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Analysis of the relationship between interictal electrical source imaging and PET hypometabolism

C. Person, L. Koessler, V. Louis-Dorr, D. Wolf, L. Maillard, P.Y. Marie

Abstract—The aim of this paper is to compare interictal EEG source localizations with statistical analysis of hypometabolisms in PET brain imaging. Both methods are currently used in the pre-surgical evaluation of drug-resistant partial epilepsy, but the relationship between electrical source localizations and hypometabolic areas has not been well defined yet. At the present time, these two methods have been performed on five patients in order to develop a comparative quantitative study with these first results which should be then extended to a larger patient database.

I. INTRODUCTION

Pre-surgical evaluation of epilepsy consists in the localization of the epileptogenic zone which causes epileptic seizures. Different techniques exist to identify and characterize this zone such as electroencephalography (EEG) and Positron Emission Tomography (PET). To improve the intracerebral source localizations, high resolution (HR) EEG (at least sixty-four sensors and 1 KHz sampling rate) combined with inverse problem methods have been developed in the past few years (see [1] for review). Several studies have demonstrated that interictal and ictal spikes, which are characterized by a high signal-to-noise ratio, can be accurately localized with equivalent current dipole models [2, 3, 4].

On the other hand the study of glucidic metabolism by the ^{18}F -FDG (^{18}F -fluorodeoxyglucose) PET has been used in the analysis of temporal lobe epilepsies for more than 20 years [5], but it was only recently validated in clinical practice. Interictal PET allows the identification of reductions in cerebral metabolism, which complements elements provided by the HR-EEG and other modalities such as MRI or SPECT for example. Despite its clinical practice use, there is no real consensus about the optimal method to analyze this exam: the basic method of visual analysis was used for a long time [6], but is subject to important inter-observers variability.

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Other approaches were proposed, in particular voxel-to-voxel quantitative analysis such as SPM (Statistical Parametric Mapping) [7]: the values of each voxel of the cerebral image of a patient are compared with the values of the voxels of the images of a reference population. This supposes a preliminary deformation of the images so that each voxel corresponds to the same anatomical area for all the subjects: it is spatial normalization. The advantage of this procedure is the whole automation of the treatment which does not require any subjective intervention of the operator. On the other hand, spatial normalization can sometimes lead to aberrant deformations of the images with the SPM method because of the much dispersed detection of the hypometabolic areas obtained.

We propose to apply in this process a new spatial normalization method [8] which has been used in particular for the registration of pelvis CT scans, in order to optimize the identification of hypometabolic areas. We then compare anatomical localizations of the hypometabolic areas with the electrical sources localized from the HR-EEG. This comparison should compensate for the imprecision of each modality while considering the joint information provided by both of them.

II. MATERIALS AND METHODS

Five patients with temporal lobe epilepsy were compared to a reference population of 14 subjects without neurological abnormalities. All the images have been acquired with the same Siemens PET camera. These 14 subjects were patients with a lymphoma in remission and their neurological examination did not detect any anomaly.

The images were first of all spatially normalized in order to register them with a template used as an anatomical reference. The template was built from our reference population database. The images were then smoothed by convolution with a Gaussian kernel of 12 mm of full width at half maximum, to improve signal to noise ration and to reduce the interindividual variations of the signal. Then, voxel-to-voxel Student tests were carried out with SPM5 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK) [7] in order to highlight the hypometabolic areas, i.e. the voxels of significantly lower value than the normal population.

The image of the hypometabolic results was then transformed into the initial PET space, while applying the inverse transformation of the spatial normalization. Finally, a

registration was performed by SPM between the MRI of each patient to analyze and his CT scan provided by the PET-CT camera (PET and CT were already registered due to the acquisition). This registration was applied to the hypometabolism image, allowing comparisons between PET hypometabolisms and electrical source localizations in the same MRI coordinates system. Figure 1 shows an example of a patient's hypometabolisms displayed on his individual MRI.

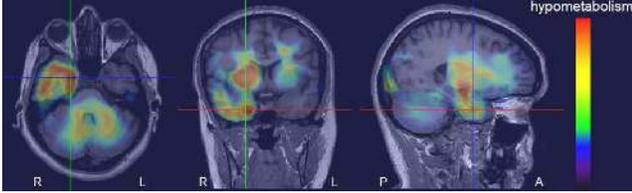


Fig. 1. Localization of the maximum T-score PET hypometabolism displayed on the individual MRI

A. EEG source localization

The five patients analyzed in this study had lesional temporal lobe epilepsy (two schizencephalies, two dysplasias and one temporal cortectomy), either right or left. The epileptogenic zone was medial temporal for the five patients and the basal temporal area was also involved for two of them (no. 2 and 5). This group was retrospectively selected from patients who had both a HR-EEG and a cerebral ^{18}F -FDG PET in the university hospital of Nancy (France), and a SEEG (Stereo-EEG) had then confirmed the diagnostic of temporal lobe epilepsy. The HR-EEG signals were recorded using 64 electrodes and a sampling frequency of 1024 Hz. The electrical source localization was performed with ASA software (ANT Software, Enschede, Netherlands) which also allowed semi-automatic segmentation of the MRI of the patients to build their own realistic head model. Five interictal spikes per patient were analyzed with a rotating dipole method (i.e. during the time windows of analysis the position of the dipole is fixed for each spike and its magnitude, moment and direction are calculated) and the sources positions were co-registered in each individual MRI. Equivalent current dipoles are well adapted for spikes analysis because of the restricted cortex area activated during a short time window [4, 9, 10].

B. PET spatial normalization

Several methods of spatial normalization can be applied in this context [11]. To improve the one implemented in SPM [7], we chose to apply a local iconic method (based on the intensities of the voxels), called Block-Matching [8], in order to obtain more robust transformations with the presence of pathologies.

The first step of this method corresponds to a simple affine registration. Afterwards, the calculation of the transformations is based on the pairing of blocks between the image to standardize and the template. The principle is to be able to move an image area in a neighborhood, and to put it

in correspondence with the block of the template located at the same position. This process is carried out iteratively in a multi-resolution process, in each of which the size of the blocks is fixed [12].

The similarity measurement between the blocks B_x of the image and B_y of the template is quantified by:

$$CC^2(B_x, B_y) = \frac{\text{Cov}^2(B_x, B_y)}{\text{Var}(B_x) \cdot \text{Var}(B_y)} \quad (1)$$

If x is the centre of the block B_x in the image to normalize, and y the centre of the block B_y in the template for which the similarity (1) is maximum, a displacement field D can be defined, for each couple (x, y) :

$$D(x) = y - x \quad (2)$$

A scalar confidence field in pairings C is also defined, thanks to the values of the similarity measurements between paired blocks B_x and B_y respectively centred in x and y :

$$C(x) = \arg \max_{y \in V_x} CC^2(B_x, B_y) \quad (3)$$

where V_x stands for the neighbourhoods of block B_x .

The fields D and C are thus null in all the points which are not the centre of a block: the objective is then to lead to a dense transformation starting from these scattered fields D and C . Thereby, an interpolation δT^p (calculated with the iteration p) between pairings is obtained by convolution of the field D with a Gaussian:

$$\delta T^p = \frac{G_\sigma * C \cdot D}{G_\sigma * C} \quad (4)$$

Weighting by C emphasizes in this interpolation pairings for which the similarity is important. In addition, the standard deviation σ of the Gaussian allows a standardization of the displacements by a more or less important interpolation. Thus, a dense field δT^p is obtained starting from various pairings of blocks.

However, errors on these pairings can be made, in particular because of a pathological area located in one of the images. A comparison between the initial field D and the interpolation δT^p of displacements makes possible to measure their average difference e and the variance σ_e^2 of this difference:

$$e = \frac{1}{N} \sum_i \left\| D(x_i) - \delta T^p(x_i) \right\| \quad (5)$$

$$\sigma_e^2 = \frac{1}{N} \sum_i \left(e - \left\| D(x_i) - \delta T^p(x_i) \right\| \right)^2 \quad (6)$$

The following criterion allows then to define aberrant pairings:

$$\left\| D(x_i) - \delta T^p(x_i) \right\| > e + \alpha \cdot \sigma_e \quad (7)$$

All pairings for which the difference between the fields D and δT^p exceeds too the average are considered aberrant and

are removed from the field D , the parameter α allowing to reject more or less pairings.

The new field D obtained is then interpolated again (according to equation 4) in order to lead to a new dense field of corrections δT^p which is then composed with the transformation calculated with the preceding iteration:

$$T^p = T^{p-1} \circ \delta T^p. \quad (8)$$

Practically, $p=10$ iterations are enough to produce an acceptable transformation and each block is a cube of $7 \times 7 \times 7$ voxels, these parameters having been validated by medical expertise on TEP results.

III. COMPARISON BETWEEN PET HYPOMETABOLISMS AND EEG ELECTRICAL SOURCES

A. Hypometabolism around the electrical sources

The electrical source localizations and PET hypometabolisms were globally consistent with intracerebral exploration used as a reference in pre-surgical evaluation. To compare quantitatively the results between the PET hypometabolisms and the electrical sources modeled by the rotating dipoles method, we first calculated the T-scores in the neighborhood of the 25 source localizations (5 spikes for each of the 5 patients). In order to take into account the errors in source localizations especially due to the resolution of the inverse problem (ill posed), we defined for each patient 5 spheres centered at the 5 electrical sources and made their radius vary from 1 to 31 mm to pick out all the associated Student T-scores inside these spheres. Figure 2 shows a boxplot of these results where all the values of the T-scores inside the 25 spheres have been picked out for each radius.

This figure tends to prove that the electrical sources and the PET hypometabolism are actually linked, since while letting the radius of the spheres increase, the average T-score decreases which can be explained by the fact that the largest T-scores are closer to the center of the spheres. In addition,

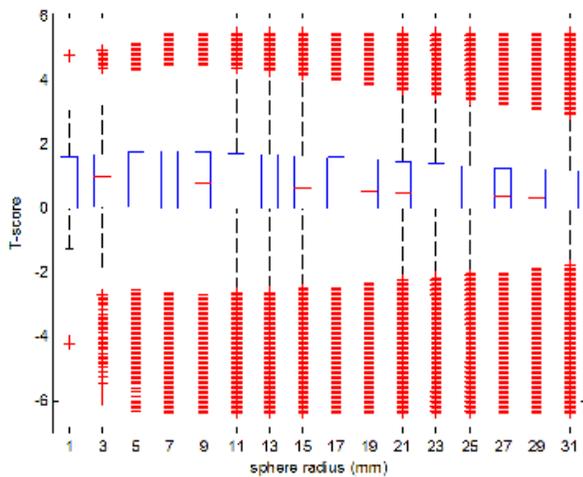


Fig. 2. Boxplot of all the hypometabolic Student T-scores in spheres centered at the 25 electrical sources localized with Rotating dipole

the upper quartile is also slightly decreasing, being generally bigger than 1.77 which corresponds to the hypometabolic significance threshold $p=0.05$ in our unilateral Student test (with 13 degrees of freedom). Furthermore, the number of outliers increases with the radius of the spheres since a larger volume should contain more dispersed values.

The distances between the electrical sources and their barycenter were calculated in order to estimate the dispersion of the rotating dipoles localizations: the mean values were between 13 and 21 mm and their standard deviations between 4 and 7 mm. These results are concordant with the sublobar precision of the source localization method.

The same boxplot study was also made separately for each of the 5 patients with only his own data and led to similar results, although the statistical robustness would be more opened to criticism in these cases because of the low number of points, especially for the smallest spheres.

B. Distance between electrical sources and hypometabolic volumes

To study more precisely the relationship between the electrical source localizations with the rotating dipole method and the hypometabolism obtained by the Student tests on the PET images, an evaluation of the Euclidean distance between the results of the two modalities was performed. First of all, the hypometabolic volume had to be clearly defined. We used two thresholds in the T-scores images in order to keep only the voxels corresponding to significant probabilities ($p=0.01$ and $p=0.05$). Then the maximum T-score was localized in this threshold image to define a volume of contiguous voxels. A second and a third volume were also defined when other foci existed, and they were classified thanks to their maximum T-score. A distance between each of these contiguous volumes and the electrical source localizations could be defined as the minimum Euclidean distance between the sources and the voxels belonging to these volumes. The results of these measurements can be found in table I for a significant threshold $p=0.01$. The rank of the maximum in the hypometabolic volume indicates if this considered volume is the cluster with the maximum T-score, or if it is the second or the third volume with the largest T-score. The volumes we chose in the table I are the closest to the electrical sources and not especially the ones with the maximum T-scores.

The hypometabolic volumes are obviously more extended with a less restrictive threshold which explains that more electrical sources are inside them (3/25 if $p=0.01$, 5/25 if $p=0.05$) and that the sources outside these volumes are closer. If $p=0.05$, the closest hypometabolic volume to the electrical sources is the one with the maximum T-score in 4 cases of 5, and this is the second hypometabolic focus in the last case. If $p=0.01$, the maximum T-score is not anymore the closest to the source in 3 cases of 5, because of the low threshold which let local maxima appear.

TABLE I
DISTANCES BETWEEN EEG SOURCES AND PET HYPOMETABOLISMS
($P=0.01$)

	hypometabolic volume (HV)	number of sources in the HV	average distance of the sources outside the HV	rank of the maximum in the HV
patient 1	14.45 cm ³	0/5	15.9 mm	3
patient 2	10.18 cm ³	1/5	11.9 mm	1
patient 3	0.18 cm ³	0/5	32.8 mm	2
patient 4	-	-	-	-
patient 5	19.46 cm ³	2/5	6.1 mm	1

IV. DISCUSSION

The results of the distances measurements between electrical sources and PET hypometabolism tend to prove the close relation between the anatomical localizations brought by these two methods. The localizations of the former are indeed consistent with the ladder modality, even if there are however some variation in the positions. It has to be kept in mind that the brain hypometabolic areas and the sources of interictal spikes are not necessarily localized in the same place. The electrical sources found with the rotating dipole method can have various positions according to the considered spikes and the inverse problem resolution shows its limits in terms of accuracy. On the other hand, PET shows metabolical dysfunctions in the lesional zones which are not necessarily localized in the same area as the epileptogenic zone, and this can provide some explanations about the differences between the results brought by the two modalities. Temporal resolution of these two methods can also influence the anatomical localizations. Indeed, PET has a low temporal resolution which can explain a diffuse hypometabolism whereas HR-EEG can identify separately different sources in a same cerebral area thanks to his millisecond time scale. Our results are in adequacy with [10] which demonstrated that the interictal spiking suggests the presence of preferential epileptogenic networks inside the hypometabolic temporal lobe.

The Block-Matching spatial normalization [8] used in PET analysis led to reliable results and made them easier to interpret since it only let the most significant hypometabolic zones appear whereas the results provided by the SPM spatial normalization often lead to a diffuse and extensive detection of hypometabolism. It has also to be noticed that the choice of the threshold for PET hypometabolism has a major effect on the detected volumes since low values let extended areas appear whereas upper values restrict them to smaller and more significant volumes. The differences in term of hypometabolic volume between the five patients are due to their various significativenesses and the size of the volumes should not be directly compared from one patient to another one since the results of the PET statistical comparisons do not only describe the extent of the pathological area but it also provides information about its severity.

Finally, the PET hypometabolisms have been localized with objective criterions in areas close to the EEG electrical sources and are consistent with the epileptogenic zones defined by invasive investigations.

V. CONCLUSION AND PERSPECTIVES

This preliminary study shows that HR-EEG and PET can be combined to improve the localization of the epileptogenic zones. Even if the two methods do not lead exactly to similar results, information about the imprecision of each of them is brought, which should finally allow a better understanding of the anatomical localization of the epileptogenic zone which causes epileptic seizures.

These results have to be validated with a larger number of patients and with other interictal or ictal patterns like rhythmic activities. Co-registration of PET and electrical source imaging could be a promising tool in the pre-surgical investigations.

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