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Metabolic Changes in Medial Temporal Lobe Epilepsy Compared to Healthy Controls Using Advanced [^{18}F] FDG PET SPM Analysis Techniques

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Abstract

Objectives: [^{18}F] FDG PET imaging has emerged as an established modality in the evaluation of medically refractory temporal lobe epilepsy. Advanced techniques improve the sensitivity and detection of abnormalities. We sought to measure changes in metabolic activity using [^{18}F] FDG PET in Medial Temporal Lobe Epilepsy (MTLE) patients compared to healthy controls and evaluate changes in the Seizure Onset Zone (SOZ) and remote areas.

Methods: We evaluated a cohort of 14 MTLE patients. Following a standard brain [^{18}F] FDG PET acquisition, images were co-registered to a healthy control database using the Neuro-MIM software. Z scores were generated for different temporal and extra-temporal lobe structures for significant p values <0.05. Seizure laterality was determined by experienced epileptologists (>10 years) using intracranial or surface depth electrodes.

Results: The mean age of our patient cohort was 33.9 years (range: 9-52 years). We evaluated 7 left MTLE, 1 bilateral MTLE, and 6 right MTLE patients. Significant hypometabolic changes were seen in the amygdala, the hippocampus, and overall, the medial temporal lobe region (Z score of -2.2, -2.3, and -2.1 respectively). There was a smaller decrease in metabolic activity observed in the parahippocampal gyrus, fusiform gyrus, and the lateral temporal lobe (Z score of -1.4, -1.2, and -1.1 respectively). There were no significant differences in the basal ganglia, thalamus, prefrontal cortex, or cingulate gyrus.

Conclusions: Measurable significant differences in FDG brain metabolic activity exist in medial temporal lobe epilepsy patients compared to healthy controls. Our study shows the most significant changes are hypometabolism in the amygdala, hippocampus, and overall, the medial temporal lobe region compared to the lateral temporal lobe.

Keywords: MTLE; Epilepsy; SOZ; FDG PET

Introduction

Epilepsy is a chronic debilitating condition. Its comorbid impact can be as significant as that of severe diabetes. It has a significant socioeconomic impact on the individual patient as well as a prominent health care cost burden [1-3]. In North America, epilepsy incidence is approximately 50/100,000 per year and prevalence is 5-10/1000 [4]. The CDC estimates that about 2.0 million people in the United States have epilepsy and nearly 140,000 Americans develop the condition each year with an increase in patients with symptomatic epilepsy [4]. The lives of epilepsy patients are negatively impacted at multiple levels, with decreased independent living, and limited financial independence, due to their reduced income and less-likeliness to have full-time employment; they have driving restrictions, neuropsychological impairment, and suffer from persistent stigma

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in developing as well as developed countries [2-6]. The best studies found an overall standardized mortality ratio of 2.3 for epilepsy relative to the general population [4]. There is a need for more research into ways to improve epilepsy management and global awareness of the disproportionate resources allocated to other diseases and lack of funding into epilepsy progress.

Medical treatment has not been shown to impact clinical outcomes or cost-effectiveness [7-9]. While useful, Antiepileptic Drugs (AEDs) exhibit a substantial long-term health care cost and are associated with debilitating side effects [10,11]. Many epilepsy patients and young females of childbearing age, in whom a pregnancy is contemplated, may be affected directly or indirectly by their epilepsy condition itself or by the adverse effects and teratogenicity related to AEDs [12]. In the case of the one third of epilepsy patients who do not respond to AEDs, respective surgical alternatives or minimally invasive novel intracranial devices may be beneficial.

Since the late 1800's, surgery for epilepsy has been shown to be successful in seizure control [13-15]. Since then major advances have been made [16-21]. Quality-of-life outcomes are high, and morbidity/mortality post-surgery are low [11,22-37] especially in temporal lobe epilepsy, but are dependent on the preoperative localization of the Seizure-Onset Zone (SOZ) [22,38]. Seizure freedom is usually high at 2 years [39,40]. A prospective, randomized study demonstrated the superiority of surgical versus medical treatment in temporal lobe epilepsy [39]. Surgical success rates can be improved by better noninvasive techniques to define the SOZ, such as what we are proposing here.

The SOZ, while challenging to identify, is traditionally identified by expert epileptologists using several measurement/techniques, each evaluating a certain aspect of the clinical, structural, functional, or electric-magnetic activity of the brain, in order to determine the boundaries of the SOZ. These methods vary widely in their temporal and spatial resolution. Given that there is no single perfect technique that assesses the SOZ reliably with both high temporal and spatial resolution, combining different approaches is currently the mainstay for modern pre-surgical evaluation. This involves inpatient 24-hour video monitoring of seizures while the patient is undergoing additional scalp or Intracranial Electrocorticography (IEC) or both. These data are analyzed in conjunction with MRI, MEG, and functional imaging studies including PET and SPECT, and used to guide final definition of the SOZ with or without intracranial electrode mapping. This process is challenging even in expert hands. It is guided by clinically heterogeneous and imperfect data and patients.

While MRI is used with great success, it is not always informative in cases where no lesion is found, or multiple lesions are seen. Defining a SOZ in the absence of a lesion evident on an MRI scan is challenging and can adversely impact outcomes [26,41-55]. This is where functional PET imaging with [^{18}F] FDG, [^{11}C] Flumazenil, [^{11}C] AMT and [^{18}F] MPPF has proven superior to MRI in identifying the SOZ necessary to be resected [56-81]. Traditionally, PET evaluation is done through visual review and interpretation of the scan. However, semi-quantitative or quantitative brain PET evaluations have proven more useful with numerous radiotracers including FDG. Hence, we aim here to measure and present the changes in metabolic activity using [^{18}F] FDG PET in MTLE patients compared to healthy controls and to evaluate changes in the SOZ (i.e., medial temporal lobe) and remote areas.

Materials and Methods

Fourteen patients (with an age range of 9-52 years) with Medial Temporal Lobe Epilepsy (MTLE) were evaluated. Presurgical evaluation was carried out, whereby the patients were required to have MRI, Stereo-Electro-Encephalography (SEEG), and interictal FDG PET scans performed.

Each patient underwent a PET scan with [^{18}F] FDG 0.1mCi (3.7MBq)/kg. [^{18}F] FDG was administered 35-45 minutes prior to imaging. A 10-minute static scan was acquired using a PET/CT scanner. PET images were reconstructed using an Ordered-Subsets Expectation Maximization (OSEM) algorithm. The appropriate corrections such as detector dead time scatter and random events, and radioactive decay were applied, in addition to attenuation correction using CT scans. The images were then co-registered to the patient's MRI and a healthy control database using the MIMneuro (MIM Software, USA).

Consequently Z-scores were generated for different temporal and extra-temporal lobe structures for significant p values <0.05. Scans were processed and reviewed by an experienced nuclear medicine physician.

Results

A total of fourteen patients were evaluated with a mean age of 33.9 Years (range: 9-52 years). There were 7 left MTLE, 1 bilateral MTLE, and 6 right MTLE patients. The Z scores from the scans were evaluated.

As shown in (Figures 1 and 2), significant hypometabolic changes were seen in the amygdala, the hippocampus, and overall the medial temporal lobe region (Z score of -2.2, -2.3 and -2.1 respectively).

There was a smaller decrease in metabolic activity observed in the parahippocampal gyrus, fusiform gyrus, and the lateral temporal lobe (Z score of -1.4, -1.2 and -1.1 respectively). A small decrease was also found in the temporal lobe and pole, as well as the globus pallidus, shown in (Figure 3).

There were no significant differences in the basal ganglia, thalamus, prefrontal cortex, cingulate gyrus, or paracentral lobule as shown in (Figures 4, 5 and 6).

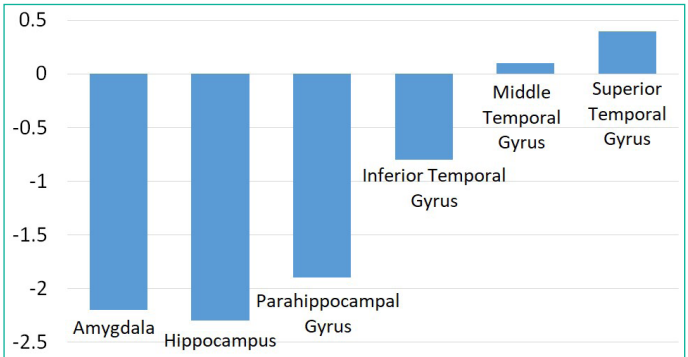

Figure 1: Z score comparison of medial temporal lobe epilepsy patients compared to healthy control patients in thalamus and basal ganglia.

Discussion

While there are several tools used in the pre-surgical evaluation of medically refractory epilepsy patients to define cortical zones of epileptic abnormality [82], currently MRI is the most reliable and accurate in providing information with regards to the epileptogenic zone. The inconsistent use of FDG PET clinically

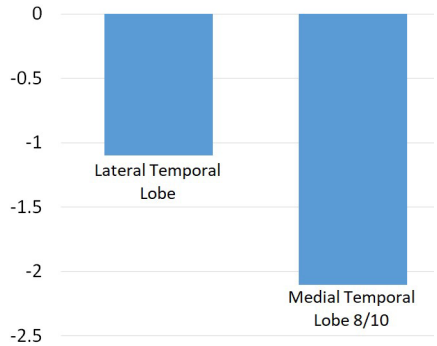

Figure 2: Z score comparison in medial and lateral temporal lobe structures.

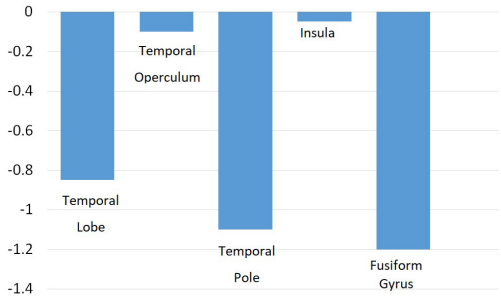

Figure 3: Z score comparison in the temporal lobe, operculum, pole and insula and fusiform gyrus.

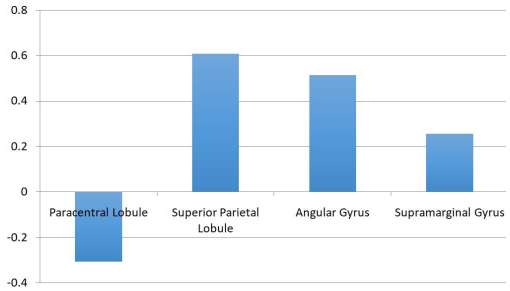

Figure 4: Z score comparison in paracentral and superior parietal lobules and angular and supramarginal gyrus.

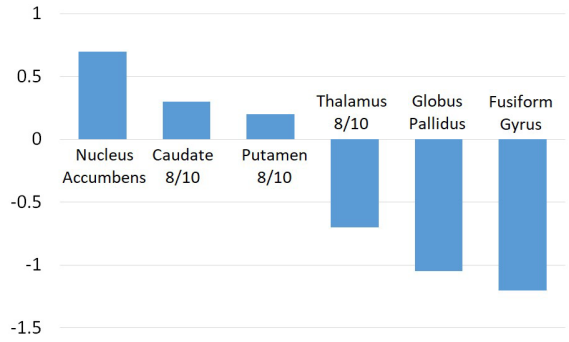

Figure 5: Z score comparison in thalamus and basal ganglia.

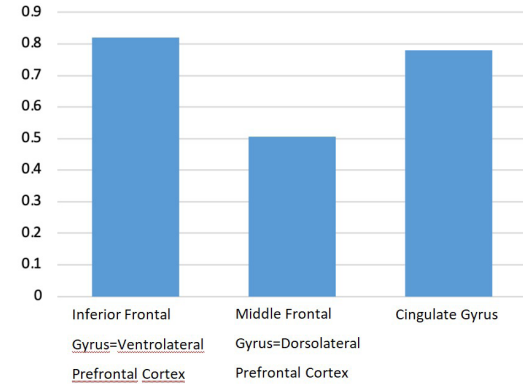

Figure 6: Z score comparison in prefrontal cortex and cingulate gyrus.

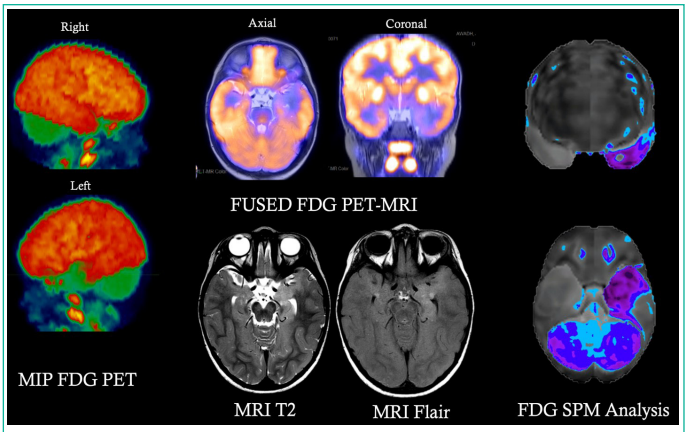

Figure 7: An FDG PET/MRI co-registered scan for an epilepsy patient showing a well-defined area of focal hypometabolism.

is due to the limited sensitivity and specificity of visual qualitative reads. Interpretation is challenging in non-experts' hands. Even nuclear medicine specialists with extensive expertise and experience can have a difficult time with accurate visual/qualitative interpretation. Even more so in the medial temporal lobe owing to baseline mild physiologic hypometabolism. The latter is due to patient variation in medial temporal lobe metabolism as well as the fact that deep brain structures may display less radiotracer uptake due to technical parameters. Hence, it makes sense to use fully quantitative or semiquantitative techniques with advanced tools such as subtraction and SPM analysis.

The main finding of this study was that the Z scores comparing MTLE patients to healthy controls provided measurable significant differences in [^{18}F]-FDG brain metabolic activity. This technique is accurate, reliable, and reproducible. It provides high inter-reader agreement. It offers increased sensitivity and specificity compared to traditional visual/qualitative interpretations, as shown in (Figure 7). We show that in our cohort using advanced statistical mapping can differentiate lateral temporal lobe from MTLE with lower non-significant z scores in the lateral temporal lobes. Changes in other temporal lobe structures outside the medial temporal lobe were not significant.

This increases the confidence in proceeding with surgery in these MTLE patients. Lack of changes outside the medial temporal lobe structures is something that cannot be ascertained visually/qualitatively with certainty. Although if present these changes would have negative prognostic determinants. Changes along the epilepsy network (basal ganglia, thalami and extratemporal cortical regions) were not significant in our cohort.

In essence, measurable significant differences in [^{18}F] FDG brain metabolic activity exist in medial temporal lobe epilepsy patients compared to healthy controls and advanced techniques offer a superior diagnostic performance.

Conclusions

Measurable significant differences in FDG brain metabolic activity exist in medial temporal lobe epilepsy patients compared to healthy controls. Our study shows the most significant changes are hypometabolism in the amygdala, hippocampus, and overall, the medial temporal lobe structures compared to the lateral temporal lobe. SPM analysis allows for an accurate and highly sensitive evaluation of medically refractory temporal lobe epilepsy patients and should be used as a standard in surgical epilepsy centers.

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