Published in final edited form as:

Biomark Med. 2011 October ; 5(5): 577–584. doi:10.2217/bmm.11.68.

α -[¹¹C]-methyl-L-tryptophan PET for tracer localization of epileptogenic brain regions: clinical studies

Ajay Kumar^{1,2}, Eishi Asano^{1,3}, and Harry T Chugani^{1,2,†}

¹Departments of Pediatrics & Neurology, Children's Hospital of Michigan, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI, USA

²Positron Imaging Center, Children's Hospital of Michigan, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI, USA

³Department of Electroneurodiagnostics, Children's Hospital of Michigan, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI, USA

Abstract

Of several molecular probes used in PET, only α -[¹¹C]-methyl-L-tryptophan (AMT) is able to pinpoint the epileptic focus itself in the interictal state, by revealing a focus of increased AMT uptake, even when an MRI or glucose metabolism PET demonstrates normal findings. AMT PET appears to be particularly useful in patients with tuberous sclerosis complex and in patients with cortical developmental malformations. Although the sensitivity of AMT PET in finding the epileptic focus is about 70%, its specificity is almost 100%, indicating that if AMT PET identifies an area of increased uptake, it likely represents the epileptic focus which needs to be resected for better surgical outcome. In nontuberous sclerosis complex patients with cortical dysplasia, increased AMT uptake is usually associated with cortical dysplasia type IIB and a very good surgical outcome. Previously, no imaging modality has been able to predict the exact pathology subtype or differentiate between epileptogenic and nonepileptogenic lesions interictally. The neuropathological similarities between tubers and type IIB cortical dysplasia suggest a common mechanism of epilepsy, for which AMT PET is a biomarker. Due to the limited access to AMT PET, as presently it is labeled with ¹¹C, which has a half-life of only 20 min and therefore has to be synthesized on site using a cyclotron, most of the AMT experience has originated primarily from only two centers. Therefore, there is a need for more clinical studies from other centers and this can be greatly facilitated if AMT can be labeled with ¹⁸F, a PET radionuclide widely available with a half-life of 110 min.

Keywords

α -methyl tryptophan; cortical dysplasia; developmental cortical malformations; epilepsy; PET; tuberous sclerosis

Almost 25% of people with epilepsy develop refractory seizures [1–3] and can benefit from epilepsy surgery, as this may lead to better social, psychological and cognitive development,

© 2011 Future Medicine Ltd

[†]Author for correspondence: Children's Hospital of Michigan, 3901 Beaubien Blvd, Detroit, MI 48201, USA, Tel.: +1 313 993 2605, Fax: +1 313 745 0955, hchugani@pet.wayne.edu.

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

particularly in children [4]. However, epilepsy surgery is often delayed or not possible in a large number of these patients due to difficulty in accurate presurgical localization of the epileptogenic zone. PET has little localization role in cases where MRI-visible structural lesions are concordant with electrophysiological and clinical data. However, in cases of discordant results, or normal MRI, or multiple lesions with inconclusive EEG, PET can play a very important role. In cases of multifocal lesions associated with partial seizures demonstrating a consistent semiology, the goal of PET (using selected radiotracers) is to identify the epileptogenic lesions. Sometimes, the epileptogenic lesion may be medially located and be associated with generalized epileptiform activity due to secondary bilateral synchrony. In such cases, PET may allow a surgical option when otherwise the patient may not be considered for surgery.

One of the several PET tracers (Table 1), used in epilepsy to provide an accurate assessment of the brain regions to be resected in order to achieve seizure freedom, is α -[^{11}C]-methyl-L-tryptophan (AMT), which traces the tryptophan metabolism via serotonin and/or kynurenine pathways. AMT can pinpoint the epileptic focus in the interictal state by revealing a focus of increased AMT uptake. This is in contrast to other more commonly used radiotracers, such as 2- ^{18}F -fluoro-2-deoxy-D-glucose (FDG) or ^{11}C -flumazenil, which usually demonstrate a larger area of decreased radiotracer uptake or binding associated with epileptogenic regions. The increased AMT signal is also easier to interpret visually and can circumvent the interpretation difficulties associated with both visual and voxel-based analyses of decreased signal, caused by partial volume effects when focal atrophy is present in the epileptogenic region. Furthermore, increased AMT uptake is not affected by recent seizure activity or frequent interictal spiking on the scalp EEG [5,6], making it convenient to perform, without any need for EEG monitoring. The mechanisms of increased AMT uptake in the epileptic focus are discussed in detail in an article by Chugani in this issue of *Biomarkers in Medicine* [7]. The present article will discuss the clinical role of AMT PET in the surgical evaluation of epilepsy.

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by hamartomas in various organs including the brain. Epilepsy is the most common neurologic presentation of TSC, present in more than 90% of cases [8,9]. The mechanisms of epileptogenesis in TSC are not fully understood, but it is likely that the tuber and associated cortical dysplasia participate in the pathogenesis of seizures [10,11]. Seizures become refractory in approximately 60% of cases [8] and may result in an epileptic encephalopathy and poor cognitive outcome, particularly in young children. Therefore, an aggressive treatment approach including consideration of all possible therapeutic options is desirable in these children. Despite the presence of multifocal tubers scattered throughout the brain, surgery should also be an early consideration, as not all cortical tubers are epileptogenic and seizure-freedom can be achieved after selective resection of the epileptogenic tubers [12–16]. However, identifying the epileptogenic tuber(s) among multiple brain tubers is challenging, as most of the patients demonstrate multifocal epileptiform abnormalities on scalp EEG. Although MRI can delineate the number and locations of tubers in great detail, it cannot identify the epileptogenic tubers. FDG PET demonstrates hypometabolism in tubers, both epileptic and nonepileptic, believed to be caused by the decreased number of neurons and simplified dendritic pattern in the tubers [17,18]; thus, it is not very useful for selecting the epileptogenic tuber. In some cases, ictal single photon emission computed tomography may identify an epileptic tuber [19]; however, the seizures in TSC are often quite brief and not ideally suited for ictal single photon emission computed tomography studies. Consequently, many patients are denied surgical treatment because of insufficient localizing data. AMT PET appears to be helpful and promising in these patients [13,20–22]. AMT PET

is unique in that it can differentiate epileptogenic from nonepileptogenic tubers, demonstrating increased AMT uptake interictally in only epileptogenic tubers [20,21]. It can be particularly useful in patients with bilateral EEG changes caused by a medial location of the epileptogenic tuber (Figure 1) or deeply located tubers giving rise to diffuse or no EEG changes on scalp EEG (Figure 2).

α -[^{11}C]-methyl-L-tryptophan PET can identify epileptogenic tuber(s) in almost two thirds of children with tuberous sclerosis and intractable epilepsy [13,20–22]. In contrast, the specificity of AMT PET is very high, at almost 100%. Kagawa *et al.* reported that a cutoff threshold of AMT uptake ratio of 1.03 (i.e., at least 3% higher AMT uptake in tubers compared with normal cortex) results in a sensitivity of 74% and a specificity of 100% with an accuracy of 82% for detecting epileptogenic tubers as defined by seizure-free outcome [13]. It appears that the tuber with the highest AMT uptake is always located in a region of ictal EEG onset and all tubers with at least 10% increase in AMT uptake are epileptogenic [13,20]. This demonstrates that AMT is an accurate biomarker for the epileptic focus in TSC. The 50–70% sensitivity of AMT PET in identifying the epileptogenic tuber appears to be related to the method of image analysis. One study reported that the MRI-based quantitative assessment can increase the sensitivity of AMT PET to 77% [13]. This apparent discrepancy is due to the fact that nonepileptogenic tubers typically demonstrate decreased AMT uptake, and that some epileptogenic tubers showing relatively increased AMT uptake cannot be easily differentiated from adjacent normal cortex without quantitative analysis. Occasionally, more than one tuber may be observed with increased AMT uptake; however, in such cases, usually the tuber with the highest AMT uptake ratio appears to have the best correlation with the ictal EEG [13]. It is possible that tubers with an intermediate AMT uptake ratio may evolve eventually into epileptogenic ones, but this remains to be demonstrated and needs further investigation.

α -[^{11}C]-methyl-L-tryptophan PET has also increased our understanding of the neurobehavioral characteristics of TSC, which include autism, attention deficit hyperactivity disorder and cognitive impairment. AMT PET, along with FDG PET, has suggested a role of both cortical and subcortical dysfunction in the pathophysiology of autism in TSC [23]. Increased AMT uptake in the caudate nucleus has been found to be related to stereotypical behavior, impaired social interaction as well as communication disturbance [23]. Another study, using both AMT and FDG PET, found that children with cerebellar lesions had higher autistic features overall [24]. Furthermore, children with right-sided cerebellar lesions were found to have higher social isolation and communicative and developmental disturbances compared with those with left cerebellar lesions, suggesting a crucial role played by the cerebellum in autistic symptomatology.

Cortical developmental malformations

Increased AMT uptake may be observed in patients with developmental brain malformations, and can localize the epileptic focus interictally in one fourth of patients with nonlocalizing MRI (Figure 3) [5,6,25]. This may have particular relevance and implication for the pediatric population, who usually have a higher incidence of cortical developmental malformations compared with adults presenting for surgery. For these patients, the best postoperative outcome is expected when a MRI-visible cortical lesion is consistent with the ictal EEG focus, and can be completely resected [26,27]. However, high-resolution MRI can identify a structural lesion in only 60–90% of patients with intractable focal epilepsy [28]. The remaining patients often demonstrate subtle malformations of cortical development on neuropathologic studies and these are the patients who can benefit most from the AMT PET scan. Fedi *et al.* found increased AMT uptake, corresponded to the epileptogenic area, in four out of seven patients with cortical dysplasia and intractable partial epilepsy, in whom

conventional MRI and FDG PET had failed to detect any abnormality [25]. Subsequently, Juhász *et al.* reported increased AMT uptake in eight out of ten patients with histopathologically confirmed cortical developmental malformations [5]. They also found that the areas of AMT PET abnormalities were typically smaller than the FDG PET hypometabolism, and AMT PET could detect epileptogenic regions missed by both MRI and FDG PET [5]. Like in tuberous sclerosis, AMT PET scan appears to be highly specific (97%) but only moderately sensitive (47%) in identifying seizure onset lobe in patients with intractable neocortical epilepsy and malformations of cortical development [6]. Contrary to Fedi *et al.*, who found a correlation between AMT uptake and frequency of interictal spikes during AMT PET scan in a small number of patients (n = 15) [22,25], Juhász *et al.* [5] and Wakamoto *et al.* [6] did not find such correlation in relatively larger patient cohorts (n = 17 and 52, respectively). In fact, they both reported very high AMT uptake in several patients with very low spike frequency. Furthermore, looking at the scatter plot between AMT uptake and spike frequency, as published by Fedi *et al.*, the mild correlation appeared to be driven by only one out of eight patients [22]. Therefore, it appears that the AMT uptake is not affected by interictal spiking during AMT PET scan, thus avoiding the need for continuous EEG monitoring during AMT PET scan, making it more convenient to perform.

Increased AMT uptake can be observed in different types of cortical developmental malformations. Although Natsume *et al.* did not find increased AMT uptake in four patients with periventricular nodular heterotopias [29], increased AMT uptake was reported in patients with focal cortical dysplasia, subependymal heterotopia, congenital perisylvian syndrome and polymicrogyria [6,30]. Although these different malformations can be classified into three different categories of cerebral malformations, depending on the interrupted developmental stage during fetal life, these major developmental steps are not temporally separate. Cellular proliferation continues after neuronal migration begins, and neuronal migration continues as cortical organization commences [31] and therefore, it is not surprising that the affected patients share some common epileptic mechanisms related to increased AMT uptake in various forms of cortical developmental malformations. Among all these malformations, AMT uptake appears to be significantly higher in cases of cortical dysplasia compared with other malformations [6,30]. Subsequently it has been demonstrated that increased AMT uptake is more specific to cortical dysplasia type IIB, which is associated with balloon cells and a good surgical outcome (Figure 3) [30]. This finding is not surprising considering the histopathological similarities between cortical dysplasia type IIB and epileptogenic cortical tubers, which also contain a large number of balloon cells and may imply a common role of the inflammatory kynurenine pathway of tryptophan metabolism in seizure generation in these lesions, for which AMT PET is a biomarker (discussed in detail in [7])

Increased AMT uptake may sometimes be observed in apparently normal cortex, evidenced by either normal MRI or both normal MRI and normal postsurgical histopathology [5,6,25,30], and it appears that the patients with increased AMT uptake but normal MRI and histopathology may have poor surgical outcome [30]. Although reasons for increased AMT uptake in this subgroup of patients are not clear, it may be related to genetic disorders such as channelopathies presenting with focal epilepsies.

Surgical failure

When epilepsy surgery fails to provide substantial relief from seizures, reoperation may be considered in some cases. However, accurate identification of residual epileptogenic cortex becomes even more challenging following an initial resection. Interpretation of ictal scalp EEG is difficult due to alterations in the original brain anatomy as well as effects of skull and dural scarring. The current imaging modalities have serious limitations. The usefulness

of MRI is reduced by the above mentioned reasons or if epilepsy was cryptogenic to start with, and FDG PET typically reveals large areas of hypometabolism, most of which may be consequent to surgical tissue damage or diaschisis from deafferentation. Ictal single photon emission computed tomography and magnetic source imaging may be useful in some cases, but again may be hard to interpret. AMT PET appears to be useful for the detection of residual epileptogenic cortex in some of these patients (Figure 4). In a study involving 33 patients with failed previous neocortical resection, it was found that, if performed at least 2 months after the surgery, AMT PET can detect epileptic foci in almost 30% of cases, corroborated by ictal EEG and good surgical outcome in all of these patients (seizure freedom or considerable improvement) [32]. Although limited by small number and a modest sensitivity, this study demonstrated that AMT PET can identify nonresected epileptogenic cortex in patients with a previously failed neocortical epilepsy surgery and can assist in planning reoperation.

Postoperative AMT PET scans have also provided some new insights into brain plasticity following cortical resection for epilepsy. Following removal of epileptic brain tissue, AMT uptake in the ipsilateral lentiform nucleus is increased compared with the contralateral side, suggesting functional reorganization of cortical–striatal projections associated with increased serotonin expression [33]. This phenomenon appears to be time-related, as more intense AMT uptake was found during the early periods after surgery and, interestingly, does not appear to be driven by the extent of surgical resection.

Conclusion

The concept that a neuroimaging technique can differentiate between epileptogenic and nonepileptogenic lesions in the brain, or that it can pinpoint an epileptic focus interictally, is novel and intriguing. Yet, it should not come as a surprise, since the chemical milieu in the epileptic focus must be different from the rest of the brain and it should only take an appropriate chemical probe to highlight the focus. The neuropathological similarities between cortical tubers and cortical dysplasia type IIB and the observation that both these epileptic lesions manifest increased AMT uptake suggest a common mechanism of epileptogenicity for which AMT PET is a biomarker. This mechanism involves induction of the kynurenine pathway of tryptophan metabolism, which is probably only one of many possible biochemical pathways leading to epilepsy. These observations bring to light the likelihood that other biochemical disturbances associated with epilepsy might also be imaged using the appropriate molecular probe to yield suitable biomarkers.

Limitations & future perspective

α -[^{11}C]-methyl-L-tryptophan PET is not only a valuable tool in the surgical management of intractable epilepsy, but can also play a very important role in advancing our knowledge of the basic mechanisms of epileptic disorders. Unfortunately, although PET scanners are now widely available, few centers have access to AMT and therefore, most of the experience and information concerning the role of AMT PET has primarily originated from only two centers. One reason for this is that AMT is labeled with ^{11}C , which has a half-life of only 20 min and therefore has to be synthesized on site using a cyclotron. AMT would be much more readily available if it could be labeled with ^{18}F , which has a half-life of 110 min, allowing it to be transported as in the case of FDG. This effort is underway at a few centers, including ours, which hopefully will facilitate more widespread use and independent validation of the usefulness of this tracer by different centers. Another disadvantage is the relatively low sensitivity despite the high specificity. This issue can be addressed by developing PET probes with similar mechanism but higher avidity for the epileptic focus or epileptogenic regions, or other alternative molecular probes to image other biochemical

disturbances, thought to be underlying epileptic processes. This will not only enable us to understand better the pathomechanisms behind different epilepsy subtypes, but will also lead to the eventual development of more specific therapeutic interventions.

Executive summary

- α -[^{11}C]-methyl-L-tryptophan (AMT), which traces the tryptophan metabolism via serotonin and/or kynurenine pathways, can pinpoint the epileptic focus in the interictal state by revealing a focus of increased AMT uptake, even when the MRI or glucose metabolism PET scans are normal. AMT PET is, therefore, unique in that it is an important biomarker of the epileptic focus itself.
- AMT PET is particularly useful in patients with tuberous sclerosis complex and in patients with cortical developmental malformations.
- AMT PET is the only PET tracer capable of differentiating epileptogenic from nonepileptogenic lesions in the interictal state in patients with tuberous sclerosis by showing increased AMT uptake in the epileptogenic tubers.
- Increased AMT uptake can be observed in different types of cortical developmental malformations, including focal cortical dysplasia, periventricular heterotopia, congenital perisylvian syndrome and polymicrogyria.
- In nontuberous sclerosis complex patients with cortical dysplasia, increased AMT uptake is usually associated with cortical dysplasia type IIB and a very good surgical prognosis. Never before has an imaging modality been able to predict exact pathology subtype.
- AMT PET can identify nonresected epileptogenic cortex in patients with a previously failed neocortical epilepsy surgery and can assist in planning reoperation.
- Postoperative AMT PET scans can also provide some new insights into brain plasticity following cortical resection for epilepsy.

Acknowledgments

Some of the work discussed in this article was supported by grants from the NIH to H Chugani (R01-NS34488, R01-NS064989) and E Asano (K23-047550, R01-064033).

Bibliography

Papers of special note have been highlighted as:

- of interest
 - of considerable interest
1. Arroyo S. [Evaluation of drug-resistant epilepsy] [Article in Spanish]. *Rev. Neurol.* 2000; 30(9): 881–886. [PubMed: 10870204]
 2. Guerrini R, Sicca F, Parmeggiani L. Epilepsy and malformations of the cerebral cortex. *Epileptic Disord.* 2003; 5 Suppl. 2:S9–S26. [PubMed: 14617417]
 3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N. Engl. J. Med.* 2000; 342(5):314–319. [PubMed: 10660394]

4. Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: state of the art, Part I: General principles and presurgical workup. *Eur. J. Paediatr. Neurol.* 2009; 13(2):102–114. [PubMed: 18692417]
5. Juhász C, Chugani DC, Muzik O, et al. α -methyl-L-tryptophan PET detects epileptogenic cortex in children with intractable epilepsy. *Neurology.* 2003; 60(6):960–968. [PubMed: 12654960]
6. Wakamoto H, Chugani DC, Juhász C, Muzik O, Kupsky WJ, Chugani HT. α -methyl-L-tryptophan positron emission tomography in epilepsy with cortical developmental malformations. *Pediatr. Neurol.* 2008; 39(3):181–188. [PubMed: 18725063] . • This study, in a large number of pediatric patients with intractable epilepsy, demonstrated that α -methyl-L-tryptophan (AMT) PET can be very useful in children with malformations of cortical development and if a focus of increased AMT uptake is detected, it likely represents the epileptogenic region to be resected.
7. Chugani DC. α -methyl-L-tryptophan: mechanisms for tracer localization of epileptogenic brain regions. *Biomarkers Med.* 2011; 5(5):567–575.
8. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia.* 2010; 51(7):1236–1241. [PubMed: 20041940]
9. Jozwiak S, Schwartz RA, Janniger CK, Bielicka-Cymerman J. Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. *J. Child Neurol.* 2000; 15(10):652–659. [PubMed: 11063078]
10. Crino PB. Molecular pathogenesis of tuber formation in tuberous sclerosis complex. *J. Child Neurol.* 2004; 19(9):716–725. [PubMed: 15563019]
11. Uhlmann EJ, Wong M, Baldwin RL, et al. Astrocyte-specific TSC1 conditional knockout mice exhibit abnormal neuronal organization and seizures. *Ann. Neurol.* 2002; 52(3):285–296. [PubMed: 12205640]
12. Jansen FE, Van Huffelen AC, Algra A, Van Nieuwenhuizen O. Epilepsy surgery in tuberous sclerosis: a systematic review. *Epilepsia.* 2007; 48(8):1477–1484. [PubMed: 17484753]
13. Kagawa K, Chugani DC, Asano E, et al. Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with α -[1 C]-methyl-L-tryptophan positron emission tomography (PET). *J. Child Neurol.* 2005; 20(5):429–438. [PubMed: 15971355] . •• Demonstrates that AMT PET can identify epileptogenic tuber(s) in almost two thirds of children with tuberous sclerosis and intractable epilepsy, and a cutoff threshold of AMT uptake ratio of 1.03 (i.e., at least 3% higher AMT uptake in tubers compared with normal cortex) results in a sensitivity of 74% and a specificity of 100%, with an accuracy of 82% for detecting epileptogenic tubers as defined by seizure-free outcome.
14. Teutonico F, Mai R, Devinsky O, et al. Epilepsy surgery in tuberous sclerosis complex: early predictive elements and outcome. *Childs Nerv. Syst.* 2008; 24(12):1437–1445. [PubMed: 18704447]
15. Weiner HL, Carlson C, Ridgway EB, et al. Epilepsy surgery in young children with tuberous sclerosis: results of a novel approach. *Pediatrics.* 2006; 117(5):1494–1502. [PubMed: 16651302]
16. Wu JY, Salamon N, Kirsch HE, et al. Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex. *Neurology.* 2010; 74(5):392–398. [PubMed: 20124204]
17. Rintahaka PJ, Chugani HT. Clinical role of positron emission tomography in children with tuberous sclerosis complex. *J. Child Neurol.* 1997; 12(1):42–52. [PubMed: 9010795]
18. Szelies B, Herholz K, Heiss WD, et al. Hypometabolic cortical lesions in tuberous sclerosis with epilepsy: demonstration by positron emission tomography. *J. Comput. Assist. Tomogr.* 1983; 7(6):946–953. [PubMed: 6415136]
19. Koh S, Jayakar P, Resnick T, Alvarez L, Liit RE, Duchowny M. The localizing value of ictal SPECT in children with tuberous sclerosis complex and refractory partial epilepsy. *Epileptic Disord.* 1999; 1(1):41–46. [PubMed: 10937131]
20. Asano E, Chugani DC, Muzik O, et al. Multimodality imaging for improved detection of epileptogenic foci in tuberous sclerosis complex. *Neurology.* 2000; 54(10):1976–1984. [PubMed: 10822440] . • Evaluated various neuroimaging modalities, such as MRI, 2- 18 F-fluoro-2-deoxy-D-glucose PET and AMT PET together and demonstrated that cortical tubers with AMT uptake greater than or equal to normal cortex are significantly related to epileptiform activity in that lobe.

21. Chugani DC, Chugani HT, Muzik O, et al. Imaging epileptogenic tubers in children with tuberous sclerosis complex using α -[^{11}C]methyl-l-tryptophan positron emission tomography. *Ann. Neurol.* 1998; 44(6):858–866. [PubMed: 9851429] . •• AMT PET is the only PET tracer capable of differentiating epileptogenic from nonepileptogenic lesions in the interictal state in patients with tuberous sclerosis by demonstrating increased AMT uptake in the epileptogenic tubers.
22. Fedi M, Reutens DC, Andermann F, et al. α -[^{11}C]methyl-l-tryptophan PET identifies the epileptogenic tuber and correlates with interictal spike frequency. *Epilepsy Res.* 2003; 52(3):203–213. [PubMed: 12536053]
23. Asano E, Chugani DC, Muzik O, et al. Autism in tuberous sclerosis complex is related to both cortical and subcortical dysfunction. *Neurology.* 2001; 57(7):1269–1277. [PubMed: 11591847]
24. Eluvathingal TJ, Behen ME, Chugani HT, et al. Cerebellar lesions in tuberous sclerosis complex: neurobehavioral and neuroimaging correlates. *J. Child Neurol.* 2006; 21(10):846–851. [PubMed: 17005099]
25. Fedi M, Reutens D, Okazawa H, et al. Localizing value of α -methyl-l-tryptophan PET in intractable epilepsy of neocortical origin. *Neurology.* 2001; 57(9):1629–1636. [PubMed: 11706103] . • Demonstrated the potential usefulness of AMT PET in delineating epileptogenic area in patients with cortical dysplasia and intractable epilepsy.
26. Sisodiya SM. Surgery for malformations of cortical development causing epilepsy. *Brain.* 2000; 123(Pt 6):1075–1091. [PubMed: 10825348]
27. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P. Seizure outcome after epilepsy surgery in children and adolescents. *Ann. Neurol.* 1998; 44(5):740–748. [PubMed: 9818929]
28. Bingaman, WE.; Cataltepe, O. Epilepsy surgery for focal malformation of cortical development. In: Luders, HO.; Comair, YG., editors. *Epilepsy Surgery*. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2001.
29. Natsume J, Bernasconi N, Aghakhani Y, et al. α -[^{11}C]methyl-l-tryptophan uptake in patients with periventricular nodular heterotopia and epilepsy. *Epilepsia.* 2008; 49(5):826–831. [PubMed: 18363710]
30. Chugani HT, Kumar A, Kupsky W, Asano E, Sood S, Juhász C. Clinical and histopathologic correlates of ^{11}C - α -methyl-l-tryptophan (AMT) PET abnormalities in children with intractable epilepsy. *Epilepsia.* 2011; 52(9):1692–1698. [PubMed: 21569023] . •• Reported, for the first time, that in nontuberous sclerosis complex patients with cortical dysplasia, increased AMT uptake is usually associated with cortical dysplasia type IIB and a very good surgical prognosis. Previously no imaging modality had been able to predict the exact pathology subtype. The concept that molecular neuroimaging can be so specific for a particular histopathological subtype is intriguing and opens up the possibility that other types of histopathology can be predicted noninvasively with preoperative neuroimaging.
31. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. *Neurology.* 2005; 65(12):1873–1887. [PubMed: 16192428]
32. Juhász C, Chugani DC, Padhye UN, et al. Evaluation with α -[^{11}C]methyl-l-tryptophan positron emission tomography for reoperation after failed epilepsy surgery. *Epilepsia.* 2004; 45(2):124–130. [PubMed: 14738419]
33. Chugani HT, Juhász C, Chugani DC, et al. Increased striatal serotonin synthesis following cortical resection in children with intractable epilepsy. *Epilepsy Res.* 2008; 78(2–3):124–130. [PubMed: 18083006]

Figure 1. Usefulness of α -methyl-L-tryptophan PET in tuberous sclerosis patients with nonlateralizing EEG

(A) Fluid attenuated inversion recovery MRI showing a large tuber in the right sensorimotor cortex near midline (purple arrow), in a 5-year-old male child with tuberous sclerosis, intractable seizures and bilateral epileptiform activity on scalp EEG. Also seen are multiple small tubers, bilaterally (small red arrows). (B) α -methyl-L-tryptophan (AMT) PET scan showing increased AMT uptake only in the large right tuber, which was hypometabolic on 2- 18 F-fluoro-2-deoxy-D-glucose PET scan (C). All other small tubers are showing decreased AMT and 2- 18 F-fluoro-2-deoxy-D-glucose uptake (small red arrows). (D) Coregistration of AMT PET and intracranial electrodes (red circles: seizure onset; white circles: no seizure activity) on a 3D rendered brain MRI showing seizure onset (E) from the region of this large right tuber with increased AMT uptake (purple arrow). Close proximity to the midline was the likely reason for bilateral synchrony on scalp EEG. The patient underwent resective surgery, including this epileptogenic tuber, with a good surgical outcome.

Lt: Left; Rt: Right.

Figure 2. Localization of epileptic focus in a tuberous sclerosis complex patient with lateralizing but nonlocalizing EEG

(A) Fluid attenuated inversion recovery MRI, (B) 2-¹⁸F-fluoro-2-deoxy-D-glucose PET and (C) α-methyl-L-tryptophan PET in a 3-year-old female child with tuberous sclerosis and intractable seizures. MRI and 2-¹⁸F-fluoro-2-deoxy-D-glucose PET showed multiple tubers, scattered throughout the brain, with diffuse nonfocal EEG changes over the left hemisphere on scalp EEG. α-methyl-L-tryptophan PET scan revealed increased α-methyl-L-tryptophan uptake in the left inferior frontal region at the periphery of a large left inferior frontal tuber (arrows), adjacent (lateral) to the left caudate nucleus and buried inside the left sylvian fissure.

Lt: Left; Rt: Right.

Figure 3. α -methyl-L-tryptophan PET predicts histopathology in a child with molecular coincidence detection of epileptogenic focus by α -methyl-L-tryptophan PET in patients with cortical dysplasia and intractable seizures

(A) α -methyl-L-tryptophan PET scan showing increased tracer uptake in left parietal lobe in an 8-year-old girl with intractable seizures and (B) normal MRI. (C) Postsurgical histopathology revealed cortical dysplasia type IIB with balloon cells (magnification 25 $\times$, hematoxylin and eosin stain). The child remained seizure free for 7 years after surgery.

Figure 4. Role of α -methyl-L-tryptophan PET in patients with failed epilepsy surgery
(A) α -methyl-L-tryptophan PET scan showing a focal area of increased α -methyl-L-tryptophan uptake posterior to the surgical margin in the right frontal area in a 3.5-year-old boy with failed epilepsy surgery. All other imaging investigations, including (B) spoiled gradient echo MRI and 2- ^{18}F -fluoro-2-deoxy-D-glucose PET (not shown here) were noncontributory.
Lt: Left; Rt: Right.

Table 1

Mechanism of uptake/binding pattern of various PET tracers in epileptogenic foci.

PET tracer	Mechanism/target	Uptake/binding pattern in epileptogenic foci
FDG	Glucose metabolism	Interictal decrease Ictal increase
¹⁵ O-H ₂ O (water)	Blood flow	Interictal decrease Ictal increase
AMT	Tryptophan metabolism to serotonin or quinolinic acid	Interictal increase [†]
FMZ	GABA _A /benzodiazepine receptor (antagonist)	Interictal decrease
¹¹ C-PK11195	Peripheral benzodiazepine receptor (antagonist)	Increased
¹¹ C-(S)-[N-methyl]-ketamine	NMDA receptor (antagonist)	Decreased
¹¹ C-L-deprenyl	MAO-B (inhibitor)	Increased
¹¹ C-doxepin	H ₁ receptor (antagonist)	Increased
¹¹ C/ ¹⁸ F-FCWAY	5HT _{1A} receptor (antagonist)	Decreased
¹⁸ F-MPPF	5HT _{1A} receptor (antagonist)	Decreased
¹⁸ F-altanserin	5HT _{2A} receptor (antagonist)	Decreased
¹¹ C-carfentanyl	μ-opioid receptor (agonist)	Increased
¹¹ C-methylnaltrindole	δ-opioid receptor (antagonist)	Increased
¹⁸ F-cyclofoxy	μ,κ-opioid receptor (antagonist)	Increased
¹¹ C-diprenorphine	μ,δ,κ-opioid receptor (antagonist)	Decreased
¹¹ C-NMPB	mACh receptor (antagonist)	Decreased
¹²³ I-iododexetimide	mACh receptor (antagonist)	Decreased

[†] AMT is the only tracer that can delineate and identify the 'epileptic focus' in the 'interictal' state in patients with tuberous sclerosis.

Ach: Acetylcholine; AMT: ¹¹C-α-methyl-L-tryptophan; FCWAY: Trans-4-fluoro-N-2-[4-(2-methoxyphenyl) piperazin-1-yl] ethyl-N-(2-pyridyl) cyclohexanecarboxamide; FDG: 2-¹⁸F-fluoro-2-deoxy-D-glucose; FMZ: ¹¹C-flumazenil; H: Histamine; HT: Hydroxytryptamine; MAO-B: Monoamine oxidase-B; MPPF: 4-(2-methoxyphenyl)-1-[2-(N-2"-pyridinyl)-p-fluorobenzamido] ethylpiperazine; NMDA: N-methyl-D-aspartic acid; NMPB: 4-N-methylpiperidiny benzilate; PK11195: 1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide.