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Making the Case for Brain ^{18}F-FDG PET Subtraction in Medically Refractory Epilepsy. A Novel, Useful Tool. Practical Points?

Mehdi Djekidel MD

Running Title: Brain PET subtraction with FDG.

Corresponding author:

Dr Mehdi Djekidel

QMC. Michigan. USA.

Email: mehdjeki@gmail.com

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^{18}F-FDG PET plays a major role in the pre-surgical evaluation of medically refractory epilepsy patients. The current standard of care is performing interictal evaluations of glucose metabolism. This is mostly related to the tracer kinetics of ^{18}F-FDG owing to a long uptake phase which would translate into ictal injections having low sensitivities and low specificity and demonstrating not only ictal but post-ictal changes. It has been reported that this limitation can be overcome in some status epilepticus scenarios where prolonged seizures can then correlate better with ^{18}F-FDG uptake kinetics. In these cases, focal visual qualitative hot spots are suggestive of the seizure onset zone (SOZ). However, we note that by using advanced subtraction techniques, the prolonged ^{18}F-FDG uptake phase can be overcome in a variety of other cases as well. This opens the door to a slightly larger set of patients that may benefit from this higher resolution PET method. We present 4 cases where a novel subtraction ^{18}F-FDG PET technique was used and elucidate its impact in these specific cases.

<u>Introduction</u>:

About one third of epilepsy patients are resistant or not well controlled on multiple medications (*1-5*). This subset of medically refractory patients may have improved outcomes with surgery (*1,4-6*). Surgical success requires accurate delineation of the SOZ. Imaging plays a major role with MRI, SPECT and PET being essential elements of the work-up (*1,7*). Current nuclear medicine standard of care for PET (*1,2,5-8*) is to image patients interictally since the long uptake phase of ^{18}F-FDG in contrast to the short duration of seizures limits evaluation of the ictal phase (*8-11*). On the other hand, ictal PET has been reported in status epilepticus scenarios where prolonged seizures can correlate better with slow ^{18}F-FDG uptake kinetics (*12*). In these cases, focal visual qualitative hot spots are suggestive of the seizure onset zone (SOZ) (*12*). Additionally, subtraction Ictal-Interictal ^{99m}Tc-HMPAO or ^{99m}Tc-ECD SPECT not PET is used successfully in select cases owing to the very short uptake phase -a few seconds- of the cerebral blood flow SPECT radiopharmaceuticals (*9-11,13*). We propose to outline the benefit of using advanced imaging subtraction techniques with ^{18}F-FDG PET. Subtraction is defined as two time points and these can be represented by the ictal-interictal time points or two different ictal or interictal phases along the continuum of the patient's disease including during the pre and postoperative period as well as during and following a brain insult such as encephalitis or other. Advanced semiquantitative or processing techniques are essential tools in the nuclear medicine epilepsy practice.

Using advanced techniques allows not only to understand the seizure onset zone but also uncover propagation pathways and the severity of the seizures (*1,14-16*). Subtraction **^{18}F-**FDG PET is novel and can localize the SOZ for intracranial recording or for surgical resection in lesional and non lesional epilepsy. It may also directly guide management or lesionectomy if multiple lesions are present.

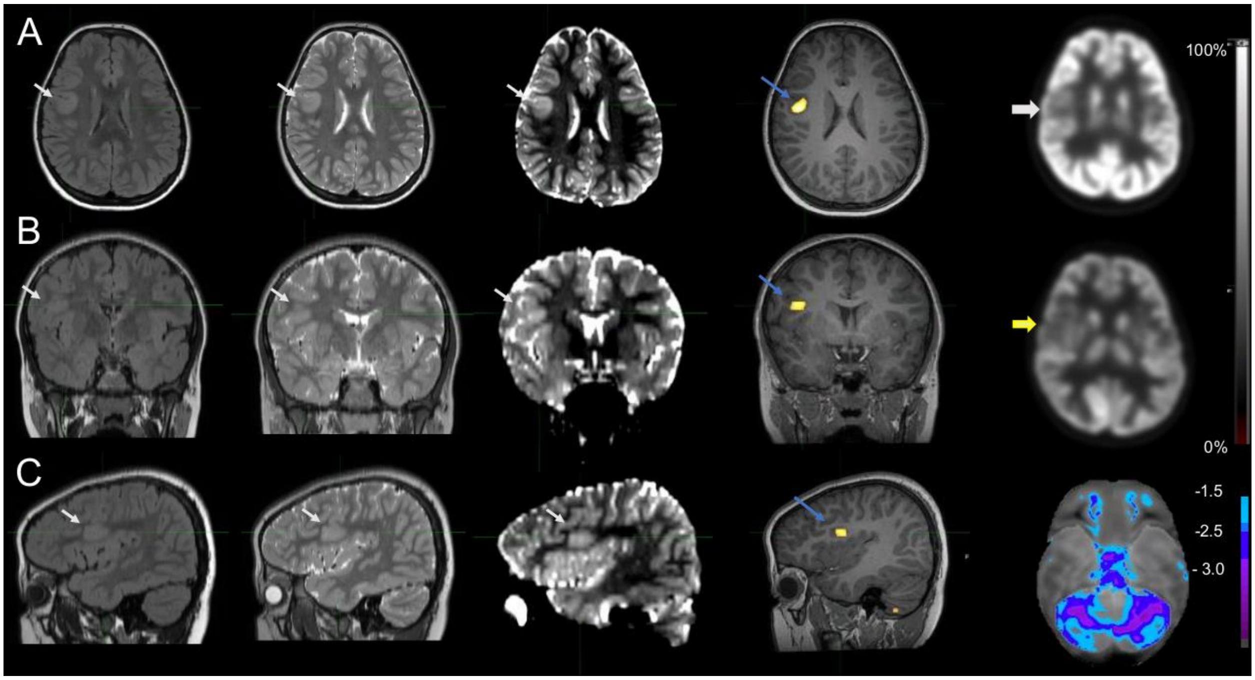
Methods:

We performed subtraction ictal-interictal ^{18}F-FDG PET. ^{18}F-FDG PET scans were obtained in the ictal and interictal phase following injection of radiopharmaceutical activities according to SNMMI/EANM guidelines. Subtraction was performed using Neuro MIM software. Co-registration of both PET volumes and the patient's most recent MRI was performed. Subtraction of both PET scans was followed by a cluster statistical analysis to define the area of highest significance. Results were co-registered and displayed on the patient's MRI scan. Further evaluation of the patient's clinical and imaging results was performed at a multidisciplinary epilepsy team meeting. MRI images as well as ^{18}F-FDG PET ictal and interictal scans were reviewed qualitatively. ^{18}F-FDG PET scans were also reviewed semi-quantitatively using a normal healthy database control with z score results displayed on stereotactic surface projections of the patient's MRI. Subtraction fused ^{18}F-FDG PET-MRI results were also discussed.

1. **Case Presentation 1:**

We present the case of a 6-year-old right-handed boy with intractable seizures. Onset of seizures was at 4 y.o. Seizure semiology is represented by tonic seizures of the upper limbs lasting 25-30 seconds and occurring about 30-40 times a day. Generalized seizures also occur twice a week. Historically, he had a trial of 9 different anti-epileptic drugs (AED) and is currently on triple AED treatment. His stay in the epilepsy monitoring unit (EMU) revealed evidence of focal epileptic seizures arising from the right frontal region.

Figure 1. A. Left to Right: Axial scans successively Flair, T2, DWI, Subtraction ^{18}F-FDG PET fused with a T1w MRI and Inter-Ictal ^{18}F-FDG PET. B. Left to Right: Coronal scans successively Flair, T2, DWI, Subtraction ^{18}F-FDG PET fused with a T1w MRI and axial Ictal 18F-FDG PET. C. Left to Right: Sagittal scans successively Flair, T2, DWI, Subtraction ^{18}F-FDG PET fused with a T1w MRI and z score Stereotactic Surface Projection (SSP) of FDG PET hypometabolism.



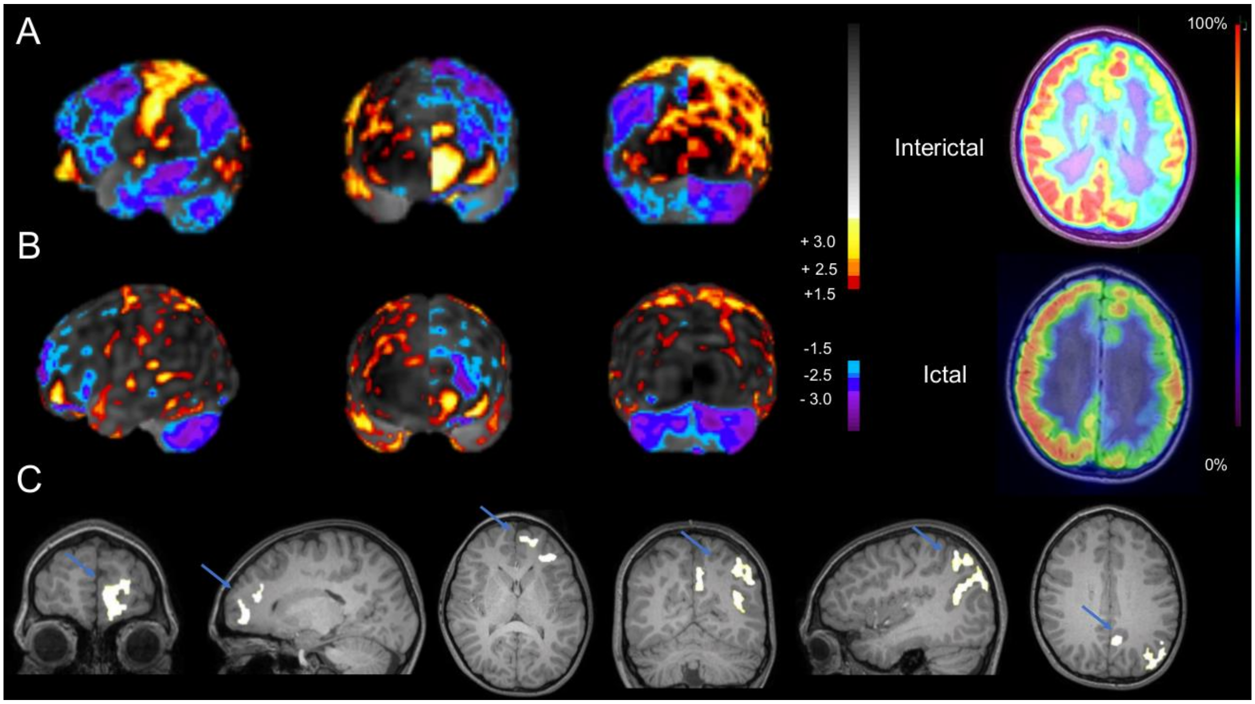
Here we showcase the value of subtraction ^{18}F-FDG PET in uncovering the SOZ in the right Rolandic operculum (Figure 1). A small lesion was initially missed on the MRI due to technique and the subtle nature of the lesion and was reported only on follow-up MRI (Figure 1, thin white arrow) and only after the subtraction PET revealed the lesion/SOZ. Of relevance, is that the interictal ^{18}F-FDG PET scan (Figure 1A) shows visually somewhat a large area of mild hypometabolism in the right frontal lobe (Figure 1A, thick white arrow). This area has slightly improved metabolism ictally (pseudo-normalization of glucose metabolism) (Figure 1B, thick yellow arrow). Of significance is that there are no areas of increased glucose metabolism noted on the ictal PET, so no obvious ictal focus to report. However, the subtraction ictal-interictal technique reveals the cluster of significance in the right Rolandic operculum corresponding to the SOZ (Figure 1, blue arrow). The subtraction technique accurately detects the SOZ as well as the extent of the SOZ which is much larger on the raw PET data.

2. **<u>Case Presentation 2</u>:**

Our second case is a 13-year-old boy with intractable seizures. Onset of seizures was at 1 y.o. in the form of a febrile seizure. First unprovoked seizure was at 2 y.o. Seizure semiology was in the form of loss of consciousness and loss of muscle tone for about 10 seconds and occurring about 20-25 times a day. Historically, he had a trial of 4 different anti-epileptics and was on two AED's during work-up. His autoimmune/inflammatory workup was negative. Interictal EEG showed left frontal slow disturbance and abundant epileptic discharges arising from the left anterior frontal region. Ictal EEG showed multiple seizures recorded with onset from the left frontal region with spread to the right frontal region. No generalized seizures were noted. Patient was injected in the nuclear medicine department approximately 1 minute after having a seizure. Then 2 minutes after the injection he had another seizure and had an additional 3 seizures during the remainder of the uptake phase before his scan. MRI showed subtle loss of gray-white matter differentiation in the entire left frontal lobe most apparent after review of the ^{18}F-FDG PET scan but initially reported as unremarkable. However, no anatomic/morphologic discernable changes were seen in the left parietal and parietooccipital regions. Additionally, ictally no obvious ictal region with increased glucose metabolism was noted.

In this case we note that the raw inter-ictal and ictal ^{18}F-FDG PET data showed a much higher sensitivity at detecting abnormalities in the left hemisphere which are very subtle on the MRI. Additionally, SSP projections show changes in metabolism (hyper: yellow red color scale and hypo: blue-purple color scale) across the entire brain and how they change during the ictal phase. The subtraction technique allowed here to identify two potential areas for the SOZ in the left frontal and left parieto-occipital lobe (Figure 2, blue arrows). This guided patient management significantly by allowing for a better definition of the SOZ than the MRI in this case and raising the possibility for multifocal seizures. It also allowed for an improved selection of the proper surgical approach (lesionectomy, disconnection or other) including the contemplation of intracranial mapping that would cover both seizure clusters.

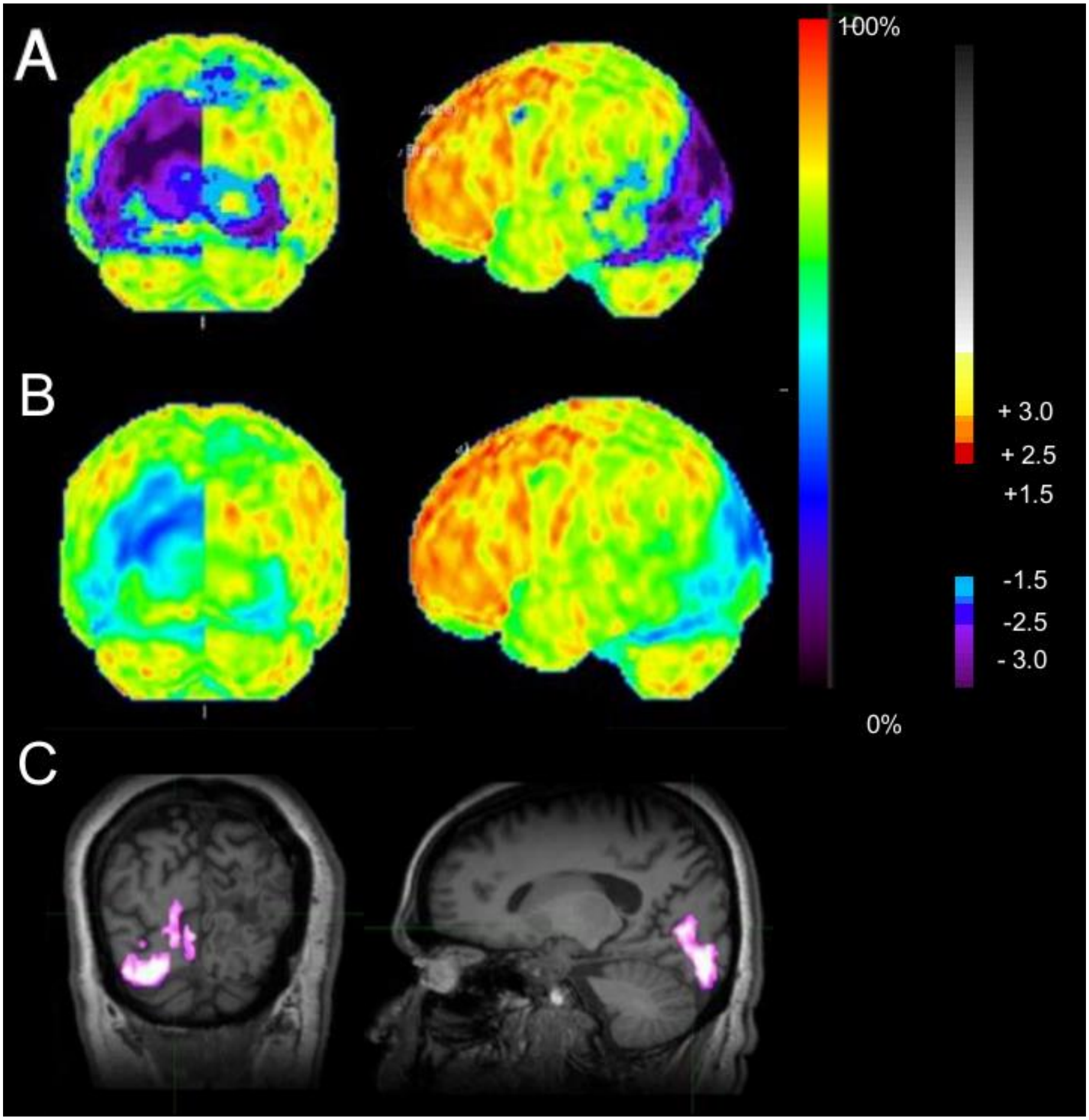
Figure 2. A. Left to Right: z score Stereotactic Surface Projection of ^{18}F-FDG PET hypometabolism and hypermetabolism and axial Inter-Ictal fused ^{18}F-FDG PET-MRI. B. Left to Right: z score Stereotactic Surface Projection (SSP) of ^{18}F-FDG PET hypometabolism and hypermetabolism and axial Ictal fused ^{18}F-FDG PET-MRI. C. Subtraction fused ^{18}F-FDG PET-MRI in all 3 planes showing two sites of clusters of significance in the left frontal and left parieto-occipital lobe.



3. **Case Presentation 3**:

Our third case is a 40 yo man with medically refractory epilepsy due to prior encephalitis. Seizure semiology consisted of simple partial visual seizures. Seizures started in his 30's. There were no generalized seizures. ^{18}F-FDG PET scans were performed ictally and interictally. We point out in this case that ictal ^{18}F-FDG PET (Figure 3B) does not show any areas suggestive of increased glucose metabolism when reviewed as a single study or even when compared to a normal healthy control database. It shows persistence of hypometabolism. However, when compared to the interictal exam (Figure 3A) we can see the improvement in hypometabolism in the left occipital region ictally. So, there's a so called **relative** increased glucose metabolism ictally that is only uncovered when compared to the interictal study. The subtraction technique allows us to clearly uncover and define a cluster of significance in the left occipital lobe (Figure 3C). As one must consider that looking at the ictal phase ^{18}F-FDG PET alone shows changes in the SOZ and along the propagation pathway (network effect). So, the pseudo-normalization can also occur in other areas of the brain, hence the value of the subtraction technique. In essence, the ictal ^{18}F-FDG PET scan as an independent exam is limited. However, this limitation can be overcome through comparison to the interictal scan and especially with the use of advanced techniques such as normal healthy controls statistical mapping and subtraction as demonstrated here (Figure 3).

Figure 3. A. 3D SSP maps showing significant areas of hypometabolism in the left occipital lobe interictally. B. 3D SSP maps showing no areas of hypermetabolism in the left occipital lobe ictally or elsewhere, however the severity of the hypometabolism in the left occipital region has diminished (pseudo-normalization of glucose metabolism). C. Subtraction Ictal-Interictal fused ^{18}F-FDG PET-MRI shows a cluster of significance in the left occipital lobe (SOZ).



4. <u>Case Presentation 4</u>:

Our fourth case is a 10 y.o. right-handed girl with intractable left temporal lobe epilepsy, status post left anterior temporal lobectomy and left medial amygdalo-hippocampectomy. Seizures started at the age of 5 y.o. She continued to have seizures following the surgery, with a similar semiology to the pre-operative seizures. Scalp EEG recordings post-surgery showed mild focal intermittent slow disturbance of cerebral activity seen in the right fronto-temporal region as well as a multifocal epileptic abnormality seen independently in the left and right anterior head regions. During her EMU stay six stereotyped seizures were noted with no definite localizing or lateralizing features. Some seizures were associated with subtle delta slowing in the bifrontal region, and at times with left frontopolar predominance whilst others were associated with a clear right fronto-temporal postictal slowing. These findings from multidisciplinary epilepsy team consensus suggested a deep left hemispheric epileptogenic focus (orbitofrontal versus insular) although an independent right sided focus couldn't be excluded considering EEG findings. Further evaluation with invasive recordings was performed to further localize the SOZ. Prior to intracranial mapping an inter-ictal postoperative ^{18}F-FDG PET scan was performed (supplemental Figure 1). Subtraction images of pre- and post-operative inter-ictal ^{18}F-FDG PET scans (Figure 4B) excluded any contralateral right hemisphere focus allowing intracranial grids, strips and depth electrodes to be placed in the left hemisphere only: orbitofrontal, left insular, left cingulate and left posterior temporal region (Figure 4C). Subtraction also suggested that the SOZ extended posteriorly in the left temporal lobe (Figure 4B). Contralateral right sided medial temporal lobe hypometabolism seen on pre-operative ^{18}F-FDG PET scan improved post-operatively (Figure 4A white arrow). This change is reported to be associated with better Engel outcomes.

Supplemental Figure 1. A. Left to right: Axial Preoperative Fused ^{18}F-FDG PET-CT, Axial Postoperative ^{18}F-FDG PET fused with preoperative MRI, Axial Postoperative ^{18}F-FDG PET-CT B. Left to right: Coronal Preoperative Fused ^{18}F-FDG PET-CT, Coronal Postoperative ^{18}F-FDG PET-CT, Postoperative ^{18}F-FDG PET SSP Right Hemisphere and Right Temporal Lobe and Postoperative ^{18}F-FDG PET SSP Left Hemisphere and Left Temporal Lobe.

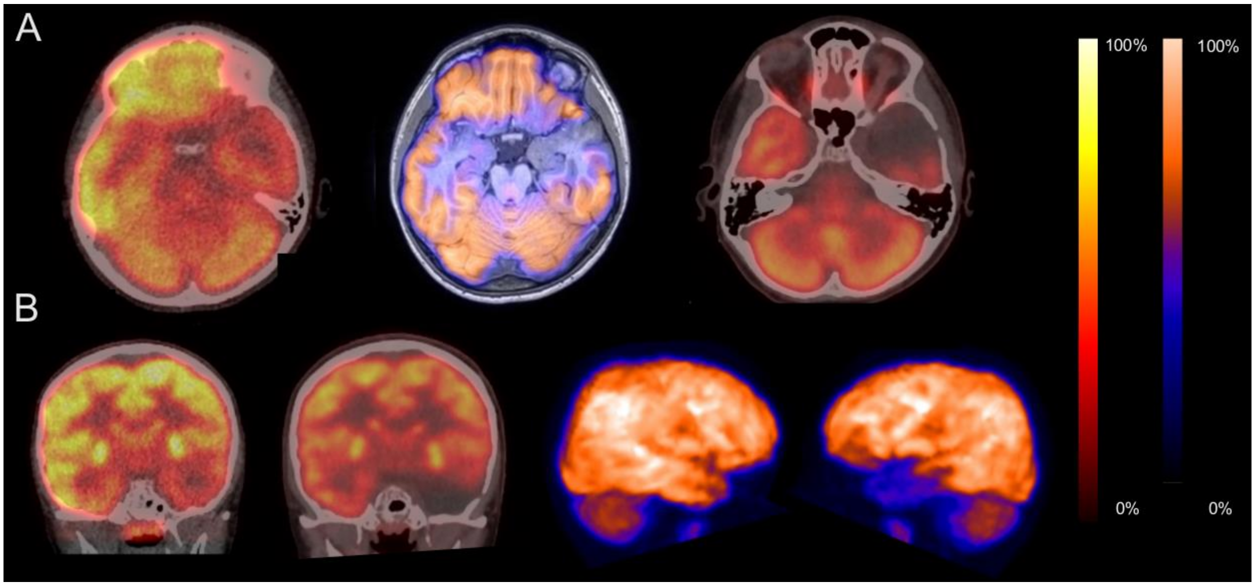
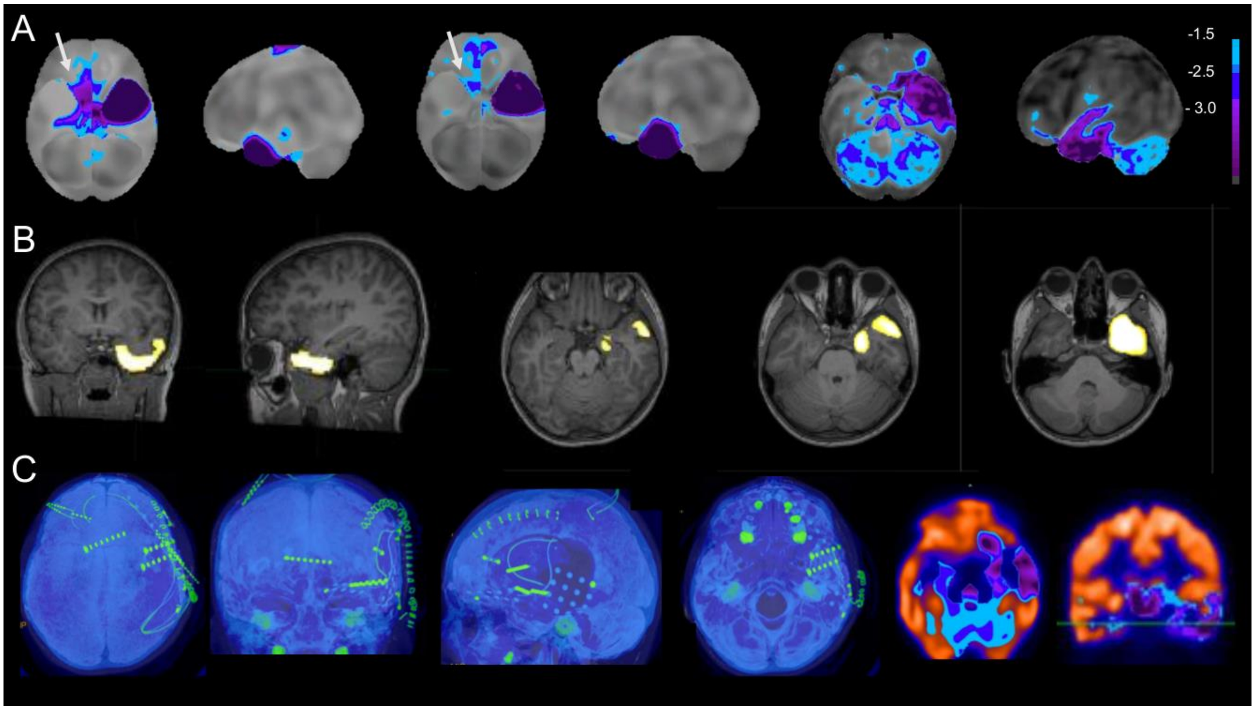


Figure 4. A. Left to right: z score SSP of preop cerebral blood flow ^{99m}Tc-HMPAO SPECT, postop cerebral blood flow ^{99m}Tc-HMPAO SPECT and postop FDG PET B. Subtraction pre and post-op fused ^{18}F-FDG-MRI PET C. Left: Intracranial mapping with grid, strip and depth electrodes; Right: Z score hypometabolism on preoperative ^{18}F-FDG PET.



Conclusion:

^{18}F-FDG PET subtraction techniques offer a significant advantage over traditional inter-ictal ^{18}F-FDG PET evaluations and can be used successfully to delineate the SOZ and guide the management of medically refractory epilepsy patients. We hope our results will encourage larger use and bigger datasets for proper comparison and further expansion of the pool of patients that may benefit.

Key Points:

-- Question: Can advanced novel PET imaging techniques impact clinical management in medically refractory epilepsy patients?

-- Pertinent Findings: Advanced FDG PET subtraction techniques allow better delineation of the SOZ in medically refractory epilepsy patients.

-- Implications for Patient Care: Advanced FDG PET subtraction techniques enhance clinical management in medically refractory epilepsy patients.

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Graphical Abstract: