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Voxel-based Morphometric MRI Post-processing in MRI-negative Focal Cortical Dysplasia Followed by Simultaneously-recorded MEG and Stereo-EEG

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Summary

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We aim to report on the usefulness of a voxel-based morphometric MRI postprocessing technique in detecting subtle epileptogenic structural lesion. The MRI post-processing technique was implemented in a morphometric analysis program (MAP), in a 30-year-old male with pharmacoresistant focal epilepsy and negative MRI. MAP gray-white matter junction file facilitated the identification of a suspicious structural lesion in the right frontal opercular area. The electrophysiological data by simultaneously recorded stereo-EEG and MEG confirmed the epileptogenicity of the underlying subtle structural lesion. The patient underwent a limited right frontal opercular resection, which completely included the area detected by MAP. Surgical pathology revealed focal cortical dysplasia (FCD) type IIb. Postoperatively the patient has been seizure-free for 2 years. This study demonstrates that MAP has promise in increasing the diagnostic yield of MRI reading in challenging patients with “non-lesional” MRIs. The clinical relevance and epileptogenicity of MAP abnormalities in patients with epilepsy have not been investigated systematically; therefore it is important to confirm their pertinence by performing electrophysiological recordings. When confirmed to be epileptogenic, such MAP abnormalities may reflect an underlying subtle cortical dysplasia whose complete resection can lead to seizure-free outcome.

Keywords

epilepsy; MRI-negative; voxel-based morphometric MRI post-processing; magnetoencephalography; MEG; stereo-EEG; focal cortical dysplasia

Introduction

It is not uncommon that pharmacoresistant focal epilepsy (PFE) patients have negative MRI findings, even with a 3-Tesla magnet and dedicated epilepsy protocol. It is often challenging to formulate an adequate surgical hypothesis in some of these patients. Subsequent implantation coverage with intracranial electrodes may therefore be insufficient or excessively extensive, which may lead to failed localization and/or increased morbidity. Moreover, some of these patients may not even be referred for intracranial EEG investigations since they are often considered unfavorable surgical candidates. Despite substantial pre-surgical workup efforts, the absence of a lesion on MRI has consistently been shown as the most prognostically important indicator of compromised surgical outcomes (Bien et al., 2009; Jeha et al., 2007). In this challenging group of patients, any additional tool that will support a more robust presurgical hypothesis is important. Here we present the utility of a voxel-based morphometric MRI post-processing technique, as implemented in a morphometric analysis program (MAP), to identify a subtle abnormality in an “MRI-negative” case.

Case report

A left-handed 30-year-old male presented with a history of pharmacoresistant seizures starting at the age of 12 years. Birth and developmental history were unremarkable. Seizures were usually preceded by an aura of tingling sensation deep in his throat, spreading to his left face, then followed by left face clonus and occasional left arm posturing. Salivation and incomprehensible speech were also reported during some seizures. Notably, consciousness was preserved during these events, which lasted around 30 seconds and occurred several times a day.

Multiple scalp-EEG monitoring showed no interictal abnormalities and non-localizable (obscured by muscle artifact) EEG seizures. Three previous MRIs were normal, with the most recent examination using a 3-Tesla magnet with a focused 32-channel head coil. An

interictal FDG-PET study showed subtle hypometabolism involving both the right frontal and temporal operculum. Subtraction ictal SPECT coregistered to MRI (SISCOM) analysis was nonlocalizing (ictal SPECT injection time: 19 sec; seizure duration: 30 sec). The case was presented at a multidisciplinary patient management conference, and a hypothesis of focal epilepsy possibly arising from the right frontal lobe (operculum with propagation to the precentral region) was proposed. Further investigations with MEG and stereo-EEG (sEEG) monitoring were recommended. MAP was also performed as an exploratory tool to assess for areas of subtle gray/white matter changes.

As part of a research protocol we were able to obtain simultaneous interictal MEG-sEEG recording. MEG single dipole was modeled at the peak of the global field power of each interictal activity using vendor software (Neuromag, Helsinki, Finland). All dipoles were estimated within the right frontal as well as parietal opercular areas with consistent orientation, as shown in the third row of Figure 1. The simultaneously recorded sEEG consistently showed maximal spike activity (Figure 2) involving contacts R5 and R6 (positions indicated in Figure 1, red contacts on fourth row). Figure 2 shows an example of source localization of the simultaneously recorded MEG spike at the time of one sEEG-recorded spike. The interictal MEG activity is localized to the same sublobar area that encompasses the maximally involved depth electrode contacts (compare Figure 1, third and fourth row). Note that each dipole in the third row of Figure 1 comprises of one individual source modeling process, which is exemplified in Figure 2 bottom panel; and that the MEG dipole cluster illustrates the results of all interictal MEG spikes noted during the period of recording.

During sEEG monitoring, continuous repetitive interictal discharges were seen exclusively within the right frontal operculum (Figure 1, red contacts on fourth row) assuming a polyspike-appearance 10% of the time. During typical spontaneous seizures sEEG showed initial involvement of the same contacts within the right frontal operculum (R5 and R6), as well as early involvement of contacts within the right parietal operculum and middle precentral areas. Stimulation of the right frontal opercular contacts R5 and R6 using 25Hz biphasic square-wave pulses of constant current stimuli induced a habitual seizure with identical ictal EEG pattern at an intensity of 6mAmp.

MAP study was performed on T1-weighted MPRAGE images obtained from the patient's pre-operative 2009 MRI, which had been formally read as negative by our dedicated epilepsy neuroradiologists and neurosurgeons following focused re-review of the study during the multidisciplinary patient management conference. MAP analysis was performed with methods described by Huppertz et al. (Huppertz et al., 2005; Huppertz et al., 2008), using SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK) implemented in Matlab version 2007a (MathWorks, Natick, Massachusetts). The T1 input images were first normalized to Montreal Neurological Institute space, bias corrected for field inhomogeneity, and segmented in different tissue types including gray matter and white matter. The distribution of gray and white matter was then analyzed on a voxel basis and compared to a normal database, which consists of 90 normal controls acquired using the same 3T scanner in our institution (Huppertz et al., 2010). A 3D z-score gray and white matter junction map was generated as one of the outputs of the analysis, which is sensitive to blurring of the gray-white matter junction. We identified in the junction file an abnormality within the right frontal operculum. This abnormal region had a z- score greater than 4 (Figure 1, second row) and coincided with the MEG dipole cluster, as well as the sEEG-defined interictal and ictal onset zones.

Based on the available and highly concordant multi-modality data, the patient underwent a limited resection of the right frontal operculum. Post-operative MRI (bottom row of Figure

1) indicated complete removal of the area corresponding to contacts R5 and R6, as well as the abnormality region on MAP. Surgical pathology revealed balloon-cell focal cortical dysplasia (type IIb FCD, Figure 3). To date the patient has remained seizure-free for more than 2 years.

Discussion

Sensitivity of MAP to Subtle Cortical Dysplasia

Presented here is a unique case in which MAP successfully uncovered a solitary subtle lesion within the frontal operculum characterized by blurring of the gray-white matter junction in an “MRI-negative” patient. The concordant anatomic and electromagnetic localization data, as supported by MAP and simultaneously recorded MEG and sEEG indicated that this subtle lesion was abnormal not only structurally but also electrophysiologically. The lesion was later histologically-proven to represent FCD. Notably, the MAP study was based on a high-resolution MRI that showed no identifiable structural abnormalities on several conventional, detailed visual analyses. The capability of this post-processing technique to identify subtle gray/white matter abnormalities in some patients with negative MRIs is consistent with previous studies (Fauser et al., 2009; Huppertz et al., 2005; Huppertz et al., 2008). We emphasize that retrospectively we were able to identify this subtle lesion on the patient’s previous MRIs, i.e., the postprocessing analysis does not generate new information, but rather directs the reviewer to suspicious areas needing further scrutiny.

In contrast to traditional voxel-based morphology (VBM) techniques, which excel at group comparisons but are often criticized for low sensitivity or specificity for individual application, MAP is designed to be more suitable for individual analysis (Huppertz et al., 2009). The sensitivity of MAP to area of subtle cortical dysplasia has been studied in several patient series. In a 2005 study, which was the first to introduce this algorithm, 21/25 confirmed FCD lesions were shown to be associated with either blurring or abnormal extension of gray matter; three MRI-negative cases showed MAP+ abnormalities (Huppertz et al., 2005). A 2009 study presented 5 unusual patients with suspected multi-focal cortical dysplasia. MAP indicated additional abnormalities in 3 out of these 5 patients (Fauser et al., 2009). In a recent study of 91 FCD patients MAP increased the detection rate in patients with confirmed type IIa from 65% with visual MRI analysis alone to 82% after MAP. When combined with conventional visual analysis MAP provided complementary information and identified FCD type II lesions in 98% (89 of 91) of patients (Wagner et al., 2011). Doelken et al. recently reported a multimodality study of 51 patients with cryptogenic epilepsy and a suspected uni-lobar focus using MAP as well as MEG, SPECT, and PET, and found MAP to be 24% sensitive and 96% specific (Doelken et al., 2011).

Epileptogenicity of MAP Abnormality

The relevance and epileptogenicity of MAP abnormalities in patients who are referred for epilepsy surgery have not been evaluated systematically (Fauser et al., 2009). Therefore it is important to confirm their pertinence by performing appropriate electrophysiological recordings. Previous studies utilized invasive evaluations to confirm the potential epileptogenicity of abnormalities identified with MAP (Fauser et al., 2009; Huppertz et al., 2005; Huppertz et al., 2008). Here we were able to uniquely combine a noninvasive MEG with an invasive sEEG investigation. The ability to simultaneously record MEG and sEEG signals is rather unique. There have only been a few studies comparing simultaneously recorded MEG with results of electrocorticography (ECoG) (Mikuni et al., 1997; Oishi et al., 2002; Sutherling et al., 2001). The inherent limitation of ECoG is that only the surface of the brain can be sampled and therefore activities from deeper structures (such as the

opercular region in this case) can not be recorded directly. To our knowledge, this is the first report of source localization from simultaneous MEG-sEEG recording.

The two sEEG contacts (R5 and R6) that were closest to the abnormal area detected by post-processing exhibited almost continuous repetitive interictal spikes (Figure 2). One should be aware that, one limitation of sEEG recordings is the inherent “tunnel vision” of depth electrodes (Badier and Chauvel, 1995), which can miss sources distant to the site of implantation. In our case, concordant results from the simultaneously recorded MEG, which provides a more global whole-head survey of epileptiform activities, suggest that there were no other major interictal abnormalities.

Invasive intracranial EEG (ICEEG) is regarded as “gold standard” for accurate localization of the epileptogenic focus. An inherent challenge of ICEEG studies is the question of *where* to implant the necessary electrodes. Overall, ICEEG is most efficient when properly guided by other (noninvasive) modalities, such as a lesion on MRI. In MRI-negative cases, MAP has the potential to identify more subtle lesions, thus increasing the yield of ICEEG.

Resection of MAP Abnormality and Surgical Outcome

Complete resection of FCD offers a good chance for seizure freedom (Bingaman, 2004; Fauser et al., 2004; Kral et al., 2007; Widdess-Walsh et al., 2005). The importance of detecting these lesions and delineating their extent in potential surgical candidates cannot be overemphasized. It is possible to incorporate the MAP findings into the intraoperative neuronavigation and stereotaxy system to allow for a more precise targeting and resection of the lesion (Wellmer et al., 2010). Complete resection of the pathologically confirmed type II dysplastic lesion was possible in our case. Moreover, based on the available data, the surgeon was able to perform a limited resection tailored to the patient’s epilepsy, thus minimizing the risks for functional deficit, while still rendering the patient seizure-free. Although the data is compelling in this case, it is still unclear whether complete resection of MAP+ abnormality correlates with seizure-free outcome in a large number of MRI-negative patients. This will be the focus of our future work, with the hypothesis that MAP+ abnormalities, when confirmed to be epileptogenic, may reflect an underlying subtle cortical dysplasia whose complete resection can lead to seizure-free outcome.

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Figure 1.

Top row: Patient's conventional high-resolution 3-Tesla MRI. There are no identifiable abnormalities on detailed visual review of these images. Second row: gray-white matter junction z-score file as output of MAP processing, which is coregistered with the conventional MRI in the top row. The red crosses in top and second rows indicate the location of the subtle abnormality. Third row: composite image of MEG single-dipole source localization results, with each dipole representing a single interictal spike captured at different times of the recording. Fourth row: position of the stereo-EEG (sEEG) electrode in the vicinity of the lesion, with red indicating maximally involved contacts among all implanted electrodes (green). Fifth row: post-surgical MRI indicating a limited resection encompassing the electrically-defined epileptic focus within the right frontal operculum.

Figure 2.

Simultaneously recorded sEEG and MEG source localization. Top left: Invasive implantation map, with 10 sEEG electrodes and 1 depth electrode mainly targeting the right opercular, perisylvian, insular and precentral areas. Top right: sEEG tracings from the R electrode, showing maximal repetitive interictal discharges involving contacts R5 and R6 (cf Figure 1 fourth row for contact locations on the MRI). Bottom: MEG source localization analysis at the time of enclosed simultaneously-recorded sEEG spike. Magnified MEG spike waveform, contour map of MEG-recorded signals, and spike dipole superimposed on the patient's individual MRI are shown. The green arrow on the contour map indicates the estimated dipole projected to the helmet surface. The red isocontour lines represent efflux, and the blue lines represent influx of the magnetic field with respect to the helmet.

Figure 3. Surgical pathology showing areas with features of a type IIb (balloon- cell) focal cortical dysplasia (hematoxylin and eosin staining; original magnification = 200).