Noninvasive Localization of Electromagnetic Epileptic Activity. II. Demonstration of Sublobar Accuracy in Patients with Simultaneous Surface and Depth Recordings

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Summary: Seven patients with complex partial epileptic seizures undergoing invasive video/EEG-monitoring were investigated with a combination of 10 subdural strip electrode contacts (subtemporal + lateral temporal), and 22 extracranial recording sites. In each patient spikes with different intracranial distributions were identified, and for those with similar distributions the extracranial activity was averaged. A new inverse solution method called EPIFOCUS (Grave et al. 2001, this issue) was used to reconstruct the sources of both single and averaged spikes in a standard 3D-MRI, and a statistical analysis was performed in order to demonstrate location differences between spikes with different intracranial distributions. The results revealed significantly more anterior and ventral source locations for subtemporal compared to lateral temporal spikes. Within the subtemporal group, medial spikes had more mesial and dorsal locations compared to lateral ones. In the lateral temporal group, more anterior and ventral locations were obtained for anterior compared to posterior spikes. The results demonstrate the applicability of EPIFOCUS in the localization of sources in the temporal lobe with sublobar accuracy. This possibility may become important in the future, for instance in identifying cases where amygdalo-hippocampectomy or other limited temporal lobe resections may replace the standard en bloc resections.

Key words: Source reconstruction; Inverse solution; Epilepsy; Sublobar; EPIFOCUS.

Introduction

During the past ten years methods for 3-dimensional source localization through inverse solution procedures have been applied to interictal epileptiform activity. Most investigators have used the model of approximating the activity of the epileptic focus, recorded with EEG or MEG, with one or a limited number of dipolar sources (Barth 1982; Ebersole 1991, 1992, 1994; Ebersole and Wade 1991; Wong 1991; Stefan et al. 1992, 1994; Lantz et al. 1994, 1999; Lantz and Ryding et al. 1997; Nakasato et al. 1994; Baumgartner et al. 1995; Boon et al. 1996; Diekmann et al. 1998; Shindo et al. 1998; Scherg et al. 1999). In order to assess the correctness of the source localizations, the results have usually been compared to those of other clinical, structural or functional imagery exams, related to the outcome of surgical resection of the suspected area, or in some cases directly confirmed by intracranial recordings from subdural and/or depth electrodes. A major drawback of investigations using dipole models, however, is that the sublobar differentiation has been based mainly on the orientation of the dipoles (for instance tangential dipole orientation for mesiobasal temporal sources and radial orientation for lateral temporal sources, (Ebersole 1991)). Dipole locations have not permitted comparable spatial separation (Ebersole 1997).

Recently distributed inverse solutions, which estimate 3D current density distributions rather than dipolar sources, have been applied to interictal and ictal epileptic data (Lantz and Michel et al. 1997; Lantz et al. 2001; Seri et al. 1998; Fuchs et al. 1999; Michel et al. 1999; Blanke et al. 2000; Spinelli et al. 2000; Worrell et al. 2000). Distributed source models are supposed to more realistically repre-

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sent active brain regions than dipole models since they are less restrictive concerning the number of sources. While all the distributed methods that have been proposed so far have in common that they estimate the activity on a large number of discrete grid points inside the head, they have slightly different properties concerning their spatial resolution power. This has repeatedly been demonstrated in artificial and real data (e.g. Fuchs et al. 1999; Michel et al. 1999; Grave de Peralta et al. 1998). Some of these studies have demonstrated a spatial resolution that reaches sublobar precision (Lantz and Michel et al. 1997; Fuchs et al. 1999; Michel et al. 1999). For example, in Fuchs et al. (1999) current source density reconstructions in a realistic boundary element (BEM) model, allowed the demonstration of an intracranially verified spread of epileptiform activity from the temporal tip to mid temporal regions.

In some investigations simultaneous recording of intra- and extra- cranial epileptiform activity has been combined with dipole or distributed source modeling to localize mesiotemporal sources or to differentiate between mesial and lateral temporal sources in patients with temporal lobe epilepsy (Lantz et al. 1996; Lantz and Michel et al. 1997; Pacia and Ebersole 1997; Merlet et al. 1998). In the two studies performed in our laboratory, the same data set was used. This data set consisted of patients recorded with 10 intracranial electrodes, including 4 subtemporal and 3-6 lateral temporal electrode contacts on the side where the ictal onset had been found. Surface activity was recorded from 22 electrodes, placed according to the 10-20 International system with special coverage of the temporal lobes. In the first of these studies (Lantz et al. 1996) differentiation between subtemporal and lateral temporal spikes was possible from dipole orientations, whereas dipole locations were not clearly different between the groups. In the other investigation (Lantz et al. 1997), where LORETA (Pascual-Marqui et al. 1994) was used for the source reconstructions, it was possible to statistically demonstrate source location differences between subtemporal and lateral temporal spikes. In neither of the two investigation was it possible to obtain a more detailed sublobar differentiation.

In epilepsy surgery candidates, the aims of the workup are to verify the existence of one single focus, and to determine the location of this focus with highest possible accuracy. We have developed an inverse solution which, provided a single source can be postulated, tries to localize this single focal source with the highest possible accuracy. The method, EPIFOCUS (Grave et al. this issue), scans the whole 3D-solution space and calculates for each solution point the probability that this point is the only active point in the brain.

In the present study the EPIFOCUS-method was applied to the same data set of simultaneously recorded subdural and surface data that has been used in our previous investigations. The purpose of the study was to determine whether EPIFOCUS would permit a more detailed source separation within the temporal lobe than has been demonstrated in previous studies.

Patients and methods

Seven patients (aged 18-43; mean 31; 4 males and 3 females) with drug- resistant partial epilepsy undergoing invasive video/EEG-monitoring with subdural electrodes were investigated at a separate session after the monitoring had been completed. Previous non invasive investigations had in all patients indicated seizure onset in one of the temporal lobes (two left, five right). Intracranial recordings were therefore comprised of subdural strips over subtemporal and lateral temporal cortex on the side where seizure onset was expected. Wyler electrodes (Ad-Tech Medical Instrument Corporation, Racine, WI, U.S.A) with 4-6 electrode contacts, and with an inter electrode distance of 10 mm were used for the subdural investigations.

After the video-EEG monitoring had been finished, the electrode montage was altered in the following ways. Ten of the 32 recording channels were used for intracranial electrodes. The 10 intracranial electrodes that were used included the 4 subtemporal and 3-6 of the lateral temporal electrode contacts on the side where the ictal onset had been found. The remaining 22 were used for scalp recordings that were positioned according to the 10-20 International system with special coverage of the temporal lobes.

EEG was recorded from a 32-channel Neuroscan system (Neuroscan Inc.), using an average reference and 256Hz A-D digitization rate. The EEG was digitally filtered off line from 2-20Hz. The intracranially recorded epileptiform discharges were identified by visual inspection of the traces. EEG epochs of +/- 500 ms centered around the intracranial peak of the discharges were collected and categorized according to their intracranial distribution. Epileptiform discharges with 4 different intracranial distributions - medial subtemporal, lateral subtemporal, anterior lateral temporal and posterior lateral temporal - were identified, if present. In one patient all four spike categories were found, whereas in the other cases only one or two of the four categories could be identified.

For each category of each patient, between 12 and 157 spikes with similar intracranial distribution were averaged, with a corresponding average of their simultaneous extracranial activity. The latency for averaging was the peak of the intracranially recorded discharge. This procedure was repeated for all patients, resulting in 1-4 averaged potentials for each of the 7 patients. The total number of averaged potentials was 14, comprising 5 mesial subtemporal, 2 lateral subtemporal, 5 anterior lateral tem-

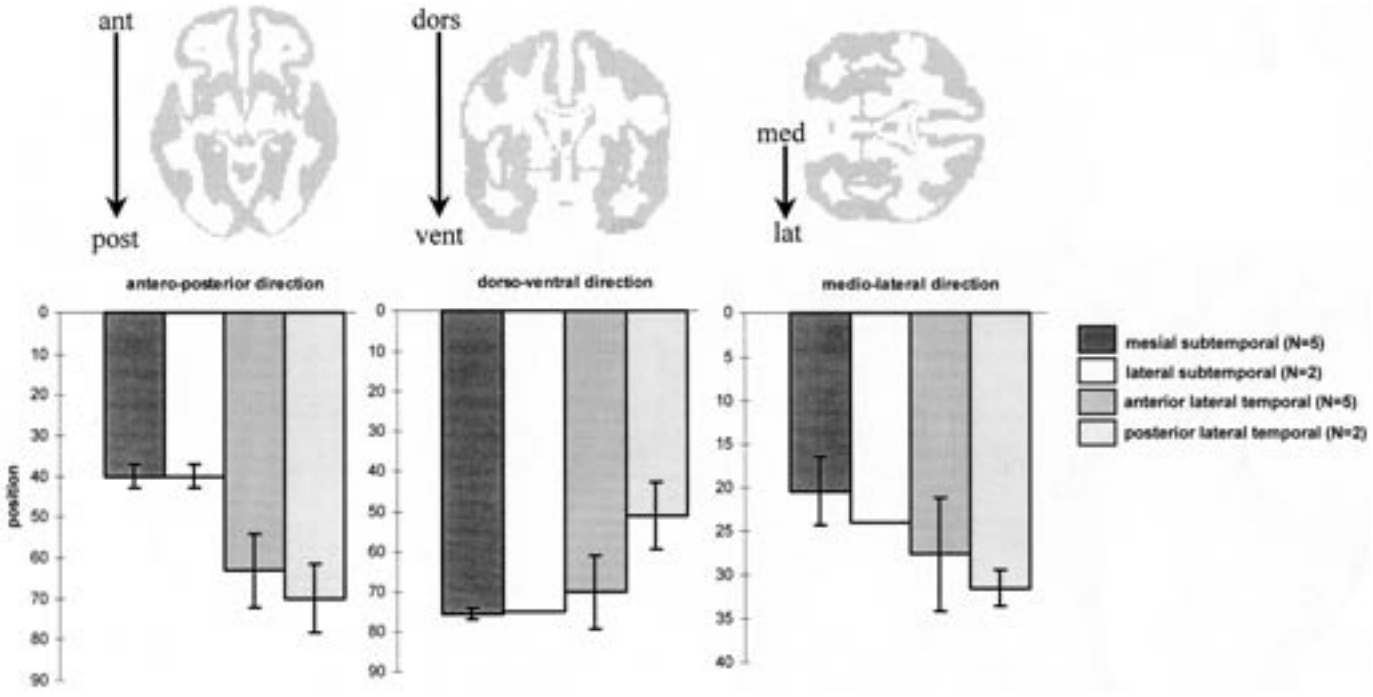

Figure 1. Location in antero-posterior, dorso-ventral and medio-lateral direction of the EPIFOCUS maximum for averaged epileptiform potentials of mesial subtemporal, lateral subtemporal, anterior lateral temporal and posterior lateral temporal origin.

poral and 2 posterior lateral temporal. In addition 8-14 single spikes with a favorable intracranial signal-to-noise-ratio were selected from each category of each patient.

For the source reconstructions EPIFOCUS was computed on a realistic head model based on the average MRI used by the Statistical Parametrical mapping (SPM) software. 3,256 solutions points were selected in regular distances within the gray matter of this MRI. Since EPIFOCUS requires the presence of one single dominating source, this was first verified by applying a distributed source model applicable for multiple sources (LAURA, Grave et al. 2001, this issue).

Two different analysis approaches were used. For the averaged spikes a single time point analysis was performed at the latency corresponding to the peak of the intracranial spike, and the location in 3 dimensions (antero-posterior, dorso-ventral and medio-lateral) of the EPIFOCUS-maximum was determined for this timepoint. For the individual spikes the EPIFOCUS-maximum was determined for each time point from -250 to +250 ms from the intracranial peak. The results for the different spikes were then statistically compared (unpaired t-test) for each time point in order to reveal significant location differences between the 4 different categories, as well as the over time variability of these location differences. Although the spikes were in some cases collected from different areas in the same patient, they were, for the statistical evaluations, regarded as independent measures, and t-tests for independent samples were performed.

Results

Four different groups of averaged spikes were compared at the timepoint of maximal intracranial amplitude with respect to their location in the antero-posterior, dorso-ventral, and mesio-lateral directions, respectively: mesial subtemporal (N=5), lateral subtemporal (N=2), anterior lateral temporal (N=5), and posterior lateral temporal (N=2). The results from these comparisons are displayed in figure 1. In the antero-posterior direction, subtemporal spikes (mesial and lateral) have a more anterior location than the lateral temporal (anterior and posterior). In the dorso-ventral direction posterior lateral temporal spikes differed from the other 3 groups in by having a more dorsal distribution. Finally, in the mesio-lateral direction, mesial subtemporal spikes had the most mesial location followed by lateral subtemporal, anterior lateral temporal, and posterior lateral temporal, respectively. Due to the limited number of averaged spikes, statistical comparisons were not possible. The results in one patient (pat 4, the only patient with spikes of all categories), are displayed in figure 2.

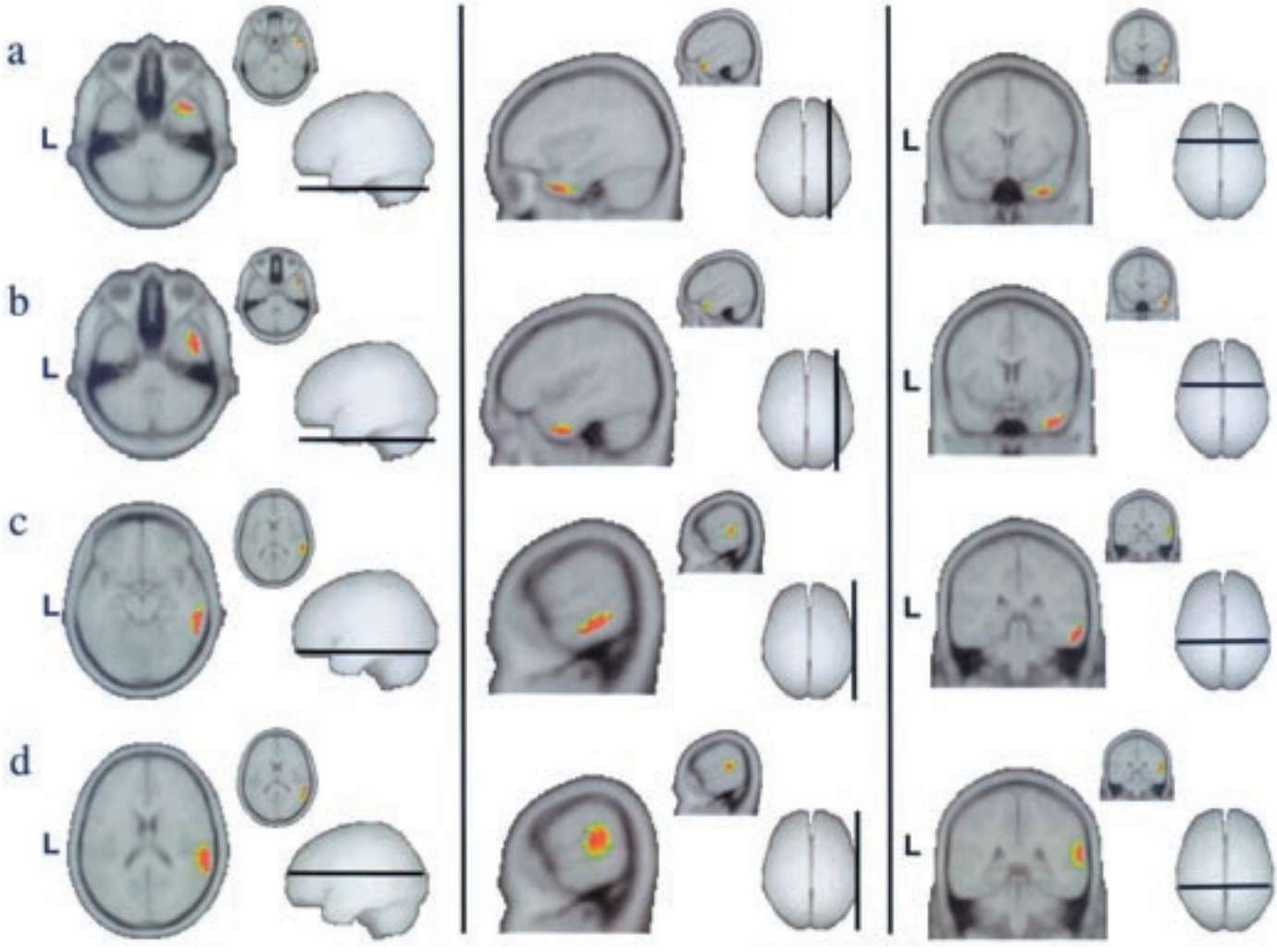

Figure 2. Localization in the realistic brain model (SPM) of averaged epileptiform potentials of a: mesial subtemporal, b: lateral subtemporal, c: anterior lateral temporal, d: posterior lateral temporal origin. Left: EPIFOCUS maximum. Right: slice where the maximum was found. Small figures on top: the results of the LAURA investigation used to demonstrate the presence of a single source. Note the clearer separation between different sources with EPIFOCUS, especially in the coronal plane.

For the individual unaveraged spikes, source reconstructions were performed for several timepoints around the timepoint of maximal intracranial amplitude, and, for each timepoint, the 4 spike categories were compared statistically for differences in source location. The results of these comparisons are shown in figure 3.

When comparing subtemporal (mesial+lateral) to lateral temporal (anterior+posterior) spikes, statistical differences were found for antero-posterior location (subtemporal more anterior than lateral temporal during 40 ms around the GFP peak, figure 3a), and for dorso-ventral location (subtemporal spikes more ventral than lateral temporal during 10 ms around the peak, figure 3b). Between medial and lateral subtemporal spikes significant differences were seen for dorso-ventral location (medial subtemporal more dorsal than lateral subtemporal during 10 ms around the peak, figure 3c) and for medio-lateral location (medial subtemporal more medial than lateral subtemporal during a few ms after the peak, figure 3d). Comparison between anterior and posterior lateral temporal spikes revealed significant differences for antero-posterior location (anterior lateral spikes more anterior than posterior lateral during 20 ms around the peak, figure 3e), and for dorso-ventral location (anterior lateral spikes more ventral than posterior lateral during a period of 15 ms starting 5ms after the

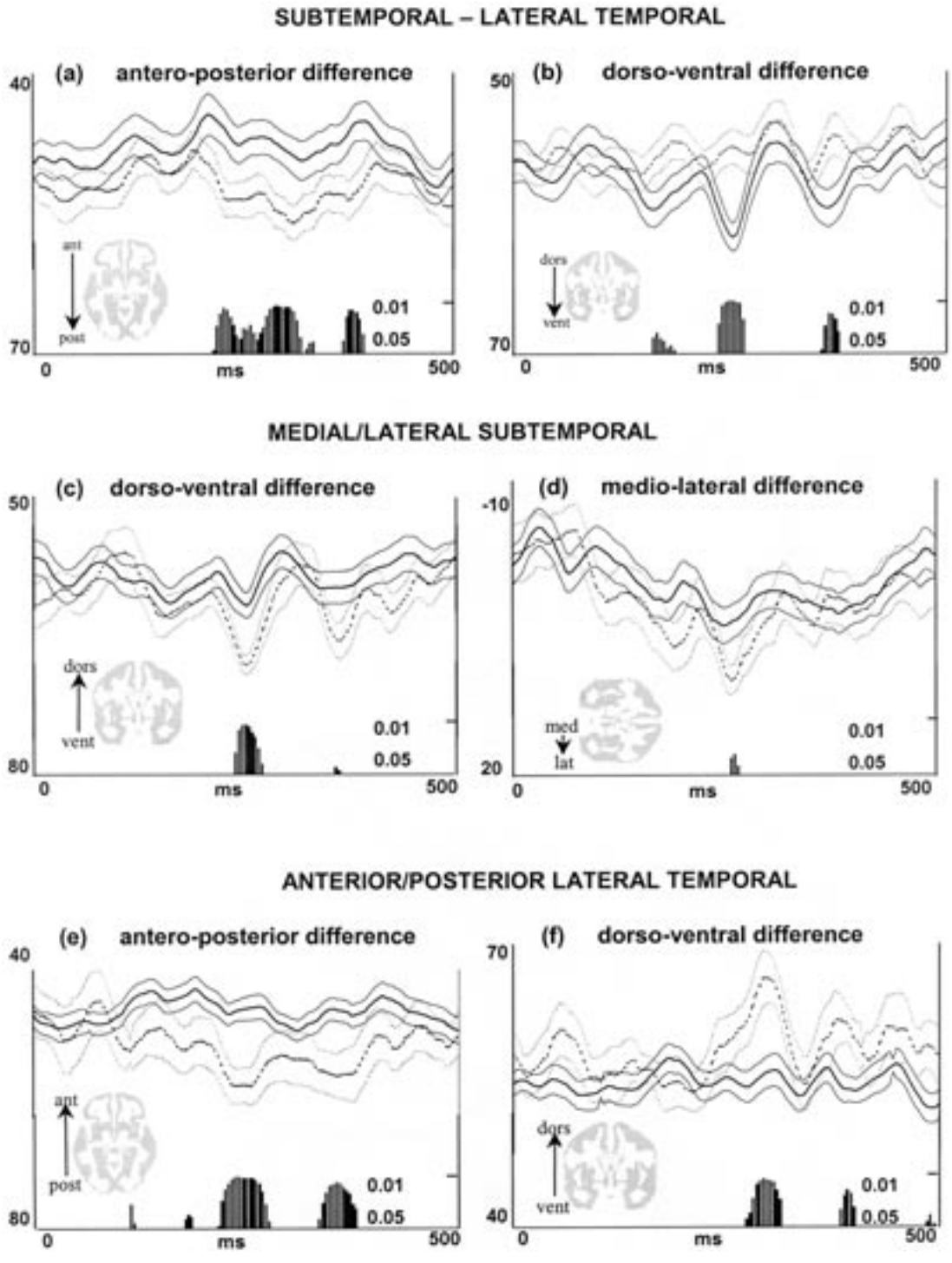

Figure 3. Results of the statistical analysis of individual unaveraged spikes. On the x-axis time is shown, with the spike peak at approximately 250 ms. On the y-axis location of inverse solution maximum (given in grid units). Vertical bars indicate periods of significant difference between the two spike catagories (p-value). Each figure (a-f) shows the comparison between two spike categories, one shown with continuous lines and the other with dotted lines. Standard deviations are indicated with thinner lines. For subtemporal (continuous line) versus lateral temporal spikes (dotted line) the antero-posterior (a) and the dorso-ventral differences (b) are displayed. For the comparison between medial (continuous line) and lateral subtemporal spikes (dotted line) the dorso-ventral (c) and medio-lateral (d) differences are displayed. For the comparison between anterior (continuous line) and posterior lateral temporal spikes (dotted line) the antero-posterior (e) and the dorso-ventral (f) differences are displayed. For details concerning interpretation, see text.

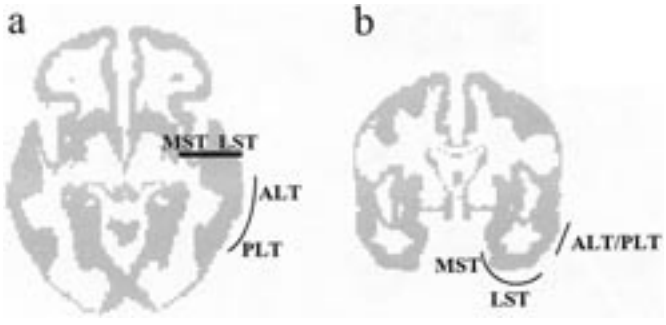

Figure 4. Schematic drawing indicating the approximate position of the subdural electrodes in the horizontal (a) and coronal (b) planes. MST=medial subtemporal, LST=lateral subtemporal, ALT=anterior lateral temporal, PLT=posterior lateral temporal.

spike peak). In addition to these differences, which were all seen around the intracranial spike maximum, some cases showed one period of significant differences after the spike (figure 3a,b,e,f). Significant differences before spike onset were very short and are probably explainable by artifacts in one or a few of the included spikes.

Discussion

The use of dipole reconstruction methods to differentiate between mesial and lateral temporal epileptic foci, has been demonstrated by several authors (Ebersole 1991, 1992, 1994; Ebersole and Wade 1991; Stefan et al. 1994; Lantz et al. 1996; Lantz and Ryding et al. 1997; Baumgartner et al. 1995; Boon 1996; Scherg et al. 1999). A considerable drawback of these techniques, however, is that the interpretations about focus localizations are based mainly on the orientation rather than the location of the dipoles (Ebersole 1997), thus giving only an indirect estimation of the focus area.

In the present investigation reconstruction of sources in different parts of the temporal lobe was performed in an approximate realistic brain model using a new source localization technique (EPIFOCUS). The analysis was made in two ways, by comparing the localization results of averaged spikes of different intracranial distributions at the timepoint of maximal spike amplitude (the average analysis), and by statistically comparing the localizations of individual unaveraged spikes during several consecutive timepoints (the statistical analysis).

In the comparison of subtemporal and lateral temporal spikes, a more anterior location for the subtemporal spikes was found. This result, which was obtained both in the average (figure 2) and in the statistical (figure 3a) analysis, is what would be expected from an anatomical point of view (figure 4a). Also the second difference between these groups, the more ventral location of subtemporal spikes compared to lateral temporal, (figure 2, figure 3b), is what would be expected (figure 4b).

Comparing mesial and lateral subtemporal spikes revealed a more dorsal location for the mesial subtemporal, a difference which was seen in the statistical (figure 3c), but not in the average analysis (figure 2). This finding is also in line with what would be expected based on temporal lobe anatomy (figure 4b). In addition, a more mesial location for the mesial subtemporal compared to the lateral subtemporal spikes was significantly different during a short period in the over time statistical analysis (figure 3d), but was not present in the averaged data (figure 2). This difference is particularly important for source separation in the temporal lobe, and a more clear separation might be obtained if reconstruction in the patients' own MRIs, is performed. For the patients presented here, the MRI data were unfortunately not available in digital form.

The comparison between anterior and posterior lateral temporal spikes also showed differences in two dimensions. First, a more anterior location of anterior lateral spikes (figure 2, figure 3e) is evident. A second, very significant, difference, a more dorsal location of posterior lateral compared to anterior lateral spikes (figure 2, 3e), is more difficult to explain. One possible reason could be that the dorsal strips may be inserted in a slight dorsal direction, making the most distant electrodes on this strip record activity with a more dorsal location. It is also not clear why this difference is not synchronous with the peak of the spike, but rather follows it 10 ms later.

The recordings in this investigation were performed with rather few electrodes, 10 intracranial and 22 surface electrodes. The reason for using this particular data set is that the same data has been used in two previous articles from our lab (Lantz et al. 1996; Lantz and Michel et al. 1997), and that we wanted to enable direct comparison between the results with the different techniques. An example of EPIFOCUS results from a data set with denser electrode coverage is given in figure 5, where two patients, one with a mesiotemporal and one with a lateral temporal focus have been recorded with 125 electrodes. The results confirm the ability of EPIFOCUS to differentiate between mesial and lateral sources in the temporal lobe.

We can think of EPIFOCUS as a hybrid of a linear distributed source model (LDSM), the single dipole model (SDM) and the MUSIC method (Mosher et al. 1992), inheriting drawbacks and features from all of them. Like LDSM the solution is computed by applying an inverse matrix to the data. This matrix is constructed under the assumption that there is a focal source, and thus, like SDM or MUSIC it aims to localize concentrated sources. In contrast to SDM, the focal source is not punctual and

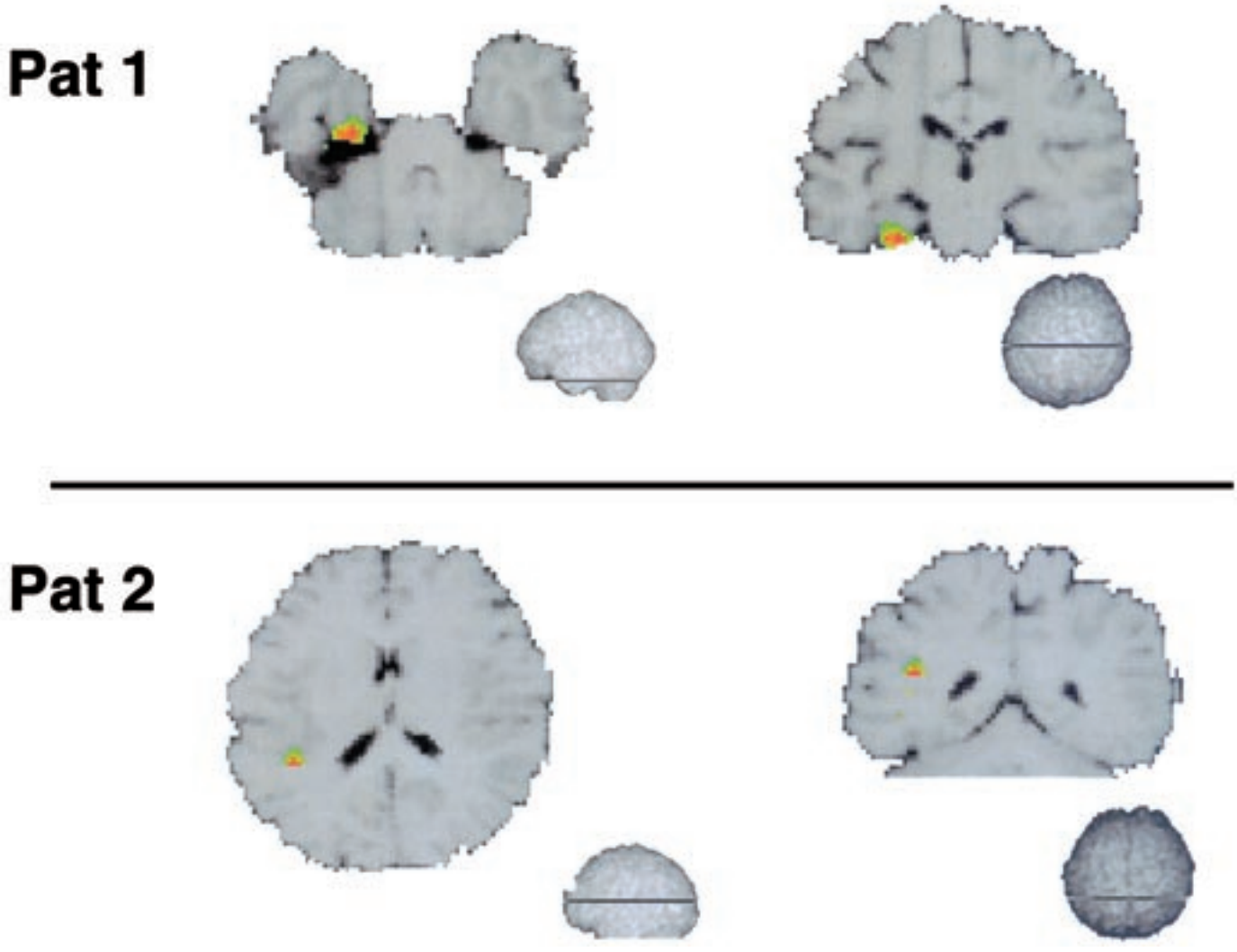

Figure 5. Examples of EPIFOCUS results for interictal epileptiform activity recorded with 125 electrodes. Pat 1 is a male age 53, in whom MRI has shown left hippocampal sclerosis and left temporal atrophy. Ictal onset is left temporal, and the patient is seizure free after left temporal resection. EPIFOCUS localizes the epileptiform activity to the mesial parts of the left temporal lobe. Pat 2 is a female age 20, in whom MRI shows dysplasia in the left posterior temporal area. Ictal onset is left posterior temporal and, due to the proximity of the focus to eloquent area, the patient will be subject to invasive recordings: in this case EPIFOCUS localizes the activity to the left posterior temporal area, in good agreement with the location of the dysplasia.

can extend over a compact region of the brain. It also avoids the use of nonlinear optimization algorithms that are very difficult to implement in a realistic head model (the solution space is discontinuous and non convex) where solutions can get erroneously trapped in local minima. Similar to MUSIC the recorded data are projected on each solution point disregarding the fit to the data. In contrast to MUSIC the projector is constructed independent of the data and does not need data covariance matrices for its implementation, allowing the application of the method to single and/or independent maps.

The a priori assumption of EPIFOCUS, that is the existence of a concentrated source, can create problems if several sources (epileptic or otherwise) are active at the same time. To circumvent this problem we propose the two following preprocessing alternatives. 1) Confirming the existence of a single source. For that we propose to apply the distributed inverse solution LAURA (Grave de Peralta et al. 2001, this issue) to the data, which has been shown to estimate the number and location of all active sources with high accuracy. If this first analysis indicates a single dominating source, EPIFOCUS can be applied in

order to further increase the spatial accuracy of the solution. 2) Second, decompose multi-channel data into simpler maps through the use of the non-stationary source approximation techniques (Gonzales et al. in press).

On the basis of the results presented here we can conclude that EPIFOCUS is a source localization method able to reconstruct sources in the temporal lobe with sublobar accuracy. This technique may be particularly useful as an adjunct means of identifying cases where amygdalo-hippocamectomy or other limited temporal lobe resections may be performed in lieu of the standard en bloc resections.

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