Summary

Using the example case of a former patient as a guiding line, the article gives an overview of several novel methods of computer-assisted MRI postprocessing and their clinical application in non-invasive and invasive presurgical evaluations of epilepsy patients. Morphometric MRI analysis facilitates the detection and delineation of subtle focal cortical dysplasias and other cortical malformations by highlighting typical structural alterations like thickening of the cortical ribbon, blurring of the grey-white matter junction, and abnormal gyration. Automatic curvilinear reformatting of 3D MRI data calculates serial convex planes across the brain in different depths from the cortical surface. This method improves the display of the gyral structure, permits a precise localization of lesions, and helps to identify subtle abnormalities difficult to detect in planar slices. Pre-operative planning of subdural electrode implantation for invasive EEG recordings by means of realistic 3D representation of electrode contacts is a novel method that allows calculating electrode positions directly on the convexity of the individual cortical surface and in correct spatial proportions with respect to brain size. Thereby it permits rapid and exact determination of optimal electrode positions and supports planning and execution of electrode implantation. After implantation, the positions of subdural electrodes can be determined by help of an automated fast method for volume rendering of 3D MRI at the level of the implanted electrodes. The results of all presented methods can be integrated into intra-operative neuronavigation systems to support final lesion resection. After surgery, coregistration of pre- and postoperative images makes it possible to confirm the completeness of lesion resection. In conclusion, a variety of MRI postprocessing methods aids in the presurgical evaluation and surgical management of medically refractory epilepsy patients.

Key words: Epilepsy, magnetic resonance imaging, MRI postprocessing, morphometric analysis, focal cortical dysplasia, electrode implantation

Digitale Nachverarbeitung von strukturellen MRI-Aufnahmen in der prächirurgischen Diagnostik von Epilepsiepatienten

und chirurgischen Behandlung von medikamentös therapiereisistenten Epilepsie-Patienten.

Schlüsselwörter: Epilepsie, Magnetresonanztomografie, MRT-Nachverarbeitung, morphometrische Analyse, fokale kortikale Dysplasie, Elektrodenimplantation

Traitement numérique et quantitatif des images IRM structurelles dans le bilan pré-chirurgical des patients atteints d’épilepsie

Par l’exemple d’un ancien patient, l’article donne un aperçu des nouvelles méthodes d’analyse assistée par ordinateur de l’IRM cérébrale et leurs applications cliniques dans le bilan pré-chirurgical non invasif et invasif des patients atteints d’épilepsie. L’analyse morphométrique IRM facilite la détection et la différenciation des dysplasies corticales focales discrètes et d’autres malformations corticales en mettant en évidence les changements structurels typiques tels que l’épaisseur anormale du cortex, une limite floue entre substance grise et substance blanche, ou une gyriication anormale. Le reformatage automatique curvilineaire des données 3D IRM est calculé par une série convexe de plans de coupe à travers le cerveau à différentes profondeurs sous la surface corticale. La procédure améliore l’apparence de des gyri et sulci, permet une localisation précise des lésions et permet de détecter des anomalies discrètes qui sont difficiles à identifier dans les images planaires conventionnelles. La planification de l’implantation d’électrodes sous-durales pour les enregistrements EEG invasifs à l’aide d’une représentation 3D réaliste des contacts des électrodes est une nouvelle méthode, qui permet de calculer directement la position des électrodes sur la convexité de la surface corticale individuelle dans les rapports de taille correcte par rapport au cerveau du patient. Cela permet la détermination rapide et précise de la position optimale des électrodes et aide la planification et la mise en œuvre de l’implantation. Après l’implantation, les positions des électrodes sous-durales sont déterminées en utilisant une méthode automatisée rapide qui est un rendu de volume 3D de l’IRM au niveau des électrodes implantées. Les résultats de toutes les méthodes peuvent être intégrés dans des systèmes de neuro-navigation peropératoires pour soutenir la résection finale de la lésion. Par la suite, une coredégreation pré- et post-opératoire de l’IRM permet de vérifier si la lésion a été complètement enlevée. En résumé une variété de méthodes de post-traitement des images IRM offre une aide précieuse dans le bilan préopératoire et la planification de la chirurgie chez les patients atteints d’épilepsie pharmaco-résistante.

Mots clés : Epilepsie, imagerie par résonance magnétique, analyse complémentaire de l’IRM, dysplasie corticale focale, implantation d’électrodes

Introduction

During the past year computer-assisted digital postprocessing of structural MRI data has increasingly found entrance into routine clinical diagnostics. In epileptology, a variety of methods are available, not only to improve detection and visualization of subtle epileptogenic lesions but also to plan invasive EEG recordings, to localize implanted electrodes and to assist intra-operative neuronavigation. This article gives an overview of these methods and their clinical application in the presurgical evaluation of epilepsy patients. The methods presented here are in daily use at the Swiss Epilepsy Centre and mostly based on algorithms and standard procedures of the SPMS software package (SPM = statistical parametric mapping, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). In principle, however, they can also be implemented in other freeware image-processing environments such as, for example, the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) or the AFNI software (http://afni.nimh.nih.gov/afni). The subsequent presentation follows the typical sequence of diagnostic procedures in a former patient with drug-resistant epilepsy who underwent non-invasive and invasive presurgical evaluations. The overview roughly sketches the methods and describes what results can be expected from MRI postprocessing and how they contribute during the diagnostic workup. The available space does not allow explaining technical details of the postprocessing techniques; however, the interested reader is referred to the primary literature on this topic (cf. references).

Description of the Example Case

The example case is a former patient, a 30 year-old female, who suffered from left-sided tonic and secondarily generalized tonic-clonic seizures since the age of two years. EEG and semiology pointed to an epileptogenic focus in the right frontal or right precentral region. Results from nuclear medicine (i.e. SPECT) supported this hypothesis. However, at referral the patient’s epilepsy was considered to be cryptogenic since two MRI investigations in the past had been regarded as normal.

Abbreviations

MRI = magnetic resonance imaging
SPM = statistical parametric mapping
VBM = voxel-based morphometry
FLAIR = fluid attenuated inversion recovery
FCD = focal cortical dysplasia
SBH = subcortical band heterotopia
PNH = periventricular nodular heterotopia
HS = hippocampal sclerosis
Morphometric MRI Analysis

Although MRI techniques have markedly improved over the last years, conventional MRI frequently does not reveal the underlying pathology in focal epilepsy. The detection of an epileptogenic lesion on MRI, however, is crucial since the selection of candidates for possible epilepsy surgery is easier and postoperative outcome is significantly better in MRI-positive patients [1, 2]. Therefore, attempts have been made to facilitate lesion detection by modern image post-processing strategies like curvilinear reformatting of 3D MRI [3], quantifying the regional distribution of gray and white matter by voxel-based morphometry or autoblock analysis [4 - 9], measuring the thickness of the cerebral cortex [10], texture analysis [11 - 13], or quantitative intensity analysis [14 - 16]. In addition, there have been promising approaches for automated lesion detection, for example by searching for maximum deviations with respect to a normal database [17, 18], by using a Bayesian classifier [12], by thresholding z score maps [19], by applying classifiers based on neural networks [20], or by statistical parametric mapping either applied to structural data in the framework of voxel-based morphometry or combined with signal intensity analysis. An overview of the different approaches can be found in the review by Bernasconi and co-workers in 2011 [21].

One of these approaches is a method for morphometric MRI analysis based on algorithms of SPM5 and comparing voxel-wisely individual brain anatomy with a normal database. The whole processing is performed by a fully automated MATLAB® script. The starting point is a high-resolution 3D MRI dataset covering the whole head and brain. Usually, a T1-weighted volume data set is used which is part of the recommended routine MRI protocol for epilepsy patients [22, 23], but the technique has also been successfully applied to T2-weighted images [24]. Following the principles of VBM [25], the MRI data is normalized to the standard brain of the Montreal Neurological Institute (MNI) included in the SPM5 distribution, segmented into different brain compartments, i.e. grey matter (GM), white matter (WM), and cerebrospinal fluid, and simultaneously corrected for small intensity inhomogeneities. Normalization means that the individual brain is brought into a common anatomical space to make it comparable with a dedicated normal database, i.e. MRI data of healthy controls processed in the same way and preferably also acquired at the same MR scanner and with the same sequence as the patient’s data. The segmentation results are compared with the distribution of GM and WM in the normal database, and three new morphometric maps (called “extension”, “junction”, and “thickness image”) are derived, which characterize three different potential features of focal cortical dysplasia (FCD) and also other cortical malformations: abnormal extension of grey matter into white matter (i.e. abnormal deep sulci, abnormal gyration), blurring of the grey-white matter junction, and abnormal thickness of the cortical ribbon. By highlighting suspicious brain regions, these maps can guide a second look at the MRI and thereby increase the sensitivity for detecting subtle epileptogenic lesions [17, 18, 26 - 31]. The results can be integrated into intra-operative neuronavigational systems [32, 33] to guide the placement of subdural or depth electrodes or the final lesion resection.

Although this method has proven to facilitate the recognition of various malformations of cortical development, such as subcortical band heterotopia, polymicrogyria, and periventricular nodular heterotopia [34, 35], it is primarily meant to support the detection and visualization of FCD, which are the most frequent histopathologic substrate in children and the second most common etiology in adult epilepsy surgery patients [36]. The diagnostic yield has recently been investigated in a large study on 91 patients with histologically proven FCD operated on between 2000 and 2010 at the epilepsy centre of Bonn. Compared to visual MRI analysis alone, the additional application of morphometric analysis could increase lesion detection by about 12% [31]. However, since the study also included MRI data acquired 10 years ago, i.e. at a time when quality of MRI acquisition as well as radiological knowledge and awareness of dysplastic lesions probably were not as high as today, the study may overestimate the diagnostic yield. In addition, the detection rate is smaller in an unselected population, comprising for example also patients with non-epileptic seizures or with idiopathic epilepsies. At the Swiss Epilepsy Centre, morphometric analysis is applied to all MRI containing a T1-weighted 3D data set, and the additional diagnostic yield currently (after almost 3000 patients since 2006) ranges between 5 and 6% (unpublished data). This may appear small but for the involved patients it is most relevant. Resective surgery is considered the most effective therapy [37], and with the detection of a dysplastic lesion in a patient with formerly cryptogenic and medically refractory epilepsy it often comes within reach for the first time thus radically changing the prognosis of possible seizure freedom.

With regard to possible false-positive results it is important to take into account that morphometric analysis as well as the other postprocessing methods presented here are meant to be informative on a single patient level. In contrast to group studies with scientific goals, in which the risk of type I error (i.e. false-positive results) has to be minimized, it is more important to reduce the risk of type II errors, i.e. the possibility of false-negative results, in the clinical setting of an epilepsy surgery program. This is due to the fact that the detection of an epileptogenic lesion is often the only chance for the patient to enter such a program, and it determines the probability of being admitted to surgical therapy. The trade-off of a higher sensitivity, i.e. the increased risk of false-positive findings, is accept-
able because before surgery, the epileptogenicity of a probable lesion has to be proven not by MRI findings or postprocessing results but from compatible results of EEG and seizure semiology. Moreover, lesion detection is not the only goal. An improved visualization and delineation of lesion extent is also important because post-operative seizure freedom particularly depends on the completeness of lesion resection [38].

In our example patient, morphometric analysis highlighted a small structural alteration and possible lesion at the lower end of the right central region (Figure 1), with features typical for an FCD, such as abnormal gyration, blurring of the GM-WM junction and abnormal cortical thickness.

Quantitative FLAIR Analysis

Apart from structural changes, cortical malformations like FCDs may also be accompanied by hyperintensities in T2 images or FLAIR (= fluid attenuated inversion recovery) scans, i.e. images with T2-weighted contrast but complete suppression of the high signal intensity of cerebrospinal fluid (CSF). Since morphometric analysis only refers to structure, an additional postprocessing method for exploiting also signal alterations would be advantageous. Focke and coworkers have recently described a new method for quantitative analysis of FLAIR scans [16, 39]. Their method essentially performs a rescaling and intensity normalization of the FLAIR image to a common mean level so that the patient FLAIR image can be compared with a normal database of FLAIR scans which have been intensity normalized in the same way. The approach avoids difficulties due to partial volume effects with CSF which are to consider for alternative quantitative methods like T2 relaxometry [40 - 42]. Compared to T2 mapping with FLAIR CSF suppression [14, 15], it does not require a special FLAIR T2 map, which has a long acquisition time and is often not available, but takes a standard clinical 2D or 3D FLAIR spin echo sequence as input. The further processing includes both a spatial and intensity normalization of the FLAIR images by using internal reference regions and spatial normalization parameters derived from combined normalization and segmentation of a coregistered T1-weighted image. The normalized and rescaled FLAIR images are then the starting point for a whole brain FLAIR analysis, which has been shown to be successful in the detection of focal cortical dysplasia [16].

In our example patient, quantitative FLAIR analysis highlighted a subtle hyperintensity at the location of the suspected dysplasia which had been overlooked in the original FLAIR images (Figure 2).
As a further development of the whole brain FLAIR analysis described above, the quantitative evaluation can also be focussed on regions of interest, for example the hippocampi, to disclose or exclude an accompanying sclerosis in these structures which are known to be sensitive for secondary epileptogenesis. For that purpose, the normalized and rescaled FLAIR images are thresholded and weighted by a probabilistic hippocampal mask to determine the average FLAIR intensities of the left and the right hippocampus. In a recent study, this method was applied to MRI data of 103 patients with hippocampal sclerosis (HS) and 131 controls. A 95% confidence region calculated from the FLAIR intensities of controls was used as threshold to discriminate both groups. One hundred patients, and among those all 23 patients with histologically confirmed HS, fell outside the 95% confidence region, thus amounting to 97.1% sensitivity. All but 6 controls (= 95.4%) were found within the confidence region, corresponding to the expected specificity. Right and left HS were separated without overlap. This approach could also distin-

Figure 2: Quantitative FLAIR analysis: The original FLAIR scan (left side), which had been regarded as normal, was rescaled, intensity normalized, and compared with a normal database. In the resulting FLAIR z score image (right side) the suspicion of a dysplastic lesion was further corroborated by the finding of subtle signal hyperintensity.

Figure 3: Quantitative hippocampal FLAIR analysis: The results of the example patient falling in the middle of the 95% confidence region of healthy controls confirm the visual impression that there is no dual pathology in terms of an additional hippocampal sclerosis.

As a further development of the whole brain FLAIR analysis described above, the quantitative evaluation can also be focussed on regions of interest, for example the hippocampi, to disclose or exclude an accompanying sclerosis in these structures which are known to be sensitive for secondary epileptogenesis. For that purpose, the normalized and rescaled FLAIR images are thresholded and weighted by a probabilistic hippocampal mask to determine the average FLAIR intensities of the left and the right hippocampus. In a recent study, this method was applied to MRI data of 103 patients with hippocampal sclerosis (HS) and 131 controls. A 95% confidence region calculated from the FLAIR intensities of controls was used as threshold to discriminate both groups. One hundred patients, and among those all 23 patients with histologically confirmed HS, fell outside the 95% confidence region, thus amounting to 97.1% sensitivity. All but 6 controls (= 95.4%) were found within the confidence region, corresponding to the expected specificity. Right and left HS were separated without overlap. This approach could also distin-
ages already belonging to MRI protocols for epilepsy is economic [43].

In clinical routine, the main advantage lies in the fact that quantitative FLAIR analysis can corroborate the results of visual assessment in HS and – perhaps even more important – can strengthen confidence that the hippocampi are not affected. The presence of HS can be regarded as very unlikely when FLAIR analysis results in a location in the middle of the 95% confidence region, as in our example patient (Figure 3). This helps to rule out the possibility of a dual pathology.

Curvilinear Reformatting

Curvilinear reformatting of three-dimensional MRI data is a well-established technique to calculate serial convex image planes across the brain and parallel to the cortical surface [3]. Several advantages have been attributed to this method: a better display of gyral contours, precise localisation of lesions, improved visualization of lesion extent, and better assessment of spatial relations between lesions, anatomical landmarks, and implanted subdural electrodes [44], thus supporting surgical planning [45, 46]. Since this method also helps to identify subtle abnormalities, which are difficult to detect in planar slices due to the brain’s complex convolutional pattern, it has been proposed for detecting small FCDs [3, 47]. Alternative 2D techniques [48] and the commonly used “pancake” representation of the cortex, sometimes also called “curved reconstructions” [49] or “brain surface reformatted imaging” [50 - 52], lack the 3D visualization of the gyral surface and suffer from relative distortions of distances. However, the initial implementation of curvilinear reformatting required an interactive delineation of the brain surface contour by manual placing of supporting points at the cortical surface. Then, a program calculated several new curved cutting planes across these points and below of them, allowing an overview of the brain in different depths. To spare the manual and time-consuming placement of supporting points, a fully automated alternative approach based again on SPM algorithms has been developed [53]. When the patient’s brain is normalized to a standard brain (as has been done for morphometric analysis described above), predefined masks of different sizes can be applied in the same stereotactic space to cover and remove the skull and the outer brain regions in different depths from the brain surface. The residual inner part of the brain can then be presented 3-dimensionally by volume rendering (Figure 4). If necessary (e.g., for intraoperative navigation), the normalized data can be easily transferred back to the original stereotactic space.

Today, the results of automated curvilinear reformatting of 3D MRI data are primarily used to improve the visualization of epileptogenic lesions and the assessment of lesion extent and spatial relations to eloquent cortical regions. Lesion detection has receded in importance due to more successful methods like morphometric analysis. However, confirmation of a suspected lesion is still valuable. In our example patient, the method revealed that the suspected lesion was located at the lateral end of the right central sulcus and indeed accompanied by blurring of the gray-white matter junction (Figure 4).

Planning of Electrode Implantation

Since the suspected lesion was located in the central region, presurgical evaluations had to proceed with invasive EEG recordings and mapping of sensory-motor functions to differentiate the epileptogenic zone from possible eloquent cortical areas that are to spare in the final resective surgery. For invasive EEG recordings optimal topographic concordance of implanted subdural electrodes with suspected epileptogenic and relevant eloquent cortical areas is essential. The implantation of subdural strip and grid electrodes is usually planned by designing schematic drawings where 2-dimensional electrode images are placed on pseudo-3D images of a standard brain. The disadvantage is obvious: there is no correlation between the size of the electrodes and the size of the individual patient brain. An improvement would be an image of the individual patient’s brain surface (as derived from simple skull-stripping of 3D MRI data), brought together with electrode images of corre-
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Figure 5: Planning of electrode implantation using an image of the individual patient’s brain surface together with 2-dimensional electrode images of corresponding size in a common coordinate system, but still disregarding the convexity of the brain (figure by courtesy of Dr. Peter Hilfiker, Swiss Epilepsy Centre).

However, this approach still does not take into account the convexity of the brain, and does not indicate whether the electrode grid is large enough for the cerebral area to be mapped — or perhaps too large. An alternative method overcomes these drawbacks and calculates the geometry of the electrode three-dimensionally and in correct spatial relation to the curvature of the individual brain surface [54]. The position of the first electrode contact is manually chosen on the brain surface, and a second point is marked to indicate the direction of the strip electrode or the first row of a grid electrode. Then, an in-house-developed program automatically calculates the positions of the other electrode contacts in between and makes them follow the curvature of the brain surface. This is also possible for grid electrodes. In a mathematical sense the electrode contacts are treated like marbles that are forced to keep contact to each other and to maintain the grid structure but are free to rotate around each other and to bend to the convexity of the brain. After this calculation, the electrode positions are available as separate objects. They can be projected into another data set, for example the original image with the skull still in place. This helps the surgeon to plan the correct approach for craniotomy, i.e. the optimal area for trepanation of the skull.

Localization of Subdural Electrodes

After implantation of subdural electrodes it is important to localize the real position of electrodes and to confirm congruence with prior planning. For correct interpretation of invasive EEG data and mapping results, it is crucial to be sure about the location of each electrode contact. Planar MR sections often pose problems with regard to electrode localization due to the convexity of the cortical surface. The alternative approach, i.e. 3-dimensional rendering of the cortical surface, requires computational removal of the skull in the MRI data. Normally, one would expect that simply removing the skull by help of a brain extraction program (e.g., BET = brain extraction tool from the FMRIB Software Library) renders the underlying electrodes visible. Unfortunately, this form of skull-stripping not only removes the bone but also the signal extinction artefacts by help of which the electrodes become visible. Therefore, a trick is needed: the combined use of a pre-implantation and a post-implantation image. Both data sets (usually 3D T1-weighted images) are coregistered. The position of the electrode contacts is transferred to the second MR image acquired after implantation. In the data set acquired before implantation, the skull is removed using the aforementioned brain extraction tool [55]. The resulting “skull-stripped” image is used as a mask to also remove the skull (but only the skull) in the second MRI acquired after implantation. This leaves the signal extinction of the electrode contacts in place. By volume rendering, the extracted brain can then be presented 3-dimensionally with the electrodes directly visible because of their signal extinction artefacts.
Compared to planar MRI slices, this offers a markedly superior visualization of topographic relations between subdural electrodes and cortical structures. In addition, the possibility of different view angles facilitates the planning of operations. We can also visualize the lesion and its spatial relation to the electrodes, and we can even show electrodes at the basal surface of the brain, between cerebrum and cerebellum [56, 57]. Figure 7 displays the results of electrode localization in our example patient.

Invasive Diagnostics, Epilepsy Surgery and Histological Results

Invasive EEG monitoring confirmed the onset of habitual seizures over and in the surroundings of the suspected dysplastic lesion. As already expected from the lesion’s location in the central region, mapping of motor functions showed a partial overlap of the seizure onset zone with motor areas. However, this overlap was limited to regions responsible for tongue movement. Due to their bilateral representation, these motor functions are usually not at risk in case of unilateral resection. Finally, therefore, epilepsy surgery in our example patient aimed at complete removal of the seizure onset zone around the lesion. In the resected specimen, focal cortical dysplasia type II according to Palmini and Lüders was histologically confirmed [58].

Validation of Postoperative Results

After epilepsy surgery it is important to validate the post-operative results and to examine whether the epileptogenic lesion has been completely removed. As stated above, the completeness of lesion resection has a decisive influence on the post-operative outcome [38]. Pure visual analysis of MR images may not be sufficient to detect residual lesional tissue. The examination is greatly enhanced if pre- and post-operative MRI data are coregistered and inspected together in the same coordinate space. If the lesion is only hardly recognizable on conventional MR images, it can be advantageous to coregister also the results of morphometric analysis presented above. In patients who fail to become seizure-free after surgery the proof of residual dysplastic/lesional tissue might offer the chance to achieve complete lesion resection in a second operation [59].

In our example patient coregistration of pre- and post-operative MRI data confirmed that the lesion had been completely removed. Since then, the patient has remained seizure-free and meanwhile has also tapered off the antiepileptic medication (Figure 8).

Conclusion

Postprocessing of structural MRI data has increasingly found entrance into routine clinical diagnostics and especially into the presurgical evaluation of epilepsy patients. In cases of medically refractory epilepsy it helps to determine the underlying pathology and to identify candidates for epilepsy surgery with a correspondingly higher chance of seizure freedom and improved quality of life for these patients. However, postprocessing MRI data does not only serve to capture epileptogenic lesions that are difficult to discern by eye, but can be useful at various stages during the course of presurgical evaluations and epilepsy surgery. Overall, computer-assisted MRI postprocessing complements conventional visual analysis and helps to manage and work up the increasing load of MRI data in epileptology (Figure 9).

References

Figure 8: Validation of post-operative results: The coregistration of the pre-operative MRI data (left subfigure) and the results of morphometric analysis (i.e. junction image in the middle subfigure) with the post-operative MR image (right subfigure) helps to confirm that no residual dysplastic tissue has been left in situ.

Figure 9: Progress of the average memory consumption of a single MRI measurement in epilepsy patients (data from the Swiss Epilepsy Centre in Zurich).
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