Utilization of magnetoencephalography results to obtain favourable outcomes in epilepsy surgery

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Summary
Magnetoencephalography (MEG) is a well-known technique in the presurgical evaluation of epilepsy patients. Like EEG, it can detect and localize epileptic activity. Epilepsy surgery can be used to evaluate MEG source localizations. Resection volumes were determined in 33 epilepsy surgery patients. The resection volume, taken together with the post-operative outcome, was used to evaluate MEG results. The scattering MEG localizations of interictal epileptic activity were represented by an ellipsoidal volume. Using this MEG results ellipsoid, it was demonstrated that a high coverage by the resection volume and a small distance to the resection volume are both correlated to a favourable outcome; in addition, a homogeneous distribution of MEG localizations is correlated to a favourable outcome. This study shows that MEG source localization can help to delineate epileptic activity and, along with other techniques, should be taken into account for epilepsy surgery.

Keywords: MEG; presurgical evaluation; functional tailoring; MSI epilepsy surgery; epilepsy

Abbreviations: MEG = magnetoencephalography; MSI = magnetic source imaging


Introduction
A considerable number of epilepsy patients cannot be treated sufficiently by drugs. Epilepsy surgery is a treatment option in these pharmacoresistant cases. Its goal is to remove a minimum volume to control the seizures without cognitive impairment. Outcome after neurosurgery provides the possibility to evaluate neurophysiological results. Presurgical evaluation typically involves EEG, video-EEG monitoring, high resolution MRI, single photon emission computer tomography and neuropsychological testing. Each modality provides unique information; decision-making is based on the integration of all findings (Polkey, 2000).

Magnetoencephalography (MEG) can contribute to the presurgical evaluation. In a study by Stefan et al. (2003), interictal spikes were detected in 76% of 300 patients, the epileptic lobe was correctly identified in 89% of 455 cases and MEG yielded crucial information for decision making in 10% of these patients. In a study of 58 patients (Wheless et al., 1999), the site of surgery was correctly predicted by invasive EEG in 70%, compared with MEG (52%), interictal scalp video-EEG (45%) and ictal scalp video-EEG (33%).

MEG and EEG source localizations are faced with the ‘inverse problem’: an infinite number of source configurations could explain the measured signal. Additional constraints are then used to allow a numerical solution; for example, the source of the measured signal can be modelled by a single equivalent dipole. The corresponding algorithm calculates a location for every selected time point, which is understood as a ‘centre of gravity’ with a surrounding confidence volume.

Analysing various single epileptic spikes generates a scattering of single source localizations. Previously, the decision on how to use these MEG results for epilepsy surgery had to be made on the basis of these distributed single localizations. It would be desirable to generate a volume representing features of the irritative zone from these scattering source localizations in order to plan epilepsy surgery as well as to compare MEG results with other diagnostic methods. The investigated hypothesis is whether MEG source localizations help to determine the area of epilepsy neuropathophysiology.
Subjects and methods

All patients that met the following criteria were included:

- Epilepsy surgery was performed at the University of Erlangen between 1998 and 2003.
- A pre-operative MEG as part of the presurgical evaluation registered epileptic activity.
- A pre-operative and a six-month post-operative MRI scan of the brain were available.

A total of 33 patients (15 females and 18 males) were included in this study. The average age at surgery was 33.6 ± 9.6 years (SD, range 18–60 years). All patients gave informed consent to the scientific analysis of the acquired data. The local ethics committee (medical faculty, university of Erlangen) approved the described procedures. Six months after epilepsy surgery, all patients attended the epilepsy centre for follow-up examination. During this period, the outcome due to the classification described by Engel (groups 1–4) was determined. Proposal for revised classification of epilepsies and epileptic syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

MRI was recorded on a 1.5 Tesla Siemens Magnetom system until April 2001, and then on a 1.5 Tesla Siemens Sonata (Erlangen, Germany). For magnetic source imaging (MSI), lipophilic fiducials were applied at the nasion and preauricular points. The head was scanned with a MPRAGE sequence in 144 coronal images with a size of 256 × 256 pixels (1.09 mm/pixel resolution in both directions) and a slice thickness including gap of 1.2 mm. An isotropic volume consisting of 1.1 mm symmetric cubes was generated from these images with Curry software version 4.5 (Compumedics Neuroscan, El Paso, TX, USA). All surfaces and volumes were segmented using a computer macro. The result was checked in a 3D visualization; if necessary, corrections were performed manually. The skin surfaces from pre- and post-operative MRI were segmented and co-registered. The post-operative MRI was resliced to fit the preoperative MRI. The procedure was repeated until an accuracy of maximum 2 voxels deviation on all axes was obtained at anatomical landmarks. The resection volume was obtained from the difference between the segmentation of the pre- and post-operative cortex. If there was a notable post-operative shift of the brain towards the resection cavity, this was corrected slice by slice, visually identifying the resection margins in the pre-operative images. An estimated error of 1 voxel outlining the resection margin leads to a 3% error in the resection volume. The number of voxels in the resection volume and the centre of mass were noted.

MEG was recorded on a dual unit 74-channel biomagnetometer system (Magnes II, 4-D Neuroimaging, San Diego, CA, USA) inside a magnetically shielded chamber (Vakuumschmelze, Hanau, Germany). The system consists of two sensors with 37 first-order gradiometers with 5 cm baselines; the channels had an average distance of 2.2 cm. The position of the nasion and the preauricular points was digitized using a 3D digitizer (Polhemus, Colchester, VT, USA). Positioning of the MEG sensors was based on previous clinical findings. Recording duration depended on the amount of epileptic discharges; if no or only a few epileptic discharges were seen in the online display, recordings were extended to 30 min at every position. The included patients had an average of 3.1 ± 2.0 (±SD) recording sessions, lasting 1260 ± 605 s (±SD) per session. The signal was digitized with a frequency of 520.8 Hz and 1–100 Hz bandpassed. The MEG source localization analysis was performed or reviewed by experts who had been involved in MEG analysis for at least two years full-time. Epileptic discharges were selected offline during visual inspection of the recorded activity. A 31 channel EEG was recorded simultaneously to assist spike detection in all patients.

The MSI software (4D-Neuroimaging) uses a single equivalent dipole model in a volume conductor of three homogeneous spherical shells for source reconstruction. Curry software offers a more sophisticated boundary element method volume conductor, consisting of triangle meshes for the cortex, liquor, skull and skin surface. Source models can be adapted to the number of simultaneous sources recognized by a singular value decomposition. Distributed source models allow to crosscheck source localizations (Fuchs et al., 2004a). These controls, which were also applied as quality standards for clinical use, were considered when source localizations were entered into the used database. To retain comparability to other results, however, only source localizations calculated with the single equivalent dipole model were used in this study. These localizations were subjected to a hierarchical cluster analysis and visualized in a free rotating 3D scatter plot to check for separated clusters.

If more than one cluster was found, the following were performed for each cluster separately, generating separate MEG results ellipsoids. For each localization, the distance to the centre of the cluster was calculated. If this distance exceeded the mean plus 2 SD, a localization was considered an outlier and therefore excluded. This procedure excluded 20 out of 312 localizations. A principal component analysis of the x, y and z coordinates determined the main components, including their eigenvectors and eigenvalues. An ellipsoid was fitted to these localizations, using the eigenvectors as the orthogonal axis of the ellipsoid. The ellipsoid extend was set to the double standard deviation separately for each axis to account for 95% of the variance.

Using a C++ Curry plug-in, the MEG results ellipsoids were visualized in the isotropic image cube and overlaid with the resection volume (Fig. 1). The percentage of voxels inside the MEG results ellipsoid covered by the resection volume was then calculated. If there was only one cluster of localizations, the Euclidian distance between the mass centres of both volumes could be calculated as an additional parameter for the spatial relationship. The variance of all pairwise distances between localizations within a cluster was used as a measure for localization homogeneity. The percentage of localizations inside the resection volume was calculated. Statistical tests were performed using STATISTICA 6.0 (StatSoft Tulsa, OK, USA) and SPSS 12 (SPSS) software.

Results

The resected tissue was located in the temporal lobe (79%), frontal lobe (12%), parietal lobe (6%) and the occipital lobe (3%) of patients. In 88% of the temporal lobe epilepsy patients, the mesial temporal lobe was part of the resection volume. The resected brain tissues in the 33 patients had a volume of 20.8 ± 10.2 cm³ (±SD). MEG source localizations were represented by an ellipsoid, which we term the MEG results ellipsoid.

MEG results ellipsoids had a volume of 10.7 ± 14.1 cm³ (±SD). In a voxel-based comparison, an average of 20.8% of the MEG results ellipsoids were covered by the resection volumes. A correlation between a favourable outcome and a high coverage of the MEG results ellipsoid by the resection volume was found (n = 33, P = 0.024, Kendall’s tau-b correlation, single sided, Fig. 2A). Five patients had two clusters of
localizations. No differences were found between patients with two clusters compared with patients having only one cluster of localizations. In the 28 patients with one cluster, a distance of $29 \pm 19$ mm between both volumes was observed. A small distance between both volumes correlated with a high coverage of the MEG results ellipsoid by the resection volume ($r = -0.69, P < 0.001$, Pearson correlation, Fig. 2C). A small distance between the mass centres of both volumes also correlated to a favourable outcome ($n = 28, P = 0.024$, Kendall’s tau-b correlation, single sided, Fig. 2B). In contrast, the percentage of MEG localizations inside the resection volume did not correlate significantly to a favourable outcome ($n = 33, P = 0.052$, Kendall’s tau-b correlation, single sided). A low variance of pairwise distances between MEG localizations correlated to a favourable outcome ($n = 33, P < 0.001$, Kendall’s tau-b correlation, single sided, Fig. 2D). Neither outcome nor coverage of the MEG results ellipsoid by the resection volume, nor the distance between both volumes correlated to the absolute volumes of the MEG results ellipsoids or to the resection volumes. In addition, no correlation was observed between either the coverage of the MEG results ellipsoids by the resection volumes or the distance

Fig. 1 Results from an extratemporal and a temporal lobe epilepsy patient are shown; both had no post-operative seizures. The resection volume covered 68% and 41%, respectively, of the MEG results ellipsoid. The distances between volume centres were 13 mm in both patients. All MRI slices are positioned at the centre of the MEG results ellipsoid. The borders of the resection volume and the ellipsoid are labelled in white. Three-dimensional views of the segmented cortices: the resection volume and the ellipsoid representing the MEG results are displayed in a darker grey, also visible in part through the semi-transparent cortex.

Fig. 2 A circle represents a single patient; thick lines and boxes indicate means and standard deviations, respectively. (A) A high coverage of the MEG results ellipsoid by the resection volume correlated with a favourable Engel outcome. (B) A small distance between the centre of MEG results ellipsoid and the resection volume correlated with a favourable Engel outcome. (C) A significant correlation ($r = -0.69$) was found between inter-volume distances and coverage of the MEG results ellipsoid by the resection volume. (D) Inhomogeneous distribution of MEG localizations correlated with a less favourable Engel outcome.
between both volumes with the number of source localizations, recording positions, total recording time, sex or age at surgery. No significant differences were found between the 26 temporal lobe epilepsy patients compared with the seven extratemporal lobe epilepsies.

Discussion
A method was designed to generate an ellipsoidal volume from the scattering of single MEG source localizations to represent MEG results. This volume was compared voxelwise with the resection volume generated from pre- and post-operative MRI scans. A high coverage of the MEG results ellipsoid by the resection volume and a low distance between the mass centres of both volumes correlated to a favourable outcome.

Previous evaluation of MEG results
MEG results in presurgical evaluation have been evaluated by several diagnostic methods, especially electrocorticogram (Mamelak et al., 2002; Oishi et al., 2002). Concordance of results from these methods does not permit the conclusion that therapy of the identified region leads to a favourable outcome.

MEG results were analysed with respect to patient outcome in three studies (Smith et al., 2000; Otsubo et al., 2001; Genow et al., 2004). Chronologically:

(i) In patients with neocortical epilepsy, four of five with ‘focal’, two of five with ‘regional’ and two of eight with ‘diffuse’ MEG localizations were post-operative seizure free; no relation between MEG results and outcome was found for all 46 included patients (Smith et al., 2000).

(ii) Otsubo et al. (2001) analysed retrospectively the MEG results of 12 children with lesional epilepsy. No high-resolution comparison with MEG results was possible because the extent of resections was not measured by post-operative MRI.

(iii) The only study evaluating MEG source localizations of interictal spikes by the resection volumes and the post-operative outcome was performed in patients with lesional frontal lobe epilepsy by Genow et al. (2004). Localizations were decided to be inside or outside of the resection volume, as determined by post-operative MRI. Because the sample of five patients cannot yield significant results, we compared this method to the MEG results ellipsoid.

Reasoning for volume and chosen form
MSI of epileptic activity yields a number of localizations. These can be transferred into a computer-aided treatment system, demonstrated for radiation therapy (Hellstrand et al., 1993; Aoyama et al., 2004), frequently used for somatosensory areas in neurosurgery (Nimsky et al., 1999) and, still unpublished, for epilepsy surgery. No evaluated concept is available on how to integrate single MEG results into the decision about the extent of the volume to resect or radiate. In this respect, a volume representing the MEG results seems desirable. This notion is further supported by the fact that enclosure of a higher percentage of localizations by the resection volume did not correlate significantly with a favourable outcome.

There are many possible ways to represent scattered points by a volume. A reasonable alternative to the chosen method would be to fit spheres to the coordinates. These could be shrink-wraped and, optionally, dilated or eroded to account for different levels of variance. MEG source localization results have a confidence volume, mainly depending on the signal-to-noise ratio (Fuchs et al., 2004a). A good signal has a small confidence volume and should have an above average contribution to the overall result. However, a function between signal quality and weighting of this signal is necessary in order to consider confidence volumes or any other additional parameter. No established method to design this function is available. This would have a major impact on the results; therefore, all signals from the mentioned database were treated equally. Recent developments in this field seem promising and should be tested after further evaluation (Fuchs et al., 2004b).

These arguments led to the use of a geometrical form that could account for the centre of mass and overall variance in all directions; a single sphere meets these criteria. Inhomogeneous distributions of MEG results, having a high variance of pairwise distances between MEG localizations, were associated with a less favourable outcome. To account for the scattering of localizations, a free oriented ellipsoid was used; its orthogonal axis was given by principal component analysis. The ellipsoid diameter was set to 2 SD to account for 95% of the variance on each of the three axes separately.

Locations with a distance to the centre exceeding the selected threshold of more than the mean plus 2 SD were eliminated to avoid disturbance of the result by single outliers. 3D visualization and cluster analysis were performed without overlay to the brain to avoid possible bias. The used MEG results ellipsoid, in contrast to a (wrapped) spheres model, accounts for localizations close to each other and is less influenced by single localizations with higher deviations from the centre.

Epilepsy surgery was performed in all included cases before the method to generate a volume from MEG localizations was designed. Therefore, none of the images showing the described ellipsoids or the study results could have biased the clinical procedures of included subjects. MEG was used as part of a battery of preoperative techniques. All clinical results are integrated to delineate the focal epileptic activity.

When assessing the coverage of MEG results ellipsoid by the resection volume, it should be considered that the resection volume covers only the resected brain tissue and does not include the liquor space between the gyri, and that the MEG results ellipsoids are not confined to the nervous tissue. Some patients benefited from epilepsy surgery, although no overlap between both volumes was observed. Disconnection of neural
circuits by surgery should be discussed in these patients. To control seizures, it is not necessary to completely remove the spiking zone, but only the critical mass of epileptogenic tissue. Therefore, epilepsy surgery does not aim at a total coverage of the MEG results ellipsoid. Like other diagnostic methods, the MEG results ellipsoid can only be interpreted as an indicator of where the epileptogenic zone might be.

To evaluate MEG results and achieve comparability to other methods, we established a method to generate a volume from MEG results. More extensive work is needed to further evaluate MEG results for standard clinical use. This will allow MEG results to provide additional information for treatment planning and to optimize individual functional tailoring of epilepsy surgery.

Acknowledgements
We wish to thank Michael Buchfelder, Johann Romstoeck and Bernd Tomandl for their support.

References


