Difference Imaging of Inter- and Intra-Ictal SPECT Images for the Localization of Seizure Onset in Epilepsy

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***Abstract*—The comparison of inter- with intra-ictal SPECT images plays an important role during the diagnosis and treatment of epilepsy patients. Although there is already commercial software available to address this problem using complex clinical workflows, this article describes a different way of looking at this issue. During the examination various issues arise from differing tracer concentrations, patient movement between the acquisitions at different times and also the lack of morphological information. The goal of the presented work is therefore to present an approach that is on the one hand easy to use for the physician and on the other hand both reliable and robust enough to cope with the previously mentioned challenges. The proposed algorithm introduces methods that have already been applied successfully in digital subtraction angiography (DSA). The work comprises of several steps for the intensity normalization, image registration, difference imaging and the incorporation of an MR image for the spatial localization. As a result, information is provided about differences within the cerebral blood flow (CBF) and active brain areas between the intra- and inter-ictal states. Very new to the field of SPECT brain imaging is the application of non-rigid registration techniques. This helps to drastically reduce the artifacts within the difference images due to a bias of the standard rigid registration. Acquired results from a collective of 11 patients show that this additional feature helps to further improve the image quality.**

***Index Terms*—SPECT, epilepsy, difference, subtraction, rigid registration, nonrigid registration**

I. Introduction & Motivation

ONE of the main goals in epilepsy surgery planning is to localize the region of seizure onset. For this purpose, inter- and intra-ictal SPECT images are acquired at different times. The comparison of these images is non-trivial due to the low spatial resolution, varying image intensity ranges (standard uptake values) and different acquisition times. Conventional side-by-side visual assessments are difficult because of shifts in intensities and different patient positions during the acquisitions. We propose an alternative to the commonly used complex clinical workflow. Our method introduces digital subtraction imaging techniques that are already successfully applied in digital subtraction angiography (DSA) into the context of SPECT epilepsy imaging. The presented clinical workflow consists of a pre-processing, an alignment and a post-processing step. For pre-processing, the SPECT images are separated from the background noise and normalized. During the alignment step, an automatic rigid and non-rigid registration is performed in order to correct the patient position and orientation misalignments. In the context of brain imaging without surgery, using non-rigid registration techniques seems to be quite uncommon, however, state-of-the art rigid registrations are biased if different image context is present. In this case, it is the variation of CBF that leads to different focal regions, which directly affects the similarity measures in a negative way. Making use of additional but heavily regularized degrees of freedom that are offered by a non-parametric non-rigid registration helps to decrease this bias for better results in the post-processing step, where the aligned SPECT images are subtracted from each other. The resulting difference image directly depicts changes in the CBF between the two acquisitions. A previously acquired MRI is integrated into the workflow and used to spatially localize the differences. We justify and show that the application of a non-rigid registration algorithm leads to an increased accuracy and a better quality of the difference image. The morphological information gained through this approach can for instance be used for further surgery planning. The method is applied to a collective of epilepsy patients.

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II. Related Work

The CBF is known to increase during epileptic seizures at the areas of the seizure onset, which leads to differences between the two images. The method of subtraction imaging was introduced into the SPECT context first by Zubal et al. [1] and Spanaki et al. [2]. They applied it after rigid registration and normalization to analyze the location of seizure onset. O'Brien et al. [3], [4] additionally incorporated MR images through an image fusion with the difference image to visualize the spatial location of the focal spots. To identify statistically relevant image differences, both Chang et al. [5] and McNally et al. [6] applied a statistical parametric mapping technique. It allows for the comparison of subtraction values to a norm collective in order to identify variations due to an epileptic disease. Koo et al. [7] have shown in a preliminary study that retrospective subtraction of inter- from intra-ictal SPECT images with difference values of 75% to 100% show good concordance with seizure foci.

Varying tracer concentrations between the image acquisitions lead to different standard uptake values that have to be normalized before subtraction. Otherwise, there is a systematical error affecting the intensities of the difference image.

There exist several approaches for the normalization that are described in literature. Chang et al. [5], for instance, fit a linear mapping model into the joint histogram of both SPECT images after the registration such that the entropy of the difference image is minimized. Other methods include normalizations to the maximal image values, to the mean uptake value in the entire brain signals or only in selected regions. The normalization presented in this article approximates a linear model as proposed also by Liao et al. [8].

Regarding the rigid registration, several surveys presented in literature cover a wide range of standard approaches. Examples can be found, for instance, in Brown [9], Elsen et al.[10], Hill et al.[11], Maintz et al.[12] or others. The standard registration techniques focus on the optimization of a voxel intensity measure in order to estimate a transform that aligns the two images. Virtually all registration approaches that make use of voxel intensity measures have been successfully applied to single subject studies. For the purpose of this work, we used an approach that was presented earlier [13] in order to integrate the intensity normalization directly into the registration process. This is done by applying the fitted linear model to a transfer function that is used for an intensity transform during the registration.

The approach of comparing inter with intra-ictal SPECT images is very similar to techniques used for DSA. In DSA, an additional non-rigid registration is important in order to get rid of artifacts within the difference image that arise from movements of the patient. An overview of such motion artifacts and the techniques to avoid them are discussed in Meijering et al. [14]. For the presented approach, the non-rigid registration is introduced, as well, in order to compensate for errors of the rigid registration. Possible non-rigid registrations can be divided mainly into parametric and non-parametric techniques. Parametric approaches incorporate an inherent regularization by the choice of the parametric model, whereas non-parametric approaches have to be constrained by additional regularization terms. Comprehensive descriptions about this topic can, for instance, be found in the works of Modersitzki [15], Hermosillo et al. [16] or Clarenz et al. [17]. Regarding the regularization, Fischer and Modersitzki [18] proposed a curvature regularization for the usage of their non-rigid technique within the field of medical imaging, which we are choosing as a constraint for the non-rigid registration in the following.

III. Methods

The following section describes the several steps of the workflow in chronological ordering. The intensity normalization is the basis for the method, as it enables the comparison of intensity values between the two SPECT images directly. The rigid registration is used afterwards to align the images in a least squares manner, however, this still contains some bias in the result due to the variations in blood flow and the few degrees of freedom of the transform. The non-rigid registration performed subsequently allows for a refinement and is necessary to increase the accuracy within the subtraction. In addition, an MRI of the patient may be incorporated by registering it with the reference SPECT image. The same transform can then be applied to the subtraction image to add spatial information to the differences.

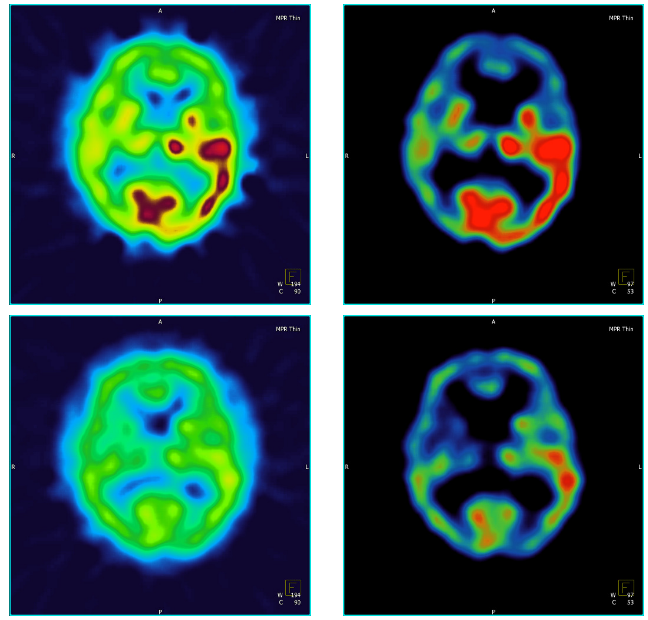

Fig. 1. SPECT images from left to right: intra-ictal, intra-ictal after normalization, inter-ictal, inter-ictal after normalization. It can be clearly seen that the same transfer function applied on the images before the normalization leads to a different visualization result, whereas the same transfer function applied afterwards leads to similar intensities.

A. Intensity Normalization

As already mentioned, for a correct interpretation of the differences between the SPECT images, the intensities have to be normalized to a common intensity range. This is due to background noise and different acquisition times that lead to changes in the overall uptake values in the images. We apply an affine intensity transform for the normalization, similar to Liao et al. [8]. The approach is designed to transform the two SPECT images to both a common mean and minimum intensity value with respect to the brain signal intensities. For the computation of the offset and brain signal mean, we make use of the visualization capabilities of transfer functions within the medical volume rendering software. This allows to specify a threshold that separates the brain signal from the background by interactive modification of the transfer function. The statistics are then computed on all image intensities above the threshold, i.e. the intensities within the brain region. The results of the normalization can be seen in Fig. 1.

B. Rigid Registration

The computation of the differences between the inter- and intra-ictal SPECT data requires that the images are suitably aligned. To correct for patient motion between the acquisitions, a rigid, image intensity-based registration between the SPECT images is performed. The optimization minimizes as objective function the sum of squared differences (SSD) between the two images with respect to a global parametric transform (rotation and translation):

$$\hat{\Phi} = \underset{\Phi}{\operatorname{argmin}} \int_\Omega \mathcal{D}[R, T, \Phi](\boldsymbol{x})\ \mathrm{d}\boldsymbol{x} \tag{1}$$

$$\begin{aligned} \Phi(\boldsymbol{x}) &= \boldsymbol{R}\boldsymbol{x} + \boldsymbol{t} && (2) \\ \mathcal{D}[R, T, \Phi](\boldsymbol{x}) &= (R(\boldsymbol{x}) - T(\Phi(\boldsymbol{x})))^2 && (3) \end{aligned}$$

Here, Φ denotes the six degrees of freedom transform (DOF) (2) consisting of a rotation matrix $\boldsymbol{R}$ and a translation vector $\boldsymbol{t}$. It maps spatial positions $\boldsymbol{x} \in \mathbb{R}^3$ from the template T to the reference SPECT image R. The parameters of this transform are estimated by a nonlinear optimization to minimize the objective function (1) with respect to the SSD intensity measure (3). $\mathcal{D}$ is defined only within the overlap domain Ω that is dependent on the transform.

This approach yields a result that can only be optimal in the sense of a least squares of the intensities. If there is a large amount of variation in the CBF at different locations, the intensity similarity measure gets biased. This tends to impair the registration accuracy at lower contrast image regions, for instance at the boundaries of the brain signal. If such a biased registration result is used as input for the subtraction stage, the difference image falsely shows these artifacts, which may lead to wrong diagnoses. Fig. 2 shows a 2D registration example that demonstrates the effect of bias on the difference image. Both reference and template image depict the same slice of an arbitrarily chosen SPECT image, however, there is a difference in the location of an artificially introduced focal spot. The left difference image in the bottom row of the figure is the result of an image subtraction after a rigid registration. The differences at the boundaries of the signal clearly shows the rigid registration's inability to compensate the local shift of the focal spot. This experiment is not only repeatable with SSD, a similar effect can also be seen for mutual information and other intensity measures.

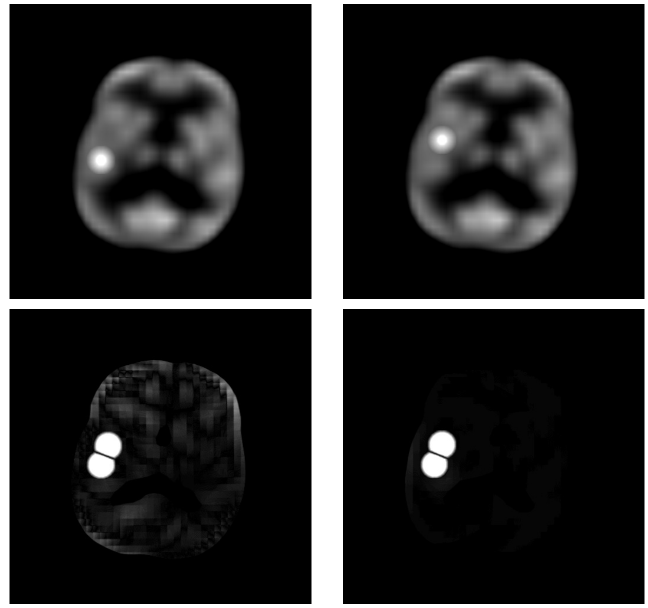

Fig. 2. The top row depicts the reference and template image, that only differ by the location of an artificially introduced focal spot. The bottom row shows the difference image results after a standard SSD rigid registration on the left and after a non-rigid registration on the right with the same stiffness parameters as used within the 3D SPECT registration. It can clearly be seen that there is a bias on the rigid registration, whereas the non-rigid registration is only locally affected by the translation of the focal spot.

C. Non-Rigid Registration

As illustrated in the previous section, the rigid registration can only result in a global least squares fit of the images. As a consequence, variations in the CBF leading to local SPECT signal changes impair the accuracy of the rigid registration. This can be compensated by a local registration technique. In our case, we make use of a non-rigid registration based on the work of Fischer and Modersitzki [15]. The regularization of this non-parametric registration (4) is provided by means of a curvature penalty term (6).

$$\begin{aligned} \min_{\boldsymbol{u}} \mathcal{J}(\boldsymbol{u}) &= \min_{\boldsymbol{u}} \int_\Omega \mathcal{D}[R, T_{\boldsymbol{u}}](\boldsymbol{x}) + \alpha \mathcal{S}[\boldsymbol{u}]\ \mathrm{d}\boldsymbol{x} && (4) \\ T_{\boldsymbol{u}}(\boldsymbol{x}) &= T(\boldsymbol{x} - \boldsymbol{u}(\boldsymbol{x})) && (5) \\ \mathcal{S}[\boldsymbol{u}](\boldsymbol{x}) &= (\Delta_{\boldsymbol{x}} \boldsymbol{u})^2 \\ &= \left(\sum_{i=1}^{3} \frac{\partial^2 \boldsymbol{u}}{\partial x_i^2} \right)^2 && (6) \end{aligned}$$

The transform $\boldsymbol{u}$ in this case defines a dense deformation field that assigns a translation vector to each voxel of the template image. The nonlinear optimization of the objective functional (4) is driven by the same distance measure as in the rigid case. The curvature term (6) weighted by α determines the amount of regularization applied to the deformation transform. The larger the value for α, the more rigid the resulting deformation will be.

Without the non-rigid registration step, slight rigid misregistrations due to the already mentioned bias would show up in the difference image and might falsely be regarded as lesions. This step is therefore necessary to reduce these artifacts within the subtraction image that can be computed after the registration.

D. Fusion with MRI

After applying the difference computation, the remaining intensities can be directly interpreted as changes in blood flow activity. As the subtraction image only depicts functional information, the morphological and spatial components can for instance be contributed by an additionally acquired MRI. The direct registration of the difference image with the MRI is generally an ill posed problem due to its lack of morphological information. Instead, we make use of the fact that the difference image is contained within the same frame of reference as the two registered SPECT images. The fusion of the MRI with the difference image can therefore be realized indirectly by its registration with the intra-ictal SPECT. This is done by calculating a rigid transform that maximizes the mutual information between the MRI and the SPECT [19], [20]. This transform can finally be applied to align the difference image with the MRI for the spatial localization of the lesions, which yields valuable information for surgical planning.

IV. Results

The proposed method has been applied to a collective of 11 epilepsy patients and assessed by physicians. The difference images have been analyzed visually and compared to results gained from EEG measurements. In one case, the MRI features a clearly contrasted lesion that highly correlates with the results of this algorithm. In a double blind case study, the outcome of the EEG measurements, as well as a side-by-side assessment of the SPECT images, resulted in the same diagnosis as performed only on basis of the difference image using the presented approach. The entire approach takes less than 5 minutes in the currently non-optimized implementation on an Intel Pentium M 2.26 GHz with 2 GByte of main memory. The effects of the two registration algorithms on the resulting difference images are depicted in Fig. 3. The top four views show artifacts at the boundaries of the brain signal due to a wrong rigid image registration result. The four views on the bottom have been generated after an additional non-rigid registration, which leads to a higher overall image quality in the subtraction image. In Fig. 4, the outcome of two interesting cases within the collective are presented. The images atop show a lesion within the left brain hemisphere that could clearly be located in both the SPECT difference images and the MRI, whereas for the images below the MRI did not show any significant lesions at all. However, the focal spots shown in the SPECT difference image correlated with the EEG measurements and the results from visual side-by-side assessment.

V. Summary

Introducing digital subtraction methods into the domain of epilepsy SPECT brain imaging provides valuable insights into spatial location, emanation and quantity of uptake changes between inter- and intra-ictal stages. The workflow presented within this article is based on an image normalization to the mean standard uptake value within the brain signal, both, a rigid and non-rigid image registration and the fusion of the subtraction image with an MRI. Although the brain itself is a rather rigid structure if no surgical operations are involved, it can be shown that the standard rigid registration approach is not able to register two images from different times without a bias if a local variation in CBF is involved. This bias affects the accuracy of the six DOF rigid transform in a negative way and leads to artifacts in the subtraction image. The bias cannot be compensated by other similarity measures because it is mainly due to the inability of the rigid registration to robustly cope with local intensity variations. The non-rigid registration technique used in the approach, on the other hand, can remove the bias up to a certain amount. This is due to its large number of DOF that enables it to incorporate local information within the registration transform, therefore also keeping the bias local. The general formulation of the non-rigid objective functional requires a regularization in order to remain well conditioned.

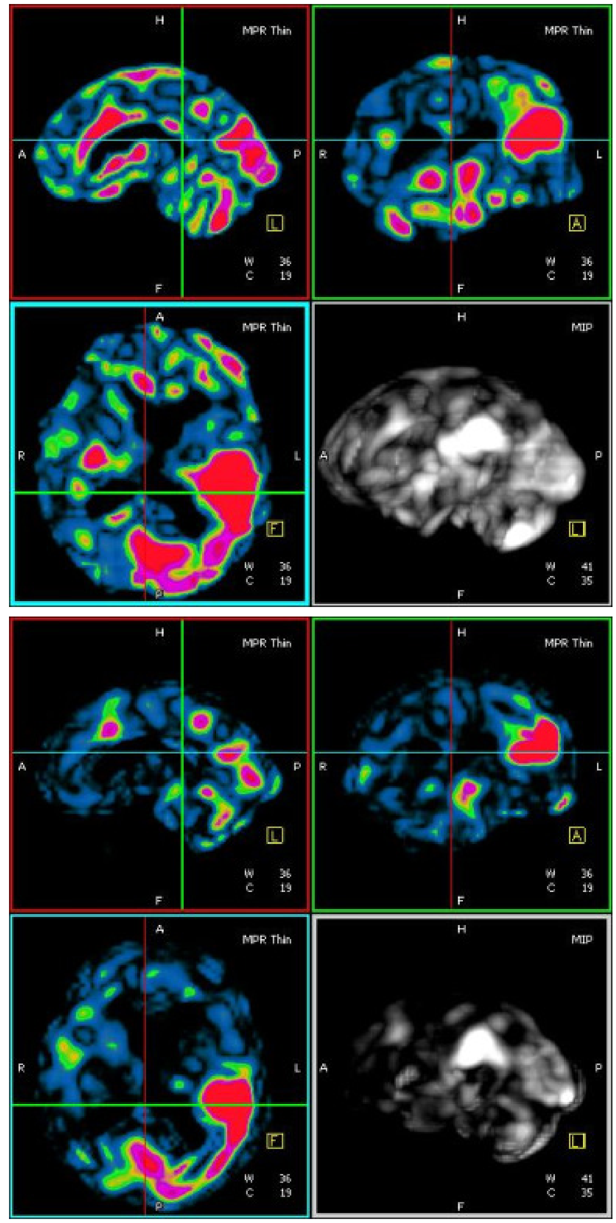

Fig. 3. The four images on the top show a SPECT difference image after the rigid registration with clearly visible artifacts that have no physical meaning and that can be explained by the bias inherent to the approach. The enhanced difference image in the bottom views was computed using both rigid and non-rigid registrations and features a higher image quality.

A high weighting for the regularization constraint was chosen for the approach in order to maintain the local CBF variations in the image. The quality of the difference image is therefore greatly enhanced. To provide additional morphological information, the fusion with an MRI has directly been incorporated into the workflow. The entire approach has been integrated into a commercially available software for clinical evaluation.

VI. Conclusions

SPECT difference imaging has been shown to greatly support the localization of seizure onset in the diagnosis of epilepsy patients. The problem of the common approach is an inherent intensity bias in the rigid registration necessary to

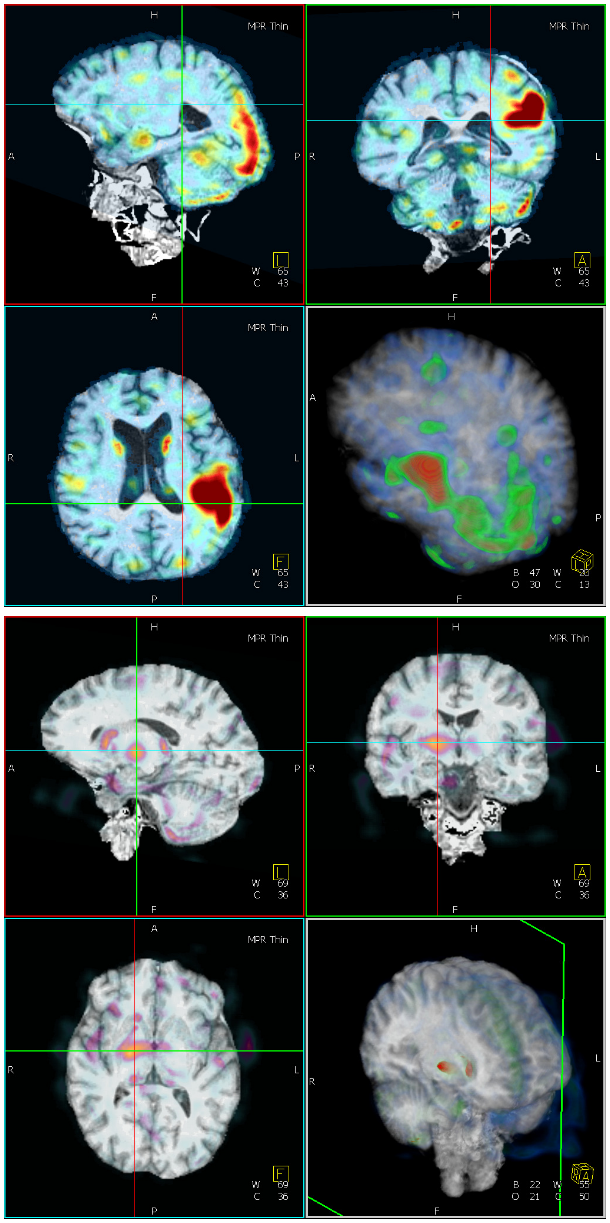

Fig. 4. These two representative cases show results of the proposed algorithm on two patients from the collective used for the results. Depicted are the corresponding MR images of the epileptic patients fused with the difference images of the according SPECT images.

perform the difference imaging. This can be addressed by a subsequent non-rigid registration of the SPECT images, which greatly reduces the visible artifacts in the difference image.

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