sLORETA Allows Reliable Distributed Source Reconstruction Based on Subdural Strip and Grid Recordings

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Abstract: Source localization based on invasive recordings by subdural strip and grid electrodes is a topic of increasing interest. This simulation study addresses the question, which factors are relevant for reliable source reconstruction based on sLORETA. MRI and electrode positions of a patient undergoing invasive presurgical epilepsy diagnostics were the basis of sLORETA simulations. A boundary element head model derived from the MRI was used for the simulation of electrical potentials and source reconstruction. Focal dipolar sources distributed on a regular three-dimensional lattice and spatiotemporal distributed patches served as input for simulation. In addition to the distance between original and reconstructed source maxima, the activation volume of the reconstruction and the correlation of time courses between the original and reconstructed sources were investigated. Simulations were supplemented by the localization of the patient's spike activity. For noise-free simulated data, sLORETA achieved results with zero localization error. Added noise diminished the percentage of reliable source localizations with a localization error ≤ 15 mm to 67.8%. Only for source positions close to the electrode contacts the activation volume correctly represented focal generators. Time-courses of original and reconstructed sources were significantly correlated. The case study results showed accurate localization. sLORETA is a distributed source model, which can be applied for reliable grid and strip based source localization. For distant source positions, overestimation of the extent of the generator has to be taken into account. sLORETA-based source reconstruction has the potential to improve the localization of distributed generators in presurgical epilepsy diagnostics and cognitive neuroscience. *Hum Brain Mapp* 33:1172–1188, 2012. © 2011 Wiley Periodicals, Inc.

Key words: invasive electrodes; source localization; epilepsy; simulation

INTRODUCTION

The use of source localization algorithms in epilepsy diagnosis and cognitive neuroscience derived from EEG and

MEG recordings is, on the one hand, well-established but, on the other hand, still under debate with respect to the reliability and the neurophysiologic interpretation of the results. A comprehensive review about the different algorithms, head models needed for forward computation, and application areas is given in Michel et al. [2004]. A recent increase in the application of source localization methods is documented in a review by Plummer et al. [2008], which reports about 150 articles in the area of source localization based on EEG recordings. The use of MEG almost always comes along with the application of source localization algorithms [Barkley and Baumgartner, 2003].

The application of source reconstruction algorithms in recordings based on intracranial electrodes used in

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presurgical evaluation of patients suffering from pharmacoresistant focal epilepsy is rare up to now. However, an increasing interest is documented by a couple of simulation studies [Chang et al., 2005; DümpeImann et al., 2009; Fuchs et al., 2007a,b; Zhang et al., 2008] and case studies [DümpeImann et al., 2009; Fuchs et al., 2007a; Rullmann et al., 2009; Zhang et al., 2008;]. Besides these studies, which have the main objective to prove the feasibility and reliability of source reconstruction based on intracranial electrodes first studies have applied source reconstruction based on invasive electrodes in cognitive neuroscience. Korzyukov et al. [2007] reconstructed generators of the P50 component in an auditory sensory gating experiment on the basis of the LORETA algorithm from subdural grid data. Sammler et al. [2009] investigated the localization of an ERP component related to syntactic violations in language and music by a source density reconstruction on the brain surface based on subdural recordings from perisylvian brain areas.

The studies of Fuchs et al. [2007a,b] and the P50 study [Korzyukov et al., 2007] used a source model consisting of cortical patches. The study by Sammler et al. [2009] is also based on a cortical source configuration. As an extension, the studies by Zhang et al. [2008] and DümpeImann et al. [2009] addressed the question, whether three-dimensional source reconstruction of deep sources gives reliable results without the need for the application of constraints related to the 3D distribution of the sources. The optimistic results of Zhang et al. [2008] derived from a weighted minimum-norm least squares algorithm were weakened by DümpeImann et al. [2009] using a more systemic placement of probe sources in the entire brain in the sense that results using the minimum-norm least squares (MNLS) algorithm [Hämäläinen and Ilmoniemi, 1984] were systematically attracted to the positions of the adjacent intracranial electrodes. Only generators close to electrode contacts were reconstructed with a small localization error. The attraction of localizations toward the electrode contacts could not be prevented by standard means usually applied in scalp recording based source localization methods [Fuchs et al., 1999]. Reliable localization results for simulated sources in the entire brain were reported for the application of the MUSIC (Multiple Signal Classification) algorithm as described by Mosher et al. [1992, 1999]. This supports the simulation results of the earlier study from Chang et al. [2005] which used the MUSIC-derived RAP-MUSIC algorithm and beamforming [Van Veen et al., 1997] based on intracerebral depth recordings.

The article by Zhang et al. [2008] and the case study by Rullmann et al. [2009] used a finite element (FEM) model to describe the properties of the head in as well forward simulation as well as in source reconstruction. These studies showed that the use of this sophisticated type of models is nowadays feasible for source reconstruction tasks in general but and for localization based on intracranial electrodes in particular.

The objective of this study is to investigate whether the popular sLORETA algorithm, which was introduced by

Pascual-Marqui [2002] and belongs to the group of distributed source models, gives reliable source reconstruction results in intracranial recordings. This is of special interest, because the standard distributed source model given by the minimum-norm solution, did not show reliable results in the previous study by DümpeImann et al. [2009]. Nevertheless, a distributed source model is requested to represent complex source distributions, as they can be expected for intracranial recorded potential distributions [Fuchs et al., 2007b]. sLORETA is a promising candidate for source localizations free from systematic errors for single point-like sources, since the problem of the attraction of reconstructed sources toward the electrodes does not exist. Further, it could be shown that sLORETA results even show a zero localization error for simple source configurations and moderate signal-to-noise ratios [Pascual-Marqui, 2002; Wagner et al., 2004].

Simulations were performed for a set of artificial sources distributed in the entire brain and two different three-dimensional activation patches using a boundary element (BEM) head model derived from a patient undergoing presurgical epilepsy diagnostics by means of subdural grid and strip electrodes. The simulation results were supplemented by source reconstruction results of averaged spike activity of the patient.

This study aims to establish a source localization method suited to reconstruct complex, as well as focal and distributed source configurations based on invasive recordings and with the potential to enhance the investigation of spatiotemporal processes in the brain both for clinical diagnosis and neuroscience research.

METHODS

Simulation

A head model and the positions of subdural grid and a subdural strip electrodes were derived from a three-dimensional MRI data set of a 40-year-old male patient suffering from focal epilepsy with nocturnal simple and complex partial seizures since the age of 8 who underwent presurgical evaluation at the Epilepsy Center of the University Hospital Freiburg, Germany. MR imaging and PET did not show pathological alterations. Scalp EEG showed bifrontocentral epileptiform activity with spiking, rhythmic slowing, and beta bursts with the maximum amplitude at electrode FC1. Especially during sleep an expansion of the electrical field to Fz, F3, and sometimes CP2 was observed. Semiology of simple partial seizures did not give any lateralizing information, whereas EEG showed initial rhythmic beta activity at contacts FC1-Cz. Based on the hypothesis of a frontomesial or frontolateral seizure onset, invasive presurgical evaluation was performed to delineate the epileptogenic zone with a left frontocentroparietal 64-contact grid electrode, four interhemispheric frontocentral 4-contact strip electrodes and one 4-contact strip electrode in the left fronto-lateral-anterior region (Fig. 1b). Invasive

Figure 1.

Case study of patient with left frontal grid and 4-contact strip electrodes. (a) Averaged spike, showing amplitude maximum in contacts G_B2–G_B4, (b) curvilinear reformatting of brain surface with overlaid grid and strip electrode contacts and interhemispheric strip electrode contacts, (c) sLORETA localization result, (d) postoperative MRI showing the resection volume. The crosshair points in (c) and (d) to the maximum of the sLORETA solution.

Figure 2.

First configuration used for distributed simulation study and reconstruction volume. (a) Number of active source positions increases linear up the middle of the activation interval and decreases again in the second half of the interval. (b) Positions of the sources

underneath the grid used for the simulation of the spatiotemporal patch shown as orange balls. (c) Activation volume of the sLORETA reconstruction for radial source at time points with increasing number of active source positions $t = 4$, (d) $t = 8$, (e) $t = 10$.

recordings showed continuous spike activity in contact B2 of the grid with extension to contacts B4 and C2 and propagation to contacts C1-4 and A1-4. The recorded seizures started with polyspikes in the anterior part of the grid rows A to C. Amplitude maxima of ictal polyspikes were seen in the contacts B2 and A2-4, C1-4. As a result of invasive recording including functional mapping of motor and language areas, a tailored resection in the left frontal lobe was performed (Fig. 1d). Histological examination identified a focal cortical dysplasia of type 2b [Palmini et al., 2004]. So far, the patient has remained seizure-free for a period of 10 months.

The electrode positions were determined from a three-dimensional T1 MRI dataset with 1 mm isotropic resolution acquired after electrode implantation on the same scanner system as the preimplantation MRI. Individual stainless steel, i.e. ferromagnetic electrodes cause a local magnetic field inhomogeneity, which produces a local signal void ("black hole artifact"). These circumscribed susceptibility artifacts were used to determine the individual electrode positions. To this aim, the center of each susceptibility artifact was manually marked using self-developed three-dimensional visualization software.

A boundary element (BEM) head model was derived from a three-dimensional T1 MRI dataset registered before electrode implantation: The MRI data set was normalized to the standard brain of the Montreal Neurologic Institute (MNI) included in SPM99 and skull stripped [Kovalev et al. 2005] in a subsequent step. The BEM model was created using the ASA (A.N.T. Software B.V., Enschede, The Netherlands) package [Zanow and Knösche, 2004] on the basis of the preprocessed MRI. It consisted of one homogeneous compartment made up of 3,446 vertices and 6,888 triangles. This head model was used for simulation purposes (forward computation of potentials at contacts of strip and grid electrodes), as well as for subsequent inverse localization of the simulated sources.

First, point-like sources were used for simulation with an impulse-like time course consisting of 20 data points. The potentials of the electrode contacts were calculated for 92 different source positions distributed on a regular three-dimensional lattice (edge length 24 mm) inside the entire brain with radial dipole orientations. Radial source orientation was approximated by the vector between the origin of the coordinate system and the source position. The origin of the coordinate system was defined by the preauricular points and the nasion. In addition to the described noise-free simulated potentials, two further sets of realizations of simulated data with added noise with a signal-to-noise power ratio (SNR) of 10.0 and 4.0 were presented to the sLORETA source reconstruction algorithm implemented in the ASA package. The used SNR ratios were equivalent to effective amplitude value ratios of ~ 3.1 and 2.0 between signal components and noise, which corresponds to unambiguously visually detectable signal components. The source space for the sLORETA algorithm consisted in the simulation study of

4,228 source points distributed on a regular cubic lattice (8-mm edge length).

The same configuration was also used to determine localization MNLS source reconstruction and MUSIC scan results to have a direct comparison between the methods. Minimum-norm results and MUSIC results were computed as described in Dümpelmann et al. [2009].

Second, two activation patches consisting of 43 neighboring points on a regular lattice with 7 mm edge length (Fig. 2) were used for simulation. Here, the spatial resolution was slightly finer than for the simulations with the point-like sources. The first patch was located underneath the anterior superior part of the grid electrode, which corresponded to regions with recorded spike and seizure activity of the patient. The patches were presented with radial and tangential source orientations. Tangential orientation approximation was derived by replacing the x component of the radial orientation vector with the y component and the y component— with the negative x component. The z component of the tangential orientation vector was set to zero. The spatiotemporal activation patterns consisted in a linear increasing number of active sources around the center of the patch in the first half of an interval of 20 samples with an amplitude of 1 nAm. The number of active sources decreased in the second half of the interval, respectively. The second source patch was located in the middle frontal gyrus of the left hemisphere, which represents an area not covered by the grid but with a reasonable distance for a generator configuration to be investigated for clinical or scientific purposes by the given electrode configuration. sLORETA was used to reconstruct the sources using the simulated data generated by this source configuration, as well as simulated data with added noise with a SNR of 10.0 and 4.0. Under investigation were the maximum of the reconstructed activity compared with the source position in the center of the patch, the overlap between the activation patch and the reconstructed activation volume and the time course between the source activity and the reconstructed activity for a subset of the corresponding sLORETA reconstruction points. The latter was computed using Pearson correlation coefficients as implemented in the SPSS version 15.0.1. Further, since the input activation function consisted of two states instead of a continuous time-courses a non-parametric test (Mann-Whitney) was applied to check, whether it is possible to group the sLORETA reconstruction values related to the input magnitudes of the sources used for simulation. U -values and significance levels again were determined using SPSS version 15.0.1.

In the following, a short derivation of the sLORETA algorithm is given. For distributed source models, it is convenient to use the leadfield matrix to describe the relationship between the sources and signal strength at the sensors:

$$F = LQ \quad (1)$$

F is the matrix with measured values, Q consists of the source strengths and L describes the sensitivity of

measurement sensors with respect to each source strength. Every row of F and L is associated with a particular measuring channel. The columns of F and Q represent the time samples. Each column of the leadfield matrix L represents the (normalized) contribution of one particular source to the data. Generally, there is no unique solution of this equation for the determination of the sources Q and additional constraints are needed. The minimum-norm least squares constraint proposed by Hämäläinen and Ilmoniemi [1984] is widely used and results in the following equation to determine the source strength:

$$Q = L(LL^T + \lambda I)^{-1}F. \quad (2)$$

here, λ is a regularization parameter used to make the result less sensitive to noise and I is the unary matrix. sLORETA expands the concept of MNLS solution by a location-wise weighting of the results of the linear estimation inverse solution with their estimated variance [Pascual-Marqui, 2002]. The sLORETA algorithm takes into account two sources of variance, first, the variance of the actual sources and second variation due to noisy measurements. Both sources of variation are assumed to be independent and additive.

Thus, the variance of the measurement is given by

$$S_F = LS_QL^T + S_{DM}. \quad (3)$$

S_F is the total variance of the measured data, S_Q is the variance of the sources and S_{DM} —the variation due to noisy measurements. Assuming the measurement covariance matrix to be the identity matrix, S_Q can be estimated by

$$\hat{S}_Q = L^T(LL^T + \lambda I)^{-1}L. \quad (4)$$

Then, sLORETA at the l th voxel corresponds to

$$\hat{Q}_l^T \hat{S}_{Q_{ll}} \hat{Q}_l, \quad (5)$$

where $\hat{Q}_l$ is vector with three components of the source estimate at one voxel given by the MNLS algorithm and $\hat{S}_{Q_{ll}}$ is the l th 3×3 diagonal block matrix of $\hat{S}_Q$. Finally, the regularization parameter λ is determined as described in Dümpekmann et al. [2009].

To get a more profound insight into what could be expected in general for the application of linear inverse models used for source localization based on invasive electrodes, the source visibility was determined for the given configuration. The source visibility evaluates to what extent an arbitrary current distribution can be detected by a given sensor configuration. It is defined as the ratio between the size of the visible part and the size of the source [Grave de Peralta-Menendez and Gonzalez-Andino, 1998]. For single point sources, the visibility is given by

$$V_i = \|L^{-1}L_i\|^2 \quad (6)$$

where L_i is the i th column of the leadfield matrix. This measure only depends on the leadfield matrix, and no further assumptions on the used inverse model are made here.

Case Study

sLORETA was applied to the averaged spikes of the patient whose data were used for the simulation study. The EEG-data were obtained using a Neurofile NT (TM) digital video-EEG system with 128 channels at a sampling rate of 1,024 Hz, and a 16-bit A/D converter. The signal was filtered in the recording system with a high-pass filter with a time constant of 1 second and a low-pass filter with a cutoff frequency of 344 Hz. The spikes were visually identified and averaged with the ASA package. The spike average showed prominent peaks in the grid contacts G_A2-4, G_B2-5, G_C1-3. Maximum of the spike average was at contact G_B2. The interval used for the sLORETA algorithms was ± 12 ms around the peak of the spike average. To be able to take the interhemispheric contacts into account for localization, a head model of the brain surface was derived, which consisted only of the left hemisphere of the patient. The source space for the sLORETA algorithm consisted of the 2,114 left hemispheric source points, which also served as the left hemispheric source points in the simulation study.

Informed consent for data analysis was obtained from the subject and approved by the local ethics committee. The procedure complies with the Declaration of Helsinki on human investigation.

RESULTS

Simulation

Maps for the source visibility, which gives information to what extent an arbitrary current distribution can be detected by the sensor configuration for linear reconstruction techniques are given in Figure 3. The maps show high values of the source visibility close to the grid electrode with a steep descent to distant brain areas.

The source visibility only depends on the leadfield matrix of the given configuration. Summaries of the simulation results for complete source reconstruction procedures are given in Table I. To quantify the results, the localization error was defined as the distance between the global maximum position of the sLORETA algorithm and the original source position used for forward computation of the potentials at the electrodes. Since sLORETA gives independent results for each time point, the localization result of the sample with the maximum amplitude of the simulated data was taken into account for the comparison. To quantify the amount of the brain volume, for which a

Source visibility

Figure 3.

Source visibility evaluating to what extent an arbitrary current distribution can be detected by the sensor configuration by leadfield-based reconstruction techniques.

reliable localization can be achieved, the percentage of original source positions was computed, which had a localization error ≤ 15 mm. Since the result maxima were located on a discrete grid with an edge length of 8 mm, it was verified from the simulation results, that no reconstruction maxima had a distance of two-grid units to the point-like source used for simulation. Thus, it was checked that no result bias was introduced by the threshold selection just below the distance of two grid units. As a third

quality measure the activation volume was defined as the percentage of sLORETA grid points with a reconstructed magnitude, which is greater than 0.66 times or two-thirds of the maximum reconstruction magnitude. Since for simulations a point-like dipolar source was used, a small activation volume represents the original sources better than extended activation regions. Table I presents the mean values of the activation volume averaged over the original source points in percent.

TABLE I. Simulation results for the configuration used in the simulation study

	Mean localization error (mm)	Max. localization error (mm)	Reliable localizations (%)	Mean activation volume (%)
sLORETA both hemispheres				
No noise	0.0	0.0	100.0	68.3
SNR 10.0	7.0	49.3	81.1	64.2
SNR 4.0	11.8	63.0	67.8	55.4
sLORETA left Hemisphere				
No noise	0.0	0.0	100.0	24.7
SNR 10.0	4.1	33.0	87.8	23.2
SNR 4.0	9.5	52.5	75.0	22.6
MNLS both hemispheres				
No noise	65.3	126.5	2.2	1.0
SNR 10.0	65.2	126.5	2.2	1.1
SNR 4.0	64.7	126.5	2.2	1.2
MUSIC both hemispheres				
No noise	0.0	0.0	100.0	0.01
SNR 10.0	2.8	33.0	93.3	0.7
SNR 4.0	7.5	51.2	81.1	1.7
sLORETA contralateral extra strip electrode				
No noise	0.0	0.0	100.0	55.3

Reliable localizations are defined by a distance ≤ 15 mm between original source and reconstruction maximum. The activation volume is defined as the percentage of source reconstruction points having an amplitude of $> 0.66 \times$ maximum reconstruction amplitude. sLORETA results for the whole brain and the left hemisphere, which was covered by the grid and the strip electrode, are compared with the MNLS and the MUSIC algorithm. The last column shows the influence of an hypothetical additional contralateral 4-contact electrode on the activation volume (see Fig. 5).

In case the simulated data were presented without noise to the sLORETA algorithm, the original source positions were reconstructed with zero localization error. Adding noise to the simulated data with a SNR of 10.0 resulted in a mean localization error of 7.0 mm and a maximum localization error of 49.3 mm. The percentage of reliable localizations was 81.1%. Increasing the noise level to a SNR of 4.0 increased the mean localization error to 11.8 mm and the maximum localization error to 63.0 mm. The percentage of reliable localizations diminished to 67.8%. Figure 4 shows the localization error as three-dimensional maps overlaid to the MRI image. For a SNR of 10.0, a small localization error is shown for almost the complete hemisphere covered by the grid and strip electrodes and further reaching to central and parietal areas of the contralateral hemisphere. A SNR of 4.0 reduced the brain volume with reliable localizations to a volume underlying the grid, but located more than 2 cm in depth below in the cingulate gyrus and the SMA.

Taking a look at the hemisphere which was covered by grid and strip electrodes, the mean localization error diminished to 4.1 mm for a SNR of 10.0. The maximum localization error was 33.0 mm. The percentage of reliable localizations was 87.8%. A SNR of 4.0 gave a mean localization error of 9.5 mm and a maximum localization error of 52.5 mm. Reliable localization positions were reduced to 75.0%.

To have a comparison with other frequently used source reconstruction techniques, the results for MNLS algorithm and MUSIC are also shown. Mean localization error were for MNLS 65.3 mm (without added noise), 65.2 mm for a SNR of 10.0, and 64.7 for SNR of 4.0. In all three cases, the maximum localization error was 126.5 mm. Reliable source localizations could be achieved only for about 2.2% of the original source positions independent of the level of added noise. The amount of the activation volume was between 1.0% and 1.2%. Figure 4c shows that reliable source localizations could be achieved only directly underneath the grid electrode.

MUSIC source localization results showed no localization error for the reconstruction without added noise. A SNR of 10.0 resulted in a mean localization error of 2.8 mm and respective for a SNR of 4.0 a mean localization error of 7.5 mm. The maximum localization error was 33.3 mm for a SNR of 10.0 and 51.2 for a SNR of 4.0. The noise diminished the percentage of reliable localizations to 93.3 for a SNR of 10.0 and 81.1 for a SNR of 4.0. The activation volume increased from 0.01 to 1.7 from reconstructions in the noise-free case to reconstructions for a SNR of 4.0. Figure 4d shows that reliable localizations can be achieved also in large parts of the contralateral hemisphere even for a SNR of 4.0.

Figure 5 gives three examples for the activation volume for an original source close to the grid, a respective contralateral source, and a frontobasal source ipsilateral to the grid. Source reconstruction was performed for data with added noise with a SNR of 4.0. The simulated data

showed a clear elevation in contacts G_F3-4 for the source close to the grid electrode. The reconstructed source had a zero localization error and showed a focal activation volume. The contralateral source resulted in a small elevation over a large number of the grid contacts. The reconstructed source maximum again had zero localization error. However, the activation volume included the whole hemisphere of the original source and reached into the hemisphere with the grid and the strip electrodes. For the ipsilateral frontobasal source, which is more probable to be under investigation in a clinical practice, the source position was reconstructed with a zero localization. The activation volume was not restricted to the ipsilateral frontobasal area, but it also spread over the complete contralateral frontal lobe. To quantify the activation volume, FWHM (full width at half maximum) values were estimated for the configurations. First, the volume of the sLORETA activation with a magnitude greater than 50% was determined. Then, the diameter of a sphere with a corresponding volume was used as an estimator of the FWHM. The FWHM for the source close to the grid was 18.3 mm, for the contralateral source 137.0 mm and 138.4 mm for the frontobasal source.

The mean activation volume for both hemispheres for simulated data without noise was 68.3%. For data with noise, the activation volume was 64.2% for a SNR of 10.0 and 55.4% for a SNR of 4.0. Reducing the volume of interest to the hemisphere covered with invasive electrodes, activation volumes were given by 24.7% for data without noise, 23.2% for simulated data with a SNR of 10, and 22.6% for simulated data with a SNR of 4.0.

For an overview of the distribution of the activation volume, Figure 6 shows three-dimensional maps of the activation volume for two electrode configurations. Figure 6a reveals that for the actual electrode configuration of the patient, only the volume underneath the grid and some ipsilateral frontal areas have a small activation volume. The configuration with a hypothetical contralateral strip electrode presents globally reduced activation volumes and small activation volumes close to the contralateral strip contacts (Fig. 6b).

For the distributed source configuration patch underneath the grid (Fig. 2.) with radial source orientations, the sLORETA reconstruction is shown for three different time points in the interval with an increasing number of active sources for a SNR of 10.0. The reconstruction maximum kept at a fixed position over time. The magnitude of the activation increased in amplitude corresponding to the number of active sources used for simulation. In parallel, the activation volume increased. Table II gives quantitative information about the reconstruction results for the investigated configurations. For all configurations (radial, tangential source orientations, noise levels), the distance between the maximum of the activation patch and the reconstruction maximum was at maximum one grid point (7 mm) of the reconstruction grid. Between 72% and 100% of the original source points were included in the

(a) sLORETA localization error (SNR 10.0) [mm]

(b) sLORETA localization error (SNR 4.0) [mm]

(c) MNLS localization error (without noise) [mm]

(d) MUSIC localization error (SNR 4.0) [mm]

Figure 4.

Three-dimensional mapping of localization error for simulated data. Brain areas with a localization error ≥ 15 mm for a SNR of 10.0 (a) and a SNR of 4.0 (b) are shown in red. sLORETA results are shown for a SNR of 10.0 and 4.0. (c) MNLS results are shown for the most optimistic case without noise. (d) MUSIC results are shown for a SNR of 4.0.

Simulation examples: SNR 4.0

Figure 5.

sLORETA source localization with zero localization error for simulated data with a SNR of 4.0. (a) Simulated ECoG for original source position close to grid electrode contacts, and sLORETA reconstruction showing the maximum (crosshair) in center of small activation volume, (b) simulated ECoG for original source position contralateral to grid electrode contacts. Though cross-

hair points at correct position of original source, the huge activation volume does not give a realistic impression of the original point-like source. (c) Simulated ECoG for frontobasal source ipsilateral to grid. Again the maximum is correctly reconstructed. Activation volume covers ipsilateral frontobasal structures but also spreads over the complete contralateral frontal lobe.

activation volume of the sLORETA reconstruction. Only for the radial source configuration without added noise, the activation volume had almost the same size as the original activation volume. In all other cases, the activation volume covered much wider brain areas. The ratio between the reconstructed activation volume and the volume used for simulation was between 19.7 and 23.9. The Pearson correlation coefficient between the time-courses of the sources of the activation patch and the reconstruction results at corresponding positions was significant on the level of 0.01 (two-tailed significance). For radial source configurations the correlation was between 0.54 and 0.56, for tangential source configurations—between 0.34 and 0.40. The U values of the Mann-Whitney test are given in Table II. All values correspond to significance levels <0.001 .

Original source configuration and reconstruction results for the activation patch in the middle frontal gyrus are presented in Figure 7. Similar to the reconstruction results

underneath the grid, the reconstruction maximum kept fixed over time. The magnitudes and the activation volume were increasing corresponding to the number of active sources of configuration used for simulation. For all configurations, the maximum distance between reconstruction maximum and the center of the activation patch was one grid point. For all configurations the original activation volume was completely covered by the reconstruction volume. The ratio between the volume of the reconstruction and the original activation patch was between 13.0 and 14.5 for the activation configuration with radial source orientation, and 34.1 and 35.5—for the activation configuration with tangential source orientation. Again, the Pearson correlation coefficient between the time-courses of the sources of the activation patch and the reconstruction results at corresponding positions was significant on the level of 0.01 (two-tailed significance). For radial source configurations, the correlation was between 0.53 and 0.55, for tangential source

(a) Activation volumes [%]

(b) Activation volumes with contralateral 4 contact electrode [%]

Figure 6.

Comparison of sLORETA activation volumes for electrode configuration as given by patient in case study and with additional contralateral 4-contact electrode.

configurations—between 0.36 and 0.41. As for the activation patch underneath the grid, U values of the Mann-Whitney test corresponded to significance levels <0.001 .

Case Study

The maximum of the sLORETA result of the average spike was located underneath the contacts G_A2-3 and G_B2-3. The distance between the grid contact with maximum averaged spike amplitude (G_B2) and the sLORETA maximum was 15.7 mm. G_B2 was also the contact showing maximum amplitude for polyspikes at seizure-onset. The sLORETA algorithm showed a focal activation volume with a percentage of 4.1% of grid points with a reconstructed magnitude, which is greater than 0.66 times the maximum reconstruction magnitude. Postoperative MRI showed that the maximum of the sLORETA solution well coincided with the resection volume. The activation area overlapped both with posterior parts of the resection volume and adjacent areas of the precentral gyrus.

DISCUSSION

Though the quality of imaging methods improved tremendously during the last years, recordings with subdural

grid and strip electrodes remain necessary in case noninvasive studies remain nonconcordant or inconclusive regarding the irritative zone, the seizure onset zone or the eloquent cortex [Rosenow and Lüders, 2001]. Furthermore, subdural recordings become more and more popular for neuroscientific studies due its superior signal quality as compared to non-invasive measures [Ball et al., 2009]. In general, grid and strip electrodes only cover restricted parts of the brain surface and leave, in some cases, doubts about the generators of epileptogenic activity. Thus, it would be helpful if source localization algorithms could contribute to the resolution of the following basic questions. First, can generators of epileptogenic activity which are not well-sampled with electrodes be localized? Second, can reliable depth information of generators be derived? Third, can source reconstruction contribute to information about the extent of the generators? These questions are only the basic ones, which neglect e.g. the aspects of propagation or the separation of multiple independent or coupled generators of epileptic activity.

The application of invasive electrodes in epilepsy diagnosis gives a unique opportunity for cognitive research by recording neuronal activity directly from the brain surface or even within brain structures. Cognitive studies [Korzyukov et al., 2007; Sammler et al., 2009] applied localization

TABLE II. Reconstruction results for the two activation patches with either radial or tangential source orientations

Simulation configuration	Distance reconstruction maximum center of source patch (mm)	Overlap between patch volume and reconstruction volume %	Ratio between patch volume and activation volume	Pearson correlation coefficient	Mann-Whitney <i>U</i>
Underneath grid					
Radial source orientation					
No noise	0.0	72.0	1.3	0.56	27,781.0
SNR 10.0	7.0	100.0	22.7	0.54	28,365.5
SNR 4.0	7.0	100.0	23.9	0.54	29,303.0
Tangential source orientation					
No noise	0.0	97.7	21.7	0.34	42,946.0
SNR 10.0	0.0	97.7	20.2	0.40	38,177.5
SNR 4.0	0.0	97.7	19.7	0.37	40,443.0
Middle frontal gyrus					
Radial source orientation					
No noise	0.0	100.0	13.0	0.55	29,168.0
SNR 10.0	7.0	100.0	13.7	0.53	39,010.0
SNR 4.0	7.0	100.0	14.5	0.53	31,345.0
Tangential source orientation					
No noise	0.0	100.0	34.1	0.41	37,075.0
SNR 10.0	7.0	100.0	34.9	0.36	41,771.5
SNR 4.0	7.0	100.0	35.5	0.37	44,053.5

Besides distances between the center of the patches to the reconstruction maximum, relations between the activation volumes, the correlation between the time-courses of the original and reconstructed source magnitudes and the Mann-Whitney *U* values for the distinction between the sLORETA results based on the two magnitude values of the sources. All correlation results were significant on a level of 0.01. All values of the Mann-Whitney test correspond to significance levels <0.001.

procedures to ERP components using a cortex- or brain surface-based distributed source model. This study aimed to expand the range of methods to sLORETA, which gives a three-dimensional representation of source activity. Answers with regard to the same question as for clinical diagnosis would improve tremendously localization related studies in neuroscience research: is it possible to reconstruct generators distant from grid and strip contacts, to derive information on the exact depth and spatial extension of generators of measured activity? Interaction and coupling of generators are next steps in analysis, which can be investigated with a higher spatiotemporal resolution by source reconstruction from invasive EEG recordings, as compared to functional MRI.

Recent simulation studies tried to answer some of the mentioned questions using different source models and head models of different complexity. Since the assumption of point-like dipolar sources, which is a good approximation for the farfield distributions measured by EEG or MEG, is no longer valid in the close vicinity of the sources, as for invasive recordings [Fuchs et al., 2007a], this source model was not investigated in any of the studies. Nevertheless, in a case study [Rullmann et al., 2009], a dipole fit localization result, which was close to a lesion border and congruent to the localizations of other source reconstruction methods was reported. Similar to dipole fit, the MUSIC and the derived RAP-MUSIC algorithm use the

assumption of focal sources and have as a result a two-dimensional or three-dimensional distribution, which gives at each scan point information about the existence of one active source which is spatially/temporally uncorrelated to any other active source. Compared with dipole fit, no assumption about the number of underlying sources has to be made. Instead, an upper boarder of independent sources has to be specified by the number of SVD components taken into account as belonging to the signal subspace. MUSIC [Dümpelmann et al., 2009] and RAP-MUSIC [Chang et al., 2005] showed favorable results in published simulation studies based on invasive electrodes. These results were not restricted to sources close to the electrode contacts. Thus, it can be concluded that MUSIC and MUSIC-based algorithms have the potential to localize sources even apart from the electrodes and can give reliable depth information. Due to the focal nature of the algorithm only limited information about the extent of the generators can be given.

Revealing information about the spatial extent of generators of brain activity is the domain of distributed source models. Studies by Fuchs et al. [2007a,b] used cortex-based source activity configurations, which they call "cortical patches." These patches are moved along the cortex to reconstruct the activity distribution. These types of models allow deriving information about the extent of sources. Little information is given in the studies about the potential

a) Source positions underneath grid used for simulation

b) Reconstructed activation volume at $t = 6$ (SNR 10.0)

c) Reconstructed activation volume at $t = 8$ (SNR 10.0)

d) Reconstructed activation volume at $t = 10$ (SNR 10.0)

Figure 7.

Second configuration used for distributed simulation study and reconstruction volume. (a) Positions of the sources in middle frontal gyrus used for the simulation of the spatiotemporal patch shown as orange balls. (b) Activation volume of the sLORETA reconstruction for radial source directions in the middle of the

interval matches source configuration also for activation patch not directly covered by grid and strip electrodes. Activation volume at time points with increasing number of active source positions $t = 6$, (c) $t = 8$, (d) $t = 10$.

to reconstruct sources, which are remote from grid and strip electrodes.

The studies by Zhang et al. [2008] and Dümpelmann et al. [2009] used a source space which included deep

brain structures, which is of importance to localize e.g. generators of epileptic activity in temporomesial areas, suspect for the generation of spikes in a high number of candidates for epilepsy surgery, and in the insular region.

The investigation of these brain areas is of outstanding interest in cognitive research [Fernández et al., 1999; Mutschler et al., 2009]. A further recent example of interest in noncortical brain structures is a study which used ERP analysis and source reconstruction based on invasive recordings to get insight in the role of the nucleus accumbens for the processing of unexpected events [Axmacher et al., 2010]. Both studies did not constrain the source space but used three-dimensional regular grids for the localization of source positions including source positions distant from the electrode contacts. The optimistic results for the weighted minimum-norm least squares algorithm used in the study by Zhang et al. [2008] could not be confirmed in the more extensive simulation study of Dümpelmann et al. [2009] which showed that the localization maxima were systematically attracted to the nearest electrode contacts. Only source positions adjacent to a grid or strip electrode were reconstructed with acceptable exactness, which was defined in this, as well as the preceding studies, as a localization error ≤ 15 mm. Standard compensation algorithms were not able to reduce this systematic miss-localization of the sources.

Therefore, the objective of this study was to investigate whether sLORETA is a reliable and accurate distributed source localization algorithm for recordings based on subdural grid and strip electrodes, which allows to estimate the depth and extent of generators, probably also for brain areas, which are not well-covered by the grid and strip electrodes. The zero localization error property of sLORETA for noise-free data [Pascual-Marqui, 2002; Wagner et al., 2004] could be replicated for grid and strip based source localization for probe sources in the complete brain volume. This result is not surprising since the zero localization property of sLORETA is inherent due to the used formula [Grave de Peralta et al., 2009]. Adding noise reduced the proportion of the brain volume to 67.8%, for which localizations with an acceptable exactness could be performed. In case the hemisphere covered with subdural electrodes is defined as the region of interest for 75.0% of the original positions reliable localization were achieved. A qualitative evaluation of the error maps showed that for up to moderate signal-to-noise ratios for the brain segment of the hemisphere, which was covered by the grid and strip electrodes, reliable source reconstruction can be achieved. It can be concluded that under this restriction of the region of interest, reliable reconstruction of the source position can be achieved also for generators distant to electrode contacts including correct information about the depth of the generators. For simulation, this study used sources with a radial orientation. A previous study [Dümpelmann et al., 2009] showed no relevant differences for dipolar sources with radial and tangential orientation in reconstruction results based on invasive recordings. This can be confirmed by the source sLORETA reconstruction results using the two distributed patches with radial and tangential orientations of the sources used for simulation.

This study revealed a tremendous dependency of the activation volume on the distance to the electrodes. This is in general in line with the properties of sLORETA as described by Pascual-Marqui [2002]. Yet, in the context of this simulation results, it has to be concluded that the point-like sources which were used for the simulations were only reconstructed as focal sources in the vicinity of the electrode contacts. Taking a look at the maps of the source visibility, the maps appear to be reciprocal in comparison. This may lead to the conclusion that the increased activation volume is the other side of the medal of the correct localization. Due to the low visibility of source points distant from the electrodes, point-like sources can only be localized as blurred activation volumes. These results are in-line with results of a recent comprehensive simulation study related to distributed source models applied to reconstructions from MEG recordings by Hauk et al. [2011]. Their study confirms the finding that the zero localization error of sLORETA comes along with a high spatial dispersion for source configurations distant from the sensors. In summary, it can be concluded that for the segment of the hemisphere of interest limited by the extent of the surface covered with electrode contacts reliable source reconstruction including depth information can be obtained, but information about the extent is only valid for generators close to electrode contacts.

Simulations for a distributed generator located underneath the grid showed that the maximum of the patch, as well as the time course of the activation pattern could be reconstructed. For noise-free data and sources with a radial orientation—also the extent of the patch was well reconstructed. Adding noise resulted in an overestimation of the active area. The same holds true for the source patches with tangential source orientations, which were used for simulation. The maximum was well-reconstructed, and the original patch was completely in the activation area. But again, the activation area overestimated the regions involved in the generation of the simulated invasive measurement data. The results of the correlation analysis and a nonparametric test to distinguish between the input values by the reconstruction result indicated that sLORETA is capable to reconstruct not only point-like source but also extended sources with a spatiotemporal pattern similar to an epileptic spike. Similar results were found for a second patch in the middle frontal gyrus, which was not covered by the grid, showing that the generators in areas not so well-sampled by electrodes can be reliably reconstructed. Nevertheless, limitations in the spatial resolution with respect to simultaneous active sources can be expected, as they were shown in simulations for scalp recordings [Wagner et al., 2004] and for MEG [Hauk et al., 2011]. The overestimation of the activation volume in the reconstruction results may hide independent sources also for reconstruction based on invasive recordings.

Noise was added to the simulated data to check the robustness of the sLORETA source reconstruction results. The analysis of patients' recordings may be even more

demanding. Instead of random values added to the simulations the superimposed activity of neural generators, which may generate, on the one hand, oscillations and on the other hand—singular peaks and signal complexes, has to be separated from the activity of interest. The property of sLORETA to have a zero localization may be overruled by cross-talk and point-spread properties of sLORETA of the additional generators of neuronal activity [Liu et al., 2002]. A further source of uncertainty of the results is the possible cancellation of sources for generators, which extend to opposite walls of sulci and gyri [Ahlfors et al., 2010]. Systematic investigation of cancellation effects of generators underneath the grid electrode should be encouraged for cortex-based distributed source analysis. In this study, the added noise did not reduce the number of correct localizations of the activation maximum for large parts of the hemisphere covered by the grid electrode. Interestingly, the added noise did not increase the mean activation volume, which represents the blurring of the point-like original sources by the sLORETA algorithm.

In scalp recordings of epilepsy patients, spikes can be seen in many cases as activity generated by a dominant source with added noise. Transferring this assumption to recordings based on intracranial recordings, the simulation results for the point-like sources and the source patches are promising that dominant point-like and, probably, also distributed sources can be reconstructed. The same can be assumed for circumscribed peaks of evoked or event-related activity. For complex patterns, which maybe quite frequent in grid-recorded data, also the application of MUSIC or the derived RAP-MUSIC algorithm have the potential not to describe the generators by a distributed activation pattern but by the superposition of focal generators. The successful application of RAP-MUSIC to scalp recorded data to the EEG of patients suffering from epilepsy has been already shown by Kobayashi et al. [2002a,b]. The expansion to intracranial recordings would be an interesting topic for future research.

The presented simulation study and the case study used a BEM head model, which is the current standard compromise between accuracy and computational expenses. The studies by Zhang et al. [2008] and Rullmann et al. [2009] showed that the use of FEM models is already feasible. This would allow accurate modeling of tissue conductivity anisotropies, especially anisotropic white matter conductivity, tumor tissue, and the silastic isolating base pads of the subdural electrodes containing the actual contacts. Thus, the use of FEM models is highly recommended for future studies in source localization based on invasive electrodes in case reliable conductivity values are available.

Further concerns about the study could refer to the way the electrode positions were determined based on pre- and postimplantation MRI data sets. Properties of the alternative using the combination of CT and MRI are discussed in the study of Winkler et al. [2000]. At the epilepsy center in Freiburg CT imaging after electrode implantation is not a standard procedure since electrode artifacts visible in the

MRI allow the assignment of the contacts to anatomic structures directly in the images without the need of a coregistration of the postdata sets and without additional radiation exposure of patients. A detailed description and discussion of the properties and the accuracy, which can be achieved by the used method to derive the positions of the electrodes is given in Schulze-Bonhage et al. [2002] and Kovalev et al. [2005].

The presented study uses two margins, which cannot be derived with full rigor. The margin for reliable source localizations was set to 15 mm. This is very close to the reported distance between source localizations and the maximum of the activity in intracerebral electrodes (11 ± 4.2 mm) in an accuracy study by Merlet and Gotman [1999]. The reported results were discussed as reliable and using intracranial electrodes for source localization, at least a similar margin for accurate source localizations should be set. The second margin is the threshold of 66% used for the activation volume. Unfortunately, a theory to derive thresholds for activation volumes in source reconstructions on profound statistics is missing. An example of how a statistical measure to perform statistical parametric mapping for MNLS results on repeated events can be derived is given in Sperli et al. [2006]. To derive similar rules for sLORETA, results on single events should be encouraged to get more profound rules to define sLORETA activation volumes.

The case study showed the maximum of the sLORETA result inside the post-op resection volume of a patient who underwent invasive recordings with subdural grid and strip electrodes during his presurgical work-up. The averaged spike showed high amplitude activity for a restricted set of electrode contacts of the grid electrode. The focal sLORETA activation underneath the grid electrode could reasonably explain the spike activity. A part of the sLORETA activation volume overlapped with non resected tissue. Nevertheless, the patient is seizure free. This is in line with the notion that the irritative zone does not exactly overlap with the epileptogenic zone and that its complete resection may not be necessary for seizure control [Rosenow and Lüders, 2001].

Though, methodological restriction were discussed related to source reconstruction based on methods investigated in this and previous studies, these methods can add decisive information to the pure visual investigation of spike activity. As well as MUSIC as sLORETA provide reliable localization also for generators, which are not close to the regions covered by subdural electrodes and give information about the depth of the sources. MUSIC gives by nature focal results and one value for a complete time interval. sLORETA can show the activity distribution for the single samples and allows investigating the development of the activation over time, which is of high interest in spike and event-related potentials analysis. With regard to the estimation of the extent of the generators care has to be taken for generators distant to the electrode contacts. Despite the algorithms investigated by Dümpelmann et al. [2009] cortex-based patch analysis [Fuchs et al., 2007a,b] using a minimum-norm approach gives a third option for

source reconstruction based on invasive electrodes. The selection of one of them should depend on assumptions about the location, extent, and spatiotemporal complexity of the generators underlying the measured activity.

It has to be noted that the activation volumes cannot be directly compared between the methods under investigation. The improvement in the localization accuracy of sLORETA is due to the normalization of the MNLS results by the source and noise variances rendering the current densities into f -statistics. Three-dimensional distributions of these statistics cannot be directly translated into the distribution of the underlying currents, which might be tempting looking at sLORETA maps. The spatial extension of sLORETA results rather depends on the signal-to-noise ratios and distance to the electrodes. Thus, this study presented as recommended [Hauk et al., 2011] also maps showing the source visibility and simulation results for the activation volume providing estimates of the blurring of the sLORETA results. Similar MUSIC does not give currents but a probability measure. Since the probe source is a point-like source it may reconstruct focal sources as focal for sufficient signal-to-noise ratios. Extended MUSIC maxima on the other hand do not allow to draw the conclusion of an extended generator of the activity.

Until now, besides simulation studies, mainly case studies have been published. The encouraging results of the simulations and the cases now give a solid basis to apply source localization to clinical data recorded from representative groups of patients who need invasive recordings during presurgical workup. The objective should be to investigate how source localization derived from invasive recordings can improve the delineation of the epileptogenic zone. A second option in the evaluation of source analysis is the use of evoked potentials with known generator structure. This will give, in the extension, new unique opportunities for cognitive research, which can be performed accompanying the presurgical procedure.

The present study thus supports a wider application of three-dimensional source localization based on invasive recordings in epilepsy diagnosis and cognitive research and, hopefully, it will stimulate further studies using real data in the near future.

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