**Summary**

**Objective:** The objective of the study was to characterize interictal 18-fluorodeoxyglucose–positron emission tomography (18FDG-PET) whole-brain voxel-based metabolic patterns among distinct subtypes of temporal lobe epilepsy (TLE), as defined by stereo–electroencephalography (SEEG) and to determine predictive value of PET result on postoperative outcome.

**Methods:** Fifty-four consecutive patients with pharmacoresistant TLE were enrolled retrospectively after a comprehensive presurgical evaluation. This evaluation defined: 7 lateral TLE, 17 mesial TLE, 14 “plus” TLE, and 16 bilateral TLE. Whole-brain voxel-based brain metabolism was studied in each group of patients, in comparison to 23 healthy subjects, and individual classification was evaluated by cross-validation using the found clusters. An 18FDG-PET index was moreover calculated for each patient, based on the individual Z-score of the most significant cluster extracted on the comparison between patients’ subgroup and healthy subjects. Logistic regression analysis was used to estimate factors associated with postoperative outcome (Engel’s classes III–IV vs. I–II), including age, gender, disease duration, seizure frequency, as well as magnetic resonance imaging (MRI) and PET findings.

**Results:** Different patterns of hypometabolism were found inside and outside the epileptogenic zone, among patients with distinct subgroups of TLE, in comparison to healthy subjects (p < 0.001, corrected for the cluster). At individual level, cross-validation showed satisfactory discrimination between the four groups with 71.4–88.2% overall accuracy. Multivariate analysis shows that 18FDG-PET index was the only significant predictor of postoperative outcome to distinguish between Engel’s classes I–II and III–IV (p = 0.037).

**Significance:** Overall, this whole-brain voxel-based analysis validates specific patterns of hypometabolism, inside and outside the EZ, in distinct subgroups of patients with TLE, as defined by SEEG gold standard, and in relation with postoperative outcome.

**KEY WORDS:** Temporal lobe epilepsy, Stereoelectroencephalography, Positron emission tomography, Epileptogenic zone, Postoperative outcome, Statistical parametric mapping.
Temporal lobe epilepsy (TLE), which is the most common form of localization-related epilepsy, is pharmacoresistant in approximately 45% of adult patients, with uncontrolled ictal seizures and interictal neuropsychological deficits that are physically and socially disabling. In this context, temporal lobectomy as a therapeutic option has dramatically improved the quality of life of patients with TLE. For example, seizure freedom rates have been reported to be between 46% and 81% at 1 year following surgery, and up to 72% at 10 years. The efficacy of surgery has been moreover demonstrated in a randomized controlled trial, versus medically managed controls.

Prior to surgery, evaluations are performed to identify the epileptogenic zone (EZ; i.e., the brain area necessary and sufficient for the generation of habitual ictal events; by definition less extensive than the whole irritative zone), to distinguish this from propagation pathways, and to determine its relationship with functional cortical areas. This noninvasive evaluation includes brain magnetic resonance imaging (MRI), interictal and ictal scalp electroencephalography (EEG), video-monitoring, neuropsychological tests, interictal 18-fluorodeoxyglucose–positron emission tomography (18FDG-PET), and ictal single photon emission computed tomography (SPECT) when possible. Stereo-electroencephalography (SEEG) recording with intracerebral electrodes is sometimes necessary to identify the brain area triggering the seizure when complex organization of the EZ is suspected. This technique is, however, limited by its invasiveness and its sampling. Invasive and noninvasive presurgical investigations have thus permitted to identify TLE with distinct EZ (and propagation pathways; mesial, lateral or temporal plus subtypes, bilateral), leading to distinct temporal resections.

Among the noninvasive evaluation, interictal 18FDG-PET, which evaluates the cerebral metabolic rate for glucose (CMRGlc), visually demonstrates temporal hypometabolism (unilateral or bilateral asymmetric) in >70% of patients with refractory epilepsy. Using quantitative analysis, detection of significant temporal lobe hypometabolism may exceed 90% in these patients. Although the relationships between interictal brain hypometabolism and involvement of these structures during seizures are complex, previous studies argue that interictal hypometabolism topography may be related to the neuronal networks involved by ictal discharge onset and spread pathways. However, until now, very few PET data have been available in comparison with a gold standard—technique (here the SEEG), and especially in the different subtypes of TLE. On the other hand, and besides the direct comparison to SEEG, validation of 18FDG-PET may also depend on predictive study. In this way, follow-up data have shown that 18FDG-PET is a predictor of postoperative outcome, but again this value has been little studied within the different subtypes of TLE.

The objectives of the present study are: (1) to characterize interictal 18FDG-PET whole-brain voxel-based metabolic patterns among distinct subtypes of TLE as defined by SEEG as the gold standard for localization, (2) to determine their individual diagnostic value by cross-validation among patients, and (3) to determine their predictive value on postoperative outcome.

**Methods**

**Subjects**

Fifty-four consecutive patients with pharmacoresistant TLE were retrospectively enrolled after a comprehensive presurgical evaluation, including at least brain MRI, 18FDG-PET, surface video-EEG electroclinical exploration, and SEEG recordings (33.3 [mean] ± [standard deviation] 13.4 years). 18FDG-PET was especially used with MRI and surface video-EEG electroclinical exploration to guide SEEG recordings. 18FDG-PET analysis was at this step based on a visual interpretation without quantification. The EZ was defined as the “regions of primary organization of the ictal discharges,” essentially taking account of the form of rapid discharges. Rapid discharge that occurs at seizure onset was delimited by visual inspection. In most cases, a time–frequency representation of signals (spectrogram computed from short-term fast Fourier transform) was used to accurately determine the beginning of the rapid activity.

Subtypes of TLE were defined according to the current categories proposed in previous studies: (1) mesial TLE, in which the EZ is limited to the mesial temporal lobe; (2) lateral TLE, in which the EZ is limited to the temporal neocortex; (3) “temporal plus,” in which the EZ extends to the adjacent cortex (operculoinsular, orbitofrontal, or temporo-occipital region). We also defined bilateral TLE when the EZ was found to be bilateral (characterized by seizures starting either from one or the other side or seizures starting immediately or rapidly <1 s on both temporal lobes). In details, our group of patients included 7 lateral TLE, 17 mesial TLE, 14 “plus” TLE, and 16 bilateral TLE. Characteristics of patients are presented in Table S1.

Twenty-three healthy subjects similar with respect to age with the whole group of patients (33.9 ± 7.8 years; p = 0.83) were also included. They were free from neurologic/psychiatric disease and cognitive complaints, and had a normal brain MRI. Informed consent was obtained with a protocol approved by the local ethics committee and conforming to the Declaration of Helsinki on human investigation (registration number of the clinical trial: NCT00484523).

**18FDG-PET acquisition**

Interictal brain metabolism was studied in all patients, under the same conditions as in healthy subjects. PET scan was performed using an integrated PET/computed tomography (CT) camera (Discovery ST; GE Healthcare,
Waukesha, WI, U.S.A.), with 6.2 mm axial resolution, allowing 47 contiguous transverse sections of the brain of 3.27 mm thickness. A total of 150 MBq of $^{18}$FDG were injected intravenously with the patient in an awake and resting state, with eyes closed, in a quiet environment. Image acquisition started 30 min after injection and ended 15 min later. Images were reconstructed using ordered subset expectation maximization algorithm, with 5 iterations and 32 subsets, and corrected for attenuation using CT transmission scan.

**Statistical analysis**

Whole-brain statistical analysis was performed at voxel-level using SPM8 software (Wellcome Department of Cognitive Neurology, University College, London, United Kingdom), by flipping the EZ to the same side, as shown previously. In details, ipsilateral and contralateral brain PET metabolism, related to EZ side, was compared at voxel-level to the mean left and right brain PET metabolism obtained in healthy subjects. The PET images were spatially normalized onto the Montreal Neurological Institute (MNI) atlas by using a 12-parameter affine transformation, followed by nonlinear transformations and a tri-linear interpolation. The dimensions of the resulting voxel were $2 \times 2 \times 2$ mm. The images were then smoothed with a Gaussian filter (8 mm full-width half maximum [FWHM]) to blur individual variations in gyral anatomy, and to increase signal-to-noise ratio. The resulting PET images were divided by individual fluorodeoxyglucose (FDG) uptake value of a specific reference site to control for individual variations in global PET measures. We selected the vermis as being a preserved area. The individual vermis value was obtained for each subject using the “Anatomical ROIs (regions of interest) Analysis” toolbox of SPM allowing the automatic extraction of the labeled region mean value from the Anatomical Automatic Labeling (AAL) atlas.

Significant hypometabolism was searched in comparison to healthy subjects for each subgroup of TLE patients (mesial, lateral, plus, and bilateral TLE). The SPM maps were thresholded using $p < 0.001$, corrected for multiple comparisons for the cluster. Anatomic localization of the most significant voxels was then identified by Talairach Daemon (http://www.talairach.org/daemon.html) and AAL parcellation.

A stepwise linear discriminant analysis (LDA) was performed to determine optimal functions for predicting group membership from clusters’ AAL parcellation found by comparing each group for patients to healthy subjects (see below: six clusters found, corresponding to parts of 37 anatomic AAL ROIs) and sociodemographic and clinical data (age, gender, illness duration, seizure frequency and MRI findings [presence/absence of lesion]). DA is a multivariate technique to classify study participants into groups to describe group differences and to assess the relative importance of variables for discriminating between groups. A “leave-one-out” procedure (jackknife validation procedure) was used to cross-validate the classifier, that is, the procedure successively classifies all cases but one to develop a discriminant functions and then categorizes the case that was left out, producing a more reliable functions. The analysis was performed with equal prior probability for any given subject to be classified into each of the four groups.

An FDG-PET index was moreover calculated on each patient, corresponding to the individual Z-score of the most

**Figure 1.**
Hypometabolism in patients with lateral TLE, in comparison to healthy subjects ($p$-voxel $< 0.001$). Hypometabolism in lateral TLE was ipsilateral, involving the middle and superior temporal gyrus (BA21, BA42). The medial temporal cortex was spared.

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significant cluster extracted on the comparison between patients’ subgroup and healthy subjects.

Finally, we examined the relationship between FDG-PET index and postoperative outcome using Engel class I–IV classification, while considering key preoperative and clinical factors. Patients were grouped as having a favorable postoperative outcome (i.e., Engel’s classes I and II) or a poor outcome (i.e., classes III and IV). The continuous (age, illness duration, seizure frequency, AAL cluster PET parcellation, and FDG-PET index) and categorical (gender and MRI findings [normal or not]) variables were compared between the two prognostic groups using the Mann-Whitney and chi square test, respectively. A logistic regression analysis was used to estimate the adjusted odds ratio (OR) with 95% confidence interval (CI) for factors associated with postoperative outcome (classes III–IV vs. I–II). The variables relevant to the model were selected from the univariate analysis based on a threshold p-value ≤ 0.30. Additional variables were included in the models because of its sociodemographic interest (age and gender). The final model incorporated the adjusted OR with 95% CI.

Continuous variables were expressed as means ± standard deviation (SD) or as median with range (min, max), and categorical variables were reported as count and/or percentages. All the tests were two-sided. Statistical significance was defined as p < 0.05. The statistical analyses were performed using the SPSS version 18.0 software package (SPSS Inc., Chicago, IL, U.S.A.).

Results

Patterns of hypometabolism related to TLE subtypes

In comparison to healthy subjects (p < 0.001, corrected for the cluster; Fig. 1), patients with lateral TLE showed ipsilateral hypometabolism, involving the middle and superior temporal gyrus (BA21, BA42).

In comparison to healthy subjects (p < 0.001, corrected for the cluster; Fig. 2), patients with mesial TLE showed ipsilateral hypometabolism, involving the middle and superior temporal gyrus (BA21, BA22), but also the uncus within the medial temporal lobe (BA28).

In comparison to healthy subjects (p < 0.001, corrected for the cluster; Fig. 3), patients with “plus” TLE showed ipsilateral hypometabolism, involving the middle and superior temporal gyrus (BA21, BA22, BA42), the uncus (BA28, BA36) and the parahippocampal gyrus (BA30, BA36), the lingual gyrus (BA18), the inferior parietal lobule and the supramarginal gyrus (BA40), the pre— and post—
central gyrus (BA6, BA9, BA1, BA2, BA3), the inferior and the middle frontal gyrus (BA10, BA44, BA45, BA47), the rectal gyrus (BA11), and the insula (BA13).

In comparison to healthy subjects (p < 0.001, corrected for the cluster; Fig. 4), patients with bilateral TLE showed bilateral hypometabolism, involving the inferior, middle, and superior temporal gyrus (BA20, BA21, BA38), the parahippocampal gyrus (BA30), the thalamus, the putamen, and the lateral globus pallidus.

On the whole, the medial temporal cortex was spared in lateral TLE; extratemporal cortical involvement was found only for “plus” TLE; bilateral involvement was found only for “bilateral” TLE; subcortical involvement was only found for “bilateral” TLE.

Six clusters of metabolic difference were found between each TLE group and healthy subjects (Table S2). These six clusters corresponded to parts of 37 anatomic AAL ROIs.

**Individual discriminant analysis**

The LDA revealed three discriminant functions, which were used to best discriminate the subjects into the four groups (i.e., mesial, lateral, plus, and bilateral TLE). Of the included variables, ipsilateral lingual metabolism contributed the most to the first function (correlation coefficient r = 0.868) and second function (r = 0.480), whereas ipsilateral middle temporal metabolism and contralateral middle pole temporal metabolism contributed highly to the third function (respectively r = 0.733 and r = 0.683). The group separation was satisfactory, as shown visually in Figure 5.

The cross-validated results showed significant discrimination for the four groups, with satisfactory overall accuracy (87.5% were correctly classified for bilateral and lateral TLE, 88.2% for mesial TLE, and 71.4% for “plus” TLE).

**Relation with surgical outcome**

Thirty patients underwent TLE surgery and had postsurgical seizure assessment. Follow-up ranged from 2 to 8 years (mean 4.9). Multivariate analysis shows that PET was the only significant predictor of postoperative outcome to distinguish between Engel’s classes I–II and III–IV, with better results obtained for the FDG-PET index than for the 37 ROIs (p = 0.037; Table 1): a more preserved metabolism (i.e., less hypometabolic) was associated with a poorer prognosis. No significant effect was found for age, gender, illness duration, seizure frequency, and presence/absence of MRI lesion. An additional analysis has been performed to distinguish Engel’s classes I and II–IV, and only a trend for FDG-PET index was found (p = 0.099; the single predictor with a p-value < 0.250 for this second analysis).

**Discussion**

This whole-brain voxel-based PET study shows different patterns of hypometabolism among patients with distinct subgroups of TLE, with satisfactory classification at the individual level. As previously reported with electroclinical patterns using surface EEG and whole-brain voxel-based analysis, the area of hypometabolism included the EZ as defined here by SEEG gold standard. Lucignani et al. had nevertheless shown poor agreement between quantitative FDG-PET and SEEG findings for the specific EZ, with normal metabolic rates found in up to 62% of the areas.
with abnormal SEEG activity, but using an a priori ROI approach.

Our findings show that hypometabolism is not limited to the EZ. Previous studies reported abnormal metabolic rates in up to 23% of the areas with normal SEEG activity.\(^{22}\) Of interest, we show here distinct areas of hypometabolism outside the EZ, suggesting distinct propagation pathways among TLE subgroups. Bilateral TLE was particularly characterized by bilateral subcortical metabolic involvement, including striata and thalami. These alterations may be linked to privileged pathways of propagation for this type of epilepsy.

Furthermore, we confirm the predictive value of FDG-PET in TLE; the inclusions were, however, too limited to perform the same prediction analysis in each TLE subgroup. Follow-up data have shown previously that FDG-PET is a predictor of postoperative outcome, the only significant one in comparison to MRI and to EEG in a recent TLE study,\(^ {14}\) with a greater proportion of seizure freedom after surgery in patients who had temporal hypometabolism in comparison to those without this finding. These results are concordant with our FDG-PET index data, since a more preserved metabolism (i.e., less hypometabolic) was associated here with a poorer prognosis, which

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**Figure 4.** Hypometabolism in patients with bilateral TLE, in comparison to healthy subjects (p-voxel < 0.001). Hypometabolism in bilateral TLE was bilateral, involving the inferior, middle, and superior temporal gyrus (BA20, BA21, and BA38), the parahippocampal gyrus (BA30), the thalamus, the putamen, and the lateral globus pallidus.

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has also been related to an extended hypometabolism outside the temporal lobe.\textsuperscript{23}

In addition to the FDG-PET confrontation to SEEG gold standard or to postoperative outcome, validation of PET in the presurgical evaluation of TLE has been obtained with various approaches. Although relationships between interictal brain hypometabolism and involvement of these structures during seizures are complex, previous studies argue that interictal hypometabolism topography may be related to the neuronal networks involved by ictal discharge onset and spread pathways.\textsuperscript{11–13} First, Engel et al.\textsuperscript{24} reported retrospective standardized reviews of brain PET metabolism and scalp-sphenoidal EEG ictal onsets in 153 patients, and showed that FDG-PET localization was misleading in only 3 patients. Intercital metabolic changes have been further correlated in other studies with ictal electroclinical patterns,\textsuperscript{12} initial ictal discharge frequency,\textsuperscript{13} and ictal brain SPECT perfusion.\textsuperscript{11} In particular, comparisons of patients with and without ictal symptoms showed relationships between dystonic posturing and interictal hypometabolism of putaminal and extratemporal cortical areas;\textsuperscript{25} between emotional/somesthetic symptoms and respectively anterior/posterior insular hypometabolism;\textsuperscript{26} between \textit{déjà vu} and parahippocampal hypometabolism;\textsuperscript{19} and between hyperkinetic behaviors and subcortical hypometabolism.\textsuperscript{27}

This study is the first to use a whole-brain voxel-based analysis to determine metabolic involvement in subgroups of TLE patients defined by SEEG recordings. A good concordance was found between patterns observed in PET- and SEEG-defined subtypes. In particular, extensive hypometabolism outside the temporal lobe was found in temporal plus epilepsies corroborating studies using visual\textsuperscript{8} or quantitative SEEG data. This result confirms the extensive epileptogenicity of involved brain networks. The extension of the EZ is probably an explanation for the surgical failures observed in this group. In patients with lateral neocortical epilepsies, PET hypometabolism was prominent in the superior temporal gyrus, concordant with SEEG data.\textsuperscript{9,28} Bilateral TLE were finally characterized by a more bilateral extension of the temporal hypometabolism. Taken as a whole, these findings argue for the classification of TLE epilepsies in distinct anatomic subtypes.\textsuperscript{17,29}

Statistical thresholds were corrected for multiple comparisons. The study is, however, limited by the sample size, even if the number of included patients is concordant with the previous report performed in comparison to interictal and ictal scalp video-EEG monitoring.\textsuperscript{12} Nevertheless, this sample size did not allow direct comparison between patient subgroups. Finally, our results may be affected by the profile of patients included, that is, those requiring SEEG recordings because of initial discordant findings. In our center, SEEG was systematically indicated when a bilateral or “plus” TLE subtype is suspected, and in our experience in most of the lateral TLE for delineating the limit of surgery. In these cases, the SEEG results are probably a good reflection of these subtypes of TLE. For mesial TLE, the reasons for SEEG were generally linked to the initial suspicion of the above-mentioned subtypes, without any reason to think that the organization of these mesial TLE is different from those that are not explored. Concerning the surgical results, 33% of failure for TLE is globally in the range of surgical

### Table 1. Factors associated with postoperative outcome (Engel’s classes: III–IV vs. I–II): univariate and multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Engel’s classes: I–II</th>
<th>Engel’s classes: III–IV</th>
<th>p-Value</th>
<th>Adjusted OR [95% CI]\textsuperscript{a}</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.3 (17.2)</td>
<td>29.3 (12.7)</td>
<td>0.878</td>
<td>0.99 [0.93;1.06]</td>
<td>0.770</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>55.0</td>
<td>30.0</td>
<td>0.260</td>
<td>0.24 [0.03;1.84]</td>
<td>0.171</td>
</tr>
<tr>
<td>Illness duration</td>
<td>16.9 (14.6)</td>
<td>12.7 (9.0)</td>
<td>0.758</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>14.0 (22.8)</td>
<td>13.0 (14.0)</td>
<td>0.565</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MRI (normal)</td>
<td>45.0</td>
<td>70.0</td>
<td>0.260</td>
<td>0.88 [0.10;7.52]</td>
<td>0.905</td>
</tr>
<tr>
<td>FDG-PET index</td>
<td>–7.7 (2.1)</td>
<td>–5.6 (1.2)</td>
<td>0.006</td>
<td>1.95 [1.04;3.65]</td>
<td>0.037</td>
</tr>
</tbody>
</table>

\textsuperscript{a}P, percentage; M (SD), mean ± standard deviation. Significant p-values (p < 0.05) are in bold.

\textsuperscript{a}Adjusted OR [95% CI]: adjusted odds ratio [95% CI].
results after 2 years.30 Failures are more numerous in “plus” and bilateral TLE subtypes.

Overall, this whole-brain voxel-based analysis validates the specific patterns of hypometabolism, inside and outside the EZ, in distinct subgroups of patients with TLE, as defined by SEEG gold standard, and in relation with postoperative outcome.

ACKNOWLEDGMENTS

This work was supported by Inserm (Centre d’Investigation Clinique, CIC, Hôpital de la Conception, Marseille), and AP-HM (PHRC 2007/09).

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of patients.

Table S2. Talairach coordinates of significant PET findings in subgroups of TLE patients, in comparison to healthy subjects (p < 0.001, corrected for the cluster).