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Invited review

EEG source imaging

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Abstract

Objective: Electroencephalography (EEG) is an important tool for studying the temporal dynamics of the human brain's large-scale neuronal circuits. However, most EEG applications fail to capitalize on all of the data's available information, particularly that concerning the location of active sources in the brain. Localizing the sources of a given scalp measurement is only achieved by solving the so-called inverse problem. By introducing reasonable a priori constraints, the inverse problem can be solved and the most probable sources in the brain at every moment in time can be accurately localized.

Methods and Results: Here, we review the different EEG source localization procedures applied during the last two decades. Additionally, we detail the importance of those procedures preceding and following source estimation that are intimately linked to a successful, reliable result. We discuss (1) the number and positioning of electrodes, (2) the varieties of inverse solution models and algorithms, (3) the integration of EEG source estimations with MRI data, (4) the integration of time and frequency in source imaging, and (5) the statistical analysis of inverse solution results.

Conclusions and Significance: We show that modern EEG source imaging simultaneously details the temporal and spatial dimensions of brain activity, making it an important and affordable tool to study the properties of cerebral, neural networks in cognitive and clinical neurosciences.

Keywords: EEG; Source localization; Neuroimaging

1. Introduction

Distributed neuronal networks assure correct functioning of the human brain (Mesulam, 1998). Inhibitory and excitatory feedforward and feedback processes are the basic mechanisms of interaction between different modules of these networks (Bullier, 2001). Localizing the different modules of the functional network implicated in a given mental task is the principal aim of functional neuroimaging studies. A large body of research, using positron emission topography (PET) and functional magnetic resonance imaging (fMRI), has been devoted to this aim (Cabeza and Nyberg, 2000). However, these methods are not the most suitable for addressing the question of *when* during the mental task the different modules become active and hence in what processing step(s) each module is involved. Nor can they readily answer the important questions of sequential versus parallel activation, feedforward versus feedback processes, or how information is 'bound' together to form unified percepts.

In order to investigate such temporal properties of brain circuits, methods that directly measure neuronal activity in real time are needed. Electro- and magneto-encephalography (EEG, MEG) offer this possibility by measuring the electrical activity of neuronal cell assemblies on a submillisecond time scale. Unfortunately, these techniques face the problem that the signals measured on the scalp surface do not directly indicate the location of the active neurons in the brain due to the ambiguity of the underlying static electromagnetic inverse problem (Helmholtz, 1853). Many different source configurations can generate the same distribution of potentials and magnetic fields on the scalp (for a review see Fender (1987)). Therefore, maximal activity or maximal differences at certain electrodes do not unequivocally indicate that the generators were located in the area underlying it. However, and as will be discussed in further

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detail below, the converse holds: different scalp topographies must have been generated by different configurations of brain sources. Capitalizing on this fact, a first step in defining whether and when different neuronal populations were activated over time or between experimental or pathological conditions is to identify differences in scalp topographies. Spatial enhancement algorithms, such as current source density calculations or deblurring (Babiloni et al., 1996; Gevins et al., 1991; He et al., 2001; Nunez, 1981) can help for this purpose.

While the analysis of the scalp potential or magnetic field distribution is the precursor for source localization, it does not provide conclusive information about the location and distribution of the sources. The only way to localize the putative electric sources in the brain is through the solution of the so-called inverse problem, a problem that can only be solved by introducing a priori assumptions on the generation of EEG and MEG signals. The more appropriate these assumptions are the more trustable are the source estimations. During the last two decades different such assumptions have been formulated and implemented in inverse solution algorithms. They range from single equivalent current dipole estimations to the calculation of three-dimensional (3D) current density distributions. Each approach uses different mathematical, biophysical, statistical, anatomical or functional constraints.

Several reviews on EEG/MEG source imaging exist, that explain in detail the formal implementation of the a priori constraints in the different algorithms (Baillet et al., 2001; Fuchs et al., 1999; George et al., 1995; Gonzalez Andino et al., 1999; Grave de Peralta Menendez and Gonzalez Andino, 1998; Hämäläinen et al., 1993; He and Lian, 2002; Michel et al., 1999a). While these rather mathematically oriented reviews are of utmost importance for the specialist in inverse solutions, the practical user might be more interested in a summary of the critical requirements for successful source localization. In fact, electromagnetic source imaging should involve many more analysis steps than applying a given source localization algorithm to the data. Each step should be carefully considered and selected on the basis of the information one would like to obtain from the measurements. The judgment on the validity of the results presented in a given study should be based on all these points, and not only on the choice of the inverse solution algorithm, because they are intimately linked. This review therefore not only discusses inverse solution algorithms, but also critical issues in steps preceding and following source estimation, such as the number and positioning of electrodes (including the reference electrode) and the determination of relevant time points or periods for source localization. We also discuss how the source estimations can be integrated with MRI and how one can go beyond simple pictures of inverse solutions by analyzing source localizations statistically.

This review concentrates on EEG recordings, though most of the aspects discussed here similarly concern MEG. Similarities and differences between EEG and MEG have been discussed elsewhere (e.g. Anogianakis et al., 1992; Liu et al., 2002; Malmivuo et al., 1997; Wiskwo et al., 1993; see also discussion in Barkley and Baumgartner (2003)).

EEG source imaging is not only used in cognitive neuroscience research, but has also found important applications in clinical neuroscience such as neurology, psychiatry and psychopharmacology. In cognitive neuroscience, the majority of the studies investigate the temporal aspects of information processing by analyzing event related potentials (ERP). In neurology, the study of sensory or motor evoked potentials is of increasing interest, but the main clinical application concerns the localization of epileptic foci. In psychiatry and psychopharmacology, a major focus of interest is the localization of sources in certain frequency bands. While the issue of source localization is similar for these different applications, the pre-processing of the data is somewhat different.

2. Number and positioning of the electrodes

This section discusses some of the basic questions regarding the recording of the data for EEG source imaging. It concerns the number and the distribution of the electrodes on the scalp and the spatial normalization of the individual potential maps for group averages. We will show that localization precision of epileptic sources drastically increases from 31 to 63 electrodes and also, though less drastically, from 63 to 123 electrodes. We also give an example that illustrates the importance of uniformly covering the scalp surface in order to correctly reconstruct the potential field, which is a prerequisite for correct source localization. We also discuss a point that in our opinion is irrelevant, but that is often cited as major problem of EEG: the choice of the reference electrode. We will show that the spatial configuration of the scalp potential map, and thus the localization of the sources in the brain, is independent of the position of the reference electrode.

2.1. Effect of the number of electrodes on source localization

A crucial practical question concerns the number of electrodes that are required for reliable EEG source imaging. Theoretically, a more correct sampling of the spatial frequencies of the scalp electric fields should lead to a better resolution of the topographic features. Using simulations as well as tests on real data, several authors showed that interelectrode distances of around 2–3 cm are needed to avoid distortions of the scalp potential distribution (Gevins et al., 1990; Spitzer et al., 1989; Srinivasan et al., 1996, 1998). However, still missing was a direct and systematic evaluation of the effects of the number of electrodes on source localization precision. For this reason,

we addressed whether using more electrodes, first in the case of simulated single dipoles and later in the case of interictal discharges in epilepsy, would improve source estimation results (Lantz et al., 2003a). For the simulations, 9 different electrode configurations of between 25 and 181 channels were chosen. Using a simple three-shell spherical head model (see Section 4.2), the potential maps for single dipoles in each of 1152 solution points in the sphere were calculated for the different electrode configurations. Different source localization algorithms were then applied to these potential maps, and the goodness of the localization was expressed in terms of the percentage of sources localized with zero dipole localization error. These simulations revealed that the influence of the number of electrodes on source localization precision is not linear. The precision increased from 25 to around 100 electrodes and then reached a plateau (Fig. 1). With the linear inverse solution EPIFOCUS (see Section 3.2), a nearly perfect localization was already achieved with 68 electrodes. This is due to the fact that this particular inverse solution, by default, assumes a single dominant source and thus has advantages over the other solutions in this type of simulation. The validity of dipole localization error for the evaluation of distributed inverse solutions will be discussed further in Section 3.3.

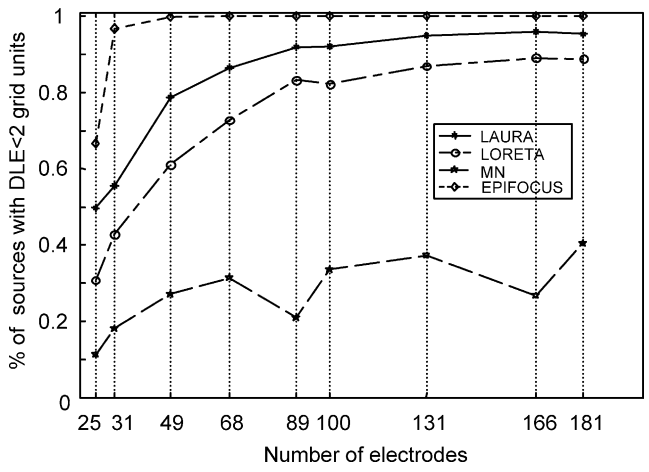

Fig. 1. Effects of the number of electrodes on dipole localization error (DLE) examined by different inverse solution algorithms with simulated data. There was a uniform distribution of 181 electrodes over a spherical surface that were down-sampled to montages ranging from 25 to 166 electrodes while keeping their distribution as uniform as possible. The lead field matrix was computed for each electrode configuration using a three-shell spherical head model with an equally spaced grid of 1152 solution points. Surface potentials were computed for dipolar sources at each of these grid points. These simulated surface potentials were subsequently localized using 4 different inverse solution algorithms: Minimal Norm (MN), Laplacian weighted Minimum Norm (LORETA), Local Autoregressive Average (LAURA) and EPIFOCUS. The percentage of sources with a DLE of less than 2 grid points are plotted for each electrode configuration and each inverse solution algorithm. This number increases non-linearly with increasing number of electrodes, reaching a plateau at around 100 electrodes for the fully distributed inverse solutions. For the linear inverse solution EPIFOCUS, which assumes a single dominant extended source, minimal localization error is already found with around 50 electrodes.

In the case of interictal discharges from 14 patients with partial epilepsy in whom the epileptic focus was unequivocally identified, EEG was recorded with 123 channels and down-sampled to 63 and 31 electrodes. EPIFOCUS was used in combination with a realistic head model derived from each patient's own MRI (the SMAC algorithm, see Section 4.2), which was then applied to the individual spikes using the different electrode densities. In these cases, localization precision was calculated from the distance between the estimated source maximum and the actual epileptogenic lesion. This analysis revealed a significant increase of the localization precision from 31 to 63 electrodes in 9 of the 14 patients, and from 31 to 123 electrodes in 11 of the 14 patients. Thus, while the 31-channel recordings were clearly insufficient for adequate source localization, the difference between 63 and 123 channels was minimal, confirming the simulation results described above. However, we would caution the reader that the conclusion drawn from this study is likely only valid for the strong, focal sources analyzed in these patients, as well as for a source localization procedure that implicitly assumes such a single focal source. The simulation study described before would suggest that fully distributed inverse solutions benefit from a larger number of electrodes, provided that noise (which increases with increased numbers of electrodes as a consequence of the ill-conditioned character of the inverse problem) is adequately accounted for.

In view of the obvious requirement of small inter-electrode distances for both the correct mapping of the electric field as well as the correct reconstruction of the sources, it has been proposed that a concentration of electrodes above the area of interest can solve the spatial aliasing problem (Spitzer et al., 1989; Srinivasan et al., 1998). This might be correct when the analyses are limited to those of waveforms. However, source localization procedures require uniform sampling of the full head surface and, by extension, the electric activity of the brain propagating to the scalp. The result of inverse solutions with non-uniform sampling of the potential field can lead to drastically wrong results, as shown in Fig. 2. Here, the P1 component of the visual evoked potential is localized progressively more frontally the fewer frontal electrodes are measured. When the number of electrodes is limited, a possible compromise can be to sample the potential field in a non-uniform way, i.e. to cover the whole head but increase electrode density in the regions of expected steepest potential gradients (Benar and Gotman, 2001).

Since both, simulations as well as experimental studies clearly indicate that at least 60 if not more equally distributed electrodes are needed to correctly sample the scalp electric field that is submitted to the source localization procedure, EEG source imaging studies with the conventional 21 channel EEG recordings have to be

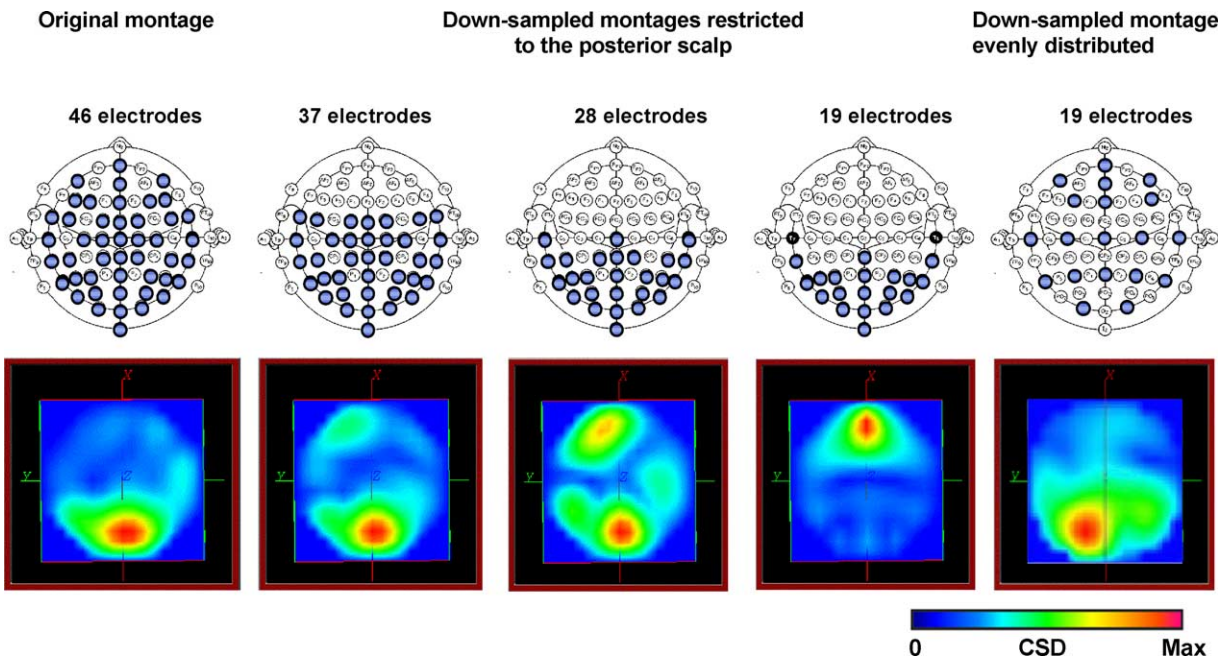

Fig. 2. Effects of the electrode distribution on the source estimation. The Laplacian weighted minimum norm algorithm (LORETA) in a three-shell model was applied to group-averaged ($N = 12$) ERP data in response to a centrally presented reversing checkerboard at the peak of the P100 component. Localization was first performed on the original configuration of 46 equally distributed electrodes (leftmost panels). We then conducted this analysis on the data where an increasing number of frontal electrodes were excluded, whereas the sampling of the occipital lobe remained the same (central 3 panels). Note that the source maximum was found in the frontal lobe when only the 19 most occipital electrodes were considered. However, when we down-sampled the montage to a set of 19 equally distributed electrodes, the source maximum was again found occipitally. Thus, a complete sampling of the electric potential is required for source imaging with distributed inverse solutions.

interpreted with extreme caution. It is not to be expected that different inverse solutions are less sensitive to spatial under-sampling. If the topographic features are not adequately sampled, none of the inverse solutions can retrieve the sources that would have generated these features. While studies in healthy subjects with high resolution EEG systems is nowadays relatively common (and inexpensive), it has repeatedly been argued that such

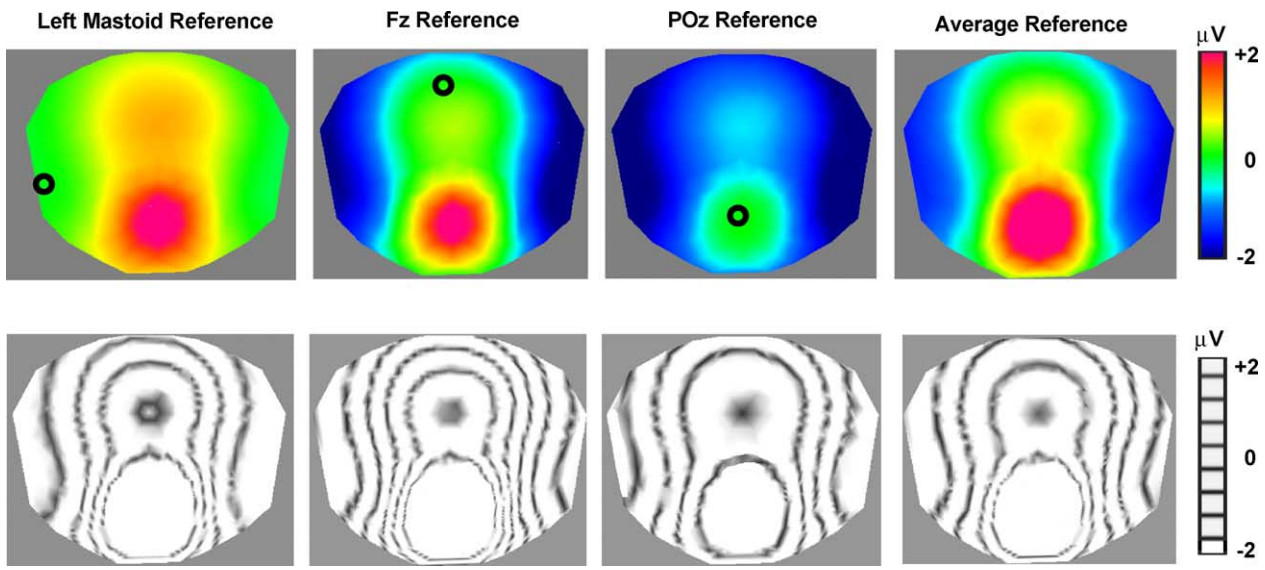

Fig. 3. The effect of the location of the reference electrode on the EEG scalp topography. Top row: Planar projection of the potential maps of a 128-channel ERP at an arbitrary time point. The 4 maps are recalculated against different reference positions as indicated above. All maps are shown using an identical color scale and are displayed from a top view with the nose upwards and left ear leftwards. The different reference locations change the color coding of the maps. However, they do not change the map topography. This is illustrated in the lower row. Here, the same maps are drawn using equipotential lines, rather than color shading. As can be easily seen, the equipotential lines and thus the topography or landscape of the map remain exactly the same. Only differences in scaling can appear. Thus, the topographic analysis of EEG and ERP as well as the source localization are reference-independent.

recordings are not feasible for clinical use because of the lengthy procedure to apply a large number of electrodes (Baumgartner, 2000; King et al., 2000; Rosenow and Lüders, 2001). Today, this argument is simply no longer valid. There are now several systems available that allow very fast electrode application and provide excellent signal quality (Lantz et al., 2003a,b; Michel et al., 2004a; Murray et al., 2004a; Praamstra and Oostenveld, 2003; Suarez et al., 2000; Tucker, 1993).

2.2. The choice of the reference

The question of the correct reference electrode has been intensively debated in the literature (Desmedt et al., 1990; Gencer et al., 1996; Junghöfer et al., 1999; Pascual-Marqui and Lehmann, 1993; Tomberg et al., 1990) and the 'reference-problem' has been taken as a major disadvantage of EEG versus MEG (Pataraia et al., 2002; Wikswo et al., 1993; Williamson et al., 1991). While the reference indeed heavily influences waveform analyses, it is actually completely irrelevant for the analysis of topographic maps and for source localization as long as the reference is correctly included in the model. This is because the configuration of the scalp topography is independent of the reference electrode (Fender, 1987; Geselowitz, 1998; Lehmann, 1987). As Geselowitz put it "The choice of a particular reference electrode, and hence the amplitude assigned to a contour, does not change in any way the biophysical information contained in the potential distribution. It does not in any way change the relation between source and potential, except for an additive constant of no physical significance" (Geselowitz, 1998, p. 132). The reference only changes the zero line. The equipotential lines remain exactly the same, and the landscape remains unaffected (Fig. 3). Therefore, any analysis method that considers the *spatial* distribution of the EEG or ERP is completely reference-independent (Lehmann, 1987). This of course also concerns the conversion of scalp potentials into sources in the brain (Fender, 1987). The quasi-stationarity that underlies the inverse solution algorithms assumes that the net source in the head is zero. The reference adds a constant potential to the recording at every electrode at any instant, leading to a non-zero net source. In order to avoid this violation of the quasi-stationarity, the data matrix has to be centered, i.e. the constant has to be removed. Interestingly, this mathematically corresponds to the calculation of the average reference of the surface potential (Lehmann and Skrandies, 1980). Thus, the average reference is usually automatically calculated in the source localization software. Therefore, if one objective of the researcher is to conduct a series of analyses on a data set that ultimately include source imaging, he/she might consider using the average reference throughout for the sake of consistency (e.g. Murray et al., 2004a for a recent example of such a step-wise approach).

2.3. Electrode positions and interpolation algorithms

Incorrect assumptions about the positions of the electrodes on the scalp can also lead to inaccurate source localization. For practical reasons, MRI scans of each subject with MRI-visible capsules at all electrode positions (Rodin et al., 1997; Wang et al., 1996) are usually not feasible. Measuring the exact 3D electrode positions with a digitizer is more practical. This procedure provides a means for taking into account inter-individual variations in electrode positions (Towle et al., 1993; Tucker, 1993). However, studies that directly evaluated the dipole localization error induced by electrode misplacements showed that the localization error is small and might be negligible compared to the error induced by noise (Khosla et al., 1999; Van Hoey et al., 2000; Wang and Gotman, 2001). Likewise, currently used electrode caps/nets conserve electrode spacing and positions (provided they are placed appropriately on the head in the first place). In such cases, the measurement of some landmarks might be sufficient to reconstruct the positions of the rest of the electrodes (De Munck et al., 1991; Le et al., 1998).

Another practical issue concerns the treatment of artifact-contaminated channels due to poor electrode-scalp contact or amplifier malfunction. In principle, these 'bad' electrodes can simply be omitted in the source localization calculation. However, this is only possible if source localization of individual subjects' data is performed. If data are averaged over conditions or over subjects, the missing electrodes must be interpolated to assure the same number of samples for each electrode. In addition, group-averaged data require normalization to the same electrode configuration before averaging (Picton et al., 2000). Such normalization is also needed when source reconstructions on head models with standard electrode positions are used to which the original data (measured on different positions) have to be interpolated (Scherg et al., 2002).

There are two widely used classes of interpolation procedures: nearest neighbor and the spline methods (Fletcher et al., 1998; Perrin et al., 1990; Soufflet et al., 1991). In nearest neighbor interpolation algorithms, the unknown values are computed as a weighted average of the potential data of the neighboring electrodes with weights that are dependent on the Euclidian distance between the neighboring site and the point to estimate. Within the class of spline interpolation methods, thin plate spline (Perrin et al., 1987) and spherical spline (Hassaina et al., 1994; Perrin et al., 1989) algorithms can be differentiated. The thin plate spline minimizes the bending energy of an infinite flat sheet passing through given data. Spherical splines use minimal bending energy in deforming the spherical surface to pass through a finite number of known points.

The quality of these different interpolation techniques has typically been investigated in terms of their ability to reconstruct given EEG maps using cross-validation criteria to estimate the interpolation error of a known potential

(Fletcher et al., 1998; Perrin et al., 1989; Soong et al., 1993; Soufflet et al., 1991). In general, spline interpolations behaved better than nearest neighbor interpolations. Within the spline algorithms, Soufflet et al. (1991) found better performance of thin plate splines as compared to spherical splines, whereas Perrin et al. (1989) reported marginally better performance of spherical splines in regions not well covered by electrodes.

3. The choice of the inverse model

This section will give an overview on some of the currently available source localization algorithms. Generally speaking, these algorithms try to most optimally explain the scalp potential field by intracranial sources. The fundamental problem of EEG/MEG source reconstruction is the ambiguity of the electromagnetic inverse problem (Helmholtz, 1853). That is, a given electric potential or magnetic field recorded at the scalp can be explained by the activity of infinite different configurations of intracranial sources. Only by introducing a priori assumptions about the sources and the volume conductor can the inverse problem be solved (Fender, 1987). These a priori assumptions are crucial, since they determine whether the solution is limited to only explaining the data or if the solution actually gives neurophysiological information about where the signals were generated in the brain. Unfortunately, the reality of how the signal was generated is not known. It is therefore up to the user to decide whether or not the constraints used in a given inverse solution are physiologically plausible. In the following sections, we will list some of the currently used inverse solutions and we will try to explain the assumptions that each of these inverse solution incorporates. As will become clear, the reason why new methods are continuously developed is mainly that new knowledge of how signals are generated is continuously incorporated as a priori constraints. Thus, the source localization problem is not yet solved, since not all information about signal generation is yet known.

3.1. Overdetermined (dipolar) models

The basic a priori assumption underlying dipolar model is that a small number of current sources in the brain can adequately model the surface measurements. To warrant a unique solution, the number of unknown parameters has to be less than or equal to the number of independent measurements (i.e. electrodes). The best location of these limited number of sources is found by computing the surface electric potential map generated by these dipoles using a certain forward model (i.e. how a dipole at a given position and orientation propagates signals to the scalp) and comparing it with the actual measured potential map. This comparison is usually based on calculating the (average) squared error between the two maps. The solution with optimal (i.e. minimal) squared error is accepted as best explaining the measurements (thus the term ‘least-square source estimation’). Since an exhaustive scanning through the whole solution space with any possible location and orientation of the sources is very demanding and nearly impossible if more than one dipole is assumed, non-linear optimization methods based on directed search algorithms are usually used (Uutela et al., 1998). A general risk of these methods is that they can get trapped in undesirable local minima, resulting in the algorithm accepting a certain location because moving in any direction increases the error of the fit (Grave de Peralta Menendez and Gonzalez Andino, 1994). The complexity of the directed search algorithms and the problem of local minima both increase with the number of dipoles. Thus, the maximal number of independent sources, which can be reliably localized for a given time point, is lower than what would be theoretically possible. Decoupling the estimation of the linear and non-linear parameters of the dipoles can reduce the complexity and help in identifying the absolute minimum in multiple source modeling (Mosher et al., 1992). However, it would be incorrect to assume that the mathematically absolute minimum is the ’correct’ solution. Among all solutions compatible with the data, the global minimum solution is at best only slightly more likely than the others. It would thus be presumptuous to automatically equate a ’correct’ solution with the absolute minimum of the residual sum of squares.

In order to increase the number of dipoles that can be fitted, Scherg and collaborators proposed incorporating the temporal domain in the dipole fitting procedure (Scherg and von Cramon, 1986). This spatiotemporal multiple source analysis technique (implemented in the BESA software) fixes the dipole locations over a given time interval and then uses the whole block of data in the least square fit. The fitting then results in time-varying modulation of the amplitude of each of these dipoles. As with all dipole models, the crucial issue in the spatiotemporal model is to assume the correct number of dipoles. Two approaches are proposed in the software (see Scherg et al., 1999): (1) The whole period is analyzed at once with an increasing number of sources. New sources are added as long as the explained variance considerably increases. (2) The period is analyzed sequentially and new dipoles are added for each additional time window if further activity remains unexplained. The second approach is exemplified in detail in the study of Foxe et al. (2003). This study illustrates how important the a priori knowledge about the number and possible location of the sources is and how much user intervention and user decision is needed in this step-wise approach. These issues have been discussed in several simulation and experimental studies (Achim et al., 1991; Cabrera Fernandez et al., 1995; Miltner et al., 1994; Zhang and Jewett, 1993, 1994).

The key question that the user of overdetermined source models has to solve is thus to obtain the correct estimates of the number of sources. Most often the choice is based on

expectancies based on physiological knowledge. For example, short-latency evoked potentials or epileptic activity is assumed to be generated by a fairly limited number of simultaneously active sources. However, even in these cases, new data on fast feedforward streams or rapid propagation of brain responses, and on parallel activation of primary and secondary sensory areas would question the appropriateness of this assumption. For example, several electrophysiological studies in primates (Bullier, 2001; Fabre-Thorpe et al., 1998; Schroeder et al., 1998) and intracranial ERP studies in humans (Blanke et al., 1999; Seeck et al., 1997; Thut et al., 2000b) indicate fast and parallel activation of different brain areas outside the visual cortex at very early latencies (for a review see Michel et al. (2004b)). Also in epilepsy, interictal activity can propagate very rapidly, leading to activation of multiple or widely distributed sources at the peak of the surface spike (Huppertz et al., 2001b; Lantz et al., 2003b; Scherg et al., 1999). Thus, rejecting dipoles that are not within the expected areas or that are explaining only a small amount of additional variance, might not always be justified.

Several studies have proposed to define the number of dipoles based on other functional imaging data such as PET or fMRI (Foxe et al., 2003; George et al., 1995; Korvenoja et al., 1999; Menon et al., 1997). However, this is not without risk given the fact that the relationship between hemodynamic changes measured with fMRI and the electrophysiological changes measured with EEG/MEG is not yet well understood (Devor et al., 2003; Logothetis et al., 2001). Mismatch between the two measures can be expected due to several plausible reasons. For example, fMRI activation can be seen in 'closed field' areas, i.e. in areas where the electrical neuronal activity pattern is such that the total current cancels out and is this invisible to surface EEG. On the other hand, EEG sources can be found without corresponding fMRI signal enhancement due to susceptibility artifacts or, more importantly, due to the thresholding of fMRI data where weak or short-lasting activities might not reach the significance level (for a discussion see Vitacco et al., 2002). This problem is particularly crucial when using fMRI not only to select the number of dipoles but also to actually fix their position to be localized on the maxima of the BOLD response and then using the spatiotemporal dipole model to reveal the time course of the activity of these areas (Korvenoja et al., 1999; Menon et al., 1997; Murray et al., 2002). More promising are approaches where the EEG/MEG source modeling is done independent and where the comparison with fMRI is used to select more likely source distributions among the possible ones (Ahlfors et al., 1999; Liu et al., 1998).

A third alternative for defining the number of active sources is to use the available mathematical approaches that aim to identify the optimal number of dipoles over a given data period automatically. For that purpose, Mosher adapted a scanning technique used in radar-technology to isolate signal from noise. The method, called multiple signal classification (MUSIC) is based on an eigenvalue decomposition of the data to identify the underlying components (the signal space) in the time series data (Mosher et al., 1992). The whole brain volume is then scanned for those source locations that contribute to the signal space. Once these sources are found, the time courses of their moments are determined in the same way as for the spatiotemporal multiple source analysis described above. Some shortcomings of the MUSIC algorithm with respect to correlated sources in the presence of noise as well as the application to realistic head models has led to improvements upon the original algorithms (RAP-MUSIC; Mosher and Leahy, 1998). Additional spatiotemporal decomposition approaches to define the source space have been proposed based on principle (Koles and Soong, 1998) or independent (Kobayashi et al., 2002) component analysis, which provide an estimator of the minimum number of dipoles.

3.2. Underdetermined (distributed) source models

In view of the intrinsic problem that the exact number of dipole sources generally cannot be determined a priori, methods that do not need this a priori assumption have received increased attention. These so-called distributed source models are based on reconstruction of the brain electric activity in each point of a 3D grid of solution points, the number of points being much larger than the number of measurement points on the surface. Each solution point is considered as a possible location of a current source, thus there is no a priori assumption on the number of dipoles in the brain (provided the grid of solution points is sufficiently large). The task to solve is to find a unique configuration of activity at these solution points that explains the surface measurements. Unfortunately, an infinite number of distributions of current sources within this 3D grid of solution points can lead to exactly the same scalp potential map. This means that the inverse problem is highly underdetermined.

This underdetermined nature of the source model further necessitates the application of different assumptions in order to identify the 'optimal' or 'most likely' solution. The distributed inverse solutions that have been proposed in the literature differ in their choice and implementation of these constraints. Some are purely mathematical, some incorporate biophysical or physiological knowledge and others even incorporate findings from other structural or functional imaging modalities. It is important to emphasize that any such constraint is only valid if source distributions fulfilling these restrictions are more likely to occur than other distributions. In other words, the validity of the a priori constraint defines the validity of the inverse solution.

Conceptually, each point in the solution space can be thought of as an equivalent dipole. However, in contrast to equivalent dipole solutions, these 'dipoles' of distributed inverse solutions have fixed positions. Only their orientations and strengths vary. Consequently, equations describing distributed inverse solutions are linear, meaning that a matrix

can be constructed that linearly relates the measured data to the estimated solution. This means that linear distributed inverse solutions have the property that the 3D current estimate (under the given constraint) exactly reproduces the measured data, i.e. the explained variance is always 100%. In practice, however, regularization parameters are usually introduced to account for the noise in the data, and thus the resulting source distribution does not fully explain the measured data. If the regularization parameter is properly based on the noise estimation, the unexplained part of the data should actually correspond to this noise. The regularization operator provides stability to the solution, such that small variations in the data do not lead to large variations in the source configuration. In the following, some (but not all) of the proposed linear inverse solutions are briefly explained.

3.2.1. Minimum Norm

The general estimate for a 3D brain source distribution in the absence of any a priori information is the Minimum Norm (MN) solution (Hämäläinen and Illmonemi, 1984, 1994). It only assumes that the 3D current distribution should have minimum overall intensity (smallest L2-norm). The method gives a unique solution in the sense that only one combination of intracranial sources can have both the lowest overall intensity and at the same time exactly fit the data. However, the restriction that the overall intensity should be as low as possible is not necessarily physiologically valid. For example, there is no proof that the solution with the second lowest overall amplitude is not actually the correct one. The algorithm thus punishes solutions that give strong activation of a large number of solution points, i.e. it favors weak and localized activation patterns. Consequently, the MN algorithm favors superficial sources, because less activity is required in superficial solution points to give a certain surface voltage distribution. In consequence, deeper sources are incorrectly projected on the surface, which can lead to erroneous interpretations.

3.2.2. Weighted minimum norm

In order to compensate for the tendency of the Minimum Norm solution to favor superficial sources, different weighting strategies have been proposed. The simplest possible weighting is based on the norm of the columns of the lead field matrix (Lawson and Hanson, 1974). In the PROMS solution proposed by Greenblatt (1993), the covariance data matrix is used to construct a weighting function within the source space. Regularized location-wise normalization has been proposed by Fuchs et al (1994). In the FOCUSS (Focal Underdetermined System Solution) algorithm, Gorodnitsky et al. (1995) proposed to iteratively change the weight according to the solutions estimated in previous step, leading to a non-linear solution. Grave de Peralta Menendez and Gonzalez Andino, 1998 proposed to impose the physical constraint that the currents are bounded to the brain volume and thus that the radial components should go to zero when approaching the surface of the brain (radially weighted minimum norm solution, RWMN). While these different depth weighting strategies overcome the problem of the surface-restricted MN algorithm, it has to be kept in mind that these weightings are based on purely mathematical operations without any physiological basis that would justify the choice of the weights.

3.2.3. Laplacian weighted minimum norm (LORETA)

Additional constraints can be added to the depth weighting. A well-known example is the Laplacian Weighted Minimum Norm algorithm (implemented in the LORETA software, Pascual-Marqui et al., 1994). The particular constraint in this case is that the method selects the solution with a smooth spatial distribution by minimizing the Laplacian of the weighted sources, a measure of spatial roughness. Since smoothness is not uniquely defined for vector fields, different definitions of smoothness (Mitiche et al., 1988) will produce different optimally smoothed solutions and thus the term 'smoothest' is unfortunate. The physiological reasoning underlying this constraint is that activity in neurons in neighboring patches of cortex is correlated. While this assumption is basically correct, it has been criticized that the distance between solution points and the limited spatial resolution of EEG/MEG recordings leads to a spatial scale where such correlations can no longer be reasonably expected (Fuchs et al., 1994; Hämäläinen, 1995). Indeed, functionally very distinct areas can be anatomically very close (e.g. the medial parts of the two hemispheres). Without taking such anatomical distinctions explicitly into account, the argument of correlation as physiological justification for the LORETA algorithm should be taken with caution. Consequently, and because of this assumption of correlation over relatively large distances, LORETA generally provides rather blurred ('over-smoothed') solutions that can include the two hemispheres or different lobes (Fuchs et al., 1999; Grave de Peralta and Gonzalez, 2000; Trujillo-Barreto et al., 2004).

3.2.4. Local autoregressive average (LAURA)

This distributed inverse solution attempts to incorporate biophysical laws as constraints in the minimum norm algorithm. According to the electromagnetic theory described in the Maxwell equations, the strength of the source falls off with the inverse of the cubic distance for vector fields, and with the inverse of the squared distance for potential fields (see also Section 3.2.8 below). The method thus assumes that the activity will fall off (or regress) according to these physical laws when you move away from the source. LAURA integrates this law in terms of a local autoregressive average with coefficients depending on the distances between solution points (therefore the name LAURA; Grave de Peralta and Gonzalez, 2002; Grave de Peralta et al., 2001, 2004a). The autoregressive average thus determines the activity at each point that cannot be estimated from the data alone. Consequently, the activity at one point

depends upon two contributions: one fixed by the biophysical laws and another free to be determined from the data.

In the implementation that we applied in our recent evoked potential studies (see Section 5.1.1) we incorporated the local autoregressive average with homogenous regression coefficients in all directions within the whole solution space. Anatomical details could be incorporated at this level of the modeling by varying the regression coefficients. Also, instead of applying the same coefficients to each individual Cartesian component of the primary current density vector (3D vector field), dependencies between the dipole moments could be taken into account (Grave de Peralta et al., 2004a).

3.2.5. EPIFOCUS

EPIFOCUS (Grave de Peralta and Gonzalez, 2002; Grave de Peralta et al., 2001) has mainly been developed for the analysis of focal epileptic activity where a single, dominant source with a certain spatial extent (determined by the data) can be assumed (Lantz et al., 2001a, 2003a,b; Michel et al., 2004a). It is a linear inverse method that scans the solution space (i.e. the total number of solution points) and calculates the current density vector by projecting the scalp potential data on each solution point. The results of this estimate (i.e. the modulus of the vector) can be interpreted (up to a scale factor) as the probability of finding a single source at each specific point. Because of its simplicity, this technique is particularly well suited for realistic (MRI based) head models. It is however better to limit its use to cases where a single dominant source can be assumed since it might fail if several sources at different places are simultaneously active. However, one important difference from the dipole model is that in later case the dipole approach will regularly yield a source with all the strength confined to one point located at the center-of mass of the distribution. With EPIFOCUS it is, in contrary, possible to visualize an activity with a certain spatial distribution, and still retrieve the maximum within this distributed activity.

As the MUSIC method and the non-linear single dipole localization method, EPIFOCUS searches for focal sources in the 3D solution space. However, in contrast to the MUSIC method, it does not require a certain time period of EEG for the analysis (i.e. a covariance matrix) but can rather be applied to instantaneous potential maps. EPIFOCUS also avoids the non-linear optimization algorithm used in the equivalent dipole localization methods. This considerably facilitates the localization in realistic head models, where the source space (gray matter) is a discrete set of scattered points. Both simulations as well as analyses of real data have demonstrated a remarkable robustness of EPIFOCUS against noise (Grave de Peralta et al., 2001). This is a consequence of the fact that this is a pseudo solution in which the reconstructed map does not need to fully reproduce the observed data.

3.2.6. Beamformer

Beamforming approaches, originating from radar and sonar signal processing, have recently been applied to the analysis of (mainly MEG) signals (Gross et al., 2001; Sekihara et al., 2001; Van Veen and Buckley, 1997). A specific non-linear form of the beamformer is implemented in the algorithm called *Synthetic Aperture Magnetometry* (SAM; Robinson and Vrba, 1999). Like other linear filtering approaches (Hauk et al., 2002), SAM can be considered as a spatial filtering of the data to discriminate between the signals that arrive from a region of interest and those originating from other points. They can thus be interpreted as a source scanning procedure that can estimate source changes over time for any arbitrary voxel (Barnes and Hillebrand, 2003; Taniguchi et al., 2000). Beamformer approaches aim to estimate the activity at one brain site by minimizing the interference of other possible simultaneous active sources. For that, the selected estimator optimizes a goal function that represents the ratio between activity and noise at the target point. This function may contain the a priori information available about the source and the data as described for example by the covariance matrices. It has been postulated that SAM does not suffer from the same limitations as the linear inverse solutions (Vrba and Robinson, 2001). Unfortunately, this claim is not entirely true. The method is actually divided into two steps. First, the sources are linearly estimated using an optimal direction that is a priori defined. Second, the result is normalized by the noise power (pseudo Z). Splitting the algorithm in these two steps makes clear that, as for any linear estimator (whatever the selected direction is), other simultaneously active sources will influence the amplitude estimation of the target point. As will become clear below, it means that a resolution kernel can be associated to the estimation in the target point. This resolution kernel predicts the influence of the other simultaneously active sources on the target point. Therefore, the beamforming approaches have the same basic limitations as the other linear inverse solutions. The second step in the approach is just a post-processing of the linear inverse solution and can in principle be applied to all the methods described above. The idea of normalization as a second step in the inverse solution has also been used by Dale et al. (2000) and by Pascual-Marqui (2002) in the sLORETA method. In contrast to these alternatives that yield non-linear estimators, we proposed in Grave de Peralta et al. (2004b) the inversion of the resolution matrix to improve the performance of linear solutions.

3.2.7. Bayesian approaches

The Bayesian approach is a statistical method to incorporate a priori information into the estimation of the sources. It can result in linear or non-linear estimators. Even if the non-linear implementations result in complex mathematical problems, it is probably the more promising one, because it allows for a more detailed description of the anatomical and/or functional a priori information. The types

of a priori information that have to date been incorporated in this approach include information on the neural current (Schmidt et al., 1999), the sparse focal nature of the sources (Phillips et al., 1997), combined spatial and temporal constraints (Baillet and Garnero, 1997) as well as strategies to penalize ghost sources (Trujillo-Barreto et al., 2004).

3.2.8. Alternative source models

The above described methods are all estimating the 3D distribution of the current density vectors (the vector fields). We recently proposed to change this source model, based on the following consideration: The total microscopic current emerging in biological tissue can be decomposed into two terms, a primary neurophysiologically driven (active) current and the volume or secondary current. The primary current is induced by ionic flow between intra- and extra-cellular space of the active neurons. The volume current refers to the passive currents that manifest as the electrical response of the media to compensate for charge accumulation at specific sites driven by the active currents. It has been shown that on the macroscopic level measured by EEG (as well as MEG) only the volume currents are measured and not the active current (Plonsey et al., 1982). Importantly, since the microscopic volume currents dominate primary currents, the currents perceived by EEG and MEG are ohmic.

Based on these neurophysiological considerations, we formulated a source model (called ELECTRA) that is implicitly only estimating ohmic currents (Grave de Peralta Menendez et al., 2000). ELECTRA is not an inverse solution, but rather a source model in which the generators of the scalp maps are the intracranial potentials instead of the 3 components of a dipole at each solution point. The advantage of using this source model is that the inverse problem is better conditioned, i.e. the number of unknowns is reduced by a factor of 3. This obviously increases the spatial resolution for the same amount of data even though the solution is still non-unique. Based on the ELECTRA source model, regularization strategies such as MN, WMN, LORETA, LAURA and any others can then be applied (Grave de Peralta et al., 2004a).

On the basis of this new source model different physical magnitudes can be estimated, such as the current source density (He et al., 2002), or the potential distribution (Michel et al., 1999a; Morand et al., 2000). Estimating the potential distribution actually corresponds to non-invasive estimation of the local field potential (LFP). Therefore, direct comparison with intracranial recordings can be made (Michel et al., 1999a; Thut et al., 2000b, see Section 5.1.2).

3.3. Evaluation and comparison of inverse solutions

In view of the many different existing source localization methods, the potential user is confronted with the question of how trustable these solutions are, and which one should be chosen. While this is of course the most crucial question, there is no direct answer to it. The problem with the evaluation of inverse solutions (dipole models or distributed source models) is the difficulty of obtaining evidence about the true location of the sources. There is no clear established gold standard that would allow judging the goodness of the result of the different inverse solutions. As discussed above, other functional imaging methods such as fMRI cannot be used as a gold standard as long as the spatial and temporal relation between electrical and haemodynamic responses are not known.

Most commonly, source localization algorithms are evaluated and compared through simulations with artificial data. These studies are based on the following basic method: a dipole is placed in the (modeled) brain, the forward solution of the scalp potential distribution is calculated, the source localization procedure is applied to this map, and the distance of the estimated source to the true source is measured. In the case of distributed inverse solutions, the distance between the source maximum and the simulated source is usually taken as a measure of error. Scanning through the whole source space reveals the so-called average dipole localization error (see also Fig. 1). This approach has its undoubted value in evaluating the behavior of dipolar models. It has, for example, been used to evaluate the variability in localization precision between different regions of the brain where larger errors for basal sources as compared to sources of more superior locations have been found (Cuffin, 2001; Cuffin et al., 2001; Kobayashi et al., 2003). Such simulations were also used to evaluate the dependency of equivalent dipoles on source depth (Yvert et al., 1996), on the noise level (Achim et al., 1991; Vanrumste et al., 2002; Whittingstall et al., 2003), on the number of recording electrodes (Krings et al., 1999; Yvert et al., 1996), and on the head model (Cuffin et al., 2001; Fuchs et al., 2002).

The dipole localization error in simulated data is also often used to evaluate the accuracy of distributed inverse solutions and to compare a newly proposed method to those that have been presented before. Usually, simple spherical head models are used in these simulated comparisons. Pascual-Marqui (1999) used the dipole localization error to compare MN, column weighted MN, LORETA, and some rather general classes of inverse solutions (Backus and Gilbert and WROP). The smallest localization errors were obtained for LORETA. Laehy et al. (1996) compared MN, WMN, LORETA, and the Bayesian solution and found best localization precision for the Bayesian method if the sources had sparse focal characteristics. Recently, a new variant of a Bayesian model was presented by Trujillo-Barreto et al. (2004) and was compared to the unconstrained and a cortical constrained version of LORETA. Higher localization precision for deep sources and (more importantly) much higher spatial resolution was shown with the Bayesian approach as compared to both LORETA versions. Grave de Peralta and Gonzalez (2002) compared MN, RWMN, LORETA, LAURA and EPIFOCUS. Due to the intrinsic assumption of single sources, EPIFOCUS behaved best in

these single source simulations, followed by LAURA. Radially weighted MN and LORETA were comparable. Phillips et al. (2002) compared a simple WMN, LORETA, and a WMN that imposes constraints derived from other imaging modalities. They showed a strong noise-dependency of the LORETA algorithm. If no noise regularization was applied, LORETA was not able to provide any proper localization, even for data with a high signal-to-noise ratio.

Unfortunately, these comparisons are not of great value for judging the goodness of the distributed linear inverse solutions. Since the argument for using distributed inverse solutions is precisely that they can retrieve multiple active sources, the dipole localization error is the most 'unnatural' test for them (Grave de Peralta Menendez and Gonzalez Andino, 1998). For example, in Michel et al. (1999a) we showed that LORETA gives a correct, though blurred, reconstruction when one single point is active and all others are zero. However, just adding a constant value to all sources in the solution space makes the LORETA algorithm fail. This is due to the general fact that all simultaneously active sources affect the estimation of the activity in one point, a situation that the dipole localization error does not consider. Such simulations can thus not predict how a distributed inverse solution deals with the reciprocal influences of simultaneously active sources.

The appropriate way to evaluate and compare linear distributed inverse solutions would be the so-called resolution matrix (Backus and Gilbert, 1970; Grave de Peralta Menendez and Gonzalez Andino, 1999; Grave de Peralta Menendez et al., 1996; Lütkenhöner and Grave de Peralta, 1997; Menke, 1989). The rows of the resolution matrix (the so-called resolution kernels) give direct information about how all other active sources influence the reconstruction of a source at a given point. From these resolution kernels, different figures of merit can be derived to evaluate the behavior of distributed inverse solution in the presence of simultaneous sources, such as the source visibility and identifiably (Grave de Peralta Menendez et al., 1996), or the cross-talk metric (Liu et al., 1998, 2002). In addition, the resolution kernels provide a general framework to design and construct inverse solutions with optimal resolution (WROP method; Grave de Peralta Menendez et al., 1997). While Liu et al. (2002), used the resolution kernels to compare EEG and MEG, Grave de Peralta Menendez and Gonzalez Andino (1998) used this framework to evaluate different inverse solutions. The MN, LORETA and an averaged solution were compared. This comparison revealed that (a) all solutions systematically underestimated the dipole moment or strength, (b) LORETA and the average solution were better than the MN in terms of their capability to localize the position of a single source, (c) all solutions behaved similarly in the presence of simultaneously active sources.

The conclusion from these simulation studies on distributed inverse solutions is that their basic limitation is the incorrect estimation of the source strength. This limitation might lead to ghost and lost sources in the instantaneous map reconstruction as well as to maxima reflecting no underlying source. This limitation might be alleviated, however, by introducing posterior analysis of the reconstruction in the temporal domain invariant to factor scales (Grave de Peralta et al., 2004a) or that aim to rectify a posteriori the estimated strength (Dale et al., 2000; Vrba and Robinson).

Mathematical simulations or measurements on phantom heads have their undoubted value, but they cannot really mimic the complex distribution and interaction of active sources as it is probably the case in reality. Thus, the more challenging test of inverse solution algorithms is their behavior in real data where the most dominant sources are known with very high probability. This is offered in the case of epileptic activity in patients where the focus localization is known from other independent sources (i.e. the pre-surgical evaluation methods including intracranial recordings if needed). Several studies actually applied inverse solutions to epileptic data, both dipole localization methods (e.g. Boon et al., 2000; Ebersole, 1997, 2000a,b; Krings et al., 1998; Merlet and Gotman, 1999) as well as distributed inverse solutions (e.g. Fuchs et al., 1999; Huppertz et al., 2001a,b; Lantz et al., 2003a,b; Michel et al., 1999a; Seri et al., 1998; Waberski et al., 2000). These studies repeatedly showed that inverse solutions could correctly define the epileptogenic zone. Thereby, the localization precision on sublobar level depends on several factors such as the number and position of electrodes, the head model, the signal-to-noise ratio as well as the inverse model applied. Using 123-channel recordings and EPIFOCUS on the SMAC-transformed individual MRI, we recently showed in a prospective study of 44 patients that the epileptic focus could be localized correctly on the lobar level in more than 90% of the cases, and on a sublobar level with the maximum laying within the resected zone in 79% (Michel et al., 2004a).

In an attempt to directly evaluate different inverse solutions on real data, different groups applied different source localization algorithms to interictal data of two epileptic patients that they received from the Editor of the *Journal of Clinical Neurophysiology* (Ebersole, 1999a). Three independent groups analyzed the data without knowing anything about the possible focus location (Fuchs et al., 1999; Michel et al., 1999a; Scherg et al., 1999). The data only contained the 27-channel recordings of an averaged spike for each patient, the position of the electrodes, and the MRI of the patients. Even with this low number of electrodes, the spatiotemporal dipole model as well as most of the distributed (linear and non-linear) inverse solutions led to correct localizations of the spikes and their propagation pattern, as confirmed by the intracranial recordings (Ebersole, 1999b). Differences were mainly seen in the amount of blurring and the retrieval of basal temporal lobe sources. Of course, the low number of electrodes that were used in these examples also contributed to a limited spatial resolution of the source estimations (see Section 2.1).

A general comment should be made with regard to the use of epileptic activity to demonstrate and evaluate source localization precision. The finding that a given source analysis procedure localizes a spike within an anatomical lesion, or in a region in which subsequent depth electrodes show spiking or seizure onset, is only indirect evidence that the source location depicts the epileptic source (we do not know for sure if the spike is generated in the lesion, if seizures and spikes have the same generator, if the depth spikes are the same events as those recorded on the scalp). More solid evidence is obtained in cases where surgical removal of the area indicated as the epileptic focus by the inverse solution renders the patient seizure free. In these cases, however, the extent of the surgical resection (sometimes major parts of a lobe), often makes it difficult to judge the spatial accuracy that actually was obtained with the inverse solution. The only direct proof that the source localization results are both valid and accurate is the direct comparison of the source model to the intracerebral field through simultaneous intra- and extracranial recordings. Several such studies in epileptic patients have shown a good correlation between the intracranial source and the inverse solution results but have also demonstrated some inherent limitations, especially concerning the localization of activity confined to deep temporal structures (Lantz et al., 1996, 1997, 2001a; Merlet and Gotman, 1999, 2001).

4. Integration of EEG source imaging with MRI

The ultimate goal of modern EEG source imaging is the localization of the EEG sources in anatomically defined brain structures so that direct comparison with other imaging methods, with lesion studies, or with intracranial recordings can be made. Most of the commercial and freely available software packages provide this possibility. Most often, it is mainly applied for visualization purposes. More recently, this information has been used to define the coordinates of the sources in terms of Brodmann areas or in Talairach coordinates and to draw conclusions about the anatomical/functional structures that were active. The accuracy of these locations depends crucially on two aspects (1) The head model initially selected to compute the inverse solution and (2) The inverse solution itself.

4.1. EEG–MRI co-registration

A prerequisite to be able to define the inverse solution results within the structural MRI is the co-registration between these two imaging modalities, i.e. the EEG space and the MRI space. This step requires that electrode positions are matched to the scalp surface defined by the MRI using some transformation (rotation and translations) operations. These parameters are usually obtained by measuring some 'common' landmarks during both the EEG as well as the MRI acquisition. Most commonly, MRI-visible markers are placed on the skin that correspond to the position of the electrodes and/or some fiduciary landmarks (e.g. nasion, inion, pre-auricular points, and vertex). These points are similarly measured during the EEG recording using a 3D digitizer. From such information, the transformation parameters can be determined for projecting the EEG sources into anatomical coordinates and displaying them on the MRI (Dieckmann et al., 1998; Lagerlund et al., 1993; Merlet et al., 1996; Scherg et al., 1999; Seri et al., 1998; Towle et al., 1993; Yoo et al., 1997). In order to avoid the labor-intensive measurement of the electrodes and fiduciary landmarks on every subject, many studies use one single template MRI (such as the MNI brain from the Montreal Neurological Institute) and assume a standard electrode coordinate system. In this case, pre-defined translation parameters are used to match the EEG to the MRI space. Individual differences in head size and electrode positions are thereby ignored, leading to a limited accuracy with regard to the anatomical precision of the source locations.

4.2. Head models

An important issue with respect to EEG–MRI co-registration is the selection of the head model for the inverse solution calculation. The head model determines the way the sources located at given brain sites produce the measurements on the scalp. It includes the electromagnetic (permeability's and conductivities) and geometrical (shape) properties of the volume within which the inverse solutions are calculated. Mathematically, these properties are expressed in what is called the lead field matrix. To solve the inverse problem, this lead field matrix is multiplied with the estimated sources (the current density vector) to produce the scalp potentials (the forward solution). The distance between these predicted scalp potentials and the measured potentials is the basis for finding the generators. Therefore, an accurate head model is essential for the solution of the inverse problem. The simplest and still most often used head model is the spherical model. Spherical head models with uniform conductivity properties allow an analytical solution of the forward problem and are thus fast and easy to calculate. However, the head is not spherical and its conductivity is not spatially uniform. Source localization accuracy is limited when using this model. Incorporations of different conductivity parameters in multishell spherical head models (Ary et al., 1981; Berg and Scherg, 1994; deMunck and Peters, 1993; Zhang and Jewett, 1993) and consideration of local anisotropies (De Munck et al., 1988; Zhang, 1995) can ameliorate the accuracy to a certain degree.

Several comparative studies have shown that accurate lead field computation can—for sources in most parts of the head—only be achieved by using realistic volume conductor models (see e.g., Cuffin, 1990, 1993, 1996; Meijs et al., 1987; Menninghaus et al., 1994; Hämäläinen and Sarvas, 1989; Roth et al., 1993; Stok, 1987; Thévenet et al., 1991; Yvert et al., 1995). However, it is worth noting that

most of these studies have been performed for single dipole localization and that similar analysis for distributed inverse solutions are largely missing. The most popular techniques for realistic head modeling are the BEM (boundary element method) and the FEM (finite element method). The BEM (Hämäläinen and Sarvas, 1989) uses triangulations of the interfaces between compartments of equal isotropic conductivities as a geometric model. In contrast, the FEM (Bertrand et al., 1991; Miller and Henriquez, 1990; Yan et al., 1991) tessellates the whole volume and allows therefore to consider individual anisotropic conductivities for each element. In practical terms this implies that contrary to the BEM model, the FEM model can take skull-breaches and anisotropies into account. However, since detailed anatomical information about tissue conductivities is rarely available (Hoekema et al., 2003), the advantages of the FEM model are not yet fully exploited.

The generation of realistic geometric models is not a trivial task, since it implies the segmentation of the MRI including the interfaces between the different head compartments (including the skull the contrast of which is not readily distinct with standard T1 weighted MRI). In addition, the tessellations have to fulfill several requirements in terms of the element size, smoothness and inter-compartment distances in order to avoid instabilities of the algorithms. Although an automatic procedure has been described by Fuchs et al. (2001), which is able to complete the whole realistic lead field computation on an standard PC in a few minutes, the computational ease of spherical head models still makes them the most used model to describe the lead field. This is particularly the case for most of the available software packages using single or multiple dipole fitting. Even if realistic source models are included in the software, they are seldom used when dipole modeling is selected. The reason is that the non-linear search of the dipole positions relies on iterative algorithms (see Section 3.1). This means that for each update of the dipole positions or change of the input data, the forward problem has to be resolved according to the new estimated parameters. This procedure, depending on the complexity of the head model, may still take a significantly long time to converge. While these issues of computational load are becoming less relevant with increasing computer power, some recent studies reported that differences between spherical and realistic models for single dipole localization decrease with increasing noise in the data (Van Rumste et al., 2002; Zanow and Peters, 1995).

Because of the obvious shortcomings of spherical head models on the one hand and the complexity of realistic head models on the other hand, efforts have been made over recent years to combine the computational efficiency of spherical head models with more realistic and accurate descriptions of the head shape. Huang et al. (1999) proposed a sensor-weighted overlapping-sphere (OS) head model for rapid calculation of more realistic head shapes. The volume currents associated with primary neural activity were used to fit spherical head models for each individual MEG sensor such that the head is more realistically modeled as a set of overlapping spheres, rather than a single sphere. Comparisons of the OS model, the BEM, and the multishell spherical model showed that the OS model has accuracy similar to the BEM but is orders of magnitudes faster to compute. Ermer et al. (2001) extended this model to EEG with improvements in localization accuracy and speed similar to those obtained for MEG.

As an alternative to the above described head models, we proposed in Spinelli et al. (2000) *a spherical head model with anatomical constrains (SMAC)*. In this approach a best-fitting sphere is calculated for the individual head surface derived from the segmented MRI. Homogeneous transformation operators are then calculated that transform the MRI to a sphere. Consequently, the inverse problem can be calculated analytically (using a spherical model), but the solutions are directly calculated for this (though slightly deformed) MRI. The major advantage (besides the simplicity of the calculation) is the fact that it directly allows excluding areas (within a sphere) that are not expected to contribute to the solution, such as white matter or lesions as illustrated in Fig. 4.

4.3. Definition of the solution space

Another important issue in EEG source imaging concerns the selection of the solution space within which the sources are allowed. For dipole solution algorithms, this refers to the space that is included in the non-linear search procedure. For distributed inverse solutions, it refers to the distribution of the fixed solution points. In most of the simple spherical head models, the whole volume within a certain radius of the sphere (excluding the space between the scalp and the brain) is accepted as solution space. Thus, white matter, ventricles and deep structures are all allowed. In realistic head models (using BEM, FEM or SMAC), the MRI is taken into account to restrict the solution space to structures where putative EEG sources can actually arise (i.e. the gray matter of the cortex and some well-defined deep structures with or without the cerebellum). The optimal selection of such a restricted solution space has to be based on the segmentation of the MRI into gray and white matter. If this is done on the basis of a general head model (such as the MNI brain described above), individual variances are not considered. The use of the subject's proper MRI is ultimately needed in clinical cases where lesions or deformations are present. Only by using the patient's own MRI can such areas be excluded from the solution space (see also Fig. 4).

It is noteworthy that a realistic gray matter selection generally leads to a non-continuous solution space. This poses particularly severe problems for dipole models with their non-linear iterative search algorithms. In such scattered solution space, the definitions of gradients and steepest descent directions are obviously undefined,

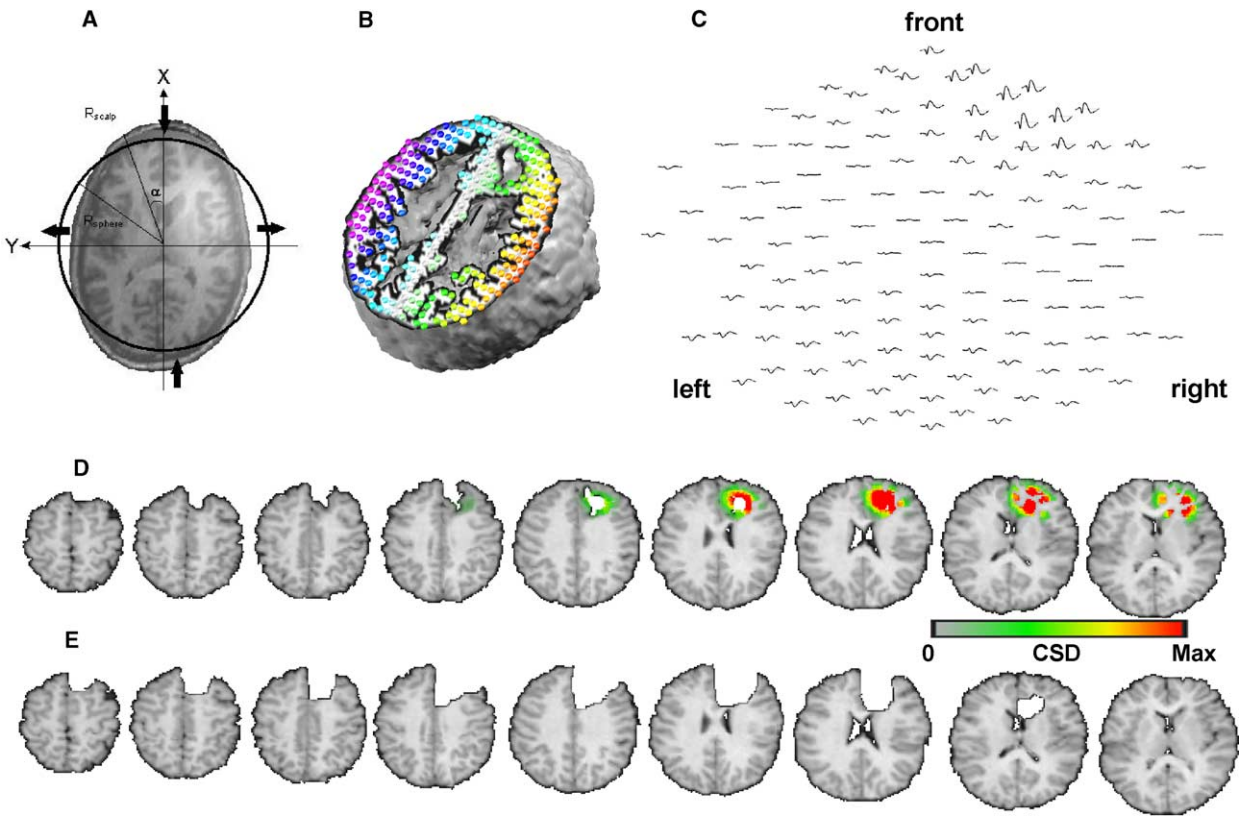

Fig. 4. Source localization in an anatomically defined spherical head model. (A) Illustration of the SMAC procedure (Spinelli et al., 2000). The MRI data are spatially transformed to the best fitting sphere by homogeneous transform operations. The back and front of the head are compressed, whereas the temporal lobes are stretched. (B) Illustration of the distribution of the solution points on the gray matter of the spherically transformed MRI of a single patient. A horizontal slice at the level of the patient's right frontal lesion is shown, illustrating that no solution points are defined within the lesion. (C) Averaged spike of this patient recorded from 123 electrodes, showing maximal potentials at right frontal electrodes. (D) Results of the application of the EPIFOCUS inverse solution to the averaged spike shown in C, displayed on the patient's MRI. Maximal source strength is observed in the vicinity of the lesion. (E) SMAC-transformed post-operative MRI of the patient allows subsequent and direct comparison between the location of the estimated source and the resected area (see Michel et al. (2004a) for details).

impeding the use of the standard mathematical solutions. On the other hand, distributed linear source models with their fixed location of solution points are straightforward to apply to non-homogeneous volumes, since the positions of the dipoles remain fixed. Also, other methods such as MUSIC and RAP-MUSIC (see Section 3.1) can be implemented in non-homogenous models.

In conclusion, if spherical head models without any anatomically defined restrictions of the solution space are used, the EEG–MRI co-registration cannot guarantee that the estimated sources will appear at reasonable positions (e.g. gray matter and not the ventricles). Such images should therefore be carefully interpreted as a mere illustrative picture without actual anatomical precision. This is especially the case for dipolar models. An erroneous impression of high anatomical precision may be given when point-like sources are displayed on the MRI, while the fact that these dipoles represent the center of mass of the actual source distribution is sometimes ignored. It can thus happen that this center of mass will be localized deeper in the subcortical white matter or superficial in the subarachnoid space. In these cases, the orientation of the dipoles and knowledge about the cortex geometry in this region has to be used to properly conclude about the anatomical area within the gray matter that is represented by this 'white matter' dipole (Ebersole, 2000a).

5. Incorporating time and frequency in source imaging

While the high temporal resolution is considered as the most important advantage of EEG/MEG measures, it carries the side effect of greatly increasing the amount of data collected, and consequently of introducing a temporal dimension to the data analysis procedures. As such, experimenters must devise methods for determining the relevant events within a continuous time series of data to which source analysis will be applied. Some of these methods are heavily influenced by the experimenter, whereas others are more driven by the data themselves. For example, these 'relevant events' can be selected a priori by searching for electrodes with potential peaks, either in evoked potentials (components) or in epileptic data (spike

maximum). They can be defined automatically as a segment of stable map topography, leading to a temporal parceling of the data into functional microstates. Alternatively to the preselection of relevant time points or periods, source localization methods can be applied to each time point and the temporal dynamics can directly be studied in the source space. Finally, the high temporal sampling of the activity also allows one to study the behavior of the sources in different frequencies by applying frequency transformation algorithms and source localization in the frequency domain. In this section we discuss some of the strategies that are used to deal with the temporal information that EEG/MEG measures provide.

5.1. Definition of components

In ERP research, a large number of studies rely on the 'component approach' to define the time point or period of interest for source localization. This approach has a long tradition in ERP waveform analysis where components are defined as peak and troughs of the waveforms at certain channels. The same approach is also used for the analysis of interictal epileptic activity, where the peak of a spike at certain electrodes is selected. This approach was reasonable at a time when electrode montages sparsely sampled the electrical field at the scalp. However, with the development and widespread use of multichannel systems, this approach is far less tenable. Concerning ERPs, different scalp sites have different peak latencies (and thus several generators), particularly for prototypical components (for detailed discussion see Skrandies, 2003; see also e.g. Foxe and Simpson, 2002; Murray et al., 2002; Picton et al., 2000). In order to circumvent this problem, the peaks of the Global Field Power (GFP, spatial root mean squared across all electrodes; Lehmann and Skrandies, 1980) are sometimes selected. GFP has the advantage of being a global measure of the electric field at the scalp, which is aided by the increased number of electrodes used, and is furthermore not biased by the experimenter's selection of a limited number or distribution of electrodes. A further strategy is the use of fixed time windows around certain 'traditional' components or around epileptic discharges and to average the activity over this period. The inverse solution is then applied to the mean map over this period.

In terms of source estimation, it is important to note that calculating an inverse solution from a mean map over time assumes that similar source(s) have been active and that therefore the mean of the maps is a good representation of the individual maps. This is a delicate assumption and minimally requires proof that the scalp topography is indeed indistinguishable and stable over the analyzed period. Interpretation of a mean topography (and the sources estimated from it) is impossible if the potential distribution changed during the averaged period (Picton et al., 2000). Such topographical changes have been shown for both long-lasting potentials such as the contingent negative variation (CNV) (Cui et al., 2000; Rohrbaugh and Gaillard, 1983) or the Bereitschaft-spotential (Cui et al., 1999), as well as for the very early sensory evoked potential such as the visual C1 component (Foxe and Simpson, 2002) and the period of an epileptic spike (Huppertz et al., 2001a; Lantz et al., 2003b). Therefore, source localization of averaged maps over the long period of sustained potentials (e.g. Kounios et al., 2001) or over the whole C1 period (Di Russo et al., 2002) without verifying map stability is not without risk. It can lead to artificial maps and thus to artificial sources. This principle also holds when comparing experimental conditions. If fixed time windows are used and the sources within these windows are compared between conditions, it has to be assured that the map topographies are stable over the period in both conditions. Simple latency shifts can result in coverage of a stable 'component' in one condition, but an inclusion of two different components with different map topographies, and by extension generator configurations, in the other. The spatiotemporal pattern analysis or 'segmentation' approach described in Section 5.1.1 solves this problem.

5.1.1. Microstate segmentation

An alternative to the direct analysis of the temporal dynamics of the estimated sources is to select time periods of interest for source analysis on the basis of the scalp potential maps. The basic idea underlying this approach is that different map topographies directly indicate different sources in the brain. By using statistical approaches that allow one to define *when* map topographies differ over time or between experimental conditions, periods where different sources in the brain are to be expected can be defined with minimal user-bias. A simple way to compare map topographies is to calculate the so-called Global Dissimilarity (Lehmann and Skrandies, 1980). It is obtained by calculating the square root of the mean of the squared differences between all corresponding electrodes, once these two maps have been recalculated against the average reference and normalized to unitary strength (i.e. divided by its own GFP). It is inversely related to the 'spatial correlation' between two maps (Brandeis et al., 1992). Global Dissimilarity ranges from values of 0 (map homogeneity) to 2 (map inversion). Using this measure, it is thus possible to quantify the stability of the maps over time and define the period over which map averages could be made (Fig. 5). It is likewise possible to use this measure to statistically compare scalp topographies between experimental conditions while maintaining EEG's temporal resolution (Murray et al., 2004a).

A striking observation when looking at this sequential dissimilarity curve of EEG and evoked potential data is that it always shows periods of several tens of milliseconds with very low values (i.e. similar topographies) interrupted by brief peaks (i.e. topography changes). When directly looking at the map series, it can be seen that the maps indeed remain stable during the periods of low dissimilarity and only increase and decrease in strength (as indicated by

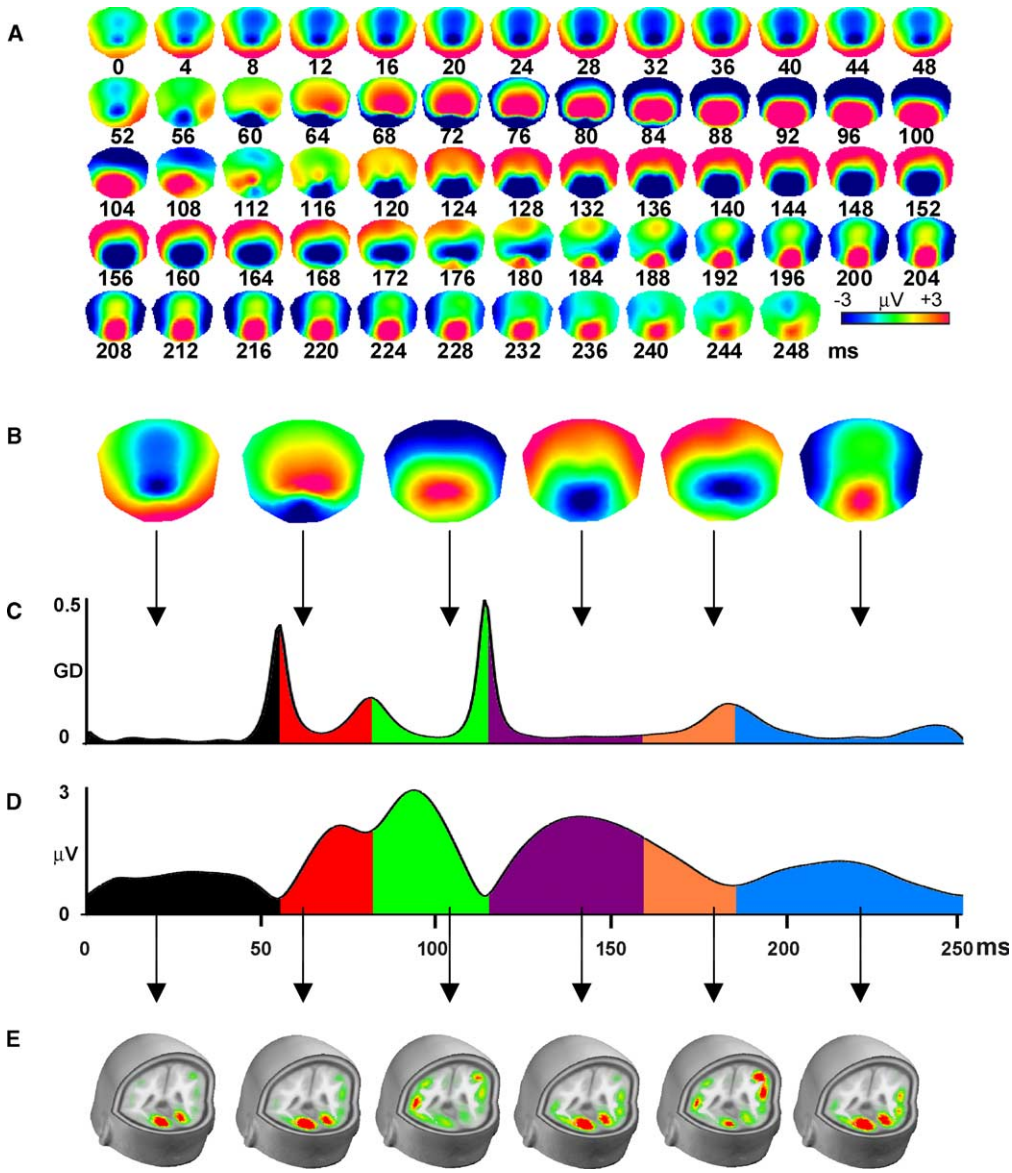

Fig. 5. Spatio-temporal ERP analysis. (A) Potential map series from an ERP in response to a reversing checkerboard and shown at 4 ms intervals. (B) Result of the spatial cluster analysis applied to the map series shown in A. A cross-validation procedure identified six maps as optimally explaining the whole data set. (C) Plot of the Global Dissimilarity (GD) for the ERP shown in A, which is a general measure of topographic similarity between two maps, here between maps of successive time points. High values indicate time points where the topography changes drastically. Colored areas under this curve denote the periods over which the above defined cluster maps best explained the data. Note that each of these maps is present for a certain time period (a functional microstate, Lehmann & Skrandies, 1980), and that transition from one stable topography to another generally corresponds to peaks of the Global Dissimilarity. (D) Plot of the Global Field Power (GFP) for the ERP shown in A, a measure of map strength. The segments defined by the cluster analysis are again indicated with colours under the curve. Note that map transitions generally appear during periods of low GFP and that these time points correspond to peaks in the Global Dissimilarity curve shown in B. (E) Distributed linear inverse solution (LAURA) of each of the six cluster maps. Only the sources in the posterior part of the head are shown here. While the most dominant activity is confined to the visual cortex during the first 80 ms (though other weaker sources are already present elsewhere), strong temporal and parietal sources are found already during the P100 segment. Feedback mechanisms might come into play at later periods with re-activation of the visual cortex.

increasing and decreasing GFP). The topography then abruptly changes (often, but not always, during a period of low GFP) to again remain in a new stable configuration (Fig. 5). Dietrich Lehmann and collaborators proposed that each of these obvious periods of stable electric field patterns represents a functional microstate of the brain or 'mind-state' during information processing (Lehmann, 1987). The mean duration of the microstates of around 80–120 ms (Koenig et al., 2002) is comparable with other reports on epochs of perceptual frames and suggests that these segments of near-stable brain activity are needed for conscious experience (John, 2002; Lehmann et al., 1998). Aside from this functional interpretation, the practical consequence of this observation in human EEG and ERP data is that it permits the summarization of the data by a series of time periods that are each described by a certain

distinct map topography. Since different map configurations must have been produced by different configuration of active (though multiple) sources in the brain, the reduction to such segments provides a means for defining the different activation patterns that can reliably be detected on the scalp surface. A statistical method based on *k*-means spatial cluster analysis and a cross-validation criterion has been proposed to define the optimal number of maps that best explain the whole data set and the time period during which they appear (Pascual-Marqui et al., 1995). By using fitting procedures based on spatial correlation analysis, a statistical method to define strength, duration, onset and offset of each of these maps and their specificity for different experimental conditions became possible (Pegna et al., 1997; for a review see Michel et al., 2001). Recently, a similar idea of component-definition has emerged (Spencer et al., 2001). However, we would note that the Principal Component Analysis that they propose has in fact been utilized in ERP research for precisely this purpose for quite some time (Skrandies, 1989).

Source localization applied to these segmentation maps is thus based on the statistical proof that the electric fields were different (and thus generated by different source configurations). Also, the method readily justifies the averaging over the period that given segmentation map was present because the maps were not significantly different. Temporal segmentation based on map topographies and subsequent source localization has been successfully applied in studies of visual and auditory perception (Ducommun et al., 2002; Khateb et al., 2000; Morand et al., 2000; Pegna et al., 1997, 2002), visuo-motor interactions (Thut et al., 1999, 2000a), language (Khateb et al., 2001, 2003; Ortigue et al., 2004), multisensory integration (Murray et al., 2004a,b), memory functions (Schnider et al., 2003) and for the definition of the primary ictal and interictal epileptic focus (Lantz et al., 2001b, 2003b) (for reviews see Michel et al., 1999b, 2001, 2004b).

5.1.2. Estimation of intracranial activation curves

The two above-described methods determine relevant time points or time periods based on the waveform or on the spatial characteristics of the electric fields and apply source analysis to these selected maps only. The alternative approach is to apply source localization to each time point and analyze the temporal dynamics of the source waveforms in the 3D-solution space.

The spatiotemporal multiple source analysis technique of Scherg and Von Cramon (1986) discussed in Section 3.1 in principle takes this approach. The basic idea is to estimate the strength of responses at a discrete number of user-defined equivalent current dipoles for each time point of a series of scalp potentials. This yields so-called source waveforms for each dipole that can themselves be analyzed in a like manner to surface waveforms (i.e. in terms of amplitude and latency). While this approach carries assumptions regarding the number and orientation of intracranial generators, it benefits from a capacity to provide information on the (possible) succession of activity across a network of brain areas, as well as the likely possibility of multiple recursive volleys of activity in one or multiple brain areas. This is particularly important for questions of sequential versus parallel and feedforward versus feedback brain processes. Indeed, this approach has been applied to the investigation of the visual (e.g. Di Russo et al., 2002; Foxe et al., 2003; Martinez et al., 2001; Murray et al., 2002; Simpson et al., 1995), auditory (e.g. Riedel and Kollmeier, 2003), and somatosensory (e.g. Buchner et al., 1995; Thees et al., 2003; Waberski et al., 2002) systems. While these studies provided several important proposals concerning the temporal properties of neuronal networks, it has to be kept in mind (see Section 3.1) that the user defines the number of sources that will present these networks and that this definition is not always necessarily correct (Achim et al., 1991; Miltner et al., 1994).

By using distributed inverse solutions, activation curves can in principle be calculated for each voxel (solution point) in the brain without an a priori decision about the areas that are expected to be active. Such millisecond-by-millisecond inverse solutions can be performed on averaged evoked potentials as well as on single sweeps. The latter approach has repeatedly been proposed by the group of Liu and Ioannides using magnetic field tomography (Ioannides et al., 2000; Laskaris et al., 2003; Liu et al., 1999). This single trial analysis is particularly appealing because it allows one to assign statistical significance to the activation at each time slice for each solution point in a single subject. This is done by statistically comparing the activation curve with the activation of this voxel during a baseline period. Of course, care has to be taken with regard to the number of statistical tests that are performed (No. of solution points × time). A pre-selection of regions and time periods of interest can reduce this problem (e.g. regions of interest defined by the maxima found in the inverse solution of the averaged data (Ioannides et al., 2000)).

In principle, the application of distributed inverse solution on each time point of the spontaneous activity attempts to perform intracranial recordings non-invasively, i.e. it attempts to estimate the activation curve that would be measured when placing an electrode within the brain. This is, however, only partly the case with the conventional inverse solutions that estimate dipole strength in the brain. Direct intracranial recordings do not measure dipoles but they measure local field potentials. Searching for steep potential gradients or phase inversions allows one to make inferences on source locations. As introduced in Section 3.2, we developed an alternative source model (ELECTRA) that directly estimates local field potentials from the surface data. This inverse solution approach is particularly suited to estimate the temporal behavior of the activity in different regions because the scale independent waveshape analysis of potentials circumvents one basic limitation of distributed inverse solutions, which is the uncertainty in estimating source amplitudes (Grave de Peralta et al., 2004a).

In previous studies, we have compared these estimated local field potentials with direct intracranial recordings in epileptic patients and could demonstrate close resemblance of the real measured and the estimated potential waveforms (Michel et al., 1999a; Thut et al., 2000b).

Single sweep analysis using the ELECTRA approach has also been used in a recent study that evaluated possible correlations between pre-stimulus activity and reaction time to the stimulus (Gonzalez Andino et al., 2004). Based on previous primate studies, we suggested correlations between pre-stimulus frequency oscillations (particularly in the Gamma range) and reaction time (Engel et al., 2001). To study such frequency oscillations we transformed the scalp EEG traces of each single sweep of each subject to intracranial potentials at 4024 discrete voxels homogeneously distributed on the gray matter. We then performed wavelet-based time-frequency analysis (see also Section 5.2) for each gray matter point for the pre-stimulus period of 300 ms. Finally, correlation analysis was performed between the reaction times and the energy for each frequency, solution point, and subject. This analysis revealed significant correlations in more than the 85% of the subjects between the energy in the gamma band (above 30 Hz) and reaction time mainly in right frontal and parietal brain areas, areas that have previously been identified as belonging to an alerting attention network. This example illustrates the possibilities that are in our hands with these new distributed inverse solutions to study intracranial time-frequency activations non-invasively.

5.2. EEG source imaging in the frequency domain

In clinical applications, many researchers are interested in localization of sources for different frequency bands, since spectral analysis of the EEG has been proven to provide important information on pathologies related to sleep disorders, epilepsy, psychiatric diseases and psychopharmacological substances (Dumermuth and Molinari, 1987). With the use of multichannel EEG systems, topographic maps of the power distribution in certain frequency bands have become popular and have been proposed as a method to quantify normal and pathological brain states (the so-called qEEG; Duffy et al., 1981; John et al., 1977). The obvious next step has consisted of attempts to localize these different EEG rhythms. Unfortunately, source localization procedures cannot directly be applied to power maps, because a) power maps represent squared potential values and thus polarity information given by the phase angles is lost, and b) power maps are reference-dependent (Lehmann, 1987). However, methods exist that allow for source analysis in the frequency domain. We proposed one such approach that we called FFT Approximation (Lehmann and Michel, 1990). The FFT Approximation calculates the Fast Fourier Transform (FFT) over a certain time epoch for each channel and then uses the complex values of all electrodes to calculate the first principal component map for each frequency point. These maps keep polarity information and can thus be subjected to source localization algorithms. Subsequent studies extended the method by showing that direct methods for frequency-domain source localization on the basis of covariance matrices are possible (Lütkenhöner, 1992; Tesche and Kajola, 1993; Valdes et al., 1992). In several experimental and clinical studies these techniques have been used to localize the sources of the different frequency bands (Michel et al., 1992), to assess spectral changes related to different mental states (Harmony et al., 1995; Isotani et al., 2001; Lehmann et al., 1993; Tsuno et al., 2002), to define EEG changes in psychiatric and neurological patients (Dierks et al., 1993a,b, 1995; Huang et al., 2000; Lubar et al., 2003; Michel et al., 1993), to characterize effects of psychopharmacological agents (Frei et al., 2001; Kinoshita et al., 1994; Michel et al., 1995) or to define the dominant frequency and its sources at onset of an epileptic seizure (Blanke et al., 2000; Lantz et al., 1999).

An interesting alternative to the FFT-based source localization is the source analysis applied to the time-frequency representation of the signal. The time-frequency representation (TFR; Lin and Chen, 1996) has two major advantages as compared to the conventional FFT. First, the TFR does not assume the signals are stationary over time and can thus be applied to non-stationary EEG periods. Second, TFR have much higher time resolution, allowing the tracing of frequency changes in the subsecond range. This allows frequency source analysis of short-lasting paroxysmal activities such as spikes, *K*-complexes and evoked responses. Sekihara et al. (1999) presented an approach for time-frequency source localization that was based on the application of the MUSIC algorithm (see Section 4.1) to the average of the time-frequency matrix over pre-selected regions of interest. Using computer simulations, they showed that the method allows estimating the locations of neural sources from each time-frequency component for given regions. We recently proposed an alternative method that consists in a generalization of the FFT Approximation to the TFR and calculation of a distributed linear inverse solution (ELECTRA, see Section 3.2) to each time-frequency point (Gonzalez Andino et al., 2001). Using computer simulations as well as applying it to data of epileptic seizures indicate that this method allows for a more spatially confined source localization, because the potential pattern specific for certain time-frequency pairs are simpler than those appearing at single time points but for all frequencies (Fig. 6). In addition, noise and signals can potentially be better separated in the time-frequency domain. This is restriction-free in contrast with approaches based on principal or independent component analysis.

6. Post-processing of EEG source images

While clinical EEG source imaging studies typically apply source localization algorithms to the individual

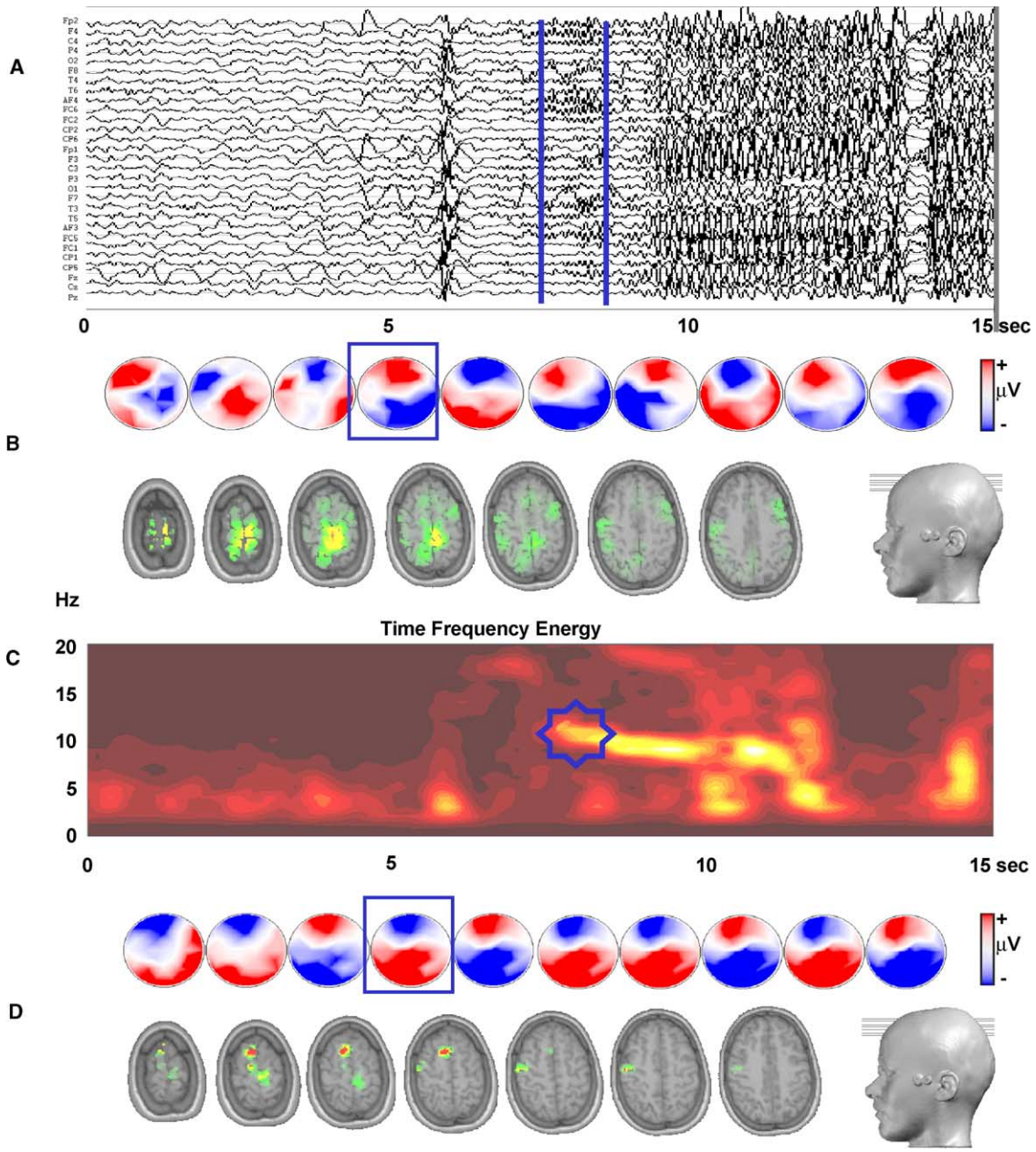

Fig. 6. Time-frequency analysis of an epileptic seizure. (A) 29-channel broadband (1–30 Hz) EEG of the beginning of a secondary generalized partial seizure. Details of the patient are reported in Seeck et al. (1998). Subsequent intracranial recordings suggested a left frontal focus. (B) (top) Sequential Potential maps during the time period marked in A are shown at 8 ms intervals. That framed in blue was subjected to the LAURA distributed linear inverse solution (bottom). Note the topographic variability of these maps and the extended medial fronto-parietal sources observed for this map. (C) Time frequency energy plot of the seizure shown in (A). High energy is observed at seizure onset with a frequency starting at ~10 Hz that decreases to ~7 Hz as the seizure evolves. (D) (top) Potential maps for the 9 Hz component during the same time period as in (B). Note the topographic stability of these maps, though with variation in polarity, which contrasts the varied scalp topography of the broadband EEG shown in (B). The map framed in blue was subjected to the LAURA distributed linear inverse solution (bottom). Source imaging of this specific frequency yielded sources that were focal to the left frontal lobe (see Gonzalez et al. (2001) for details).

patient's data, most experimental studies limit source localization to only the group-averaged data in order to illustrate putative sources at certain time points/periods (using spatiotemporal models) or their activation sequence over time. In this case, no indication about the statistical reliability of these sources or their correspondence to the actual source locations in the individual subjects is provided.

By applying the source localization algorithm to the recordings of each individual subject in a group study, statistical analyses can be performed. When using single dipole localization algorithms, statistical tests can be applied to the dipole location along each of the 3 Cartesian axes. This allows conclusions about possible significant shifts of the dipole source in one or several directions (e.g. Dierks et al., 1995; Lehmann et al., 1993; Michel et al., 1992, 1995).

Even if the single dipole itself may not adequately or accurately represent the actual sources in case of distributed activation patterns, a statistically significant shift of the 'center of gravity' of all sources due to an experimental manipulation or due to a certain drug or disease can provide indications of a change of the global activity distribution within the brain. Whether this analysis also allows interpretation about the brain areas that have been differently activated depends on the reliability of the single source assumptions. If the only conclusion were that source configuration changed, we would note that such information could readily be determined from topographic analyses of the scalp-recorded data described above in Section 5.1.1. In this case, the source estimation would not provide additional interpretational power or neurophysiological information.

With the use of distributed inverse solutions, statistical analyses similar to the ones proposed for other tomographic functional images can be applied. In fMRI studies, the so-called statistical parametric mapping (SPM) method is most commonly used. After spatially normalizing the individual fMRI images to a standard brain, a *t* test between two conditions for each voxel or region of interest is performed to determine areas of significant response differences. Several studies have applied a similar statistical procedure to the tomographic maps derived from the distributed inverse solution of each subject. A detailed step-wise description of SPM-type statistics for tomographic EEG source images is given in Park et al. (2002). It includes source estimation on the individual BEM-modeled MRI, image reconstruction, Gaussian smoothing, spatial normalization, intensity normalization and statistical parametric mapping. Using this complex method, the authors could demonstrate reductions of the mismatch negativity in schizophrenic patients as compared to healthy controls in the left superior temporal and inferior parietal gyrus. A simpler way for comparison of 3D source images is normalizing the maps to a standard head shape configuration using spherical spline interpolation (see above), solving the inverse solution for this general head model using the same solution space for all subjects, and then performing *t* test statistics for each voxel of the solution space (e.g. Fallgatter et al., 2003; Kounios et al., 2001; Michel et al., 2004b; Murray et al., 2004a). Similar to the analysis of fMRI data, an important question concerns the adjustment of

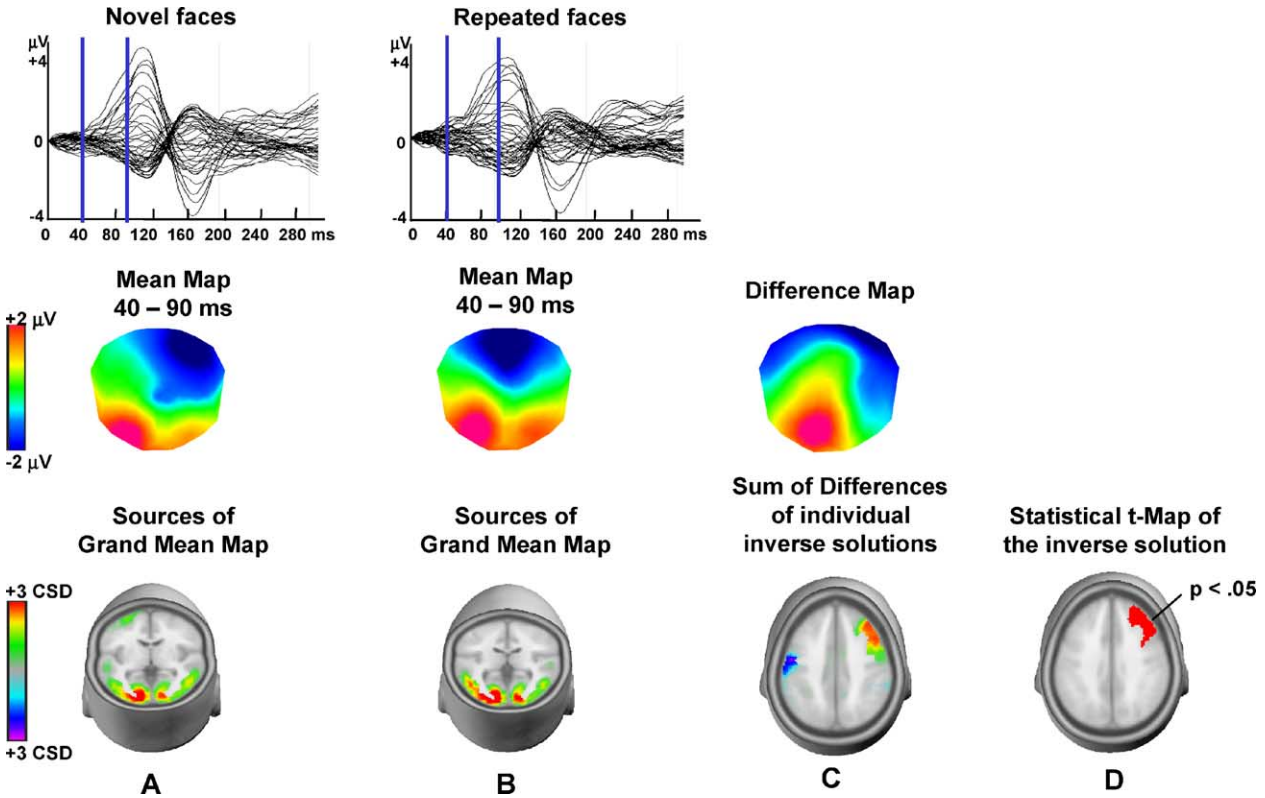

Fig. 7. Statistical analysis of distributed inverse solutions. The top panels show the group-averaged ($N = 7$) ERPs in response to a face recognition task with waveforms from the 41 electrodes superimposed. Subjects discriminated initial and repeated face presentations (see Seeck et al. (1997) for details). The middle panel shows the scalp topography of these group-averaged data for the 40–90 ms period. Spatial cluster analysis further revealed a significant difference in scalp topographies accounting for responses to initial and repeated face presentations during this 40–90 ms period at an individual subject level. The bottom panel displays the LAURA inverse solution of these group-averaged scalp topographies maps. These reveal maximal activity in the occipital lobe. However, the mean of differences of the individual inverse solutions revealed main differences in right frontal and left fronto-parietal regions during this early period. The statistical analysis using voxel wise *t* tests of the individual inverse solutions revealed that the right frontal difference was significantly more active for novel as compared to repeated faces. Thus, while occipital activity dominates during this early period, the statistical analysis reveals subtle, but significant differences in frontal areas between the two conditions (see Michel et al. (2004b) for details).

the statistical results to an appropriate significance criterion. The correction for multiple tests has to be based on the number of independent measures. In EEG source imaging, this is not the number of voxels (solution points). Rather, the number of electrodes on the scalp constitutes the number of independent measures. Therefore, the *P*-values should be corrected by the number of electrodes (Grave de Peralta et al., 2004a; Murray et al., 2004a).

The statistical analysis of the distributed inverse solution maps is straightforward. It has several advantages as compared to the inverse solution maps of the group-averaged data. For one, group-averaged data can be dominated by source maxima that are identical in two experimental conditions (for example, the occipital sources in early visual components). Consequently, weak, but consistent differences in other areas risk being overlooked or ignored due to thresholding. Secondly, distributed inverse solutions can produce spurious sources, particularly when applied to noisy data. Strong regularization operators must often be applied. However, such spurious sources usually do not survive statistical analysis due to their inconsistency across subjects. Thus, the unresolved and delicate issue of regularization when calculating the distributed inverse solution can be minimized through such statistical analysis. Finally, with paired data, the relevant information bears on the within subject differences rather than the separate averages over the conditions. These important aspects are shown in Fig. 7. It compares the ERP of two conditions (novel vs. repeated faces; see Seeck et al., 1997) at a time period between 40 and 90 ms, identified as being represented by statistically different map topographies (for details, see Michel et al. (2004b)). The mean maps over this time period as well as the difference map between the two conditions suggest a more left lateralized negativity for novel as compared to repeated faces. The distributed inverse solutions of the mean maps revealed dominant sources in the primary visual cortex for both conditions. No other sources were apparent when thresholding the data on these dominant activities. However, the sum of the difference between the inverse solutions of each subject for this time period revealed a right frontal positivity and a left fronto-parietal negativity. A paired t-test for each of the nodes showed the right frontal difference to be significant. Thus, the statistical analysis of the inverse solution revealed differnces in brain areas that are not visible in the mean images of each of the conditions.

7. Conclusion

EEG source imaging has made tremendous progress in recent years to provide statistically based neurophysiological interpretations of scalp recordings. To achieve such requires that researchers abandon ambiguous waveform analyses and the phenomenological description of grapho-elements. Instead, comprehensive analyses of the electric field at the scalp must be conducted that serve as the basis for estimating the sources underlying these fields. Many recent publications using new source analysis techniques have shown that this approach allows one to consider the temporal and spatial dimension of brain activity simultaneously. There is no doubt that this will lead to important new insights into the properties of cerebral neural networks. In addition to the progress in analysis tools and data interpretability, multichannel EEG systems have become readily affordable for nearly all clinical and research laboratories. However, a potential risk of this ease-of-access to the equipment is that it may not be paralleled by researchers fully understanding or appropriately applying these analysis tools. As a result, EEG as a field of research may become divided between those who apply only a minimal level of analysis and those who fully capitalize on the interpretational power of the technique.

Several pre-processing steps must be carefully considered and conducted, particularly in light of the extent of experimenter bias that has historically weakened EEG analyses. These start with the proper selection of the electrode montage (both for recordings and subsequent analyses) and the measurement of their location (including the reference). They continue with the selection of the time point, time period, or the frequency window. The selection of the inverse solution is, of course, the most important step. While we are extremely hesitant to proclaim a particular source localization algorithm as 'the best', we would emphasize distinctions among different approaches in terms of their a priori constraints and assumptions and would favor those that are heavily influenced by physiological principles over those that are heavily influenced by the experimenter (either directly or through the implementation of particular mathematical constraints). This is particularly important when realistic head models and displays of the sources on MRI images are used. While such images are as seductive as those of other functional imaging techniques (Ebersole, 1999b), they cannot simply be considered as the unequivocal truth. Such notwithstanding, recent work has shown that they may indeed be more warranted than traditionally thought. The spatial resolution of EEG, often considered as its biggest limitation, might actually closely approach that of standard (spatially smoothed) fMRI results. The combination of high resolution EEG, modern inverse solution approaches, realistic head shape models, and proper post-processing techniques are already leading to the use of EEG as a true neuroimaging procedure. Future research will probably be devoted to even more reasonable definitions of a priori constraints based on anatomical, physiological, and biophysical knowledge, in conjunction with the incorporation of information from other imaging modalities. This particularly concerns the more detailed incorporation of anatomical information in the physical models such that functional differences of anatomically close areas are taken into account. Another line of research that might be promising is the combination

of diffusion tensor imaging and EEG source localization. Showing direct cortical connections between areas might strengthen interpretation of the temporal succession of activity seen in the source analysis. Likewise, information about functional connectivity could be incorporated as a priori information in inverse solutions that take temporal aspects directly into account. Indeed, the inclusion of the temporal dynamics of brain activity in the inverse models is still largely missing, even though the temporal resolution of the EEG is the major advantage as compared to other functional imaging modalities.

In view of the current status of the field reviewed here and the promising future trends, there is no question that EEG and ERP source imaging is rapidly replacing conventional analyses of EEG and ERP traces and the search for peaks and troughs in these waveforms.

Acknowledgements

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