Metabolic Patterns and Seizure Outcomes following Anterior Temporal Lobectomy

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Objective: We investigated the relationship between the interictal metabolic patterns, the extent of resection of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) hypometabolism, and seizure outcomes in patients with unilateral drug-resistant mesial temporal lobe epilepsy (MTLE) following anterior temporal lobe (TL) resection.
Methods: Eighty-two patients with hippocampal sclerosis or normal magnetic resonance imaging (MRI) findings, concordant ^{18}FDG-PET hypometabolism, and at least 2 years of postoperative follow-up were included in this 2-center study. The hypometabolic regions in each patient were identified with reference to 20 healthy controls ($p < 0.005$). The resected TL volume and the volume of resected TL PET hypometabolism (TLH) were calculated from the pre- and postoperative MRI scans coregistered with interictal ^{18}FDG-PET.
Results: Striking differences in metabolic patterns were observed depending on the lateralization of the epileptogenic TL. The extent of the ipsilateral TLH was significantly greater in left MTLE patients ($p < 0.001$), whereas right MTLE patients had significantly higher rates of contralateral (CTL) TLH ($p = 0.016$). In right MTLE patients, CTL hypometabolism was the strongest predictor of an unfavorable seizure outcome, associated with a 5-fold increase in the likelihood of seizure recurrence (odds ratio [OR] = 4.90, 95% confidence interval [CI] = 1.07–22.39, $p = 0.04$). In left MTLE patients, greater extent of resection of ipsilateral TLH was associated with lower rates of seizure recurrence ($p = 0.004$) in univariate analysis; however, its predictive value did not reach statistical significance (OR = 0.96, 95% CI = 0.90–1.02, $p = 0.19$).
Interpretation: The difference in metabolic patterns depending on the lateralization of MTLE may represent distinct epileptic networks in patients with right versus left MTLE, and can guide preoperative counseling and surgical planning.

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Epilepsy surgery remains the treatment option of choice in patients with drug-resistant mesial temporal lobe epilepsy (MTLE). However, despite a thorough multimodal presurgical evaluation, a significant proportion of patients

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continue having seizures following surgery.[1,2] Accordingly, the need for reliable predictors of treatment outcomes in this era of personalized medicine remains ongoing. ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is one of the most established functional imaging modalities employed in the evaluation of epilepsy surgery candidates and offers unique insights into cerebral glucose metabolism at the synaptic level.[3–6] The cost-efficiency of ^{18}FDG-PET has long been recognized, and the wider availability of postacquisition processing techniques has increased its yield in surgical planning.[7–11]

With the advances in electroencephalography (EEG) and imaging technologies, including multimodal coregistration techniques, the role of ^{18}FDG-PET in presurgical evaluation has been enhanced beyond being a useful diagnostic tool reserved for magnetic resonance imaging (MRI)-negative cases or clinical scenarios with discordant electroclinical and structural imaging findings.[12–16] There has been a growing body of evidence suggesting that the extent of the metabolic compromise correlates with the distribution of ictal EEG discharges.[17,18] Furthermore, the findings of recent ^{18}FDG-PET and functional connectivity studies have been convergent in demonstrating the role of ^{18}FDG-PET as a metabolic biomarker of the extent of the epileptic network dysfunction.[19,20] It has also been suggested that hypometabolic changes affecting the contralateral (CTL) temporal lobe (TL) may impact on seizure outcomes in patients with drug-resistant MTLE.[21–26] Although stereoelectroencephalography and intraoperative imaging coregistration technologies open new avenues for the use of ^{18}FDG-PET in surgical planning,[8,9,27] studies on how the extent of the resection of ^{18}FDG-PET hypometabolism affects long-term surgical outcomes have been sparse and contradictory, which could be explained by a modest patient cohort size and methodological differences.[28,29] Furthermore, the results of functional and metabolic connectivity studies have been suggestive of distinct functional connectivity patterns depending on the lateralization of MTLE, including higher rates of CTL TL involvement in patients with right MTLE.[20,30–33] The higher rates of bitemporal hypometabolism have been observed in patients with unilateral right MTLE;[19] however, the effect of this distinct metabolic pattern on seizure outcomes following anterior TL resection (ATLR) has not been demonstrated.

Our study investigated the role of ^{18}FDG-PET in predicting surgical outcomes in a large, well-characterized cohort of patients with drug-resistant unilateral MTLE. The predictive value of the extent of the resection of ^{18}FDG-PET hypometabolism and the influence of CTL TL ^{18}FDG-PET changes on surgical outcomes in patients with right and left MTLE were evaluated.

Subjects and Methods

Study Subjects

This was a retrospective 2-center study. A total of 82 patients with drug-resistant unilateral MTLE who underwent an ATLR between 2001 and 2014 were included. Patients were identified from the prospectively administered Comprehensive Epilepsy Program databases at the Royal Melbourne and Austin Hospitals in Melbourne, Australia.

The inclusion criteria were: (1) age ≥ 16 years at the time of surgery, (2) preoperative MRI findings consistent with unilateral hippocampal sclerosis (HS) or no identifiable lesion ("MRI negative"), (3) concordant results of presurgical investigations and seizure semiology, (4) the presence of concordant ipsilateral TL ^{18}FDG-PET hypometabolism on visual inspection of interictal ^{18}FDG-PET, and (5) at least 2 years of follow-up following the ATLR.

The 2 centers adopted a similar presurgical evaluation protocol, which has been described previously.[12,28,34]

Briefly, this was comprised of at least one 5-day period of video-EEG telemetry including neurological examination, reevaluation of the clinical presentation and seizure semiology, expert neuroradiology review, and neuropsychiatric and neuropsychological assessment. Postoperatively, antiepileptic therapy was commonly rationalized within the first 6 to 12 months, depending on the seizure outcome. The study was approved by the Melbourne Health and Austin Health human research ethics committees.

Seizure Variables Outcomes

Seizure outcomes were assessed at the time of last follow-up and categorized using Engel classification of postoperative outcomes as seizure-free (Engel class I) or not seizure-free (Engel class II–IV).[35] The duration of follow-up varied between the patients (Table 1); however, a minimum of 2 years of postoperative follow-up was achieved for all patients, consistent with the previous published work from our group evaluating predictors of surgical outcomes.[34]

"Worthwhile improvement" was set at a ≥ 75% reduction in seizure frequency compared to the preoperative seizure burden. Acute seizures occurring within the first week following surgery were discounted.[36] Postoperatively, only seizures manifesting with impaired awareness were counted toward seizure recurrence.[37]

Neurosurgical Procedure

All patients underwent a Spencer-type resection, which is a type of ATLR also known as an anteromedial temporal lobectomy or a radical hippocampectomy.[38] In brief, it is a 2-step procedure involving the resection of the middle temporal gyrus and the inferior temporal gyrus 3 to 3.5 cm from the tip of the temporal pole, followed by resection of the mesial TL structures including the amygdala, hippocampus, and parahippocampal gyrus. It was the policy of our surgeons to do a less extensive neocortical resection, sparing the superior temporal gyrus, in patients with left (i.e., language dominant) MTLE. This is consistent with the results of previous studies that have

TABLE 1. Patient Characteristics

Variable	Right MTLE	Left MTLE	p[a]
Gender, male, n (%)	21/43 (48.8)	20/39 (51.3)	1.00
Age of epilepsy onset, yr, median (IQR)	17.0 (7.0–27.0)	16.0 (4.0–26.0)	0.50
Duration of epilepsy, yr, median (IQR)	19.0 (11.0–31.0)	19.0 (9.0–30.0)	0.91
Age at operation, yr, median (IQR)	40.0 (29.0–46.0)	34.0 (29.0–47.0)	0.58
Duration of follow-up, yr, median (IQR)	4.0 (3.0–8.0)	5.0 (2.0–8.0)	0.60

[a]Fisher exact test was used for categorical variables, and Mann–Whitney U test was performed for continuous variables.
IQR = interquartile range; MTLE = mesial temporal lobe epilepsy.

reported a smaller volume of TL resections in patients undergoing left ATLR.[39,40]

The adequacy of the hippocampal resection was determined based on a postoperative MRI performed at least 3 months following surgery.

^{18}FDG-PET and MRI Acquisition and Postprocessing

Preoperative ^{18}FDG-PET and MRI examinations were carried out as part of the presurgical evaluation. ^{18}FDG-PET scans were acquired on a Phillips Allegro (Phillips Medical Systems, Best, the Netherlands) at Austin Hospital with a voxel size of 2 × 2 × 2 mm or a GE Discovery 690 (GE Medical Systems, Milwaukee, WI) at Peter MacCallum Cancer Centre with a voxel size of 1.82 × 1.82 × 3.27 mm as described previously.[28] The median timing of the ^{18}FDG-PET scans was 5 months preceding surgery (interquartile range = 3–10.25, range = 1–23 months).

Until 2005, MRI examinations were carried out on a Genesis Signa 1.5 T (GE Medical Systems); thereafter, the scans have been performed on a Magnetom Avanto 1.5 T and a Magnetom Trio Tim 3 T (Siemens Medical Solutions, Erlangen, Germany). Three-dimensional, T1-weighted, magnetization-prepared rapid acquisition gradient echo sequences were used for post-acquisition processing. All processing was conducted using Statistical Parametric Mapping (SPM) software, version 12 (Wellcome Department of Cognitive Neurology, University College London, London, UK) mounted on a MATLAB R2012-A (MathWorks, Natick, MA).

^{18}FDG-PET Postprocessing

The images of the patients and 20 healthy controls were reoriented and nonlinearly normalized to SPM's built-in PET template using the default parameters within SPM's Old Normalise algorithm including grand mean scaling of 50 and a relative threshold of 0.8. Normalization parameters were saved for later use. Normalized images were smoothed with an 8 mm full width at half-maximum Gaussian kernel.

Hypometabolic regions of the brain were determined with reference to 20 healthy controls of an equivalent age range (16–65 years). For each patient, a general linear model was constructed to compare the patient to the 20 controls at each voxel, with a 2-sample t test carried out for each subject. To optimize the detection of the total cerebral ^{18}FDG-PET SPM hypometabolism (TCH), the modeling was conducted at every voxel within the whole brain mask (excluding the cerebellum) and a TL mask obtained from the Automated Anatomic Labeling atlas using the WFU Pick Atlas toolbox (Functional MRI Laboratory, Wake Forest University School of Medicine, Winston-Salem, NC).[41] This yielded a t statistic image for each subject. T statistic images were first transformed from the space of the PET atlas in which intersubject comparisons were made and then back to the native space of each patient's ^{18}FDG-PET using the inverse of the normalization parameters.

MRI Postprocessing

The resected tissue volume was estimated by deriving the difference through matching preoperative and postoperative MRIs. Preoperative and postoperative MRIs were nonlinearly registered using SPM's longitudinal registration toolbox with default parameters.[42] We opted for nonlinear registration because linear registration was not sufficient due to an inaccurate account of the postoperative brain changes, in particular the collapse of the brain tissue into the resection cavity. Preoperative and postoperative images were segmented into gray matter (GM), white matter (WM), and cerebral spinal fluid. The GM and WM partitions were added and thresholded at 0.1, resulting in an image of the brain tissue. A total cerebral volume image was constructed by taking the union of the preoperative and registered postoperative brain segmentations. The resection volume was measured as the difference between the preoperative and postoperative scans. To minimize the contribution of the pre- and postoperative image registration and segmentation errors, the largest cluster of the difference image was selected, which was invariably the resected tissue. To make this selection, the resected tissue was separated from the registration error by eroding the image by 2 voxels. Subsequently, the now separate resected tissue was selected, and dilated by 2 voxels to restore it to its original size. All resected tissue images were inspected by 2 independent operators to ensure the resected region on the postoperative MRI image was filled accurately. The volumes of resected tissue and of the total cerebral volume were calculated by summing the non-zero voxels and multiplying by the voxel size.

Combined MRI and PET Postprocessing

To ascertain the extent of the ^{18}FDG-PET hypometabolism resected, the patient's ^{18}FDG-PET images were matched to their preoperative MRI. ^{18}FDG-PET images were linearly coregistered to preoperative MRI using SPM's coregistration algorithm, which utilizes normalized mutual information to quantify similarity between 2 images of different modalities. The coregistered ^{18}FDG-PET/MRI images were inspected by 2 independent operators to ensure the adequacy of the coregistration. This coregistration was used to transform the *t* statistic images from the native ^{18}FDG-PET space to the native preoperative MRI space. The *t* statistic images were transformed to the preoperative MRI space, then thresholded (uncorrected $p = 0.005$, cluster extent >100 voxels) to elicit the region of hypometabolism and binarized. The optimal level of SPM thresholding was achieved through the identification of parameters whereby the ^{18}FDG-PET hypometabolism was identifiable in the ipsilateral TL in all patients. Thresholding was undertaken in the MRI space, rather than the PET template space, to allow for the application of more accurate interpolation to a continuous image (i.e., the *t* statistic image), as opposed to a discontinuous image (i.e., a thresholded *t* statistic image). This resulted in a smoother hypometabolism boundary when applying the threshold in the higher-resolution MRI space, rather than the low-resolution PET template space.

The amount of hypometabolism resected was calculated by masking the hypometabolism image in the MRI space by the resected tissue image. The total amount of hypometabolism was calculated by masking the hypometabolism image by the total cerebral volume image. The voxels in these masked images were summed and multiplied by the voxel size to derive the volume of resected TL PET hypometabolism (TLH) and the volume of the TCH.

The proportion of the TLH resected was derived as follows:

$$\%\text{TLH resected} = (\text{volume of TLH resected} \times 100)/\text{volume of TLH}$$

The proportion of the resected TCH was calculated as follows:

$$\%\text{TCH resected} = (\text{volume of TLH resected} \times 100)/\text{volume of TCH}$$

The proportion that extratemporal hypometabolism (ETH) constituted within TCH was derived by first estimating the volume of ETH by subtracting TLH volume from TCH volume, followed by:

$$\%\text{ETH} = (\text{ETH volume} \times 100)/\text{TCH volume}$$

The SPM thresholded images were also inspected for the boundaries of the ipsilateral ^{18}FDG-PET hypometabolism and the presence of ETH, including its distribution pattern.

In all patients, the ^{18}FDG-PET SPM hypometabolism identifiable in the ipsilateral TL was confined to the TL region without extension into the neighboring regions (i.e., frontoorbital, opercular, or the temporoparieto-occipital junction). The ETH areas were identified in the frontal regions (ipsilateral, CTL, and bilateral) and CTL TL region.

Statistical Analysis

Univariate analyses using Mann–Whitney *U* test for continuous variables and Fisher exact test for categorical variables were performed to first explore the differences in pertinent demographic, seizure, preoperative and postoperative neuroimaging variables in patients with right versus left MTLE, and subsequently, to explore the differences within the subgroups, depending on seizure outcomes.

Pertinent neuroimaging variables with univariate $p < 0.1$ were included in multivariate logistic regression to explore the predictive value of neuroimaging variables on seizure outcomes in patients with right and left MTLE, respectively.

A 2-tailed p value <0.05 was considered statistically significant for all tests performed unless specified otherwise. All statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY).

Results

Patient Characteristics and Seizure Outcomes

There were 43 patients with right MTLE and 39 patients with left MTLE with comparable gender composition, age of epilepsy onset, epilepsy duration, age at surgery, and duration of postoperative follow-up (see Table 1).

The median postoperative follow-up period in patients with right MTLE was 4 years, ranging from 2 to 10 years, and 5 years in patients with left MTLE, ranging from 2 to 14 years. Preoperative seizure burden did not differ in patients with right and left MTLE ($p = 0.98$; Table 2).

The seizure outcomes, excellent (Engel class I) versus unfavorable (Engel class II-IV), did not differ in patients with right and left MTLE ($p = 1.00$), with excellent outcomes observed in 30 patients (68.9%) with right MTLE and 28 patients (71.8%) with left MTLE.

The striking differences in the interictal metabolic patterns observed in patients with right and left MTLE are outlined in Table 3. Importantly, the left MTLE patients were observed to have significantly higher rates in the extent of ipsilateral TLH ($p < 0.001$), with a markedly higher proportion of TCH being confined to the ipsilateral TL ($p < 0.001$). The right MTLE patients had a significantly higher proportion of TCH falling extratemporally ($p < 0.001$), with preferential CTL TLH occurrence in right MTLE patients ($p = 0.003$).

The estimated volumes of resected TL tissue in patients with right MTLE significantly exceeded those in patients with left MTLE ($p < 0.001$), consistent with the commonly employed more sparing approach to ATLR in patients with left MTLE.[39,43]

TABLE 2. Preoperative Seizure Burden in Patients with Right (n = 43) and Left (n = 39) MTLE

Seizure Frequency	Right MTLE, n (%)	Left MTLE, n (%)
4–10/day	2 (4.7)	1 (2.6)
1–3/day	5 (11.6)	3 (7.7)
1–6/wk	17 (39.5)	15 (38.5)
1–3/mo	16 (37.2)	16 (40.9)
4–11/yr	1 (2.3)	3 (7.7)
1–3/yr	2 (4.7)	1 (2.6)

MTLE = mesial temporal lobe epilepsy.

rates of seizure freedom; however, in the right MTLE cohort it was associated with unfavorable seizure outcomes (p = 0.016; Table 5).

In the left MTLE cohort, excellent seizure outcomes were associated with greater resected TL tissue volumes (p = 0.005) as well as greater extent of resection of ipsilateral TL hypometabolism (p = 0.004; Table 6), which resonates with the findings of previous studies.[28,44]

Although the higher rates of HS on preoperative MRI (86.7% in right MTLE and 96.4% in left MTLE patients) in patients with excellent seizure outcomes were in keeping with previous studies,[34] they did not reach statistical significance in influencing seizure outcomes (p = 0.10 and p = 0.19 in patients with right and left MTLE, respectively).

TABLE 3. Summary of Pre- and Postoperative Imaging Variables in Patients with Left versus Right MTLE/ATLR

Variable	Right MTLE/ATLR, n = 43, 52.4%	Left MTLE/ATLR, n = 39, 47.6%	p[a]
HS on preoperative MRI, n (%)	34/43 (79.1)	36/39 (92.3)	0.12
Volume of preoperative ipsilateral TL SPM hypometabolism, mm^3, median (IQR)	3.79×10^3 (1.67×10^3–6.85×10^3)	9.28×10^3 (3.57×10^3–14.58×10^3)	<0.001[b]
% of TCH confined to ipsilateral TL, median (IQR)	29.9 (20.7–41.0)	63.0 (49.8–73.5)	<0.001[b]
% TCH SPM hypometabolism distributed extratemporally, median (IQR)	70.1 (59.0–79.3)	37.0 (26.4–50.2)	<0.001[b]
Presence of contralateral TLH, n (%)	17/43 (39.5)	4/39 (10.3)	0.003[b]
Volume of TL tissue resected, mm^3, median (IQR)	21.9×10^3 (17.7×10^3–28.0×10^3)	15.4×10^3 (11.8×10^3–21.3×10^3)	<0.001[b]
% TLH resected, median (IQR)	59.1 (35.9–70.9)	36.4 (23.6–58.3)	0.008[b]

[a]Fisher exact test was used for categorical variables and Mann–Whitney U test was performed for continuous variables.
[b]Statistically significant.
ATLR = anterior temporal lobe resection; IQR = interquartile range; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; SPM = Statistical Parametric Mapping; TCH = total cerebral hypometabolism; TL = temporal lobe; TLH = temporal lobe hypometabolism.

Pre- and Postoperative Imaging Variables in Relation to Seizure Outcomes

Interestingly, the presence of SPM hypometabolism detected outside the ipsilateral TL was common (54/82, 65.9%) but significantly more prevalent in right MTLE patients (33/43, 76.7%; p = 0.037). The most commonly sighted distributions of hypometabolism outside the ipsilateral TL in patients with right and left MTLE are outlined in Table 4. Hypometabolic changes in frontal regions were common and comparable in patients with right and left MTLE and were not associated with worse outcomes. The presence of CTL TLH in patients with left MTLE did not influence the

Predictors of Seizure Outcomes

The results of the multivariate logistic regression exploring the predictive value of pertinent pre- and postoperative neuroimaging features, focusing on preoperative MRI findings and ^{18}FDG-PET patterns in right MTLE patients and the extent of both the TL tissue resection and the ipsilateral TL hypometabolism in the left MTLE group, are shown in Tables 7 and 8, respectively.

In the right MTLE patients, the presence of CTL TLH was the strongest predictor of a heightened risk of unfavorable seizure outcomes and was associated with a nearly 5-fold increase in the risk of postoperative seizure

TABLE 4. Distribution of ET Hypometabolism and Its Association with Seizure Outcomes

	Right MTLE Cohort, n (%)			Left MTLE Cohort, n (%)		
ET Distribution	**Engel I, 30/43 (69.8)**	**Engel II–IV, 13/43 (30.2)**	***p*[a]**	**Engel I, 28/39 (71.8)**	**Engel II–IV, 11/39 (28.2)**	***p*[a]**
Ipsilateral frontal	13/30 (43.3)	8/13 (61.5)	0.33	8/28 (28.6)	4/11 (36.4)	0.71
Contralateral frontal	14/30 (46.7)	5/13 (38.5)	0.74	8/28 (28.6)	5/11 (45.5)	0.45
Bilateral frontal	9/30 (30.0)	4/13 (30.8)	1.00	5/28 (17.9)	3/11 (27.3)	0.66
Contralateral TL	8/30 (26.7)	9/13 (69.2)	0.016[b]	2/28 (7.1)	2/11 (18.2)	0.56

[a]Fisher exact test was used.
[b]Statistically significant.
ET = extratemporal; MTLE = mesial temporal lobe epilepsy; TL = temporal lobe.

recurrence (odds ratio = 4.90, 95% confidence interval = 1.07–22.39, $p = 0.04$).

In the left MTLE group, the predictive value of both the TL resection volume and the extent of the ipsilateral TL hypometabolism resection was explored; however, neither of the above predictors reached statistical significance ($p = 0.14$ and $p = 0.19$, respectively).

The presence of HS on preoperative MRI has long been shown to be an independent predictor of favorable seizure outcomes in patients with drug-resistant MTLE.[34] Our results corroborate with the above findings in that 76% of patients with HS on preoperative MRI achieved seizure freedom and only 42% of patients with normal MRI brain findings had a favorable outcome. The subgroup analysis of seizure outcome predictors is summarized in the Supplementary Table. The presence of CTL hypometabolism predicted an unfavorable seizure outcome ($p = 0.018$).

Discussion

The results of our study demonstrated striking differences in metabolic patterns in patients with right and left MTLE, with significantly greater rates of bitemporal hypometabolic changes observed in patients with right MTLE, whereas the patients with left MTLE had more extensive ipsilateral TL ^{18}FDG-PET hypometabolism.

Studies examining the evolution of the ^{18}FDG-PET hypometabolism over time have been sparse and mostly focused on pediatric populations. Gaillard et al studied the temporal evolution of the ^{18}FDG-PET changes in a mixed pediatric patient cohort, including a subgroup with drug-resistant epilepsy who were evaluated for epilepsy surgery, over a mean interval of 3 years.[45] They demonstrated no evidence of hypometabolism progression, with seizure frequency and time since the last seizure being the most important determinants of the differences in regional hypometabolism over the serial scans. In contrast, a recent study evaluating the interval changes in ^{18}FDG-PET hypometabolism in a heterogenous group of pediatric patients with drug-resistant epilepsy did find progression in the PET hypometabolism over time, with the median interval between the scans being >4 years, in particular in patients with ongoing drug-resistant seizures.[46] In some of these cases, unilateral hypometabolism evolved into bilateral hypometabolism on the subsequent scans. In our study, the homogeneity of our cohort and the timing of the ^{18}FDG-PET scans, with the median being 5 months preceding surgery, substantially diminish the possibility of dynamic changes influencing the findings. However, the possibility of interval changes cannot be excluded completely.

Remarkably, our findings resonate with the results of functional and metabolic connectivity studies,[20,30,32,33,47] demonstrating evidence of altered connectivity patterns in patients with MTLE, depending on the lateralization. In addition, although it remains unknown whether metabolic and functional asymmetry share the same underlying mechanisms, our findings corroborate the results of magnetic resonance spectroscopy studies by Zubler et al,[48] who demonstrated widespread abnormalities, with the involvement of CTL TL, in patients with right MTLE. It is not inconceivable, in light of the growing body of evidence demonstrating distinct aberrant metabolic and connectivity patterns, depending on the MTLE lateralization, that the right and left MTLE may represent two different entities where further research may not only advance our understanding of epileptogenesis but also influence patient management.

Our findings have shown that the overall extent of the ETH and hypometabolic changes in the frontal regions was not associated with adverse seizure outcomes,

TABLE 5. Pre- and Postoperative Seizure Variables Pertinent to Seizure Outcomes in Patients with Right MTLE (Univariate Analyses)

Variable	Engel I, 30/43, 69.8%	Engel II–IV, 13/43, 30.2%	*p*
HS on MRI, n (%)	26/30 (86.7)	8/13 (61.5)	0.10
Estimated MRI volume of resected TL tissue, mm^3, median (IQR)	22.17×10^3 (18.22×10^3–28.03×10^3)	21.08×10^3 (14.99×10^3–26.52×10^3)	0.58
Volume of preoperative TLH, mm^3, median (IQR)	3.62×10^3 (1.70×10^3–7.47×10^3)	3.94×10^3 (1.40×10^3–6.16×10^3)	0.94
% TLH resected, median (IQR)	58.67 (35.92–73.01)	60.26 (45.98–65.27)	0.63
% of TCH confined to ipsilateral TL, median (IQR)	30.72 (22.92–42.09)	24.81 (14.55–36.35)	0.17
% TCH distributed in ET regions, median (IQR)	69.28 (57.91–77.08)	75.19 (63.65–85.45)	0.17
Patients with contralateral TLH, n (%)	8/30 (26.7)	9/13 (69.2)	0.016[a]

[a]Statistically significant.
ET = extratemporal; HS = hippocampal sclerosis; IQR = interquartile range; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; TCH = total cerebral hypometabolism; TL = temporal lobe; TLH = temporal lobe hypometabolism.

TABLE 6. Pre- and Postoperative Seizure Variables Pertinent to Seizure Outcomes in Patients with Left MTLE (Univariate Analyses)

Variable	Engel I, 28/39, 71.8%	Engel II–IV, 11/39, 28.2%	*p*
HS on MRI, n (%)	27/28 (96.4)	9/11 (81.8)	0.19
Estimated MRI volume of resected TL tissue, mm^3, median (IQR)	17.78×10^3 (12.89×10^3–22.95×10^3)	11.78×10^3 (8.84×10^3–14.56×10^3)	0.005[a]
Volume of preoperative TLH, mm^3, median (IQR)	9.75×10^3 (4.60×10^3–14.73×10^3)	8.33×10^3 (3.57×10^3–11.42×10^3)	0.83
% TLH resected, median (IQR)	46.22 (31.29–60.30)	24.06 (18.01–29.42)	0.004[a]
% of TCH confined to ipsilateral TL, median (IQR)	63.31 (51.03–74.15)	62.06 (49.82–69.77)	0.62
% TCH distributed in ET regions, median (IQR)	36.69 (25.85–48.97)	37.94 (30.23–50.18)	0.62
Patients with contralateral TLH, n (%)	2/28 (7.1)	2/11 (18.2)	0.56

[a]Statistically significant.
ET = extratemporal; HS = hippocampal sclerosis; IQR = interquartile range; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; TCH = total cerebral hypometabolism; TL = temporal lobe; TLH = temporal lobe hypometabolism.

regardless of the MTLE lateralization, and may represent changes associated with seizure propagation pathways.[49]

Conversely, in right MTLE patients the presence of CTL TLH heralded unfavorable seizure outcomes, heightening the risk of postoperative seizure recurrence 5-fold. The association of poor seizure outcomes in patients with unilateral MTLE and bitemporal hypometabolism has been reported previously,[21–26] with Joo et al reporting higher rates of nonlateralizing EEG patterns in patients with bitemporal hypometabolism.[21]

We found that the patients with right MTLE had higher rates of CTL TL hypometabolism, and to our knowledge, it has not been described previously in conjunction with the lateralization of MTLE.

TABLE 7. Predictors of Postoperative Seizure Recurrence in Right MTLE Patients

Variable	OR	95% CI	*p*
MRI findings, HS vs HS-negative	2.13	0.39–11.73	0.38
Presence of CTL hypometabolism	4.90	1.07–22.39	0.04[a]

[a]Statistically significant.
CI = confidence interval; CTL = contralateral; HS = hippocampal sclerosis; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; OR = odds ratio.

TABLE 8. Predictors of Postoperative Seizure Recurrence in Left MTLE Patients

Variable	OR	95% CI	*p*
Estimated MRI volume of resected TL tissue, mm^3	1.00	1.00–1.00	0.14
% TLH resected	0.96	0.90–1.02	0.19

CI = confidence interval; MRI = magnetic resonance imaging; MTLE = mesial temporal lobe epilepsy; OR = odds ratio; TL = temporal lobe; TLH = temporal lobe hypometabolism.

Within the limitations of the current study, we therefore propose that it is not the extent but the location of the ETH that is the ultimate determinant of unfavorable seizure outcomes.

Interestingly, in the left MTLE cohort, the greater TL resection volume was associated with excellent seizure outcomes, and so was greater extent of resected ipsilateral TL ^{18}FDG-PET hypometabolism, in keeping with previous studies,[28,44] albeit none of these potential predictors reached statistical significance. It has been proposed that the extent of ^{18}FDG-PET hypometabolism is a metabolic biomarker of the extent of neural network dysfunction in patients with MTLE.[19,28,50,51] It might be, in light of potentially distinct networks implicated in right versus left MTLE, that neuronal dysfunction in left MTLE patients tends to be more confined within the ipsilateral TL, and further studies looking into the influence of the extent of resection of the ipsilateral TL ^{18}FDG-PET hypometabolism would be warranted with the focus on the left MTLE cohort.

Moreover, it has been shown that the greater TL resection volumes were associated with favorable seizure outcomes on several occasions,[44,52] and yet the quest for the optimal volume of TL resection remains ongoing to this day.[53] In reality, left ATLR procedures tend to be more sparing, with the left superior temporal gyrus being commonly preserved, resulting in a less extensive TL resection in left MTLE patients.[39,43] Our findings demonstrate distinct metabolic patterns with more extensive ipsilateral TL involvement in left MTLE patients and preferential CTL involvement in patients with right MTLE, which may help to explain the disparity between the extent of the TL resection volume and the seizure freedom rates. Further studies are warranted to explore the potential value of ^{18}FDG-PET tailored resections in patients with left MTLE.

Conclusions

Our findings demonstrate striking differences in the metabolic patterns in patients with right versus left MTLE and offer further insights into potentially distinct epileptogenic network dysfunction, depending on the lateralization of the MTLE.

From a practical standpoint, our findings call for the extended role of ^{18}FDG-PET in presurgical planning. Current guidelines reserve the use of ^{18}FDG-PET for MRI-negative cases and for patients with discordant MRI and electroclinical findings. With the results of our study demonstrating CTL TH to be a strong predictor of unfavorable seizure outcomes heralding a 5-fold increase in seizure recurrence in patients with right MTLE, the wider use of ^{18}FDG-PET can influence stratification of surgical candidates and improve presurgical counseling, in line with the expectations of personalized patient care.

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Author Contributions

V.C., T.J.O., P.K., S.F.B., B.S., and A.M.M. contributed to the concept and study design. V.C., B.S., Z.C., A.M.M., S.F.B., C.B.M., M.F.O., S.U.B., S.J.W., R.J.H., A.H.K., J.A.K., A.P.M., C.C.R., P.M.D., L.E.V., and G.C.F. contributed to data acquisition and analysis. V.C., T.J.O., and P.K. drafted the manuscript and tables. All authors approved the final version.

Potential Conflicts of Interest

Nothing to report.

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