PET imaging of brain 5-HT_{IA} receptors in the preoperative evaluation of temporal lobe epilepsy

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[18F]MPPF PET has previously been used to identify the epileptic lobe in temporal lobe epilepsy (TLE) patients at the group level. This study aims to validate the visual analysis of [18F]MPPF PET in the assessment of individual TLE patients for their suitability to undergo temporal lobe resection. Forty-two patients suffering from TLE and 18 control subjects matched for age and gender were prospectively enrolled for [18F]MPPF PET. Four subtypes were defined according to the presurgical evaluation: mesio-temporal lobe epilepsy (MTLE, 32 patients), temporal neocortical epilepsy (NC, five patients), temporo-perisylvian epilepsy (T+, three patients) and temporal epilepsy without further information (t, two patients). Parametric binding potential (BP_{ND}) images were obtained using a simplified reference tissue model. Three examiners, who were blinded to other data, visually interpreted each scan and delineated areas of decreased [18F]MPPF BP_{ND}. Statistical parametric mapping (SPM) analysis of MPPF BP_{ND} images was also performed. Visual analysis showed a low rate of disagreement between the three examiners (7%). PET scans were considered normal in four patients (9.5%). In the remaining 38 patients (90.5%), areas of focal BP_{ND} decrease were identified. A specific pattern was encountered in the MTLE subgroup, consisting of a BP_{ND} decrease involving hippocampus, amygdala and temporal pole altogether. Combining the results from the presurgical investigations and the surgical outcome, we estimated that the area of BP_{ND} decrease coincided with the epileptogenic zone in 40% of patients in the MTLE subgroup and 33% in the other TLE subtypes. This relatively low precision was due to 47% of patients who showed BP_{ND} decreases in the insula ipsilateral to the epileptogenic lobe. The SPM analysis had much lower sensitivity (67%) to detect BP_{ND} decreases in the epileptogenic temporal lobe, but revealed areas of increased BP_{ND} outside the epileptogenic zone and bitemporal BP_{ND} decreases of undetermined clinical significance, which were undetectable by visual analysis, in 29% of patients. In conclusion, visual analysis of [18F]MPPF BP_{ND} images helps in the correct identification of the epileptogenic temporal lobe in all patients showing BP_{ND} decreases, with a false negative rate inferior to 10% and no false positives in control subjects. All TLE patients with [18F]MPPF BP_{ND} decreases involving hippocampus, amygdala and temporal pole together, with or without extension to the ipsilateral insula, were good candidates for anterior temporal lobectomy. All these patients became seizure free after surgery, even when the clinical presentation was not that of a typical MTLE, or when MRI failed to detect hippocampal atrophy.

Keywords: temporal lobe epilepsy; brain 5-HT_{IA} receptors; serotonin; [18F]MPPF PET; presurgical evaluation

Abbreviations: BP_{ND} = binding potential; EZ = epileptogenic zone; FDG = [18F]deoxyglucose; MTLE = mesio-temporal lobe epilepsy; NC = Temporal neocortex; SPM = Statistical parametric mapping; TLE = temporal lobe epilepsy; PVE = Partial volume effect; 5-HT_{IA} = 5-hydroxytryptamine-IA

Introduction

Temporal lobe epilepsies (TLEs) represent the majority of drug-resistant partial epilepsies that are eligible for surgical treatment consisting of the removal of the epileptogenic zone (EZ), i.e. the area of brain necessary and sufficient to initiate seizures (Engel, 1993). There is no ‘gold standard’ criterion for delineating the cortical area to be resected for controlling seizures so that preoperative evaluation is based on convergence of data obtained through the various non-invasive and invasive investigations that are available in each epilepsy centre (Rosenow and Luders, 2001). Thus, according to series published by the different epilepsy centres, between 7% and 50% of patients are not seizure free after surgery (Sindou et al., 2006), indicating a failure to remove or disconnect the EZ completely.

Among non-invasive presurgical investigations, ¹⁸F-dideoxyglucose (FDG) PET is useful to evaluate the extent of the interictal functional deficit (Mauguie`re, 2004) and to predict the surgical outcome of temporal lobectomy in TLE (Gambhir et al., 2001). However, FDG PET has a low specificity regarding the extent of the EZ. Various radioligands of opiate, GABA-A, histamine, muscarinic and N-methyl-D-aspartate receptors have been developed to map binding changes that might be directly related to epileptogenicity (for a review, see Mauguie`re, 2004). Recent PET studies using various radioligands of 5-hydroxytryptamine-1A (5-HT₁A) receptors showed a decrease in 5-HT₁A receptor density on the side of the epileptogenic temporal lobe (Toczek et al., 2003). In TLE patients, this decrease is significantly greater, at a group level, in regions involved in the intracerebral discharge onset than in regions where only interictal paroxysms are recorded by depth-EEG (Merlet et al., 2004a). In patients showing mesiotemporal discharges on depth-EEG ictal recordings, this decrease is mostly located in mesiotemporal areas and in the temporal pole (Merlet et al., 2004b).

5-HT₁A receptors have a preferential cortical distribution in the limbic cortex, especially in mesiotemporal regions. Several preclinical studies provided some evidence for an anticonvulsant and antiepileptic effect of serotonin mediated by 5-HT₁A receptors. Serotonin binding to 5-HT₁A receptors causes neuronal hyperpolarization through the G-protein-coupled opening of K+ channels (Andrade and Nicoll, 1987; Beck and Choi, 1991; Okuahara and Beck, 1994). An excitatory/inhibitory imbalance mediated by changes in serotoninergic transmission thus represents one of the plausible mechanisms of neuronal hyperexcitability in TLE.

However, hitherto available studies supporting the concept that areas with decreased 5-HT₁A receptors could coincide with those showing interictal spikes or ictal discharges are based on group analysis or region of interest delineation, so that the reliability of 5-HT₁A receptors PET studies for mapping the EZ in individual patients remains unknown. In this PET study, we used an ¹⁸F-labelled antagonist of 5-HT₁A receptors, 4-(2'-methoxyphenyl)-1-[2'-((N-2-pirydynyl)-p-fluorobenzamido]-ethyl-piperazine (MPPF), which has an affinity close to that of endogenous serotonin (Costes et al., 2005), to estimate the binding potential of 5-HT₁A receptors in TLE patients. Patients were prospectively enrolled to undergo MPPF PET during presurgical evaluation of their epilepsy with the objectives:

1. To assess the sensitivity of MPPF PET visual analysis in the routine non-invasive preoperative evaluation of TLE.
2. To compare visual analysis and voxel-based statistical SPM analysis of individual PET data.
3. To assess the specificity of areas showing a visually detectable decrease of MPPF binding in terms of overlap with the epileptogenic area.

Methods

Patients

Forty-two fully informed consecutive patients (21 males and 21 females) were included from 2001 to 2004. Inclusion criteria were the following: (i) a clinically documented history of drug resistant TLE; (ii) Scalp video-EEG recordings of at least three spontaneous seizures associated with ictal discharges in the temporal regions; (iii) brain MRI performed in the year preceding inclusion.

Patients under medication interacting with the serotoninergic transmission (serotonin reuptake inhibitors) were excluded.

MRI

Brain MRI was performed using a 1.5 T Siemens Magnetom scanner (Siemens AG, Erlangen, Germany), and included the following sequences in all patients and normal subjects from the MPPF PET control database:

- 3D anatomical T₁-weighted sequence (TR: 9.7 ms, TE: 4 ms) covering the whole brain volume with 1 mm³ cubic voxels, providing 1-mm-thick slices in transverse bihippocampal and coronal planes.
- Six-millimeter-thick turbo-spin echo T₂-weighted sequence (TR: 2260 ms, TE: 45 and 90 ms) acquired in the bihippocampal plane.
- Turbo-spin echo T2 sequence (TR: 3000 ms, TE: 16 and 98 ms yielding 3-mm-thick slices) perpendicular to the latter.

Two independent observers, who were blinded to all other data, analysed MRI scans and reached a consensus in all patients. The MRI findings are detailed in Table 2. MRI was normal in seven patients (17%); it showed isolated hippocampal atrophy ipsilateral to the epileptogenic temporal lobe in 23 (55%); bilateral hippocampal atrophy in one (2%) and a focal lesion in 11 (26%) including nine patients with a focal dysplasia (Patients 31, 32 and 36–42); and two with an atrophic lesion (temporal pole and neocortical atrophy for Patient 34 and post-traumatic atrophy for Patient 35).

Depth stereotactic EEG recordings (video-SEEG)

Ictal and interictal intracranial video-SEEG recordings were performed in 18 patients (43%) in whom data from non-invasive...
PET findings were integrated into the presurgical discussion regarding the need for intracranial EEG recording and the surgical decision. However, for the purpose of the present study, FDG PET images have been anonymized and visually reanalysed in terms of focal hypometabolism by two independent examiners (P.R. and F.M.) blinded to all other data. Only areas reported by both examiners as showing glucose hypometabolism were considered for comparison with MPPF PET data. Any scan with at least one area reported as hypometabolic by only one of the two examiners was taken into account for calculating the rate of interobserver discrepant interpretations.

**[18F]MPPF PET study**
Ethic Committee agreement was obtained for the [18F]MPPF PET procedure (CCPPRB, Centre Léon Berard, Lyon) in accordance with the Declaration of Helsinki. Patients were fully informed and signed a written consent form.

**Data acquisition**
[18F]MPPF was obtained by nucleophilic fluoration on a nitro-precursor with a radiochemical yield of 20–25% at the end of the synthesis and a specific activity of 32–76 GBq/μmol (Le Bars et al., 1998). PET scans were performed on a CTI-Siemens HR+ scanner (Knoxville, TN, USA) during the afternoon. For tracer injections, an intravenous catheter was placed in a vein of the left forearm. A thermo-formable head holder was modelled for each subject to limit head movements during acquisitions.

Before emission acquisition, a 10-min transmission scan was performed using three 68Ge rod sources for the measurement of tissue and head support attenuation. After i.v. injection of a bolus of 171 ± 15 MBq [18F]MPPF, a dynamic emission scan consisting of 35 frames of increasing duration (20 s to 5 min) was acquired over 60-min post-injection. The PET scanner was operating in 3D mode. Images were corrected for scatter and attenuation, and reconstructed using a filtered back projection (Hanning filter, cut-off 0.5 cycles/pixels) to provide a 3D volume of 63 slices (2.42 mm thickness) with 128 × 128 voxels in plane (2.06 × 2.06 mm²). In the centre of the field of view, the NEMA (National Electrical Manufacturers Association) protocol measured a nominal axial resolution of 4.1 mm and a nominal transverse resolution of 4.4 mm for a 18F point source reconstructed with a ramp filter (Brix et al., 1997).

**Modelling**
For each subject, the MRI was coregistered with mutual information criteria with the static-weighted and summed PET image to obtain a complete data set (anatomic MRI, static and dynamic PET) with common orientation and size. Parametric images of binding potential were obtained using an analytical solution for the compartment model with a simplified reference tissue model developed for [11C]WAY100635 (Gunn et al., 1998) and validated for [18F]MPPF studies (Costes et al., 2002).

MPPF binding potential was abbreviated BPND (with the ND suffix indicating ‘non-displaceable tissue uptake’) in accordance with the recent consensus nomenclature (Innis et al., 2007). This model provides three parameters (k2, R1 = k1ref/k1ROI and BPND) without the need for an arterial input function: the free and non-specific ligand kinetic is based on the time–activity curve of a reference region (i.e. cerebellum) that is devoid of specific 5-HT1A binding. Using this model, a previous study confirmed

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**Table 1 Clinical features of patients**

<table>
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<th>Patient TLE subtype</th>
<th>Sex</th>
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<th>Handed-ness</th>
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<th>Epilepsy duration (years)</th>
<th>Side of epileptogenic zone</th>
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NC = neocortical; T+ = temporo-perisylvian; t = temporal; F = female; M = male; R = right; L = left; A = ambidextrous; mo = months; NA = non-available; B = bilateral.

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FDG PET

FDG PET was performed as a routine presurgical investigation using the same device as that used for the MPPF PET study (see below) and a standard procedure described elsewhere (Ryvlin et al., 1992). FDG PET was obtained in 38 of the 42 patients. FDG PET findings were integrated into the presurgical discussion.
that BPND was a good index of local receptor concentration in normal subjects (Kung et al., 1996). Figure 1 illustrates a normal MPPF BPND scan.

**Data preprocessing**

BPND images were spatially normalized to a BPND template built in MNI/ICBM152 space using SPM 99 (Statistical Parametric Mapping, Wellcome Trust Center for Neuroimaging, UCL, London, http://www.fil.ion.ucl.ac.uk/spm). Normalized BPND images were smoothed using a $8 \times 8 \times 8$ mm$^3$ FWHM isotropic Gaussian kernel that accommodates interindividual anatomy variability and improves the sensitivity of the statistical analysis (Ashburner and Friston, 1997).

**Control MPPF PET database**

The control database used for SPM and visual analysis consisted of MPPF BPND scans acquired in 48 healthy drug-free volunteers (24 men aged 20–68 years (mean 40.9 years), and 24 women aged...
19–67 years (mean 40.1 years) without history of psychiatric or neurological illness (Costes et al., 2005). BPND images of controls were treated using the same preprocessing as for patients. Nineteen BPND scans of control subjects matched for age and gender with the TLE patients were selected from this database and randomly intermixed with the TLE scans for visual analysis assessment.

**Surgical procedure and outcome**

Following preoperative evaluation, 35 patients (86%) were considered as eligible for epilepsy surgery and 27 have been operated upon (Table 2). Five patients (Patients 13–16 and 21) declined surgery although they were eligible, and the three remaining patients (Patients 27–29) were enrolled in a prospective study of stereotactic thermocoagulation treatment (Guenot et al., 2004).

Twenty-two patients (Patients 1–11 and 22–32) underwent anterior temporal lobectomy (Williamson et al., 1993). A selective amygdalo-hippocampectomy was performed for Patient 12. In the four remaining patients (Patients 33, 34, 36 and 37) the delineation of the temporal lobectomy was defined by results of the preoperative evaluation and involved basal or lateral temporal cortex (see Table 2 for further details).

With a mean follow-up of 25 months (7–48), 24 of these 27 operated patients (89%) were seizure free (Engel Class I) and the three others (11%) were classified under Engel Class II outcome.

**Epileptic syndrome: classification of patients**

For the analysis of BPND data, patients with mesio-TLE (MTLE), gathered in Group I, were separated from those without MTLE (Group II). MPPP PET results were not taken into account in this classification. MTLE patients should fulfill all the clinical, imaging and surface EEG diagnostic criteria for the MTLE syndrome (French et al., 1993; Williamson et al., 1993) including the following: a history of prolonged febrile seizures during childhood; first seizures in the latter half of the first decade of life; drug refractory complex partial seizures with ictal symptoms, including epigastric aura, suggesting an early involvement of mesiotemporal cortex; history of no or rare secondarily generalized seizures; unilateral rhythmic theta ictal activity on scalp temporal electrodes occurring after the clinical onset and unilateral hippocampal sclerosis on brain MRI on the side of EEG abnormalities. Patients not presenting with all criteria of the MTLE syndrome were classified in Group I if appropriate video-SEEG provided evidence for mesiotemporal onset of their seizures. Patients seizure free after anterior temporal lobectomy were also included in Group I.

In Group II, we further considered patients in whom the diagnostic criteria of a MTLE syndrome were not fulfilled or whose seizures were shown to originate outside mesiotemporal structures by ictal video-SEEG recordings. Patients with a MRI lesion outside the mesial temporal region and a strong relation between ictal video-EEG symptoms and lesion localization were also classified under this subgroup according to ictal onset. Patients with neocortical seizure onset (NC), those with temporo-perisylvian seizure onset (T+) and those with TLE without further information (t) were subsequently distinguished within Group II.

**MPPP PET analysis**

**Visual analysis**

Axial, coronal and sagittal images of BPND of the 42 patients randomly intermixed with the 19 control scans selected from our control MPPP PET database were visually analysed. Mean age and gender distribution was similar for patient and control subgroups. A set of 61 MPPP PETs was thus obtained, in which each scan was identified by a random number. Three independent examiners, who were blinded to all other data (P.R., A.H. and F.M.), were asked to report BPND decreases by drawing the visually abnormal area on individual charts showing a tridimensional picture of the brain where amygdala and hippocampus were delineated, or to specify if no BPND decrease was detectable. Only BPND decreases were analysed, because the three examiners converged on the opinion that BPND increases were not reliably visually detectable. Scans with discrepant interpretations were taken into account for calculating the rate of interobserver discrepancies and thereafter
reinterpreted by the three examiners together to reach a consensus.

**Sensitivity of visual analysis**

Patients with BP_{ND} decreases within the EZ were defined as true positives. The EZ for each subgroup was defined as follows: hippocampus, amygdala and temporal pole in MTLE, temporal neocortex in NC, perisylvian cortex in T+ and temporal lobe in t. False negatives were defined as patients in whom BP_{ND} decreases within the EZ were absent.

**Specificity of visual analysis**

Visual analysis yielded 38/42 abnormal scans. For assessing the specificity of MPPF BP_{ND} decreases in these 38 abnormal scans, Groups I and II were considered separately, since the extent of the EZ was different according to TLE subtypes. In Group I (MTLE), abnormal scans showing no BP_{ND} decrease outside hippocampus, amygdala and temporal pole were considered as specific.

In Group II, the patients with a neocortical (NC) EZ and those for whom the exact localization of the EZ within the TL was uncertain (t), specific scans were those showing no extratemporal BP_{ND} decrease. In the patients with tempo-perisylvian epilepsies (T+), scans showing no BP_{ND} decrease outside temporal lobe, insula and fronto-parietal operculum were considered as specific. Conversely, false positive scans were those showing BP_{ND} decrease outside the EZs as described above for each group.

**Voxel-based analysis of MPPF PET data**

BP_{ND} images of each patient were statistically compared with BP_{ND} images of the control subjects using the linear model at each and every voxel (Friston, 1995) and SPM99.

On the normalized smoothed images, an ANCOVA (analysis of covariance) was performed, where age, gender and global BP_{ND} were taken into account as covariates of no interest. We used a ‘Full Monty’ design modelling each patient and the control group as separate conditions. Statistical parametric maps of the t-statistic (SPM_{t}) were calculated for two contrasts per patient (controls–patient and patient–controls) with a threshold of P<0.001 uncorrected at the voxel level; an extent threshold of 100 voxels (of 2 mm × 2 mm × 2 mm) was applied at the cluster level.

**Analysis of BP_{ND} changes in relation with SEEG-recorded ictal activity**

In the 18 patients who underwent SEEG exploration, we quantitatively analysed MPPF BP_{ND} using regions of interest (ROIs) and compared data between ROIs located in and out of the EZ as defined by invasive exploration. Any ROI where SEEG showed a low voltage fast activity or a recruiting discharge during spontaneous seizures was considered as epileptogenic. Conversely, all ROIs where no ictal activity had been recorded were considered as non-epileptogenic including those unexplored by depth electrodes when clearly located outside the epileptogenic cortex.

For the comparison of BP_{ND} in anatomical ROIs, we used a frequency-based anatomical atlas (Hammers et al., 2003) based on manual delineation in 30 young adults of 83 regions (Gousias et al., 2008) concatenated into a maximum probability atlas in MNI/ICBMM152 space. Time–activity curves were automatically extracted in each ROI permitting calculation of k1, k2 and BP_{ND}.

Regional BP_{ND} values were used for statistical analysis. Only supratentorial cortical ROIs were considered for quantitative analysis (N=54). To statistically assess regional changes of 5-HT_{1A} receptor binding, patients’ BP_{ND} data were compared with those measured in the 19 subjects of our database of 48 controls, who were in the same age range as patients. Regional BP_{ND} values in male and female patients were assessed using the gender-matched subgroup of control subjects (12 males, 7 females). The mean age was identical for controls and patients of the same gender. As previous studies have shown age-related changes and gender-specific differences (Cidis et al., 2001; Costes et al., 2005), gender and age were thus taken into account.

For each ROI, individual regional BP_{ND} changes in patients were calculated as a percentage of the mean BP_{ND} value measured in the same region in the control group. This percentage (ΔBP_{ND}) was calculated using the following formula:

\[ \Delta \text{BP}_{\text{ND}} = 100 \times \frac{\text{BP}_{\text{ND}} \text{ patient} - \text{BP}_{\text{ND}} \text{ control}}{\text{BP}_{\text{ND}} \text{ control}} \]

The ΔBP_{ND} is nil when BP_{ND} values are identical in patients and controls, negative for binding decrease and positive for binding increase in patients versus control subjects.

ΔBP_{ND} in epileptogenic and non-epileptogenic regions were then compared using the Mann–Whitney test (‘R’ software: Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, http://www.R-project.org). Firstly, we performed a global analysis on all cortical ROIs (Fig. 3A): for each of the 18 patients, a mean global BP_{ND} was calculated for pooled ROIs, where ictal activities were recorded. This BP_{ND} was then compared with that measured within homologous regions of control subjects. The same procedure was performed for non-epileptogenic ROIs in patients and homologous ROIs in controls. We subsequently calculated ΔBP_{ND} for epileptogenic and non-epileptogenic ROIs.

Secondly, a regionally specific analysis was performed in the seven anatomical areas most often involved in SEEG ictal discharges. In this analysis, the ΔBP_{ND} values were pooled together in each epileptogenic region and compared with the pooled values of ΔBP_{ND} in the homologous non-epileptogenic region.

**Results**

**Clinical features**

The forty-two patients, whose clinical features, MRI data and surgical outcomes are given in Tables 1–3, were aged from 18 to 61 years (mean 35.4 years). The mean epilepsy duration was 21 years (σ = 9.5). Seven of the 34 patients, where data were available (21%), all with MTLE (Group I), had a Beck Depression Inventory (BDI II) score higher than 14 and may thus be considered as presenting depressive symptoms.

**Group I consisted of 32 patients (Patients 1–32; 76%) suffering from MTLE:**

- Patients 1–16 fulfilled all criteria described above and showed temporal hypometabolism on FDG PET. This was ipsilateral to the ictal and interictal EEG.
abnormalities and to the hippocampal atrophy. All these patients were thus considered eligible for temporal lobectomy without undergoing video-SEEG. Anterior temporal lobectomy was performed in Patients 1–11, and Patient 12 underwent selective amygdalo-hippocampectomy. All were Engel Class I after a mean follow-up of 20 (10–48 months). Four (Patients 13–16) declined surgery.

- Thirteen other patients (Patients 17–29) were included in this MTLE group on the basis of data from the video-SEEG exploration of mesial, polar and lateral temporal cortex. A mesiotemporal origin of seizures was demonstrated, although none of them presented with all criteria of the MTLE syndrome as detailed above. In five patients (Patients 17–21), brain MRI was normal. Patients 22 and 23 had a focal dysplasia located within the hippocampus. The six remaining patients (Patients 24–29) had lateralized hippocampal atrophy on brain MRI but atypical clinical history and/or ictal surface video-EEG semiology. Surgery was not indicated for Patient 17 because of the bilateral onset of her mesiotemporal seizures proved by SEEG, and Patient 18 declined surgery. Eight patients (Patients 19–26) underwent anterior temporal lobectomy. Six patients (75%) were seizure free (Engel Class I) and two (Patients 25 and 27) were Engel Class II with a mean post-surgical follow-up of 21 months (7–32 months). Patients 27–29 were not operated upon despite eligibility, because they volunteered to enter a study of stereotactic thrombo-coagulation treatment at the end of the video-SEEG recording procedure.

- Patients 30–32 were included in the MTLE group, because they presented clinically as a MTLE, but with atypical MRI findings (bilateral hippocampal sclerosis in Case 30, mesiotemporal dysplasia in Case 31 and normal MRI in Case 32). None of them underwent video-SEEG monitoring before surgery. They are all seizure free (Engel’s Class Ia) after anterior temporal lobectomy.

**Group II consisted of 10 TLE Patients:**

- Five patients (Patients 33–37) were classified under neocortical TLE (NC). In all of them, scalp ictal video-EEG recordings showed low-voltage discharges under temporal electrodes at the very onset of their seizures. Three of them (Patients 33, 34 and 36) reported ictal onset symptoms such as auditory hallucinations, vertigo or early aphasia suggestive of a seizure onset outside mesiotemporal areas and none reported epigastric auras at the beginning of their seizure. MRI was normal in one patient (Patient 33) and showed atrophy of the temporal pole and lateral neocortex in two (Patients 34 and 35) and lateral temporal dysplasia in two (Patients 36 and 37). Ictal video-SEEG recordings confirmed seizure onsets in the lateral temporal neocortex in four of them (Patients 33–36), of whom three were operated. Patient 33 underwent an amygdalectomy associated with temporo-polar, entorhinal area and T5 anterior cortectomy. Anterior lobectomy including right T1–T4, 4 cm from the pole, was performed for Patient 34, and Patient 36 underwent temporo-basal lobectomy including, from the temporal pole, 2 cm of T1, 4 cm of T2 and 8 cm of T3 and T4. Two have a Class Ia (Patients 33 and 36), and one a Class II outcome (Patient 34), 17–36 months after surgery.

The fifth patient (Patient 37) with a temporal dysplasia involving basal and lateral temporal cortex was seizure free (Engel Class Ia) 29 months after lesionectomy including the mid-third of anterior T2 and two-thirds of anterior T3. Invasive exploration was not felt to be necessary for this patient because of the strong relationship between ictal video-EEG symptoms and localization of the dysplasia.

- Three patients (Patients 38–40) with a focal cortical dysplasia were classified as temporo-perisylvian epilepsies (T+) on the basis of video-SEEG or video-EEG data showing an early implication of frontal, parietal or temporal opercular cortex in their seizures. None of these patients was considered eligible for surgery after preoperative evaluation.

- The two remaining patients (Patients 41 and 42) were classified as TLE without further information (t). In both, MRI showed a large dysplasia of the temporal cortex. Precise delineation of structures involved in seizures would have required a video-SEEG exploration that the two patients declined, so that surgery could not be offered to them.

**FDG PET data**

Results of FDG PET visual analysis for the 38 patients in whom FDG PET was performed are given in Table 2. Interobserver discrepancies occurred in 13 scans (i.e. 34%). FDG PET was considered normal in four patients (Patients 14, 18, 23 and 33), while two other patients only demonstrated hypometabolism outside the epileptogenic temporal lobe (Patients 15 and 24). Overall, 32 out 38 patients showed FDG PET abnormality within their epileptogenic temporal lobe providing a sensitivity of 84%. However, three of these patients had bilateral focal areas of hypometabolism (Patients 6, 27 and 37). Seven of the MTLE patients had a focal hypometabolism restricted to mesiotemporal structures. Extratemporal hypometabolism was reported in 13 patients and mostly involved the insula (11 patients) and the frontal lobe (eight patients).

**MPPF PET visual analysis**

Table 3 summarizes the results of the MPPF PET visual analysis. Discrepant initial PET data interpretations between the three examiners occurred for only three of the 42
patients (7%). Only structures neighbouring the epileptic hippocampus were concerned by these discrepancies. No interexaminer mismatch was observed for side or lobe identification. Furthermore, none of the 19 randomly intermixed control scans were considered as showing a focal decrease of MPPF binding by any of the three examiners, so that interpretations were fully converging for 58 of 61 (95%) PET images. This low percentage of divergences reflects the observation by the three examiners that decreases of MPPF binding (BPND) were usually unequivocal on visual analysis.

Thirty-eight of the 42 patients’ scans were abnormal on blinded visual analysis. BPND decreases involved the epileptogenic lobe and ipsilateral mesiotemporal structures in all 38 abnormal scans, i.e. there were no false lateralization on visual analysis. Hippocampus (35/38, 92%), amygdala (32/38, 84%) and temporal pole (29/38, 76%) were the structures most often involved (Fig. 2).
In 24 of 38 (63%) patients with MPPF PET abnormalities (63%), the area of decreased BPND spread beyond the mesial temporal region and involved lateral temporal, insular or perisylvian cortical areas. In particular, a BPND decrease within the insula was observed in 18 of the 38 abnormal scans (47%).

In Group I (MTLE), seven of the 32 scans (22%) showed a BP decrease limited to mesiotemporal structures (amygdala and/or hippocampus). In addition to mesiotemporal structures, the BPND decrease also spread ipsilaterally to the temporal pole in five patients (16%), to the temporal neocortex beyond the temporal pole in five (16%) and to the insular cortex in twelve (37%). The three remaining patients had no decrease of BPND.

In Group II, no patient showed a BP decrease restricted to mesiotemporal structures (amygdala, hippocampus or both), and none but one patient (Patient 40) showed a BPND decrease that involved strictly the amygdala and the temporal pole. In temporal epilepsies classified as ‘neocortical’ (NC), one patient showed no BPND decrease (Patient 33). The four others showed a BPND decrease in the hippocampus and/or amygdala and in the temporal pole that also involved the lateral temporal neocortex (Patients 34–36), and/or the insula (Patients 34, 36 and 37). In two of the three patients classified as temporo-perisylvian epilepsies (T+), there was a BPND decrease outside the epileptogenic temporal lobe either in the ipsilateral insula (Patient 39) or opposite to it in contralateral amygdala (Patient 38). The third patient of this subgroup (Patient 40) had a BPND decrease restricted to amygdala and temporal pole on the epileptogenic side. Both patients (Patients 41 and 42) in whom the location of the EZ was uncertain (t) showed large BPND decreases in the epileptogenic temporal lobe, spreading to the ipsilateral insula.

**Sensitivity of visual analysis**

PET scans were considered normal in four of 42 patients (9.5%) and lateralized focal decreases of BPND were visually identified in the epileptogenic temporal lobe of 38/42 patients. Thus, the global sensitivity was of 90.5%. Sensitivity was similar in Group I (29/32 patients; 90.6%) and Group II (9/10 patients; 90%). The scan of Patient 17 with bilateral MTLE and a BPND decrease on left side only was considered twice in this calculation as truly positive on the left side and falsely negative on the right side.

**Specificity of visual analysis**

**Specificity of the presence of visually identified decreases of MPPF BPND.** None of the 19 healthy controls were incorrectly identified as showing MPPF BPND decreases; therefore, visually identified decreases were 100% specific for an epileptogenic temporal lobe.

**Specificity of the extent of visually identified decreases of MPPF BPND for indicating the exact extent of the EZ.** According to our conservative criteria, only 12 of the 29 abnormal MPPF scans in the MTLE group showed a BPND decrease restricted to mesiotemporal structures and temporal pole, thus leading to a specificity of 40%. The scan of Patient 17 with bilateral MTLE was classified as a false positive, since it showed a BPND decrease spreading to the insula on the abnormal side. The 17 scans classified as false positive showed ipsilateral extension of BPND decrease to the insula in nine patients, to lateral temporal cortex in five and to both of these areas in three.

In Group II, the specificity of MPPF PET abnormalities was lower (33%), since only three of the nine patients with abnormal scan had a BPND decrease limited to the EZ. As for Group I, there was a major impact of the low specificity of insular BPND decreases, which were the only false positive data in five patients.

**MPPF PET SPM analysis**

Results of the SPM analysis are given in Table 3. Thirty-three patients (79%) showed BPND abnormalities. Most of them were BPND decreases (28/33, 85%), but 12/33 (36%)}
showed $\Delta BP_{ND}$ increases. In all patients showing at least one or several areas of $BP_{ND}$ decrease, the epileptogenic temporal lobe was involved except for Patient 15 in whom only the ipsilateral insula showed a decrease; however, in four, both temporal lobes were involved (4/28, 14%). $BP_{ND}$ increases could be ipsilateral or contralateral to the epileptogenic temporal lobe (four and seven patients, respectively) and were bilateral in one (Patient 27), but they never involved the EZ, although they could be located in its vicinity. In terms of $BP_{ND}$ decrease, the sensitivity of SPM analysis was only 67% (28/42) when evaluated with the same criteria as for visual analysis.

**$BP_{ND}$ changes in relation with SEEG-recorded ictal activity**

As illustrated in Fig. 3, the $\Delta BP_{ND}$ values were consistently negative indicating reduced $BP_{ND}$ in the SEEG-delineated epileptogenic regions, but not in non-epileptogenic regions (Fig. 3A), compared to controls. Furthermore, when compared with contralateral homotopic non-epileptogenic regions, these abnormalities were highly significant in most epileptogenic regions including hippocampus (Fig. 3B), amygdala (Fig. 3C), temporal pole (Fig. 3D), parahippocampal gyrus (Fig. 3E), and insula (Fig. 3H). Significance level was not reached in superior and middle temporal gyrus (Fig. 3F and G) primarily due to higher SD/mean ratios (coefficients of variation, CV, expressed as a percentage) in these two areas (CV = 27.6 and 24.7%, respectively) compared with other anatomical structures (hippocampus, CV = 18.9%; amygdala, CV = 16.5%; temporal pole, CV = 15.3%; parahippocampal gyrus, CV = 10.9%; insula, CV = 17.6%).

**Discussion**

**Methodological issues**

Before addressing the questions of MPPF PET sensitivity, specificity and clinical relevance in the presurgical assessment of TLE patients, several issues regarding data analysis and interpretation deserve some comments.

**Partial volume effect**

Partial volume effect (PVE) certainly had an impact on the evaluation of hippocampal $BP_{ND}$ in the majority of our patients who showed hippocampal atrophy in the epileptogenic temporal lobe (25/42; 60%). There is no doubt that visual analysis cannot make the distinction between $BP_{ND}$ decreases according to whether they reflect reduced receptor density or volume loss; the same limitation applies to atrophic regions in the ROI analysis and voxel-by-voxel analysis. However, the visual analysis did show hippocampal $BP_{ND}$ decreases in 11 of our 17 patients (65%) without hippocampal atrophy. Using the $^{18}$F-radioligand FCWAY for mapping 5-HT$_{1A}$ receptor density, Giovacchini et al. (2005) showed that BP decreases in mesial temporal structures and insula measured by ROI analysis remain significant after PVE correction in TLE patients. More generally, the clinical relevance of PVE correction is questionable in our study design that aimed to assess the diagnostic value of MPPF PET visual analysis in individual patients. PVE may fully explain our findings in only two of our patients (Patients 12 and 28) with hippocampal atrophy whose area of $BP_{ND}$ decrease was restricted to hippocampus, whereas in 95% of patients with abnormal MPPF scans (36/38), the $BP_{ND}$ decreases were seen outside the hippocampus as well; the same argument holds for non-atrophic epileptogenic regions in ROI analysis.

**Interaction between epilepsy and depression**

Previous studies of 5-HT$_{1A}$ receptors in TLE have reported correlation between PET findings and depressive symptoms. A significant inverse relation between the Montgomery-Asberg Depression rating scale and 5-HT$_{1A}$ receptor binding was reported by (Savic et al., 2004), in the anterior cingulate gyrus ipsilateral to seizure focus using $^{[11C]}$WAY100635. An inverse relation between BDI scores and 5-HT$_{1A}$ receptor binding in the hippocampus ipsilateral to seizure focus was reported with $^{[18F]}$FCWAY (Giovacchini et al., 2005; Theodore et al., 2007). In a parallel study including 24 of the 32 patients of the present series, we have demonstrated a positive correlation between depressive symptoms, as measured with BDI II, and $^{[18F]}$MPPF $BP_{ND}$ in the left insula and the raphe nuclei. We also observed a positive correlation between the intensity of the somatic symptoms of depression and $^{[18F]}$MPPF $BP_{ND}$ within the epileptogenic and atrophic hippocampus (Lothe et al., 2008). The opposite direction of the correlation observed with $^{[18F]}$MPPF $BP_{ND}$ as compared with the $^{[18F]}$FCWAY might reflect their different affinities for 5-HT$_{1A}$ receptors, whereby only $^{[18F]}$MPPF can be displaced by endogenous serotonin. In any event, these findings indicate that depression is unlikely to account for the decreased $BP_{ND}$ observed in our patients.

**$BP_{ND}$ changes in relation to SEEG-recorded ictal activity**

Quantitative analysis of $BP_{ND}$ using ROIs confirmed two of our previous findings regarding the relation between decreased 5-HT$_{1A}$ receptors binding and epileptogenicity. Firstly, the $BP_{ND}$ was reduced in areas showing ictal activity on SEEG recordings when compared with homologue cortical regions in controls (Merlet et al., 2004b). Secondly, this decrease was significant when comparing epileptogenic versus non-epileptogenic regions in patients (Merlet et al., 2004a). In addition, we showed that $BP_{ND}$ decrease also correlated with ictal activity for individual anatomical structures individually studied. Superior and middle temporal gyrus did not show significant correlation of reduced $BP_{ND}$ with ictal activity because of large SD values for these structures. However, the $\Delta BP_{ND}$ decrease...
Fig. 3  \( \Delta \text{BP}_{\text{ND}} \) changes in relation with SEEG-recorded ictal activity. Anatomical areas were defined with a frequency-based atlas (see text for details) and have been classified as epileptogenic (filled bars) or non-epileptogenic (open bars) ROIs. \( \Delta \text{BP}_{\text{ND}} \) in patients was compared with the corresponding values in 19 controls, matched for gender (e.g. a \( \Delta \text{BP}_{\text{ND}} \) in the hippocampus in a male patient was compared against the \( \Delta \text{BP}_{\text{ND}} \) values in all hippocampi in all male controls). Numbers of ROIs differ by region as a function of frequency with which they were sampled. \( \Delta \text{BP}_{\text{ND}}\% \) of \( \Delta \text{BP}_{\text{ND}} \) decrease or increase compared with gender-matched control groups. \( n = \) number of epileptogenic ROIs/number of non-epileptogenic ROIs for each comparison. Error bars represent the SD. \( * P < 0.05, ** P < 0.005, *** P < 0.0001 \), NS: not significant.
measured within superior temporal gyrus was close to significance level (P = 0.08).

**Sensitivity of MPPF PET**

**Visual analysis**

This study shows that, in individual TLE patients, visual analysis of MPPF PET data, blinded to clinical information and data from other presurgical investigations, permits to identify the epileptogenic lobe with a sensitivity of 90%. Interobserver disagreement was very low at 7%; note that the disagreement was about extent of abnormalities but never about lateralization. No sophisticated or time-consuming procedures are required to derive BP\textsubscript{ND} images, and visual analysis proved usable in clinical practice for preoperative evaluation of TLE patients. The side of the epileptogenic temporal lobe could be accurately identified in 38 of the 42 patients (90%), even in those without hippocampal sclerosis. MPPF BP\textsubscript{ND} decreases involving hippocampus, amygdala and temporal pole together were observed exclusively in MTLE patients, in agreement with our previous finding that, at a group level, these three areas were showing BP\textsubscript{ND} decrease on statistical parametric analysis in MTLE patients with hippocampal atrophy (Merlet et al., 2004b). No false seizure focus lateralization was seen on MPPF PET images, as has been described with Bmax images derived from [\textsuperscript{11}C]flumazenil PET (Bouvard et al., 2005).

In contrast to statistical SPM analysis, visual analysis is limited by the difficulty to identify regions with increased binding areas, which were often located in the hemisphere opposite to the epileptogenic temporal lobe (see below).

**SPM analysis**

Statistical analysis is a more objective way for identifying areas of abnormal MPPF BP\textsubscript{ND}. However, the sensitivity of SPM analysis of individual MPPF PET data in terms of BP\textsubscript{ND} decrease proved lower than that of visual analysis. SPM analysis with the standard settings used in our analysis may thus identify the epileptogenic lobe but is seriously lacking sensitivity, since no 5-HT\textsubscript{1A} receptor-binding decreases were detected in nearly half (17 patients, i.e. 40%) of epileptogenic temporal lobes. This low sensitivity likely pertains to the high variability of MPPF BP\textsubscript{ND} values across healthy subjects and brain regions (Costes et al., 2005). Indeed, the mean global BP\textsubscript{ND} value in healthy subjects is 0.49 ± 0.09 (range: 0.27–0.71), which rises to 0.8–1.5 in the hippocampus and to 0.5–1.2 in the limbic cortex.

The SPM analysis is based on the statistical comparison of each voxel’s BP\textsubscript{ND} value in an individual patient with those measured in the near homologous voxel in a set of control subjects. Thus, only dramatically abnormal BP\textsubscript{ND} voxel values are detected by statistical analysis when the range of normal values is large. This effect was only partly decreased by taking into account the global value of BP\textsubscript{ND} of each patient and control in the statistical analysis (see ‘Methods’ section). At an individual level, this bias may be overcome by other methods currently being validated using either asymmetry indices between homologous ROI (Kang et al., 2001), combinations of voxel-based analysis and volumes of interest (Hammers et al., 2001), or standardizations with reference to intrasubject measures (Hammers et al., 2007). However, many of these methods are still very time consuming, and do not currently lend themselves to widespread routine clinical use.

SPM has the advantage over visual analysis to reveal areas of increased BP\textsubscript{ND} areas, but in this study, all such areas were contralateral to the seizure focus when they were located in the temporal lobe, and outside the temporal lobe when ipsilateral to the seizure focus. Although these BP\textsubscript{ND} increases have a limited diagnostic utility, they might be relevant for assessing the mechanism of serotonin transmission changes in TLE. Extra-temporal increases of BP\textsubscript{ND} involve regions that are not included in the epileptogenic network and may reflect an over-expression of 5-HT\textsubscript{1A} receptors in healthy cerebral tissue. This is consistent with a possible antiepileptic effect of endogenous serotonin through 5-HT\textsubscript{1A} receptors. Although the antiepileptic effect of serotonin remains a matter of discussion (Barnes and Sharp, 1999), recent neuropharmacological studies performed on three different types of epilepsy models support this hypothesis (Lopez-Meraz et al., 2005).

**Specificity of MPPF PET visual analysis**

Specificity can be evaluated either according to the epilepsy subtypes and related extents of the EZ as assessed by presurgical explorations, or according to the surgical outcomes, with the limitation that a seizure-free outcome only indicates that the epileptogenic area was included in the resected tissue. In what follows, only the specificity of visual analysis will be considered.

**Specificity regarding epilepsy subtypes**

While the epileptogenic lobe is identified with great accuracy by visual analysis of MPPF PET, and this analysis is 100% specific in the sense that no healthy controls were considered abnormal, the specificity is <40% when the precise mapping of the EZ is at stake. Indeed the extent of BP\textsubscript{ND} decreases did not correspond exactly to that of the EZ as defined by preoperative evaluation. Areas showing a decrease of BP\textsubscript{ND} often spread outside the EZ within the temporal lobe as well as to the neighbouring structures. Thus, the area of 5-HT\textsubscript{1A} receptor-binding decrease was larger than the EZ in near a half of patients (20/42, 48%). Furthermore, in 12 of the 24 patients who have remained seizure free since their operation, the area showing reduced 5-HT\textsubscript{1A} receptor-binding extended beyond the resection area.

Insula ipsilateral to the epileptogenic temporal lobe is the extra-temporal area, where reduced BP\textsubscript{ND} was the most often visually detectable (47%) regardless of the
TLE subtype. Therefore, the similar finding previously reported at group level in MTLE patients (Merlet et al., 2004a) seems to be applicable to all types of TLE. The insulin is often involved in seizure spread in TLE patients who become seizure free after anterior temporal lobectomy (Silvenius et al., 1964; Isnard et al., 2000), whereas patients with seizure onset in the insula are rare (Isnard et al., 2004). Evidently reduced 5-HT$_{IA}$ receptor binding in the insula does not permit per se to discriminate between TLE and insular epilepsies. It is not known whether the MPPF BP$_{ND}$ decrease could be restricted to the insula in insular epilepsies, a finding that was never observed in our TLE patients.

The same conclusion applies to the extension of MPPF BP$_{ND}$ decrease to lateral temporal neocortex in MTLE. Of the eight patients with this PET abnormality, the five who underwent anterior temporal lobectomy are seizure free. Moreover, of the three patients with neocortical TLE who are seizure free after a tailored surgery involving the lateral temporal neocortex (Tables 2 and 3), one had no BP$_{ND}$ abnormality at all (Patient 33), another had no BP$_{ND}$ decrease in lateral cortex (Patient 37) and only the third one (Patient 36) had a latero-temporal BP decrease.

**Specificity regarding surgical outcome**

Sixteen of the eighteen operated patients (89%) whose MPPF PET showed a BP$_{ND}$ decrease restricted to the hippocampus, amygdala and temporal pole, with or without extension to the ipsilateral insula, are seizure free after anterior temporal lobectomy. The remaining two patients with a Class II outcome had a focal dysplasia in the epileptogenic temporal lobe (Patients 22 and 24). Thus, visual observation of this type of MPPF PET abnormalities in association with isolated hippocampal atrophy or normal MRI is highly predictive of a favourable surgical outcome. Conversely, extension of BP decrease to lateral temporal cortex entails no worse prognosis when the clinical presentation is that of a MTLE syndrome, and similarly, the absence of visually detectable PET abnormality does not preclude a seizure-free outcome (Patients 27 and 33).

**Comparison between MPPF and FDG PET**

Comparison between FDG and MPPF PET data shows a clear-cut superiority of the latter for localizing visually the epileptogenic area in MTLE patients. The rate of interobserver discrepancies was much higher for FDG (34%) than for MPPF (7%) PET. The specificity of FDG PET was also lower than that of MPPF PET with only 23% of patients showing hypometabolism restricted to hippocampus, amygdala and temporal pole, versus 38% demonstrating such abnormalities with MPPF PET. Furthermore, glucose hypometabolism spared the mesial temporal cortex and temporal pole in three MTLE patients, of whom two have been operated and are seizure free after anterior temporal lobectomy, a condition that never encountered with MPPF PET. Lastly, a glucose hypometabolism extended outside the temporal lobe and insula in 21% of patients, whereas this was never observed with MPPF BP$_{ND}$ decrease.

**Conclusion**

Presurgical neuroimaging in TLE aims at assessing each individual patient’s suitability for temporal lobectomy, if possible by producing images that can be visually interpreted at bedside. This study shows that visual analysis of MPPF BP$_{ND}$ images allows a correct identification and lateralization of the epileptogenic temporal lobe with 100% specificity (no false positives in control subjects), a false negative rate inferior to 10% and an interexaminer mismatch rate of 7%.

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