The Clinical Use of MEG Activity Associated with Brain Lesions

Vieth J.B., H. Kober H., Ganslandt O. 1), Möller M. 1), Kamada K.

Department of Experimental Neuropsychiatry and 1) Clinic of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany

Abstract

Brain lesions may influence their border zones by moving, compressing, infiltration, edema or by a mixture of all. Sources of evoked and spontaneous activity in border zones can be localized by magnetoencephalography (MEG) giving information on the function of these areas. The inherent multisource problem of the MEG can be handled by using spatial average techniques (Dipole-Density-Plot (DDP) and Current-Density-Plot (CDP)). The reliability was tested with structural lesions (tumors and infarctions). The localizing of the somatosensory, the motor, and the auditory cortex and the speech related areas in relation to adjacent tumors is established in our clinical routine. The MEG results will be fused into the neuronavigator for image guided neurosurgery. In two studies with subjects and patients our MEG results have been compared to the results of the functional MRI (fMRI). In the presurgical evaluation of epileptic patients the localization of the epileptogenic lesion is an additional valuable tool, especially when the lesion is not visible in the MRI. In patients with multiple sclerosis we could demonstrate that the white matter lesions produce abnormal activity only in the adjacent neuronal areas. In the field of cerebrovascular accidents the penumbra can be localized in infarctions and TIAs. The feasibility to localize the penumbra by the MEG was demonstrated by our two comparisons of MEG results and those of the proton magnetic resonance spectroscopic imaging (1H MRSI) of N-acetyl and lactate in patients with brain infarction and tumors.

Introduction

Brain lesions may alter the surrounding brain tissue structurally by either moving or compressing it, or by infiltration or edema or by a mixture of these. The function of these border zones might be impaired. Neurophysiological signs of this deficit might be lesional activity (focal slow and fast waves) and epileptic activity (focal spike or seizure activity). Therefore in clinical diagnostics it is of great interest to know the localization and the extent of focal sources of abnormal spontaneous activity in or around lesions.

But it is clinically also very important to know the location and the extent of the evoked and event related activity of functionally important areas around brain lesions, especially when the lesions should be removed surgically. Additionally it is of clinical interest to know whether the electrophysiological part of the function is still normal or not, and if a displacement of the area took place.

But electric or magnetic fields of brain activity not only originate from the sources of interest but also from those of the rest of the brain (background activity). Therefore in order to get reliable results the so called "multisource problem" must be handled. So this paper gives also a short description how this problem can be solved, and in the main part shows clinical applications in neurosurgery and neurology with their present progress towards clinical relevance, partly compared to results of fMRI and 1H MRSI of N-acetyl and lactate.

Methods

Biomagnetic recording and source localization: from 1990 to 1994 we used the 37 channel system (Krenikon\textsuperscript{5}) of Siemens, Erlangen (planar recording surface of 20 cm in diameter), and since 1995 the 2x37 channel system (MAGNES II\textsuperscript{5}) of Biomagnetic Technologies Inc., San Diego, CA, USA, (curved recording surface with a 14 cm open diameter). The transfer of the coordinates from the head to the recording device and to the magnetic resonance imaging (MRI) data set was done with our surface fiducial points are necessary at all. So any 3D-MRI (or CT, or PET or fMRI) scan can be used [22].

We used the sphere as the MEG volume conductor model, since it is sufficient in most cases [24,48]. Depending on the task we used either the single current dipole model or a current distribution solution. In order to apply the single current dipole in a more adequate way, the localization procedure will be done only on signal section with one component predominantly describing the signal. The principle component analysis (PCA) selects these sections out of the whole recording time of 10 minutes (typically only 1-2 %) [21]. The second approach will be used when extended or multiple sources must be assumed. We adjusted for our needs an approach which Robinson and Rose [35] first described. In our approach, the CLSF (Current Localization by Spatial Filtering), the analyzing space (a sphere) consists of 7000 voxels which is adjusted in size and location to the area of interest. The individual current flow of each voxel will be obtained by applying a (spatial) filter on the signals measured at the surface of the skull showing the current intensity for individual time instants [11].

The multisource problem: To reduce the background activity we use the alpha blocking effect during the recording (eyes open) and a kind of spatial averaging of the already localized sources, in order to show the spatial distribution of the activity over the recording time. This is possible, when the signal of interest is differing from the background by its focal nature, by its frequency band.
(slow or fast waves or epileptic activity) and by its time locked appearance (evoked responses or epileptic activity). For the dipole analysis we developed the Dipole-Density-Plot (DDP), a three dimensionally working convolution using a three dimensional Gaussian envelope, which takes into account the localization uncertainty [21,42,45]. For the current solution (CLSF) a similar technique was developed, the Current-Density-Plot (CDP) showing the current intensity over the analyzing time [14].

For details of comparing methods see for functional MRI in Stippich et al. [39], and Nimsky et al. [30], and for magnetic resonance spectroscopic imaging (1H MRSI) in Kamada et al. [17].

Results and Discussion

In the last 10 years we were able to develop clinical applications with different progress towards clinical usefulness and relevance. The applications were validated by using structural lesions when applicable.

Evaluation with structural lesions:
We tested the reliability of the DDP and the CDP of spontaneous focal activity of structural brain lesions (tumors, infarctions) and their border zones, up to now in 91 cases with focal slow wave activity (2-6 Hz) and in 32 cases with fast wave activity (12.5-30 Hz) with the tendency of less cases of infarctions than of tumors. 19 cases of each group were additionally investigated using the magnetresonance-spectroscopy (see below). On the basis of our results we found the accuracy to localize the associated sources of the abnormal brain activity considerably high when the focal activity is present [16,17,21,42,45], and we can be sure to localize at least the main portion of the area of the functionally impaired neuronal activity - with or without visible structural lesions in the MRI. It should be stressed here, that our approaches (DDP, CLSF, and CDP) also can be used with the EEG provided that the EEG source localization is accurate enough.

Clinical applications:

Normal activity:
The clinical application to determine the relation of tumors to the cortical somato-sensory, motory, auditory and cortical speech areas was developed and established in Erlangen by the Department of Experimental Neuropsychiatry with the goal of acceptance in clinical environment. Now these approaches are routinely used by the Erlangen Clinic of Neurosurgery for operation planning and intraoperative functional neuronavigation [8]. This image guided neurosurgery is performed in a "twin operation room" with a Siemens Open-MRI (Magnetom Open) in one room and the movable operation table (into the Open-MRI) and the Zeiss microscope neuronavigation system (MKM) and the additional Stealth pointer neuronavigation system in the other room [38]. So an optimum of carefulness is possible during the operation with special reference to important eloquent brain areas in order to have less postoperational neurological deficits.

Evoked Responses:
Gallen et al. [6,7] demonstrated first the clinical usefulness of this approach using somato-sensory evoked responses (SEF = somato-sensory evoked field). Subsequently this technique was used by others [8,9,10,18,28,29,33]. A coupling of MEG results to the neuronavigator was first described by Watanabe et al. [47]. The interactive use of MEG in image guided neurosurgery was reported first by Rezai et al. [34].

Event related motor responses:
Deecke et al. [5] reported first on a motor related MEG activity, the so called "Bereitschaftsfeld". Later also the localization of the motor induced activity was possible. More generally Lewine und Orrison [23] reported about this procedure. Our group developed for clinical usage in neurosurgery the clinical application to localize the cortical motor activity, which was induced by selfpaced finger
movements (MEF = motor evoked field). The trigger signal was obtained from the rectified electromyogram of the corresponding muscles of the lower arm [8,20].

Event related speech responses:
It also is possible to localize the cortical areas which are activated by speech recognition [37]. In our approach - similar to the WADA-Test [46] - we activate visually by written words and pictograms of monosyllabic concrete objects. The presentation was conducted via a glass fiber bundle from a television screen from outside the shielded room. If the term is also spoken internally the area of the speech induction (Broca's area) can be activated and localized too [12]. Also meaningless pictograms were presented in order to enhance the signals of the meaningful presentation by subtracting the signals of the meaningless presentation from that from the signals of the speech related presentation [14].

Figure 3: Speech related MEG source localizations in A and somatosensory evoked field (SEF) in B of a 69 years old male (jza) with a left temporo-parietal glioma. The speech responses were elicited by presenting pictograms of monosyllabic concrete objects for 800 ms on a television screen (conducted via a glass fiber bundle to the inside of the shielded room). 250 samples have been averaged and the CLSF (current density) of the of the response determined. Isocountour lines show the intensity of the CLSF results. The task was to recognize the object and internally speak the word of the object. The first response was at 340 ms after the onset of the presentation in the posterior part of the left superior temporal gyrus (Wernicke area) marked by W, and the second response was at 745 ms after the onset of the presentation in the left inferior frontal gyrus (Broca area) marked by B. The SEF source (marked by SEF) was localized 50 ms after the tactile stimulus at the index finger (200 samples averaged). The central sulcus is marked by CS.

In right handed people the activity density was highest in the posterior part of the left superior temporal gyrus (Wernicke area) at around 350 ms and at around 500-600 ms (internal speaking) in the left inferior frontal gyrus (Broca area) but also some at the same time in the superior temporal gyrus [14]. This procedure even can be used to show differences of two differently written languages: a phonetic oriented language (German) and a language consisting of morphograms (Kanji characters of Japanese) [14].

Experiences in Erlangen:
In our studies (up to Mai/1999) in the first group of 81 patients with temporal or frontal tumors we localized clinically successfully the somatosensory and the motor associated cortical responses. In all patients the somatosensory activity has been localized and out of these in 33 cases the motor response. In all patients the projection of the magnetic single dipole localization on the brain surface of the postcentral gyrus was coinciding with intraoperatively evoked phase reversal of the potentials measured at the surface of the cortex, which was elicited by electric finger stimulation (only possible in 90% !) [c.f. 8,9,10,40]. 67 patients out of the 81 patients were operated by using the functional neuro-navigation. 14 patients have not been operated on the basis of the MEG findings. An example of the localization of the somato-sensory evoked response in the postcentral gyrus in a patient with a meningeoma is shown in figure 1 with coupling of the result to the Stealth neuro-navigator. Figure 2 shows an example of the localization of the motor related responses and the somato-sensory evoked responses in a patient with a left astrocytoma in the pre- and post-central gyrus respectively.

In the second group of 16 patients (14 right and 2 left handed) with brain tumors in the speech related cortical areas were localized by using the average version of the CLSF, the CDP. Our approach was tested with 11 healthy subjects. The handedness was determined by the Edinburgh Handedness Inventory [31]. Our approach allowed to differ between the sensory and the motor speech areas (methods c.f. [14] ). 12 out of 16 patients suffered from transient or permanent speech disturbances. In 15 patients the sensory area and in 12 patients also the motor area could be localized.

In order to determine the hemisphere with the larger activity MEG recordings were done simultaneously on both sides. Our current density approach showed a two to four times larger activity on one side, sometimes up to eight
times larger. All patients (right and left handed) had their higher activity on the left side [26,27]. The WADA-test [46] confirmed in three cases the hemisphere with the higher intensity on the left side also in one left handed patient. Because of its invasiveness the WADA-test was applied restrictively. Up to now 3 patients out of the 16 patients were operated by using the functional neuronavigation. 3 patients have not been operated on the basis of the MEG findings [25,27]. Figure 3 shows an example of the localization of the speech areas and the somato-sensory evoked responses in a patient with a left temporo-parietal glioma.

**MEG and functional MRI (fMRI):**
Since 1991 [2] the functional magnetic resonance imaging (fMRI) is used to localize three dimensionally the local oxygen tissue deficit elicited by evoked or event related brain activity. The effect is called the "blood oxygenation level dependent contrast (BOLD)". There are some fundamental differences between both approaches, which can be the reason of misinterpretation:

![Figure 4: Localization of motor related responses in functional MRI (fMRI)](image)

(1) The signal to noise ratio is in MEG source imaging (MSI) much higher than in fMRI. (2) In fMRI always a base line recording is necessary. (3) On the basis of this fact movements in fMRI can produce a lot of new (artifact) sources. In MSI only the sources will lose sharpness. (4) In MSI the neuronal areas will be localized. In fMRI the drainage section of the venous branch shows oxygen deficits as already demonstrated by Segebarth et al. [36]. So the interpretation of the fMRI findings should be done with general caution [36]. Up to now no procedure was published to get around this situation. (5) In fMRI the time resolution depends on the diffusion time of desoxyhemoglobin, which is in the order of seconds. In MSI the time resolution depends on the electric properties of the tissue and the recording equipment, so it is in the order of one millisecond or less.

In two comparing studies with 6 subjects [39] and 15 patients [30] we found the localization of evoked cortical responses obtained by MEG and fMRI typically displaced by around 1 cm, showing the consequence of the two different aspects of the techniques: the measuring of the electric neuronal activity (MSI) and the measuring of venous drainage induced by neuronal activity (fMRI) (c.f [36]). Figure 4 shows an example of the comparison of the localization of the motor related MEG response and the motor related fMRI response.

**Clinical applications:**

**Abnormal activity:**

**Epileptogenic lesion:** One valuable application of localizing abnormal activity is in the field of the presurgical evaluation of epileptic patients: Normally the epileptogenic zone is removed to cure the epilepsy. But results with structural lesions show that the removal of the epileptogenic lesion (assumed to be the original cause of a seizure disorder) is also important for the clinical outcome [1,4]. Thus the localization of the epileptogenic lesion is of great interest. In addition it is very easy to record the spontaneous interictal activity associated with epileptogenic lesions. Neither a spike nor a seizure must be caught.

Up to now only two other groups and our group demonstrated, that the spontaneous slow wave activity can be used to localize the epileptogenic lesion of focal epilepsies, which are associated either with or without structural lesions [7,23,43,44].

In our study we had one group of epileptic patients with
structural lesions as the reason of the epilepsy, and the second group without any visible structural lesion. In the first group in the border zone of the tumors we got a strong coincidence of the MSI localizations of the three different spontaneous signal components: (1) interictal epileptic spikes, (2) slow wave activity, (3) fast wave activity. For source enhancement both the DDP and the CDP have been used. Occasionally occurring spike/wave complexes have been discarded, when slow and fast wave activity was analyzed. An example is shown in figure 5, which also very nicely shows the shell like distribution of the slow and fast wave sources around the tumor. The same coincidence of the results in all six approaches also was found in epileptic patients without any visible structural lesion [41,43,44].

Focal abnormal lesional activity even could be found associated with the (focal) Rolandic epilepsy of children [15]. Thus we demonstrated that even in these cases an epileptogenic lesion may be present, in spite of, that "per definitionem" no structural lesion is associated with this disease. So our approach to localize the epileptogenic lesion seems to be a valuable additional tool or maybe in some cases an alternative in the presurgical evaluation of epileptogenic patients, when no structural lesion is visible in the MRI. It is worthwhile to test in multicenter studies the value of this approach compared to the localization of interictal spikes and of the epileptogenic zone.

White matter lesions: The sources of the MEG are mainly the longitudinal flowing currents inside the neurons, which are generated at the synapses, the postsynaptic potentials [32]. Therefore lesions in the fiber section of the neurons (white matter) should have no significant contribution to the normal and abnormal electric activity of the brain. Since the multiple sclerosis (MS) is a disease, which mainly destroys the myelin sheath of the neuronal fibers, and gives a contrast in the MRI in the white matter, we wanted to know if these fiber lesions produce abnormal activity at all, and if it is present where the activity comes from.

In our study we included 8 patients suffering from MS and a baseline group of 8 healthy subjects. The two groups got the same recording protocol. The spatial dipole distribution was quantified and compared between the groups statistically. In all MS patients the maximum of focal abnormal slow and fast wave activity was found in cortical (neuronal) areas adjacent to the fiber lesions, whereas in the healthy subjects no focal abnormal brain activity could be found [19]. These results let assume that if subcortical fiber lesions may occur together with abnormal cortical neuronal activity, it might be difficult to differ the location of the lesion, which is responsible for the abnormal cortical activity, unless other informations are available.

Cerebrovascular accidents: Cerebrovascular accidents account for around a quarter of the total mortality and the bulk rate of the disabled people. Therefore it would be of great value to have diagnostic measures for an early detection of prestages.

In our studies we found that the MEG is able to localize not only the disturbed function around a structural brain lesion (infarction) but also that of an area with only functional - maybe reversible - impairment. These can be transient ischemic attacks (TIA) or lesions too small to be detected by the standard MRI resolution. Up to now we localized not only the pathological activity associated with brain infarctions in 23 patients, but also the activity associated with the penumbra of transient ischemic attacks (TIA) [17,42,45] in 21 cases.

Thus we are also able to localize clinically silent reversible ischemic brain deficits in accordance to silent brain infarcts [3]. This finding is clinically important for the decision, whether an extracranial stenosis of the internal carotid artery is to be assumed symptomatic or not, and in the case of a symptomatic stenosis for an indication of an endarterectomy [45]. The feasibility to localize the penumbra of infarctions is also very important, when new therapeutic approaches are available that prevent neurons to be damaged irreversibly.

Figure 5: MEG source localization of focal abnormal spontaneous interictal activity in the border zone of a right frontal astrocytoma of a 67 years old female patient (ida) with grand mal epileptic seizures. The averaging version of the CLSF, the Current-Density-Plot (CDP) was used to localize the current density during the whole recording time of 10 minutes. A: spikes, B: slow (2-6 Hz) and C: fast (12.5-30 Hz) wave activities. B and C without spike and wave activity. Especially in B and C the shell like abnormal activity can be seen.
Brain functions and metabolism: Another support, that our approaches are able to localize the penumbra comes from the two following studies:

In order to show the feasibility of the MEG to localize brain areas of impaired activity as the penumbra or edema zones we studied the relationship between electric brain functions and metabolic brain functions in patients with brain infarcts and brain tumors, using the MEG and the proton magnetic resonance spectroscopic imaging ($^1$H MRSI).

In the first study we investigated 12 patients with brain infarction in comparison to 12 normal cases, showing the MEG slow wave dipole density (DDP) in the border zone of the infarction and the signal intensity of N-acetyl (NA) and the lactate (Lac) inside the infarction, in the border zone, and in normal tissue, where NA is a measure for normal function of the brain. The signal intensity of NA was significantly reduced in the regions with the highest slow wave activity but was well correlated inter-individually with the dipole density (DDP) of the quantified maximum of slow waves. Though Lac was mildly accumulated in the lesions, the Lac level had no correlation with slow wave magnetic activity. We could assume, that preserved and metabolically active tissue with NA signal produced the abnormal slow wave activity under lactic acidosis (mild accumulation of Lac).

Figure 6 shows the spatial distribution of the intensities of the abnormal slow waves, the Lac and the NA activities in a patient with a brain infarct. Figure 7 shows an example of the same patient with the topographic development of the three activities along a line from normal to pathological tissue. It appears that all three distributions start with abnormal values relatively far away from the infarct, typically 3 cm or more. From the results of the study we could assume, that the MEG quantified slow wave sources give an indication whether a penumbra is present at all, and where it is localized [17]. The clinical importance is also in the field to prevent neurons to be damaged irreversibly.

The second study was performed on 7 patients with common brain tumors (i.e. astrocytic tumor and meningioma) compared to a group of 10 healthy subjects. The recording protocol of MEG and $^1$H MRSI was in both
groups the same as in the previous study. Increased slow, fast waves activities and spikes were observed in the neuronal area adjacent to the bulk of the tumor with a mild reduction of NA and a slight accumulation of Lac. Lac intensity was less pronounced than in the study with the infarcts.

Figure 8: Intensity of abnormal spontaneous slow wave (2-6 Hz) activity, lactate (Lac) 1H MRSI activity, and of N-acetyl (NA) 1H MRSI activity of a 53 years old female with a left meningeoma along a line drawn from normal tissue through one pole of the tumor to normal tissue again. Same recording protocol as in figure 6 and 7. C: line seen in a T1 image; D: line seen in a T2 image enclosed by a white rectangular line showing the enlarged area in B, where the line is in direct spatial relation to the four different activities for comparison. Na is decreasing from normal tissue to the tumor tissue and increasing to normal tissue again. Lac is increasing mildly (compared to infarcts) from normal tissue to the tumor tissue and does not reach the baseline in tissue outside the visible tumor on the other side. The slow wave activity has two peaks in both border zones of the tumor corresponding to the assumption that inside the tumor are no neurons to produce electric activity.

The bulk of the tumors was magnetically silent. The extension of the tumor border zone seems to depend on the invasiveness of the tumor, but it seems to be smaller than that of the infarcts, typically about 2 cm. Figure 8 shows an example of the intensity of the three activities along a line from normal tissue through the tumor and back to normal tissue. The clinical importance may be the early detection of prestages of a tumor by MEG. Details in Kamada et al. [16].

Conclusions

In our work we could demonstrate: the localization of the function of eloquent cortical areas is well established in neurosurgery. The localization of the epileptogenic lesion is a very promising tool in the presurgical investigation of epileptic patients. The penumbra of transient ischemic attacks (TIA), of infarcts and of tumors can be localized. A possible screening for asymptomatic "TIA" (reversible neuronal deficit) might also be a promising tool in the prevention of strokes.

References


[12] Grummich, P., Kober, H., Vieth, J., Matschke, J. and Ganslandt, O. Sensory speech area investigated by mag-


[34] Rezai, A.R., Hund, M., Kronberg, E., Zonenshayn, M., Cappell, J., Ribary, U., Kall, B., Llinas, R., and Kelly, P.J. The Interactive Use of Magnetoencepha-


