# Use of Prior Knowledge in Brain Electromagnetic Source Analysis

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Summary: Using multichannel measurements of EEG and/or MEG, macroscopic source activities can be estimated in the human brain using brain electric source analysis (BESA, Scherg 1990). If a discrete number of brain areas is active, functional brain images which depict the locations and orientations of equivalent dipole sources as well as the dynamics of the local macroscopic currents can be obtained from such data - in principle - without external knowledge. However, given a certain number of sources or 'neural masses' (Freeman 1975) which contribute to an event related response (ERP), it can be difficult to find the correct solution due to background noise in the data and distortions from the head model. Prior knowledge based on anatomy and physiology can be useful to constrain spatial or temporal parameters of the model and to define better cost functions for fitting locations and orientations. An analysis of the auditory evoked N100 complex and of the auditory mismatch negativity (MMN) is presented which illustrates the use of spatial constraints. Also, the use of a modified cost function is demonstrated which limits source currents in certain time intervals.

Key words: EEG, Evoked potentials, Dipole modelling, Source analysis, Source imaging.

## Introduction

Dipole source analyses of evoked potentials (EP) and magnetic fields (EF) recorded synchronously in multiple channels have demonstrated that multiple dynamic source processes underlie the gross electromagnetic activity measured from or over the human scalp after sensory stimulation in all modalities (Scherg 1984; Scherg and von Cramon 1985 a,b, 1986; Maier et al. 1987; Scherg et al. 1989a,b; Baumgartner et al. 1989; Buchner and Scherg 1991). The variation of EP waveforms and peak latencies with the location of the recording site is an indicator for the presence of the overlap from multiple sources (Scherg 1990; Scherg and von Cramon 1985a). In order to resolve this overlap a model must be defined that can decompose the surface waveforms in a way which will delineate and separate the dynamic source processes of each activated brain area.

### The Spatio-Temporal Dipole Model

The idea of a dynamic multiple source model derives from the functional organization of the human brain and

from the physical properties of dipole vector fields (Scherg and von Cramon 1985a,b, 1986). Scalp electrodes sense an equivalent dipole field from each activated area or neuronal mass (Freeman 1975) which is functionally distinct, i.e., which has a specific event-related dynamic pattern of activation. This macroscopic view holds whenever the extent of this neuronal mass is small in comparison to the distance of the recording site. Simulations have shown that this is approximately true for typical sizes of cortical sensory areas (Vaughan 1974; De Munck et al. 1988; Scherg 1990). By creating experimental conditions in which only a limited number of brain areas is activated, e.g., in evoked potential paradigms, the inverse problem can be solved in principle if there is a sufficient number of recording channels and if an appropriate model representation can be found for each activated area that contributes significantly to the scalp potentials (Scherg and von Cramon 1985a; Scherg 1990; Scherg and Picton 1991).

A direct linear transformation of the surface potentials of the olfactory bulb to equivalent deep source activities was first proposed by Freeman (1980) as a kind of "software lens". In 1984-86 we presented a spatio-temporal model with multiple stationary dipoles and variable dipole strength modelling the gross source current in the vicinity of and parallel to each source dipole (Scherg 1984; Scherg and von Cramon 1985a,b, 1986). This model can be formulated either in terms of smooth parametric functions $s_i(t)$, describing the magnitudes of the source activities e.g., by peak latencies and amplitudes:

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$$u_k(t) = \sum c_{ki} \; s_i(t) \qquad (1)$$

or by discrete time series in terms of matrix algebra (Achim et al. 1988; Scherg 1990) as

$$u_{kt} = \sum c_{ki} \; s_{it} \qquad \text{or} \qquad U = C * S \qquad (2)$$

where $u_k(t)$ is the predicted potential (or magnetic field) at the recording location $l_k$ ($k$=1....NL), $s_i(t)$ the source current strength of source i (i=1...NS) and $c_{ki} = c(l_k, r_i, o_i)$ the transmission coefficient describing the volume conduction and contribution of the signal $s_i$ of source i with location $r_i$ and orientation $o_i$ to the signal $u_k$ recorded at location $l_k$. This transmission relation holds for any time t (t=1.....T). Such a stationary dipole model has the advantage of allowing for a separation into a time independent, geometrical or anatomical part, the volume conduction model C, and into a dynamic part S describing the compound physiological activities of the NS equivalent sources following the external stimulus (Scherg and Picton 1991).

The linear relationship between source strength and surface signals, as required by electrodynamics, is evident from (1) and (2). As originally proposed by Okamoto et al. (1983) for the inverse problem in electrocardiography, this linear relationship can be used to get a fast best fit estimate of the source activities using a linear operator, i.e., the pseudoinverse of C, to invert (2). In this manner the linear source activity part $s_{it}$ is separated from the spatial weights $c_{ki}$ which depend nonlinearly on the dipole parameters $r_i$ and $o_i$ (Scherg 1990). The source locations $r_i$ and dipole orientations $o_i$ can be estimated by iterative methods minimizing the residual variance between the measured and modelled surface signals by summing the squared difference over all recording sites and time points (Scherg 1984). There are various approaches to accomplish this iteration (Scherg and von Cramon 1986; Maier et al. 1987; Achim et al. 1988; Baumgartner et al. 1989; De Munck 1990; Scherg 1990), but they are all based on the same linear model (2) and the same least squares criterion minimizing the residual variance (RV). Hence, they lead - in principle - to identical solutions.

## Problems in Finding a Multiple Source Solution

In contrast to our original spatio-temporal dipole model (Scherg 1984; Scherg and von Cramon 1985a,b), there are no physiological constraints on the waveforms of the source activities in the direct linear approach (2). Therefore the linear decomposition of a set of surface waveforms into multiple source activities has a much larger number of free parameters, i.e., independent

source current strengths for each time point. This may lead to a number of problems when equivalent sources are iteratively located within the volume conductor model.

First, when there are several distinct source processes within a small brain volume an initial approximation can be found easily by using a regional dipole source to project all the local source currents onto a 3-dimensional dipole vector field (Scherg and von Cramon 1986). However, this leaves the orientations of the 3 axes of the local coordinate system indeterminate and, hence, the source processes of the local volume are not fully resolved. The residual variance criterion does not change when rotating the axes and is only minimally affected when the dipoles are moved to their appropriate locations, as is known from simulations (Scherg 1990; Scherg and Picton 1991) and real data (Scherg and von Cramon 1986; Scherg et al. 1989a). This means that the best solution in the physiological and anatomical sense is embedded in a flat sea of low residual variance which may exhibit a large number of local minima surrounding the global minimum.

Second, with more sources to be modelled the probability increases that the inverse fit algorithm gets trapped in these local minima. This necessitates the development of better search algorithms which can escape from local minima, e.g., the method of simulated annealing (Haneishi et al. 1989).

Third, two factors, a) inaccuracies in the volume conductor model, i.e., in the estimation of the vectors of the C-matrix, and b) biological noise in the data, may prevent the complete separation of the source processes and may affect the relative depths of the global and local minima. Thus the global minimum as defined mathematically may not relate directly to the underlying physiology. The physiological solution may correspond to a local minimum or to no minimum at all. It may therefore be desirable to apply physiological criteria to compare the various source configurations that the fitting procedure has arrived at from different starting conditions.

This paper addresses the first and third of these problems by considering a priori knowledge of the physiological processes and the anatomy of the system under study. Such knowledge can result in constraints imposed on absolute or relative locations, on orientations and on source waveforms. Further, the cost function controlling the iterative process can be modified to include criteria other than the residual variance minimum.

## Methods

This study presents a simulation of bilateral source activity in the cingulate gyrus (Figure 1) and a reanalysis of grand average auditory evoked N100 and mismatch
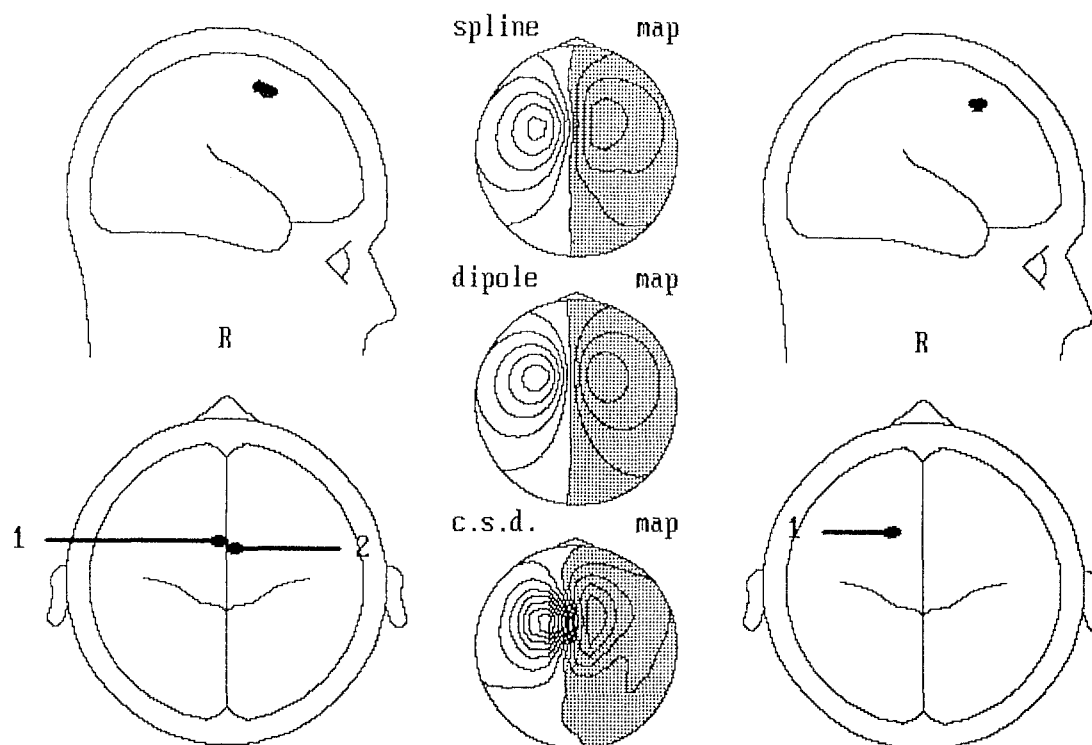
Figure 1. Simulation of the scalp potentials (using the BESA program, Scherg 1990) due to 2 dipole sources at both sides of the interhemispheric cleft as viewed in axial and sagittal projections (model on the left). The two sources are separated by 10 mm. The dipole moment of source 2 was taken to be antiparallel to and 60% of dipole moment 1. The spherical spline maps (Perrin et al. 1987) of the scalp potential (top) and of the scalp current source density (bottom) suggest the presence of a single source and do not reveal the underlying 2-dipolar source structure. In fact, a single source (model on the right, dipole map in the center) gives an excellent explanation of these maps (RV=0.23%), but it locates 12 mm lateral and 6.4 mm anterior from the larger dipole 1 of the original 2-dipole model. Conversely, the potential due to a single source in a real head may be distorted as depicted and the 2 dipole model could better account for this because of its intrinsic higher order components (see text). However, a 2-dipole model with such an interference pattern may not be acceptable on physiological grounds.

negativity data, presented in detail previously (Scherg et al. 1989a; Scherg and Picton 1991). The simulations and analyses were undertaken to illustrate the usefulness of constraints and of a modified cost function.

## Definition of Spatial and Temporal Constraints

In order to find a multiple source solution, dipole locations and orientations must be fitted in an iterative procedure, i.e., they are the independent parameters of the model. In each step dipole magnitudes over time are the dependent variables determined by (2). The number of free parameters can be reduced by letting the location and/or orientation of one source depend on another, for example, by requiring symmetry between hemispheres.

More generally, if the relative distances between various parts of the cortical gyri are known from an image of the individual anatomy, e.g., from MRI, this knowledge can be used to constrain one dipole to stay at a relative distance from another. As another form of a spatial constraint we may limit one source or a set of sources having relative location constraints to move as a joint source configuration along a certain axis, at a certain depth or within a plane or a circumscribed volume during the fit, e.g., the supratemporal plane in the case of auditory EP's. Similarly, orientations can be constrained to match predominant aspects of cortical gyri. The most simple form of such a constraint would be radial and tangential dipoles.

The definition of temporal constraints is obvious for

the spatio-temporal model (1), for which latencies or peaks of the source current $s_i(t)$ can be held constant or within certain ranges during the fit. For the linear model (2), it is only possible to constrain two or more sources to having the same waveshape, however with independent overall magnitudes. This may be justified, for example, if similar source processes occur in both hemispheres. On the other hand, the dependent waveshapes of the source activities as estimated during the fit procedure, may influence the fit if an appropriate criterion is implemented in the cost function.

### Definition of a Physiological Cost Function

To reduce potential interferences between the source currents which are estimated without any constraint in the linear model (2), one might wish to define a "cost function" to add certain penalties for various kinds of interference. Such a composite cost function can then be used instead of RV in the minimization procedure. Take for example the cost function

$$CF = (a*RV + b*Crit\ 1 + c*Crit\ 2 + d*Crit\ 3)/(a+b+c+d)$$

(3)

with 3 criteria in addition to RV and adjustable weights a-d for each criterion.

For situations as described in Figure 1 (see results) a criterion which favors small magnitudes of the source currents proved helpful. It was defined by the energy of the source potentials, i.e., the squares or their magnitudes summed over all sources and time points, divided by the total variance of the data set. This energy criterion (EC) has similarities to the minimum norm estimate required for distributed source models (Ioannides et al. 1990). However, it must be balanced against the influence of source depth on dipole moment magnitude. This can be achieved effectively by normalizing the columns of the transmission matrix C. Otherwise source dipoles tend to be shifted to more superficial locations by the energy criterion. Setting the weight of EC to 10% effectively prevented large interactions in many source analyses of multichannel evoked potentials.

For physiological reasons the probability is small that two functionally distinct sources should exhibit identical source activity waveshapes. Especially for the sensory components we might expect specific sequential onset times for the components. If we have an hypothesis about the periods throughout which sources are predominantly active, these periods may be defined as temporal constraints for each source or for a subset of sources. Then the variance in source activities outside of these periods can be taken as a penalty measure when divided by the

total variance in the data set. This variance criterion (VC) can be used to maintain a temporal separation between two or several source components. Other morphological constraints were conceived to be used as additional criterion in (3), for example penalties on proximity and collinearity of dipole pairs, but these have not yet been sufficiently tested.

## Results

### Simulation of Activity in Adjacent Cortical Folds

An example of a problem requiring additional knowledge to find an appropriate solution is simulated in Figure 1. If there are multiple sources in adjacent areas with dipole moments that are nearly parallel or antiparallel, e.g., sources in the cingulate gyri of both hemispheres (Figure 1) or in the Heschl's gyri of the supratemporal plane (Figure 2), an interference of estimated source current patterns can occur. A 1-dipole solution might be stable, whereas a 2-dipole solution might result in a dipole pair with large antiparallel dipole moments and highly similar source potential waveforms.

In analogy to sources in the cingulate gyri, a noise free forward solution was computed for 2 dipole sources at both sides of the interhemispheric cleft at a separation of 10 mm and with antiparallel dipole moments for a 33-electrode montage covering the upper part of the head. The right hemispheric dipole moment was set to 60% of the left dipole and source activity was assumed synchronous. The scalp potential distribution showed a dipolar pattern with a small distortion as observed in real data (compare spline and current source density maps in Figure 1, neither of which resolve the true simulated source configuration!). Indeed a single dipole source explained 99.77% of the data variance. However, there was a substantial difference in source locations between the 1- and 2-dipole models. The single source located 12 mm more lateral and 6.4 mm more anterior in comparison to the stronger left hemispheric dipole of the 2-dipole configuration.

Let us consider the converse situation and assume that the scalp map stems from a single dipole source. In this case the 2-dipole configuration has a net dipole moment similar to the single source. Looking at this configuration in terms of a description by a multipole series, it contains significant quadrupolar and higher order components. These can model unexplained variance at more remote scalp sites as well as distortions in the potential distribution due to inaccuracies in the head model. In this case the 2-dipole model would have to be considered as the non-physiological model as indicated by the large interference of the 2 dipole sources. In the presence of noise, however, differences in RV between such alternative
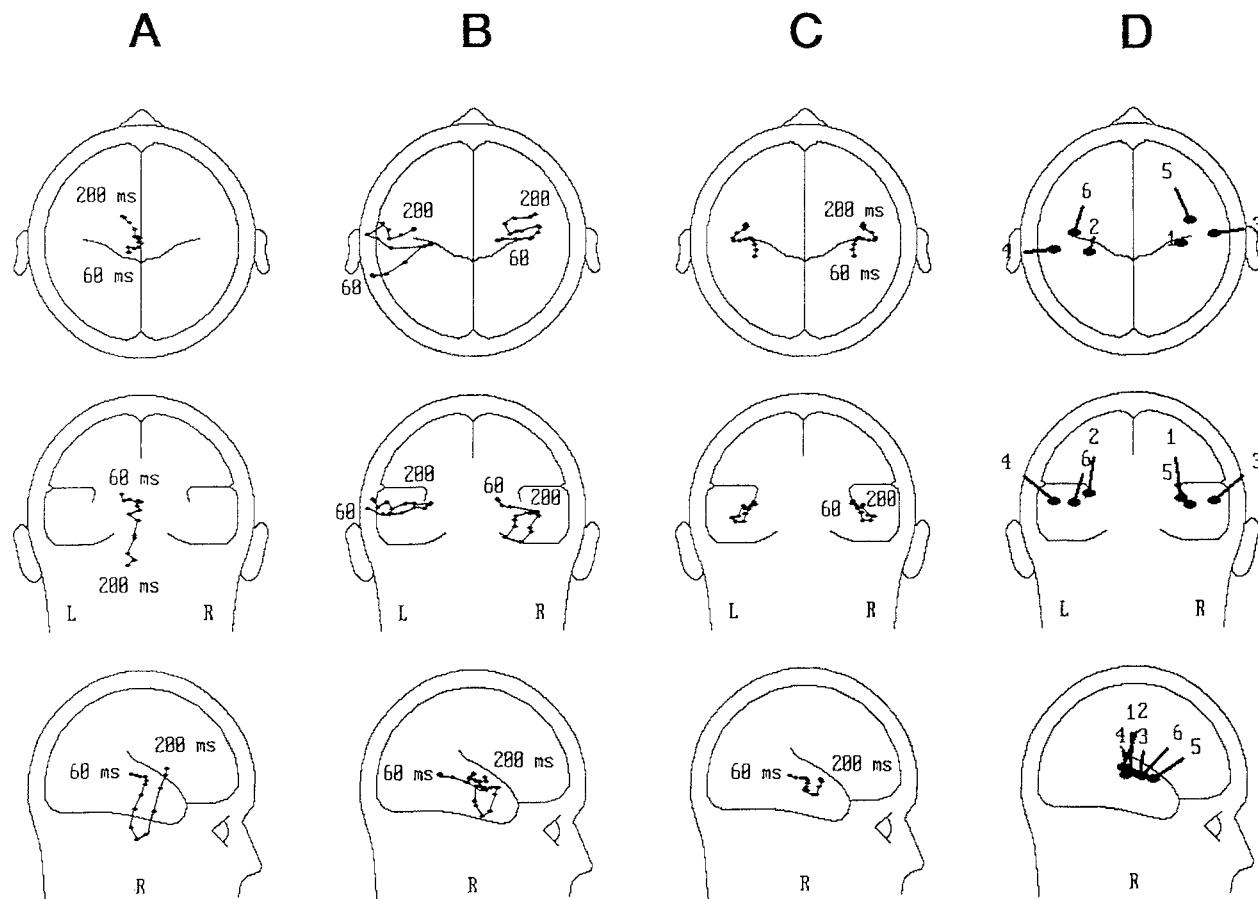
Figure 2. Comparison of moving (A-C) and spatio-temporal (D) dipole analysis. Data are a grand average of auditory evoked N100 over 5 normal subjects. Moving dipole locations (A-C) are plotted every 10 ms in axial, coronal and sagittal views. Orientations (bars) are plotted only for the spatio-temporal dipoles (D) with unit magnitudes (bars). A: single moving dipole, non-physiological solution. B: unconstrained solution for 2 moving dipoles, unstable. C: 2 moving dipoles constrained to spatially symmetric location. D: spatio-temporal 6 dipole solution showing anterior-posterior location difference between hemispheres (see text).

models may be too small to decide which model is appropriate. We would therefore have to consider external knowledge to confine the solution either by imposing spatial constraints - e.g., a bilateral source which keeps a minimum distance or which has some relative distance as defined from the individual MRI scan.

## Spatial Constraints in an Analysis of Auditory Evoked N100

An analysis of the auditory evoked N100 and sustained potential using spatial constraints is presented in Figure 2. For this 14-channel grand average data set of 5 normal subjects a 6 dipole solution (Figure 2, D) has been presented in detail previously (Scherg and Picton 1991).

It separated the onset N100 (dipoles 1 & 2), the lateral N150 (dipoles 3 & 4) and the more anteriorly originating sustained potential (SP, dipoles 5 & 6). In Figure 2 this solution is compared with a moving dipole fit with and without the spatial constraint of hemispheric symmetry.

A single moving dipole gave a satisfactory fit only for the peak of N100 (RV=2.5% at 100 ms) but not during the 120-200 ms epoch (RV=7.5% at 140 ms). In addition, the trajectory of the equivalent dipole location through the center of the brain was inconsistent with the anatomical location of relevant auditory structures (Figure 1, A). Allowing for a second independent dipole resulted in a fit of 12 parameters to the 14 voltage values at each time instance (RV=0.06 at 100 ms; 0.67% at 140 ms). This fit showed bilateral activities in the temporal lobes. How-
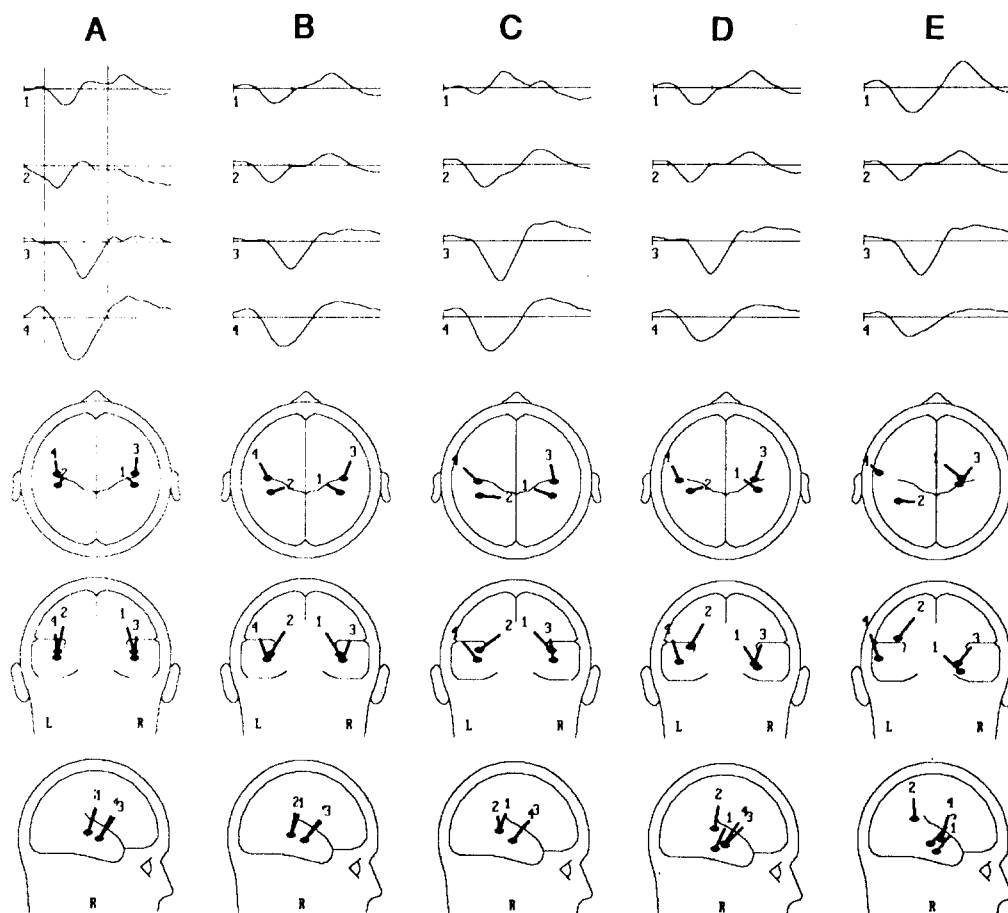
Figure 3. Comparison of 5 solutions of a mismatch negativity data set (Scherg et al. 1989a) using different constraints and cost functions. The top of each column depicts the time varying dipole magnitudes of the 4 sources required for a satisfactory explanation of the variance over time. Vertical bars mark the computation interval for the fit (48-192 ms, displayed epoch 350 ms poststimulus). Tick marks in solutions B and D indicate the periods used for the VC criterion. Below, unit dipoles show locations (dots) and orientations (lines) of the 4 sources in axial, coronal and sagittal views. The solutions A-E differ by the constraints and the cost function weights applied during the fit procedure (see text). A: original, interactively obtained solution. B: symmetric location, weights: EC & VC 30%, RV 40%. C: symmetric location, weights: RV 100%. D: weights: EC & VC 30%, RV 40%. E: weights: RV 100%.

ever, the dipole trajectories were not smooth and assumed locations outside of the brain (Figure 2, B). When dipole locations were constrained to hemispheric symmetry, the fit required only 3 location parameters and resulted in more stable dipole trajectories (Figure 2, C).

However, due to the inherent limitation of the moving dipole model we cannot ask further questions to the data, e.g., whether multiple processes overlap or whether the location of comparable source activities is more posterior in the left as compared to the right supratemporal plane. In contrast, these questions could be asked using the spatio-temporal approach (Figure 2, D). For example, we can constrain the 3 dipoles underlying N100, N150 and

SP to be located at constant relative distances along the supratemporal plane. In addition, we may require the source waveforms of the respective processes to be of similar waveshape in both hemispheres. Using these constraints with relative distances as shown in Figure 2 D, the location of the left hemispheric sources was found to be more posterior than the right hemispheric sources by 10 mm. The residual variance over the whole 60-200 ms interval was 0.4% with symmetric waveshapes and only 0.12% with independent waveshapes (RV=0.10% at 100 ms; 0.13% at 140 ms).

## Cost Function in an Analysis of the Mismatch-Negativity

In Figure 3 several best fit solutions are presented for a 14-channel data set showing the grand average of the auditory evoked mismatch-negativity (MMN) over 10 subjects elicited by a frequency change of 1000 Hz. This MMN data set and its solution using a specific 4-dipole model have been published previously (Scherg et al. 1989a). The solutions presented here differ only by the constraints imposed on hemispheric symmetry of the sources and by how the EC and VC criteria were used. Prior to the analyses presented in Figure 2 the data were band pass filtered (1-25 Hz, 24 dB/oct, zero phase shift, Butterworth type) to reduce the influence of noise on this comparison.

Solution A shows our former model of the mismatch-negativity (MMN) which was fitted with a pair of bilateral sources having hemispheric symmetry in location. The orientations were interactively adjusted such that an optimal separation of the two components was achieved, i.e., of the early MMNa component of the primary auditory cortex (dipoles 1 & 2) and of the later "true" MMNb component (dipoles 3 & 4), possibly reflecting the detection of the mismatch in a more anterior auditory association area (Scherg et al. 1989a). The solution A, as computed a posteriori, had fit criteria values of RV=1.21%, EC=0.71 and VC=0.21.

For the solutions B and C the symmetry constraint was preserved and the best fit was found without user interference by adjusting the two symmetric locations of the dipole pairs and the orientations of each dipole independently. When the cost function (3) included the EC and VC constraints with weights of 30% each (i.e., weight of RV, a=40%), the solution B was found which confirmed our interactively obtained solution A. The individual values in the cost function had all improved (RV=0.69%, EC=0.49, VC=0.05). In contrast, if merely the residual variance was used in the iterative minimization (weight of RV, a=100%), the fit reduced RV only slightly to 0.65% indicating the presence of a flat minimum space in RV. However, this solution C had much larger EC (0.86) and VC (0.28) criteria and the similarity between hemispheres in the source waveforms of the earlier and smaller MMNa component as depicted by the source potential waveforms of dipoles 1 & 2 was lost.

Finally, for the solutions D and E the symmetry constraints on source locations were released and a simultaneous and independent fit of the 3 location and the 2 orientation parameters of each of the 4 dipole sources was allowed. This implied, of course, an optimal fit of the source waveforms in each step of the direct inverse procedure. When the EC and VC constraints were used as before, the fit remained stable (solution D) and only some

asymmetries in the location of the dipoles occurred. The source waveforms were not much different from solution B apart from overall size which strongly depends on dipole depth. There was only a negligible improvement in RV from 0.69% to 0.61% with unchanged EC (0.49) and VC (0.05) criteria as compared to solution B. This suggests that the small number of recording channels does not allow for a distinction between symmetric and non-symmetric locations. In other words, the more cranial location of the contralateral dipole 2 and the more superficial location of dipole 4 as compared to the ipsilateral dipoles 1 & 3 cannot be considered significant.

Furthermore, when the EC and VC constraints were not applied during the fit (Figure 2, E), the dipoles moved to anatomically unreasonable locations, i.e., outside of the Heschl's gyri, while RV decreased only minimally to 0.56%. On the other hand, this solution E exhibited increased energy and variance criteria (EC=0.58, VC=0.20). Again, solution E did not exhibit sufficient similarity in source potential waveshape between hemispheres as did the physiologically constrained solutions B and D.

For these reasons the solution B may be accepted as the most reasonable one in physiological and anatomical terms. There was no substantial decrease in the RV, EC and VC criteria which would have justified the acceptance of one of the model solutions C-E. The small decrease in RV from solutions B to E is probably a consequence of the fact that the latter models had more degrees of freedom in the fit procedure allowing for a better explanation of the noise in the data.

## Discussion

A priori knowledge can be useful in solving the inverse problem of EEG and MEG for several reasons:

First, the functional organization of the brain justifies the use of a discrete multiple equivalent dipole model with each dipole representing the activity of a neural mass.

Second, a discrete multiple dipole model has a (mathematically) unique solution, given a sufficiently large number of channels and source activities with temporally different patterns. In contrast, inverse models aiming at solving the infinitesimal current distribution in the whole brain or in planes at predefined depth for each time instance separately require a statistical assumption, e.g., the minimum norm criterion (Ioannides et al. 1990).

Third, anatomical and geometrical knowledge of the individual brain and its cortical folds can be used to impose spatial constraints on source locations and orientations. Because of the limitations in presently available head models, absolute localization may be biased systematically. Therefore, spatial constraints which maintain the relative distances between sources constant

according to anatomical knowledge appear more useful as compared to predefined locations or constrained source regions, e.g., on the basis or individual MRI scans. The usefulness of this concept was evident in our reanalysis of the auditory N100.

Fourth, some progress seems to be possible when adequate physiological constraints can be imbedded in a cost function in addition to the residual variance or goodness of fit criterion. For the MMN example, the expanded cost function was helpful and necessary to confine the solution. The VC and EC constraints were also helpful in solving the source problem of median nerve somatosensory evoked potentials for which a sequential onset of the source components can be assumed (Scherg and Buchner 1991).

This paper has only addressed some of the problems inherent in the inverse estimation of multiple source configurations in EEG and MEG. Our experience suggests that the interactive testing of various physiological hypotheses on real data is still needed as an important control for the validity of a multiple source model. The presented approach of using constraints and a more complex cost function instead of a single goodness of fit criterion appear to be a useful and perhaps necessary adjunct to achieve the goal of computer based automatic solutions of the inverse source problem in evoked potentials.

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