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Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases

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Summary

Epilepsy surgery is based upon the minute assessment of brain tissue generating epileptic activity. A number of diagnostic methods are employed in the process of presurgical evaluation, supplying information on various morphological and functional aspects, ultimately integrated into the general result fundamental to the final treatment decision. Magnetic source imaging (MSI), combining structural (MRI) and functional (MEG) data, has been playing an increasingly important role among the tools of presurgical epilepsy evaluation. However, in spite of a considerable number of publications, the samples used have hardly exceeded 50 cases. Therefore, we present a synopsis of 455 epilepsy patients who underwent MSI investigations. Analysis of this substantial data revealed that the average sensitivity of MEG for specific epileptic activity was 70%. Among 131 patients who underwent surgical therapy in addition to antiepileptic drug medication, MSI identified the lobe to be treated in 89%, with results for extratemporal cases being even superior to those with temporal lobe surgery. Introducing a measure to quantify the contribution of MSI to the general result of presurgical evaluation that was applied to 104 patients, the results showed that MSI supplied additional information in 35% and information crucial to final decision making in 10%. Accuracy as well as contribution findings underlined MSI appropriateness even for extratemporal epilepsies, which otherwise frequently prove difficult with respect to focus localization.

Keywords: magnetoencephalography; magnetic source imaging; focus localization; presurgical epilepsy evaluation

Abbreviations: AED = antiepileptic drug; ETE = extratemporal lobe epilepsy; GFE = global focus estimate; MSI = magnetic source imaging; SED = specific epileptic discharge; SNR = signal-to-noise ratio; TLE = temporal lobe epilepsy; VNS = vagal nerve stimulation

Introduction

As a basic rule, potentially harmful diagnostic procedures must be avoided whenever the clarification of a diagnostic problem appears feasible using less severe methods. Thus, in the course of presurgical evaluation of localization-related epilepsies, invasive assessment should be applied only as a last resort (Ebner and Lüders, 1996).

Although routine surface EEG has been established as the specific test for the detection of focal epileptic activity, it may still fail to define the site of epileptic brain tissue (Niedermeyer, 1988) and it provides a somewhat 'blurred image' (Gloor, 1975). Therefore, invasive recordings were introduced to improve localization approaches. These, though helpful in a considerable number of cases without inconclusive non-invasive findings (Spencer *et al*., 1982; Spencer, 1992; Binnie *et al*., 1994; Munari *et al*., 1994), generally bear an increased risk of side-effects, e.g. bleeding and infection, in addition to the hazard of general anaesthesia. Furthermore, each invasive method also has specific disadvantages with respect to localization, offering merely limited views, compared with the rather global if 'blurred' view of scalp EEG. Intracerebral depth electrodes (Talairach *et al*., 1974; Wieser, 1981), while permitting access to deep, otherwise hardly accessible structures of the brain, yield only a sort of 'tunnel view' (Gloor, 1975; Quesney and Gloor, 1985). Subdural or epidural electrodes may be compared to a 'magnifying lens', providing detailed insight but only into a small superficial

portion of the cortex. According to these considerations, invasive recordings remain restricted to a carefully chosen selection of patients.

The worldwide increase in epilepsy surgery requires non-invasive approaches that can be performed with minimal risk in a large number of patients. As a new method that meets these requirements, MEG was introduced in epilepsy research during the 1980s (Barth *et al*., 1982, 1984; Modena *et al*., 1982; Ricci *et al*., 1987; Rose *et al*., 1987; Sutherling *et al*., 1987).

As MEG is not an imaging technique, it quickly became the custom to combine MEG localization results with co-registered MRI data. This MEG/MRI fusion, known as magnetic source imaging (MSI), has since been established as an additional non-invasive tool offering a three-dimensional (3D) view comprising anatomical and functional aspects and thus providing new perspectives concerning the assessment of intralobar relationships between functional and morphological changes in focal epilepsies (Stefan *et al*., 1990, 1991; Tiihonen *et al*., 1990; Nakasato *et al*., 1994; Ebersole *et al*., 1995; Smith *et al*., 1995; Brockhaus *et al*., 1997; Knowlton *et al*., 1997; Ishibashi *et al*., 1998). However, despite an increasing number of publications in recent years (Minassian *et al*., 1999; Paetau *et al*., 1999; Wheless *et al*., 1999; Morioka *et al*., 2000; Otsubo *et al*., 2001; Shiraishi *et al*., 2001; Ishibashi *et al*., 2002; Iwasaki *et al*., 2002; Mamelak *et al*., 2002; Pataraia *et al*., 2002), papers on MEG localizations have mainly reported data of small samples of patients. Therefore, the aim of the present study was to report MSI experiences with a large patient group, including patients with temporal lobe epilepsies (TLEs), frontal lobe epilepsies and other extratemporal lobe epilepsies (ETEs). Specifically, the study addressed the question of what MEG contributes to the process of presurgical epilepsy evaluation.

Subjects and methods

Two different biomagnetic devices were used for MEG investigations in two periods. Both had first-order axial gradiometers and were installed in a magnetically shielded chamber (Vakuumschmelze, Hanau, Germany).

The first device was a 37-channel system with a sensor array of 19 cm and gradiometer baseline of 6 cm [Krenikon (subsequently referred to as K); Siemens, Erlangen, Germany]. As it was the first multichannel biomagnetometer installed in a clinical environmant worldwide, the period of its usage was characterized by the exploration of MEG's applicability with respect to focus localization.

The second device was a dual-unit 74-channel biomagnetometer [Magnes II (subsequently referred to as M); 4-D Neuroimaging, San Diego, CA, USA] with a 5 cm gradiometer baseline. The installation of this instrument, which permitted simultaneous recordings of both hemispheres, marked the beginning of another era of MEG investigations, dedicated to the assessment of the role of MEG among the diagnostic tools used for presurgical epilepsy evaluation.

Recordings were performed under varying conditions. Spontaneous magnetic activity was continuously recorded for focus assessment purposes under antiepileptic drug (AED) withdrawal according to individual clinical requirements. Pharmacological and sleep deprivation approaches were tried in order to provoke specific epileptic discharges (SEDs) (Kettenmann *et al*., 2002).

Patients were usually positioned lying on their side, with their head either beneath the sensors (K) or between the sensor units (M). Sitting upright or half-reclining positions were chosen for recording activity from central and midline regions, with the area of interest beneath the sensors, in single-unit mode. Sensors were adjusted with respect to the presumed area of epileptogenicity, the sensor array being centred above the 10/20 position with predominant spiking activity. If no preliminary focus hypothesis was available, or if the scope provided by a single sensor position was either insufficient to record any SEDs (spikes/sharp waves) or inappropriate with respect to showing dipolar distributions of SEDs, repetitive recordings were performed with different sensor locations. Variations of sensor positions were carried out in small steps of a few centimetres in order to improve dipolar distributions of SEDs identified in the preceding position or, in the absence of previously obtained SEDs, by choosing a position that provided only a little overlap with the previous one.

Minimum recording time was usually 30 min. Depending on the time elapsed until a sufficient number of epileptic discharges had been recorded (if any), and the number of repeated measurements with different sensor positions, the duration of recordings would sometimes extend to several hours. Occasionally, in patients with high spiking frequencies, data acquisition was completed after <30 min. Due to the requirement of a fixed head position and hence the limited duration of recordings, the data obtained was mostly interictal.

Standard acquisition parameters (sampling frequency 512.8, band pass 1–100 Hz and additional 50 Hz notch filter) were modified according to special requirements.

In order to constitute MSI (the combination of MEG and MRI), two approaches were used. Early on, co-registration was set up by means of dental impressions attached to acrylic glass frames that held clues for 3D spatial identification in both MEG and MRI environments. As this method not only caused slight discomfort for the patients but was also prone to produce erroneous spatial transformations due to the device lacking rigidity, it was replaced by another procedure based upon anatomical landmarks (nasion and pre-auricular points). These were digitized prior to MEG recordings with a 3D digitizer (Polhemus, Colchester, VT, USA) with relation to the MEG sensors and identified in MRIs by means of self-adhesive radiographic markers. Reproducibility of reference points was verified by digital photography. Thus, a common spatial coordinate system could be established in order to merge MEG findings with individual anatomical conditions. MEG/MRI co-registration failed in only <5% of patients who

had MEG recordings, due to repeated seizures during MRI scans or contraindications to MRI investigations. In these cases, either a spherical sketch (K) or a graphical display of the head's surface digitization (M) was used for provisional visualization of MEG localizations.

Continuous data was band-pass filtered offline (3–70 Hz) and visually inspected for specific epileptic patterns. In order to obtain the earliest possible dipole localizations, rising slopes and peaks of spikes and sharp waves were selected for localization procedures. Standard evaluation was based upon the model of an equivalent current dipole in a homogeneously conducting sphere and only applied to data sets with dipolar distributions of SEDs. Best-fitting dipoles were selected by filtering dipole results using a 0.98 map correlation and a 3 cm^3 confidence volume threshold. Additionally, more sophisticated techniques were applied in an ongoing study aimed at the comparison of MEG and EEG results (Fuchs *et al*., 1998*a*) using different strategies of analysis, including realistically shaped head models (boundary element method; Fuchs *et al*., 1998*b*) and current density reconstructions (Curry software, Neuroscan, Sterling, VA, USA).

In order to automatically detect SEDs of high similarity, cross-correlation algorithms were available that could be applied to any selection of channels. If a sufficient number of highly correlating epileptic signals were found, they were averaged and the mean subjected to the same localization procedures as single SEDs. The choice of patterns to be submitted to averaging was made with respect to correlation coefficient as well as amplitude thresholds, which were individually defined depending on the signal-to-noise ratio (SNR).

Altogether, 475 epilepsy patients underwent MEG investigations, 129 patients with the K system and 346 with the M system (267 males, 74 K, 193 M; and 208 females, 55 K, 153 M). The overall mean age was 34 years (median 31 years, ages ranging from 7 to 79 years; K, 12–79, mean 32, median 28 years; M, 7–63, mean 34, median 33 years). The selection of patients for the K and M systems varied, with the aspect of spike occurrence in EEG recordings being more stressed as an inclusion criterion for MEG investigations with the K system than later on with the M system.

The vast majority of patients (455 = 96%) suffered from epilepsies with evident or suspected pharmacoresistance. These patients constituted the main group of the entire sample. The remainder comprised 20 postoperative patients who participated in a study of disruptive effects of surgical treatment upon subsequent MEG recordings (Tilz *et al*., 2002).

A small proportion (75 = 16.4%) of the main group were out-patients, whereas the bulk comprised hospitalized patients. Approximately half of the patients (229; one with primary generalization and 228 with partial epilepsies, of which 199 were monofocal and 29 multifocal cases; 186 patients had secondary generalized seizures) underwent treatment additional to AED medication: 85.7% of these had focal treatment, and the remainder (14.3%), suffering from multifocal or primarily generalized seizures, respectively, were provided with a vagal nerve stimulation (VNS) device or had callosotomy. Focal treatment encompassed resections and/or multiple subpial transections (93%) and radiation (7%). Focal neurosurgical procedures were applied to temporal lobes in 146 patients (82%), frontal lobes in 24 (13.5%) and other lobes in eight (4.5%).

The therapeutical strategies were decided upon according to the consensus concerning global focus estimates (GFEs), issued through the interdisciplinary epilepsy conferences. This forum consisted of all the experts participating in the process of epilepsy evaluation presenting their respective findings, discussing them and, where possible, integrating them into a conclusive focus hypothesis. Diagnostic tools included video-EEG monitoring, MRI, single photon emission computer tomography (SPECT), neuropsychology and, occasionally, invasive recordings and PET scans, with optional ictal results from scalp EEG, invasive EEG and SPECT.

During the first (explorative) period, the usefulness of MEG was tested in terms of agreement of MSI localizations with the GFE.

In the second period, the contribution of MSI to the GFE was assessed. If MSI results gave more detailed information than the GFE with regard to lateralization, lobar or intralobar localization, they were considered to contribute additional clues. For the assessment of this contribution, a rating scale was introduced: code –2 = disagreement, –1 = no contribution, 1 = agreement, 2 = additional information and 3 = influence upon neurosurgical procedures. Code –1 was assigned in cases where no SEDs were identified in the MEG data sets or where they were too few or the signal quality too poor to permit meaningful analysis. The remaining codes were reserved for cases where MSI yielded localizations: code 1 where the information obtained by MSI did not differ from the GFE; code –2 where MSI disagreed with the other diagnostic results; code 2 where MSI contributed additional clues; and code 3 where MSI findings had an impact on the final decision upon further treatment, i.e. if this decision would probably have been different had MSI not been available.

The coding was performed by two expert team members who were intimately familiar with the MSI data, the patients' histories and the findings of the remaining diagnostic procedures and had participated in the interdisciplinary conferences. They assessed the MEG contribution codes heuristically, in analogy to the process of establishing the GFE.

Results

Sensitivity

Out of 455 patients who had MEG investigations for localization purposes, 320 (70.3%) yielded results. The remainder comprised cases without specific epileptic patterns

(89 = 19.5%) and cases where artefacts and/or technical problems thwarted data evaluation (46 = 10.1%). Taking into account only the number of investigations without disturbances and unhindered analysis, sensitivity amounted to 78.2%. However, although the percentage of recordings failing analysis was higher during the first period of investigations (20 = 15.5%) than later on (26 = 7.9%), the proportion of cases without SEDs increased. Thus, the most reliable estimate of sensitivity appears to be that derived from data collected during the second period, where 229 out of 300 successful recording sessions yielded SEDs (76.3%). An increase of spike activity could be observed after sleep deprivation and, even more pronounced, after clonidine medication (Kettenmann *et al*., 2002).

Out of 229 patients who underwent treatment additional to AED medication, MSI yielded localization results in 167 (73%). This overall percentage nearly equals that for patients with temporal lobe surgery (72%); the respective rate for extratemporal focal operations was 67%. The sensitivity for frontal lobe surgery cases was 70% and for patients with focal neurosurgical treatment of other lobes only 57%, whereas 80% of the cases with other than focal neurosurgical therapy yielded MSI findings. Among these 27 cases were 12 monofocal, 11 multifocal and four diffuse localization results.

A considerable number of patients (226) received no treatment other than AED, 81 of which underwent MEG investigations during an early stage of epilepsy exploration without entering presurgical evaluation proper. MSI localizations were established in 70% of the 226 cases with AED therapy only and in 55% of the subgroup of non-presurgical exploration. The latter subgroup comprised 77 presumed focal epilepsies (54 with secondary generalization) and four cases with primarily generalized seizures. MEG localizations yielded monofocal results in 26, multifocal findings in 13 and diffuse distribution of dipoles in six cases. This finding enhances the potential role of MSI as a screening method for epilepsy evaluation.

Sensitivity considerations are shown in Fig. 1.

Primary assessment of MSI localizing value

K period

Various comparisons of MSI localizations and both presurgical results and neurosurgical treatment sites were carried out to determine the value of MSI in terms of focus localization.

During the first period (K), MEG findings were established in 90 cases. Lobar congruence between MSI and the GFE was found in 72 cases (80%). Among these, 43 MSI localizations (59.2%) agreed with the general result on a more detailed, intralobar basis, including 21 cases where dipoles lay within 3 cm of the border of a lesion. Out of these 21 cases, the distance between dipole sites and lesion was <2 cm in 16 and <1 cm in 10.

In 13 out of the remaining 18 cases with MSI findings, no conclusive focus results were produced by other diagnostic tools; four of these patients had callosotomies, and one was supplied with a VNS device.

MEG localizations did not agree with the lobe established by the other methods in five out of 90 patients (5.6%).

MSI localizations of 21 patients who had undergone invasive exploration prior to surgery, and whose outcome after neurosurgical treatment represented categories 1 or 2 in Engel's classification, were compared with findings obtained from ictal scalp EEG data by visual inspection. Although only four cases were non-localizing with MSI, no lateralizing clues were detected in ictal EEG in 12 cases. The lobe to be operated on was correctly identified from ictal EEG in six cases and from MSI in 15, with 14 out of 15 cases yielding correct information even on the intralobar level, whereas five out of the six EEG localizations were merely informative on a lobar basis. These findings are summarized in Table 1.

Total sample

Among the entire sample, 131 patients had MEG spikes and underwent focal surgery. MSI localization agreed with the treated lobe in 89% of cases. Among 109 cases with temporal lobe surgery, MSI yielded correct lobe identification in 94 (86.2%). In all 22 patients who underwent neurosurgery of other than temporal lobes, MSI results indicated the source of epileptic activity in the operated lobe.

Accuracy of lobar information was in the same range, if the subgroup of successfully operated patients was considered, with successful outcome represented by categories 1 and 2 in Engel's classification. The general rate of correctly identified lobes was 89.2%, and the respective rate for temporal lobes was 87.3%. In all 10 extratemporal cases, the lobes were correctly identified by MSI localizations.

MSI contribution in presurgical focus evaluation (M period)

Data of 104 patients investigated during the second period (M) and subsequently given surgical treatment was categorized according to the rating scale for assessment of the contribution of MSI findings to the final results and decision process of presurgical evaluation. Among these, 56 (54%) were assigned code 1, 25 (24%) code 2 and 11 (11%) code 3. Thus, in 35% of these operated cases, MSI provided additional clues as to the location of epileptogenic activity. Furthermore, in 11%, MSI contributed crucial information for the decision about surgical procedures. In only two out of the 104 cases, MSI findings were incompatible with the GFE (code –2). The remaining 10 cases (10%) were assigned code –1, referring to a failure to produce useful localization results, due to poor data quality in six and missing co-registered MRI scans in four cases. The two cases with code –2, as well as nine out of 10 which failed MSI contribution, were TLE

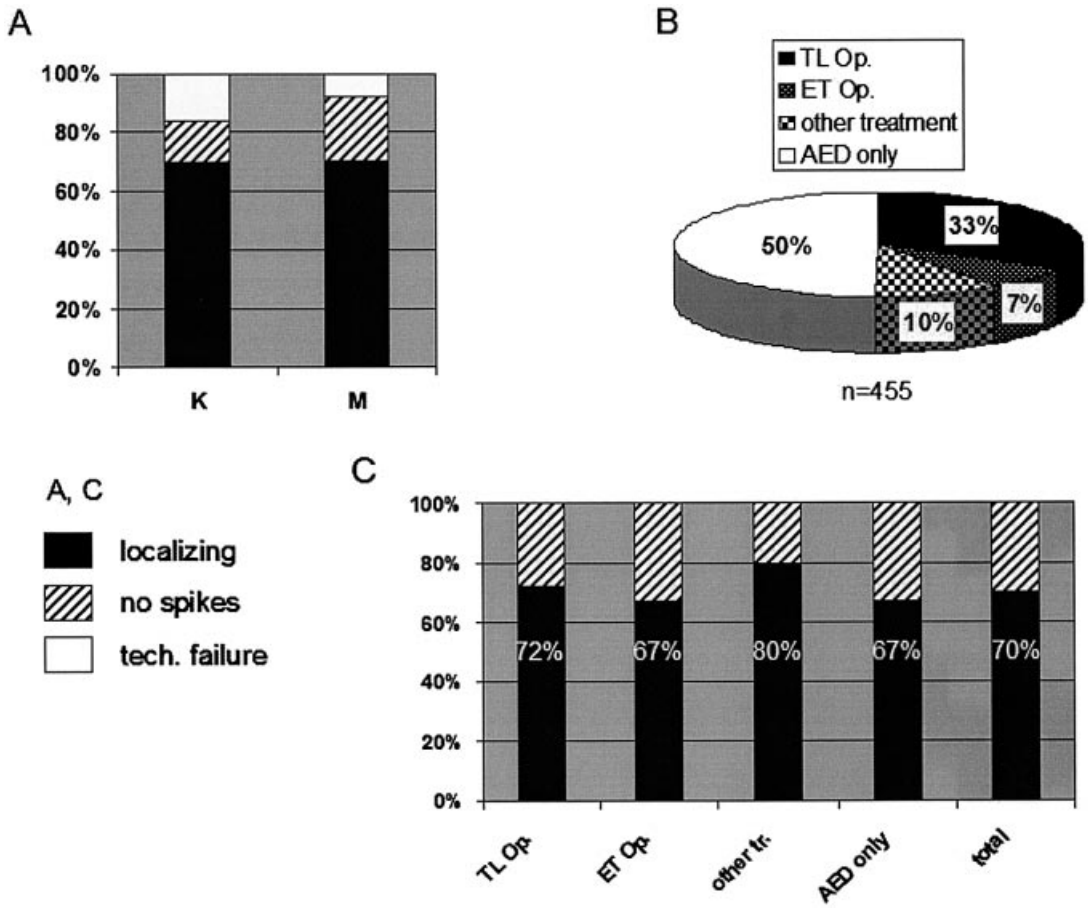

Fig. 1 MEG sensitivity with respect to specific epileptic activity. (**A**) Comparison of two consecutively used MEG systems, Krenikon (K) and Magnes II (M): localizing = MEG spikes detected and localized; no spikes = no specific epileptic activity detected in MEG data; tech. failure = hardware/software problems preventing analysis of MEG recordings. (**B**) Distribution of investigated cases with respect to treatment: TL Op. = temporal lobe operation; ET Op. = extratemporal operation; other treatment = radiation, callosotomy and implantation of vagal nerve stimulation device; AED only = treatment with antiepileptic drugs only. (**C**) Sensitivity distribution with respect to epilepsy treatment, as displayed in **B**.

Table 1 *Comparison of MSI and ictal-onset EEG localizations in 21 successfully operated patients*

Ictal-onset EEG	MSI				
	Intralobar	Lobe	Lateralization	Non-localizing	Total
Intralobar	1				1
Lobe	2	1	1	1	5
Lateralization	2			1	3
Non-localizing	9		1	2	12
Total	14	1	2	4	21

Level of information: 'intralobar' = side and lobe as well as intralobar area identified, with the site of subsequent surgery as the respective criterion; 'lobe' = both side and lobe identified; 'lateralization' = only side of focus identified.

cases; the tenth failed case belonged to the subsample with non-focal treatment. The proportion of TLE cases among the treated sample (67%) was approximately in the same range as the percentage of TLE cases among those with marked MSI contribution (codes 2 and 3 combined, 61%). Only two patients treated with non-focal procedures appear among the group with MSI contribution codes 2 or 3. Cases with extratemporal therapies figuring among the treated sample with 15%, amounted to 33% in the group of worthwhile MSI contribution. Results concerning the contribution codes are shown in Fig. 2.

Special aspects of focus localization

In general, localizations of averaged SEDs agreed with the results of single pattern localizations but had superior features

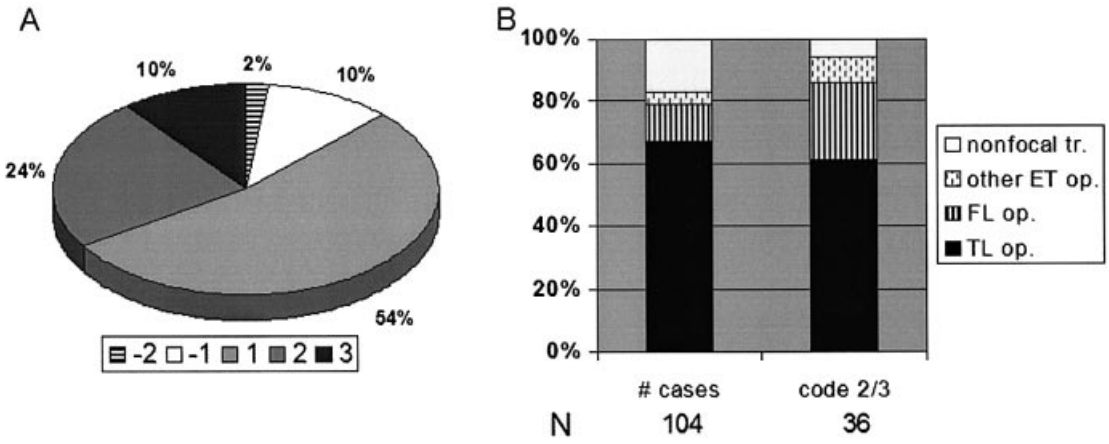

Fig. 2 MEG contribution to presurgical evaluation. (**A**) Distribution of contribution codes among 104 patients who underwent treatment in addition to antiepileptic drug medication. Codes relate MSI findings to the overall results of non-invasive presurgical exploration: –2 = contradiction; –1 = no contribution (no spikes); 1 = confirmation; 2 = additional information; 3 = additional information affecting decision about treatment and/or invasive recordings. (**B**) Distribution of treatments: among the sample of 104 Magnes II cases with treatment (left bar) and the 36 cases assigned codes 2 or 3 ('marked contribution', right bar): tr. = treatment; ET op. = extratemporal operation; FL op. = frontal lobe operation; TL op. = temporal lobe operation.

in terms of confidence volumes and map correlations, pinpointing the centre of epileptic activity around which localizations of unaveraged signals would be scattered. Furthermore, by averaging spikes with rather small amplitudes (e.g. from temporal mesial sources), their poor SNRs were increased. Thus, the improved averaged signals would yield useful localizations, whereas the unaveraged ones would fail the localizing process.

Occasionally, averaging enabled the identification of early components of epileptic discharges. In the more unfavourable SNR conditions of unaveraged patterns, these 'prespikes' were too small to be distinguished from background noise. An example with temporal mesial localization is shown in Fig. 3.

Likewise, MEG spikes were helpful as templates to detect discharges in simultaneous EEG recordings hidden in the background noise unless averaged (Fig. 4). This phenomenon was reciprocal: in some cases, the occurrence of spikes was reversed, with EEG spike templates triggering the identification of corresponding patterns in averaged MEG data.

In a small proportion of the sample (7.2%), ictal data was recorded during MEG investigations, with localization results agreeing remarkably well with interictal findings; details of comparisons of ictal and interictal data are reported in Tilz *et al*. (2002). Figure 5 shows concurring localizations of interictal spikes, theta activity and ictal onset in the temporal neocortex, as well as fast ictal spread from the initial sources to mesial temporal ones.

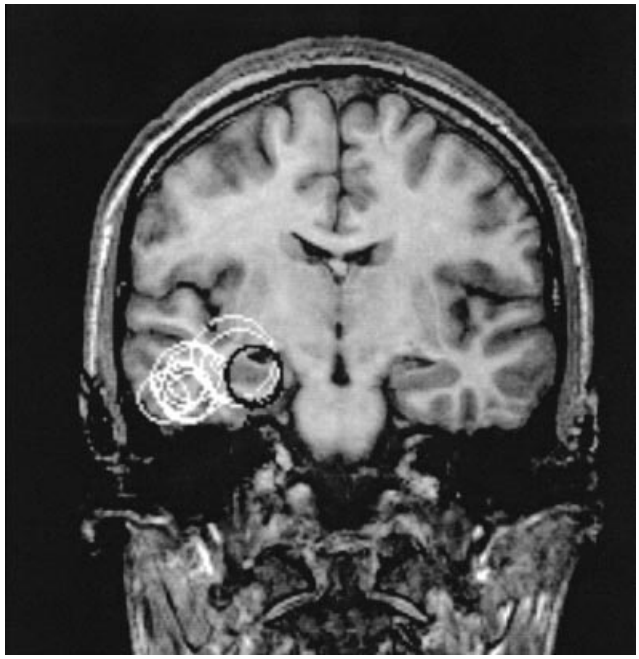

Fig. 3 MSI localizations of single spikes (white circles) and prespike activity identified in averaged signal (n = 9; black circle); circles represent confidence volumes of dipole clusters.

Discussion

The data presented here, obtained from a large sample of 455 patients, show that MEG is sensitive to interictal epileptic activity in at least 70% of cases with presumed focal epilepies. This result puts MEG in a very favourable range, compared with other non-invasive localizing tools used during presurgical epilepsy assessment: Spanaki *et al*. (1999) found a higher sensitivity only for SPECT subtraction analysis, whereas PET sensitivity was in the same range as that of MEG demosntrated here, and the remaining methods tested ranged rather below that.

Even if the investigation is carried out in non-hospitalized patients without AED withdrawal, more than half of the cases

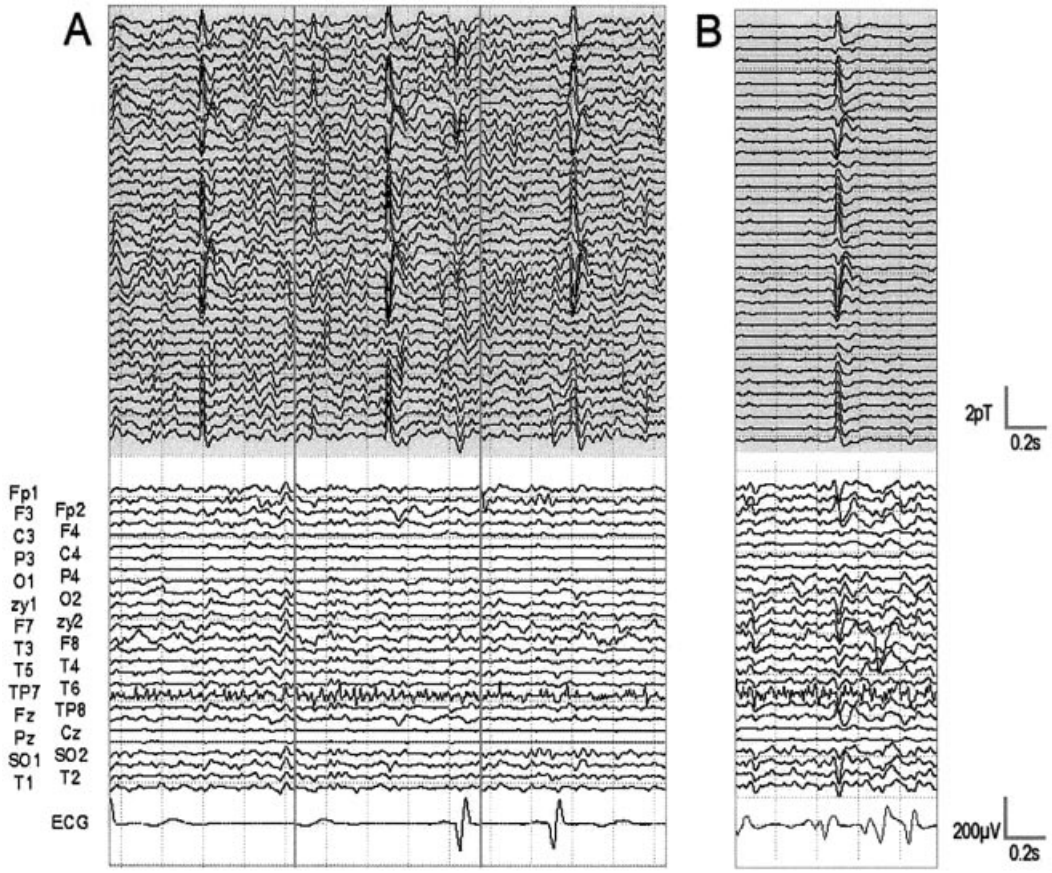

Fig. 4 Example of simultaneous MEG (*top*) and EEG (*bottom*) recordings. (**A**) Three MEG spikes recorded over the left hemisphere without corresponding patterns in unaveraged surface EEG. (**B**) Averaged signals (n = 11) reveal the spike in the EEG.

yield localizing results. This underlines the applicability of MEG in the field of screening investigations for newly diagnosed epilepsies, offering the possibility of identifying and classifying focal cases from an early stage.

The finding of MEG sensitivity being 67% in ETE cases enhances the suitability of MEG for ETE evaluation, confirming our previous report (Stefan *et al*., 2000).

With the K system, the rate of spike occurrence was higher than with the M system. However, during the K period, the selection of patients differed somewhat from the later strategy: although mainly patients with high spiking frequencies were chosen to be investigated with the first biomagnetometer, in order to grant maximum exploitation of the then novel method, this scheme was later abandoned in favour of the maximum benefit for the patients, with the ultimate aim of investigating patients consecutively. Thus, among the M sample, there were more patients with rare interictal epileptic discharges and more cases without or with very mild AED withdrawal. Therefore, the smaller proportion of patients presenting no MEG spikes cannot be interpreted as a clue to higher sensitivity of the first biomagnetometer. On the other hand, with growing experience, the number of hardware and software problems dramatically decreased, and with them the rate of technical failures. Altogether, our extensive data permit a robust sensitivity estimate of ~70%, which indicates a useful method.

A very satisfactory agreement between MSI lobe identification and surgical site was found for the 131 patients who underwent neurosurgery and had MEG spikes. In all 22 extratemporal cases, MSI yielded localizations in the treated lobe. The ratio of correct lobe identification was 86% for temporal cases. With the 100% rate for extratemporal lobes, the general rate amounted to 89%. This result confirms the localizing quality of MSI and particularly underlines its accuracy in ETE cases.

To quantify the contribution of one method to the compound result of various diagnostic tools is a rather delicate task. It could have been performed neither blinded nor by an independent observer. Thus, the difficult assessment of the degree of MSI contribution was assigned to two experts who could be expected to dissect the process of decision making with respect to the notion of which therapeutic course would have been taken in the absence of MEG information. The results show that, among the 104 M patients who underwent neurosurgical or radiation treatment, there were only two MSI localizations contradictory to the combined presurgical findings. In the majority of cases (54%), MSI information agreed with the GFE, without

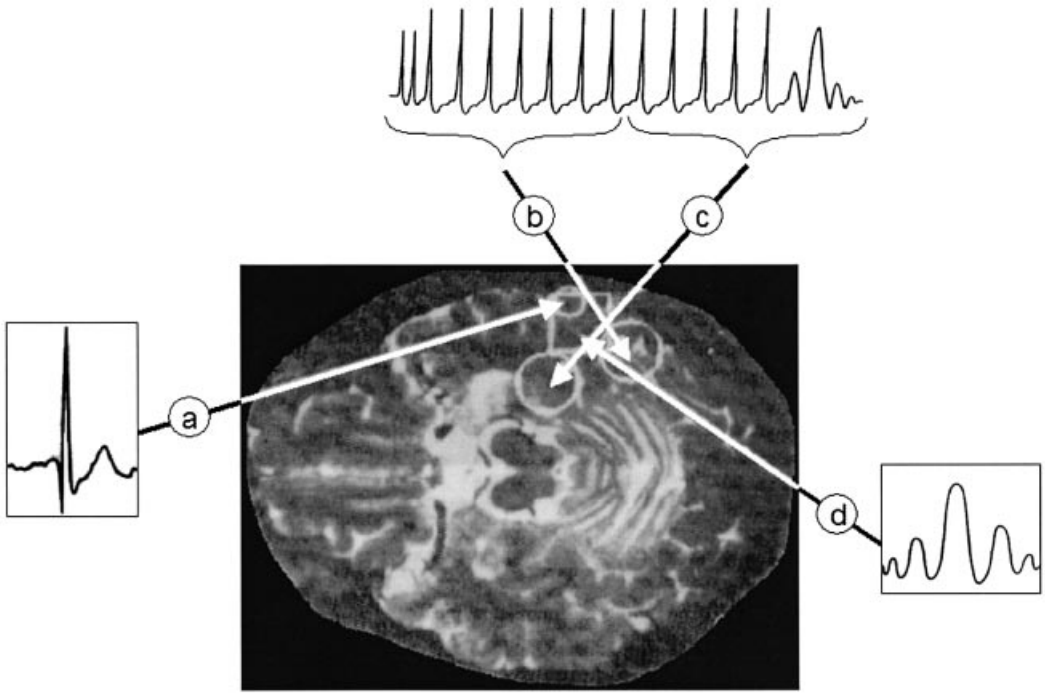

Fig. 5 Example of MSI localizations from interictal as well as ictal epileptic activity in a right temporal lobe epilepsy case. Circles and square represent sites containing dipole clusters. Arrows link examples of analysed traces with the respective localizations: (a) unaveraged interictal spike (temporal neocortex); (b) ictal onset (temporal neocortex); (c) ictal data, later than onset (mesial temporal lobe); and (d) averaged 5–6 Hz activity (temporal neocortex).

providing additional clues. Interestingly, more than one-third (35%) of the MSI findings substantially contributed to the GFE, either offering additional information on the lobar or sublobar level (24%) or assistance concerning the decision about further diagnostic or therapeutic procedures (11%). Thus, in approximately one-quarter of the patients, MSI was decidedly helpful and in 10% even crucial with respect to decision making. The high share of ETE cases among the 'substantial contribution' group again emphasizes the significance of MSI for these patients, which otherwise often present with particularly difficult problems of focus localization.

The approach of averaging patterns has proved to be rather advantageous, with respect to identification and localization of signals otherwise hardly accessible. This applies not only to signal detection across modalities (MEG and EEG), using templates from one data group to identify corresponding patterns in the other, but also to facilitating access to signals from deep sources (particularly from the mesial temporal lobe) that are difficult to obtain with MEG (Shigeto *et al*., 2002). Compared with the often rather scattered dipole clusters resulting from single pattern analysis, localizations of averaged signals, due to decreased variability, clearly mark the centre of SED generation.

Simultaneous recording of MEG and EEG is certainly a propitious approach, considering not only the mutual assistance with spike identification but also the optimization of localization analyses, taking advantage of the different features of both neurophysiological methods.

Although the direct comparison of interictal MEG and EEG data, as obtained from simultaneous recordings, is being assessed in a special study and will be published separately, preliminary results indicating that, under identical recording conditions, different contributions of both methods yield a complementary gain of information are in accordance with recent publications by other groups (Pataraia *et al*., 2002; Zijlmans *et al*., 2002).

The comparison of interictal MSI localizations and ictal-onset EEG results in 21 cases where additional results from invasive recordings were available also revealed relationships in favour of MSI. Although in two-thirds of the cases MSI was able to correctly (compared with invasive findings) pinpoint centres of epileptic activity on an intralobar level and was non-localizing in only four cases, ictal-onset EEG failed to produce clues in 12 cases; MSI mainly identified the side or lobe of seizure generation in the remaining nine cases; and intralobar information could be obtained in only one case.

Notwithstanding the fact that ictal data represent the ultimate information about epileptogenicity, the disadvantage is that the data are hard to obtain and, if available, frequently fail to yield results. Furthermore, analysis of ictal onset mostly consists of visual inspection of data contaminated with artefacts and is not as feasible by means of computerized localization tools as interictal spike analysis. Taking into

account these considerations, the results reported here indicate that MSI localizations offer a good alternative when ictal information is poor.

Based on our experience and that of others, MSI offers promising results for the interictal approximation of potential generator sites in the irritative tissue (Chauvel *et al*., 1987, 1996; Sutherling and Barth, 1989; Stefan *et al*., 1991). As MSI localizations of interictal and ictal data show considerable overlap (Tilz *et al*., 2002), reflecting a close spatial relationship between the irritative and seizure onset zone, it appears that future research should concentrate more on the subtle analysis of the interictal irritative zone than has been the case in the past.

In addition to previous reports recommending the MSI method for presurgical epilepsy evaluation (Wheless *et al*., 1999; Baumgartner *et al*., 2000; Otsubo *et al*., 2001; Iwasaki *et al*., 2002), our data provide evidence of the good sensitivity and localizing ability of MSI, derived from a substantial sample of patients.

Rather than being suited to compete with EEG for priority in presurgical epilepsy evaluation, MEG will in all likelihood remain an auxiliary technique, due to its limits regarding ictal recordings and pecuniary aspects. But if it is indispensable in difficult cases and appropriate as a screening method, the assessment of complementarity of EEG and MEG is still a challenge. Thus, the next step towards optimization of presurgical epilepsy evaluation is the comparison of simultaneously recorded EEG and MEG. Studies on this issue are currently underway.

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