome, although there is increasing evidence from imaging studies that many of these children have previously unappreciated focal cortical abnormalities (often in the form of focal cortical dysplasia), and resection of these focal epileptogenic regions can alleviate spasms in a subset of patients (14, 16, 34, 49). In addition to showing cortical abnormalities, FDG PET studies showed interictal activation of the lenticular nuclei in some infants with West syndrome (15); a pattern that has not been seen in other forms of epilepsy. This constellation of metabolic findings suggests that infantile spasms result from cortical abnormalities interacting with subcortical structures, and a potential

neuronal circuitry involved in the generation and propagation of infantile spasms has been proposed (15, 52) (Fig. 6). In short, the primary cortical abnormality interacts through epileptiform discharges with *brainstem structures*, e.g., with the raphe nuclei at a critical stage of brain maturation. This serotonergic brainstem region has abundant projections throughout the brain (1, 57, 64). Raphe-cortical and cortico-cortical projections can mediate the hypsarrhythmic changes on EEG. The prominent raphe-striatal pathway in primates (88) represents strong connections between raphe neurons and putamen bilaterally, and this pathway may be responsible for activation of the striatum. Activation of this pathway as well as descending spinal pathways may be responsible for secondary generalization of the cortical discharges to result in symmetric spasms.

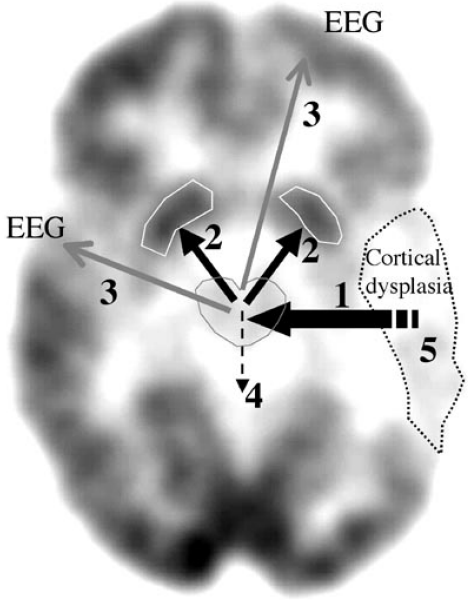

Fig. 6. Putative cortico-subcortical circuitry activated during infantile spasms (15). **1**: Cortical epileptic discharges from an area with cortical dysplasia (severe hypometabolism on FDG PET) triggering the brainstem, presumably the dorsal raphe area, a brain region with large number of serotonergic cell bodies; **2**: Bilateral, serotonergic raphe-striatal projections activate the striatum; **3**: Raphe-cortical interactions induce multifocal discharges on the EEG; **4**: Propagation to the spinal cord can lead to symmetric spasms; **5**: Surgical resection of the primary offending lesion (focal cortical dysplasia) can alleviate the spasms by preventing the circuit from being activated

3. Is epilepsy a progressive disorder?

Animal studies demonstrated that repeated seizures may cause neuronal injury (6, 82). To address whether chronic epilepsy causes progressive neuronal damage in humans, neuroimaging studies are well suited. Human cross-sectional MRI and pathologic studies demonstrated that patients with longer epilepsy duration and higher seizure number have more severe hippocampal volume and neuronal loss (54, 65, 91). Our PET studies on patients with neocortical epilepsy and brain lesion also showed a significant correlation between extent of perilesional hypometabolic cortex and the estimated life-time number of seizures, a composite measure created from duration of epilepsy and seizure frequency (46). A similar correlation was demonstrated in children with Sturge–Weber syndrome (a congenital neurocutaneous disorder characterized by leptomeningeal angiomatosis often associated with partial seizures), where high seizure frequency was associated with extensive perilesional hypometabolism (61). Such cross-sectional studies in patients with medically intractable epilepsy strongly suggest, but do not definitely prove the progressive nature of the observed metabolic abnormalities. Such proof would require longitudinal studies demonstrating progression.

There are several case reports with longitudinal neuroimaging showing progressive hippocampal atrophy following status epilepticus or frequent seizures (75, 76, 97). A recent longitudinal volumetric MRI study of patients with intractable temporal epilepsy who refused surgery, also showed progression of hippocampal atrophy in those who continued to have seizures, over a mean follow-up of 3.4 years (29). These studies strongly suggested that although an initial tissue damage or at least susceptibility to seizures may exist is some cases, hippocampal sclerosis can develop and/or progress as a consequence of severe and repeated seizures. A recent FDG PET study performed on children with recent onset seizures provided further ammunition to the argument that common and extensive metabolic abnormalities seen in patients with long standing epilepsy might be, at least partly, the result of repeated seizures rather than reflecting primary tissue damage causing seizures. In this study, children with recent onset seizures had a low rate (20%) of abnormal glucose metabolism in their epileptic temporal lobe (32). This rate is much lower than that reported in adults or even children with chronic temporal lobe epilepsy. An ongoing longitudinal neuroimaging study at the National Institute of Health will address whether initial hypometabolism predicts long-term outcome, and whether persistent epilepsy is associated with progressive hypo-metabolism in temporal and extratemporal areas. The current evidence, however, indicates that extensive cortical hypometabolism, often seen in adults with long-standing epilepsy, is a consequence of progressive functional deterioration that is likely related to decline in neurological, cognitive or behavioral functions.

4. Brain development, plasticity and epilepsy: metabolic correlates revealed by PET

4.1. Effects of age and epilepsy on cerebral glucose metabolism

One of the most exciting aspects of PET scanning of the human brain is the potential of mapping functional changes during normal and abnormal brain development. Functional maturation of various brain regions was characterized by PET scanning of children with minimal neurological injury in the 1980s (12, 13). These studies demonstrated a triphasic evolution of absolute regional cerebral glucose metabolic rates, characterized by rapid increase at birth, very high levels during childhood, and a subsequent gradual decline to reach adult levels by the end of adolescence. Sequential activation of regional metabolism during the first months of life followed closely the behavioral evolution of infants. Transient high cerebral metabolic rates in children were interpreted as a result of an elevated energy demand in the developing brain due to transient synaptic exuberance presumably related to developmental plasticity. High cerebral metabolic levels in children were consistent with the previously described high density of dendritic spines and cortical synapses in this age group (41, 42, 66). Despite these considerable changes in absolute metabolic rates throughout childhood, the cerebral *pattern* of glucose metabolism becomes largely fixed and shows little changes after 1 year of age.

PET studies on healthy children are difficult to perform due to ethical restraints. PET scanning on children with epilepsy, however, is often done and can address the question whether chronic presence of epilepsy affects functional maturation of the whole brain. Theoretically, brain development may be effected not only by the seizure disorder itself, but also by chronically administered drugs, e.g., antiepileptics. A study involving mostly children with benign centrotemporal epilepsy (a non-progressive benign form of idiopathic epilepsy) showed that, although the overall pattern of brain metabolism barely changes between 6 years of age and adulthood, there are a few structures that continue to develop functionally (94). In particular, a non-linear increase of thalamic activity was found, probably reflecting relative increase of synaptic activities in the thalamus, possibly as a consequence of improved corticothalamic connections. Increased metabolic activity in the anterior cingulate cortex was also detected suggesting that the limbic system is involved in the process of brain maturation.

Another study of children and adolescents with complex partial (but not generalized and not necessarily uncontrolled) seizures showed a maturational curve of glucose metabolism similar to that described in non-epileptic children, despite the fact that the included patients were taking various antiepileptic drugs at the time of the PET scanning (2). The study showed that global absolute metabolic rates were below the normal levels, presumably due to the result of chronic antiepileptic drug treatment. Previous PET studies in adults, in fact, showed that some of the conventional antiepileptic drugs (e.g., barbiturates, phenytoin, valproic acid) considerably suppress cerebral glucose metabolic rates (31, 91). Newer antiepileptic drugs, e.g., vigabatrin, were shown to have less suppressive effect (84). Our [^{11}C]flumazenil PET study on young children who were on chronic vigabatrin treatment, however, suggested that this

drug, that acts by modulating GABAergic mechanisms by elevating GABA levels, may affect maturational changes of $GABA_A$ receptors in cortical regions (50). The functional consequences of such influences remain to be determined.

4.2. PET studies of postlesional plasticity in the developing brain

Unilateral hemispheric injury in infants or young children is often associated with seizures. On the other hand, early hemispheric damage prompts reorganizational changes in the non-injured parts of the brain, including the contralateral hemisphere if it is functionally preserved. One of the unresolved issues of developmental neurology is how postlesional brain plasticity is facilitated, and why some patients show considerable reorganization (leading to relatively preserved functions) while others end up with significant neurological and cognitive deficit.

Occurrence and persistence of chronic seizures is a significant factor of developmental delay or arrest following hemispheric lesions. Recent imaging studies in children with Sturge-Weber syndrome gave some clues regarding the relationship between epilepsy, unilateral brain metabolism and cognitive outcome. Sturge–Weber syndrome is a particularly useful model for studying such processes since, it starts at an early age (but not before birth), it affects only one side of the brain in a progressive fashion, allowing the contralateral hemisphere to exert its reorganizational potential. Interestingly, children with large and severe unilateral hemispheric hypometabolism on PET had better cognitive functions than those with minor structural deficit (atrophy) on MRI, but areas of mild hypometabolism extending far beyond structural abnormalities in the affected hemisphere (61). Children with better cognitive function had shorter duration of epilepsy and larger size of severely hypometabolic cortex in the affected hemisphere. This finding appears to be paradoxical. The most plausible explanation is that in children with severe unilateral hemispheric atrophy and hypometabolism, early, rapid progression of unihemispheric neuronal loss not only ameliorated epilepsy, but forced the remaining functionally intact brain regions to effectively reorganize at an early age. In other words, the affected hemisphere underwent an early "autohemispherectomy", that was actually more beneficial than prolonged mild hemispheric dysfunction that was apparently less effective in facilitating functional reorganization. This is an exciting (and still somewhat controversial) hypothesis that requires further studies. This hypothesis gets support from earlier [^{15}O]water PET studies of cerebral blood flow activations in children with early vs. late brain lesions associated with epilepsy. These studies demonstrated that in patients with left-sided lesion (affecting language areas) occurring early in development, rightward shift of language activation (from the damaged left hemisphere) occurs more readily than in those with late onset lesions (71). In another study of children with lesions affecting the cortical motor area, reorganization of motor functions was also stronger to secondary motor and fronto-parietal non-motor cortices in the early than in the late lesion group, suggesting a greater potential for reorganization during early development than later in life (70). Longitudinal neuroimaging studies with neuropsychological correlation are on the way to further address this issue. If it is proven to be true, PET and MRI scanning of young

patients with Sturge–Weber syndrome (and, with other early, unilateral brain lesions associated with epilepsy) will allow identification of children who are at major risk for poor cognitive outcome and may require early intervention, such as resective surgery. On the other hand, it may also identify those who perform their own "autohemispherectomy" and do not require aggressive treatment. Other functional imaging studies, particularly MRS imaging measuring regional distribution of various brain metabolites, may prove also helpful for early assessment of extent and severity of early brain dysfunction extending beyond the visible structural damage (67).

Another prominent example of postlesional brain plasticity was described in children who underwent cerebral hemispherectomy between 1.5 and 4 years of age (17). Repeated glucose PET scans in these patients showed recovery of glucose utilization in the caudate nucleus following an initial period of hypometabolism postoperatively. This functional recovery is presumably related to reorganization of cortico-striatal projections following their massive disruption by the surgery. These alterations of cerebral glucose utilization are believed to reflect microscopic anatomical reorganizational changes (e.g., collateral sprouting) that have been documented following similar lesions in several animal models. For example, in a rat model of this phenomenon, it has been shown that expression of the transforming growth factor alpha in striatum following hemidecortication was much greater in P6 compared to adult animals (55). In humans, plasticity in the striatum following unilateral decortication may account for the old observation that inclusion of the striatum in the resection results in more profound hemiplegia than hemidecortication alone (59). Novel PET tracers targeting neurotransmitter (e.g. serotonin) systems may be used to further clarify the processes underlying these massive reorganizational changes in humans.

5. Metabolic correlates of cognitive and behavioral abnormalities in epilepsy

As discussed above, glucose metabolic abnormalities on PET commonly extend beyond the presumed epileptogenic zone. Still, these non-epileptogenic dysfunctional areas are of clinical interest, because they often have important neuropsychological correlates. In patients with unilateral temporal lobe epilepsy, for example, bilateral glucose hypometabolism was found to be associated with long disease duration and poor memory performance during the intracarotid amytal (Wada) test (56). In addition, temporal lobe epilepsy patients who perform worse in frontal lobe tests often exhibit frontal lobe dysfunctioning in additon to the temporal lobe epileptogenic zone. A PET study focusing on prefrontal metabolic asymmetry, that is also often present in temporal lobe epilepsy, confirmed this by showing impairment of verbal and performance intelligence measures in patients with such prefrontal involvement on their PET scan (43).

Specific patterns of abnormal brain glucose metabolism were observed in conjunction with specific epilepsy-related *behavioral abnormalities* as well. In infants with epileptic spasms, (19) demonstrated that bilateral temporal hypometabolism (typically affecting both hippocampus and lateral temporal structures) is strongly associated with autistic features. Similar observations were reported in children who "burned out" their hippocampi bilaterally and developed bilateral hippocampal sclerosis (detected by MRI and PET) following repeated episodes of status epilepticus (23). Such children fail to develop language (or lost attained language), social skills, and complex purposive or adaptive activity, even after epilepsy becomes controlled, despite retaining motor and sensory functions. The deficits are consistent with those seen in severe infantile autism (although etiology is different). These studies support that bilateral hippocampal dysfunction in early life is associated with a profound failure of cognitive capacities, including language learning and learning of complex social and adaptive skills in general.

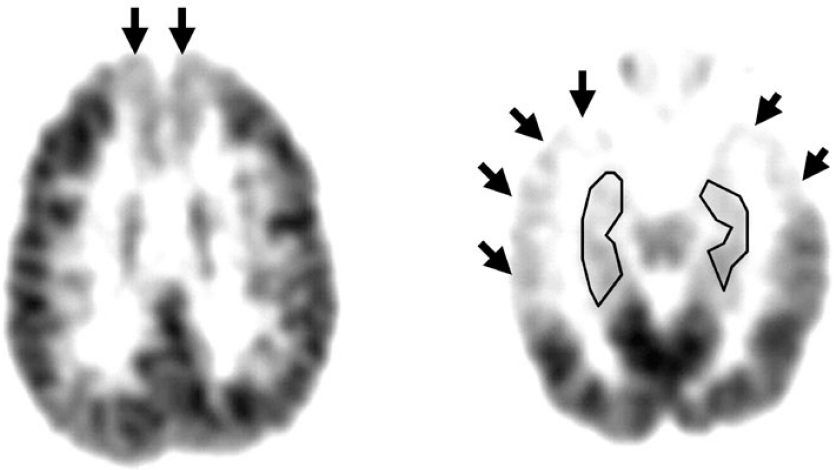

Fig. 7. Cerebral metabolic pattern commonly associated with interictal aggressive behavior in children with temporal lobe seizures. Note the bilateral hypometabolism of the temporal neocortex (arrows) with relatively preserved medial temporal (delineated in black) glucose metabolism, as well as severe hypometabolism in the bilateral medial prefrontal cortex. This pattern suggests a widespread impairment of cortical areas that normally exert an inhibitory influence to subcortical aggressive impulses. Bilateral involvement of both lateral and medial temporal structures is typically associated with autistic rather than aggressive phenotype

A different pattern of bitemporal hypometabolism has been recently linked to interictal aggressive behavior in children with temporal lobe epilepsy (51). In this group of patients with severe impulsive-aggressive behavioral abnormalities, bitemporal hypometabolism was confined to the temporal neocortex, preserving the medial temporal (limbic) structures (Fig. 7). Bilateral medial prefrontal hypometabolism was also a common finding, and severity of temporal cortical hypometabolism correlated well with the severity of aggression. These findings indicated a widespread dysfunction of neocortical areas, which normally exert an inhibitory effect on subcortical aggressive impulses. The results suggest that early dysfunction of temporal neocortex (sometimes accentuated by medial prefrontal impairment) plays a prominent role in the manifestation of aggressive behavior in children with epilepsy. If such neocortical dysfunctions are associated with hippocampal/amygdala dysfunction, the patients show autistic rather than aggressive features.

6. New directions in PET imaging of epilepsy

The above discussed studies demonstrate the potential of PET scanning in detecting and delineating not only epileptogenic brain regions, but also providing a comprehensive insight in functional abnormalities of the entire epileptic brain. Recent developments of novel PET tracers continue to add to this knowledge. One of the promising directions in PET scanning of epilepsy is imaging tryptophan metabolism and serotonergic mechanisms. *In vitro* observations showing increased serotonin (5HT) content and immunoreactivity in human epileptic tissue (77, 93) have led to the application of the PET tracer $\alpha[^{11}C]$methyl-L-tryptophan (AMT) to the study of epilepsy. AMT PET soon became an excellent imaging method to differentiate between epileptogenic and non-epileptogenic lesions in children with multifocal lesions (e.g., tuberous sclerosis (10) or multifocal cortical dysplasia), by specifically showing increased uptake of AMT in the epileptogenic region(s) (Fig. 8).

The basis for increased AMT uptake in epileptogenic cortex is not completely clear. AMT can be converted in the brain to α-$[^{11}C]$methyl-serotonin, which is not a substrate for the degradative enzyme monoamine oxidase, and therefore accumulates in serotonergic terminals. Local increase of serotonin synthesis may serve as a compensatory mechanism to decrease cortical excitability and prevent seizures. In fact, serotonin was shown to inhibit epileptiform activity in rat CA1 neurons by acting on the $5\text{-}HT_{1A}$ receptor subtypes (79). Further, it has been long known that electrical stimulation of the raphe, resulting in serotonin release, can inhibit kindled seizures in the amygdala (58, 80). Studies on surgically resected tissues from patients with tuberous sclerosis, however, have shown that, at least in some cases, increased *in vivo* uptake of AMT may be also due to an increased synthesis of quinolinic acid (11), a product of tryptophan metabolism via the kynurenine pathway. This pathway, under normal circumstances, accounts for only a very small fraction of tryptophan metabolism in brain. Quinolinic acid has a strong convulsant effect through its action as an agonist at

NMDA receptors, and may play a key role in intractable seizures in these children. Recent studies have shown focally increased AMT uptake in electrographically proven epileptogenic cortical regions even when MRI and/or FDG PET scan are non-localizing or normal (53).

In addition to using AMT for evaluating serotonin (5-HT) synthesis and tryptophan metabolism via the kynurenine pathway, an emerging method is to image 5-HT receptors by PET. Studies in temporal lobe epilepsy have found that [^{18}F]FCWAY, a selective 5-HT$_{1A}$ receptor antagonist, shows decreased receptor binding in the medial and lateral temporal lobe ipsilateral to the seizure onset (92). These decreases surpassed the degree of concomitant glucose hypometabolism and blood flow decrease in the affected regions, suggesting specific loss of 5-HT$_{1A}$ receptors in the epileptogenic temporal lobe. In addition, [^{18}F]FCWAY uptake was lower in raphe and also in the ipsilateral thalamic region of patients than controls. Another group of investigators have also reported significant 5-HT$_{1A}$ receptor changes in patients with malformations of cortical development, involving the malformed area as well as other cortical and subcortical regions, including the raphe nuclei (24). This latter finding would be consistent with a subcortical modulation of the serotonergic system in epileptic patients.

Application of functional neuroimaging can be further enhanced by multimodality imaging, e.g., by combining high resolution MRI, MRSI, fMRI and PET data. Multimodality imaging can provide complementary information regarding epileptogenic and functional deficit zones of the epileptic circuitry. Combination of structural, metabolic, electrophysiological and neuroreceptor data is a powerful way of applying clinical neuroimaging, and such studies will continue to provide further details on the pathophysiological aspects of human epilepsy.

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