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Evaluation of cortical current density imaging methods using intracranial electrocorticograms and functional MRI

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Abstract

Objective— EEG source imaging provides important information regarding the underlying neural activity from noninvasive electrophysiological measurements. The aim of the present study was to evaluate source reconstruction techniques by means of the intracranial electrocorticograms (ECoGs) and functional MRI.

Methods—Five source imaging algorithms, including the minimum norm least square (MNLS), LORETA with L_p -norm (p equal to 1, 1.5 and 2), sLORETA, the minimum L_p -norm (p equal to 1 and 1.5. When p = 2, the MNLS method is mathematically equivalent to the minimum L_p -norm.), and L_1 -norm (the linear programming) methods, were evaluated in a group of 10 human subjects, in a paradigm with somatosensory stimulation. Cortical current density (CCD) distributions were estimated from the scalp somatosensory evoked potentials (SEPs), at approximately 30 ms following electrical stimulation of median nerve at the wrist. Realistic geometry boundary element head models were constructed from the MRIs of each subject and used in the CCD analysis. Functional MRI results obtained from a motor task and sensory stimulation in all subjects were used to identify the central sulcus, motor and sensory areas. In three patients undergoing neurosurgical evaluation, ECoGs were recorded in response to the somatosensory stimulation, and were used to help determine the central sulcus and the sensory cortex.

Results—The CCD distributions estimated by the L_p -norm and LORETA- L_p methods were smoother when the p values were high. The LORETA based on the L_1 norm performed better than the LORETA- L_2 method for imaging well localized sources such as the P30 component of the SEP. The mean and standard deviation of the distance between the location of maximum CCD value and the central sulcus, estimated by the minimum L_p -norm (with p equal to 1), L_1 -norm (the Linear programming) and LORETA- L_p (with p equal to 1) methods, were 4, 7, 7 mm and 3, 4, 2 mm, respectively (after converting into Talairach coordinates). The mean and standard deviation of the aforementioned distance, estimated by the MNLS, LORETA with L_p -norm (p equal to 1.5 and 2.0), sLORETA, and the minimum L_p -norm (p equal to 1.5) methods, were over 11 mm and 6 mm, respectively.

Conclusions—The present experimental study suggests that L_1 -norm based algorithms provide better performance than L_2 and $L_{1.5}$ norm based algorithms, in the context of CCD imaging of well localized sources induced by somatosensory electrical stimulation of median nerve at the wrist.

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Brain imaging; Cortical current density; High resolution EEG; Inverse Problem; Somatosensory evoked potentials; Sensory cortex; Central sulcus

1 Introduction

Noninvasive functional imaging techniques have been widely used for functional localization and identification of cerebral functional areas in humans (Waberski et al., 2002a). Functional magnetic resonance imaging (fMRI) is well known to provide high spatial resolution in imaging brain functions (Ogawa et al., 1992;Kwong et al., 1992). However, the temporal resolution of fMRI is currently limited, due to the slow hemodynamic responses. On the other hand, electroencephalography (EEG) is an economic and easy-to-use modality to probe brain activity and offers millisecond temporal resolution. Conversely, EEG (and magnetoencephalography, MEG) are limited in spatial resolution when used to localize and image brain electric activity (Nunez & Srinivasan, 2005;He, 2004,2005).

A number of efforts have been made to solve the so-called "inverse problem" of EEG (or MEG) which aims at improving substantially the spatial resolution of EEG (or MEG). These efforts include equivalent dipole models (Scherg & Cramon, 1985;He et al., 1987;Cuffin, 1995), cortical current density (CCD) models (Dale and Sereno, 1993;Babiloni et al., 2003,2005), distributed volume current density models (Pascual-Marqui et al., 1994a), and cortical potential distributions (Gevins et al., 1994;Nunez et al., 1994;He et al., 1999,2001,2002a).

Several effective current density reconstruction (CDR) methods have been proposed for solving the EEG/MEG inverse problem. The minimum norm estimation (MNE) method is a well-known strategy (Hämäläinen and Ilmoniemi, 1984;Clarke et al., 1989;Wang et al., 1992) for estimating current density distributions within the brain. Later, this approach has been further developed into a weighted minimum–norm least squares solution (MNLS), which can avoid the intrinsic bias toward superficial currents (Pascual-Marqui et al., 1994a;Gorodnitsky et al., 1995). Among weighted minimum norm (WMN) estimations, the following solutions have been developed, including the low-resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994a), L_1 -norm (Matsuura and Okabe 1995), minimum L_p -norm (Beucker and Schlitt, 1996), minimum current estimate based on L_1 -norm (Uutela et al., 1999), standardized low-resolution electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002), and vector-based spatial-temporal minimum L_1 -norm solution (Huang et al., 2006).

Efforts have been made in an attempt to evaluate the reported EEG/MEG source reconstruction algorithms by computer simulations or experiments (Pascual-Marqui et al., 1994a;Fuchs et al., 1999;Hann et al., 2000;He et al., 2002b;Phillips et al., 2002;Stenbacka et al., 2002;Waberski et al., 2002b;Wagner et al., 2004;Yao & Dewald, 2005;Grova et al., 2006). Although a great deal of knowledge has been gained from these studies, there have been very few studies which address rigorous evaluation of source reconstruction algorithms using intracranial recordings.

In the present study, we compare and evaluate several well adopted source reconstruction algorithms in the context of reconstruction of cortical current density distribution from scalp somatosensory evoked potentials (SEPs). The CCD estimates are evaluated by comparison to ECoG recordings in 3 patients, and fMRI in 3 patients and 7 normal subjects.

2 Materials and Methods

2.1 Source Reconstruction Algorithms

The scalp EEG recordings at a single given time point obtained from m electrodes can be modeled using a discrete linear model (Dale & Sereno, 1993)

$$\mathbf{\Phi} = \mathbf{K}\mathbf{J} + \mathbf{N},\tag{1}$$

where Φ is a $m \times 1$ vector of the measured EEG signals, the $n \times 1$ **J** vector represents the cortical current density (CCD) at all the *n* discrete cortical location (the orientation of dipoles is prefixed according to the cortical surface and defined as being along the normal direction at each location over the cortex) simultaneously, **K** is the $m \times n$ lead field matrix representing the system transfer coefficients from all *n* sources to the locations of *m* electrodes, and **N** is the $m \times 1$ noise vector. The CCD distribution can be estimated by adding the constraint that the sum of the strength of all dipole sources has to be the minimal. The general solution equation of CCD can be represented by the constraint regularization as in Eq. (2),

$$\min_{\mathbf{J}} \left\{ \| \mathbf{\Phi} - \mathbf{K}\mathbf{J} \|_{p} + \lambda \| \mathbf{W}\mathbf{J} \|_{p} \right\},$$
(2)

where $\|\cdot\|$ symbolizes a norm of the *p* order, λ is the regularization parameter and **W** is the weighting matrix. Various strategies have been reported to solve Eq. (2) with different norm, weighting matrix, and regularization method.

The early CCD estimation methods are based on the L_2 norm. Eq. (2) is replaced by Eq. (3) and a MNLS method derived by Wang et al. (1992) has been widely used to solve Eq. (3),

$$\min_{\mathbf{J}} \left\{ \| \boldsymbol{\Phi} - \mathbf{K} \mathbf{J} \|^{2} + \lambda \| \mathbf{W} \mathbf{J} \|^{2} \right\},$$
(3)

where $\|\cdot\|^2$ symbolizes the squared Euclidean norm (L_2 norm), **W** is a diagonal location weighting matrix. The *MNLS* method can provide a unique inverse solution that is the best estimate in the least-squares sense (Hämäläinen et al., 1993). Subsequently, the minimum norm estimation was further extended to the L_p norm ($1 \le p \le 2$), in which Eq. (3) becomes Eq. (2). When the order *p* of norm is 2, the standard minimum L_p -norm is a L_2 norm and is mathematically equivalent to the *MNLS* method. When the order *p* of norm is 1, the standard minimum L_p -norm is a L_1 -norm. The L_1 -norm can also be solved by using a linear programming technique derived by Matsuura and Okabe (1995).

The LORETA- L_p approach is initially based on the L_2 norm (Pascual-Marqui, 1994b). Recently, it has been developed on the L_p norm, which can be expressed as Eq. (4)

$$\min_{\mathbf{J}} \left\{ \| \mathbf{\Phi} - \mathbf{K} \mathbf{J} \|_{p} + \lambda \| \mathbf{B} \mathbf{W} \mathbf{J} \|_{p} \right\},$$
(4)

where $\|\cdot\|$ symbolizes a L_p norm, the matrix **B** represents the discrete spatial Laplacian operator. A focal source reconstructed by the LORETA method usually appears over a larger region with the maxima hopefully located near the real source location (Pascual-Marqui et al., 1994b).

The *sLORETA* method is based on the L_2 norm. Eq. (2) can be replaced by Eq. (5)

$$\hat{\mathbf{J}} = \min_{\mathbf{J}} \left\{ \| \boldsymbol{\Phi} - \mathbf{K} \mathbf{J} \|^{2} + \lambda \| \mathbf{J} \|^{2} \right\} = \mathbf{L} \boldsymbol{\Phi} \text{ with } \mathbf{L} = \mathbf{K}^{T} (\mathbf{K} \mathbf{K}^{T} + \lambda \mathbf{I})^{-1},$$
(5)

where $\|\cdot\|^2$ symbolizes the squared Euclidean norm and **I** is the identity matrix. According to Eq. (5), the variance $S_{\hat{i}}$ of the estimated current density \hat{j} is given by

$$\mathbf{S}_{\mathbf{J}} = \mathbf{K}^{T} (\mathbf{K} \mathbf{K}^{T} + \lambda \mathbf{I})^{-1} \mathbf{K}$$
(6)

For the dipoles with fixed orientation, the *sLORETA* method for the dipole location k (k = 1, ..., n) can be expressed as

$$\frac{(J_k)^2}{[\mathbf{S}_j]_{kk}},\tag{7}$$

where J_k is the current density amplitude of the *k*-th dipole location and the scalar $[\mathbf{S}_{\mathbf{J}}]_{kk}$ is the *k*-th diagonal element of matrix $\mathbf{S}_{\mathbf{J}}$ (Pascual-Marqui et al., 2002).

2.2 Experimental Studies

2.2.1 Subjects—Ten subjects, three neurosurgical patients undergoing surgical evaluation and seven normal subjects without a history of neurological diseases, were studied. The P/N20 components of this data set were previously studied using a spherical dipole localization model (Towle et al., 2003). Informed written consent was obtained according to a protocol approved by the Institutional Review Boards of the University of Chicago, and the University of Minnesota. All data were collected in the Department of Neurology at the University of Chicago, including the structural MRI, CT, SEP scalp recordings, ECoG SEP recordings, scalp electrode locations and subdural electrode locations (produced by Radionics Medical Products Inc., Burlington, Massachusetts). The recordings of seven normal subjects included structural and functional MRI, SEP scalp recordings, and scalp electrode locations. Although N20 and P30 components have been used for localizing the central sulcus, previous reports (He et al., 2002a;Waberski et al., 2002a) indicated that P30 component around 30 ms after stimulation provided similar results for localizing the sensory area and identifying the central sulcus as the N20 component. In the present study, the P30 component was used for all patients and normal subjects.

2.2.2 SEP Recording—Both scalp (three neurosurgical patients and seven normal subjects) and subdural SEP (three neurosurgical patients) recordings were taken in the relaxed awake state. For the patients, the scalp SEPs were made several days before the implantation of the subdural grid. For the neurosurgical patients and normal subjects, the SEPs were elicited by electrical stimulation of the median nerve at the wrist. The stimuli were 0.2 ms-duration electrical pulses delivered at 5.7 Hz at the motor threshold. Five replications of 500 stimuli were averaged. Using a commercial signal acquisition system (Compumedics, Inc., El Paso, TX), 32-channel scalp EEGs referenced to C_z was amplified with gain of 5,000 and band-pass filtered from 1 Hz to 1 kHz.

2.2.3 Direct cortical Recordings—The cortical SEPs were recorded from a 4×8 rectangular electrode grid with an interelectrode distance of 1 cm, placed directly on the surface of the brain as part of their diagnostic evaluation for surgery. Thirty-two channel ECoGs referenced to the contralateral mastoid were also band-pass filtered from 1 Hz to 1 kHz, but a gain of 1,000 was used.

2.2.4 MRIs and boundary element modeling—The MR images were obtained from each subject with a Siemens 1.5 Tesla scanner using T1-weighted images composed of 60 continuous sagittal slices with 2.8-mm slice thickness. The three compartment (skin, skull, brain) boundary element (BE) head models (Hamalainen and Sarvas, 1989) were constructed

from the MR images of each subject, using Curry 5.0^{TM} (Computedics, Inc., El Paso, TX). The boundary element algorithm used is described in Fuchs et al., (1998). Each layer of the BE head model consisted of approximately 4,000 nodes. The cortex model consisted of about 8,000 nodes. The inter-node distance of for the surfaces of brain, skull, skin and cortex were 7, 9, 10 and 3 mm, respectively. The conductivities of the skin, skull and the brain were assumed to be 0.33, 0.0165 and 0.33 S/m, respectively (Oostendorp et al., 2000;Lai et al., 2005).

2.2.5 Registration of scalp electrodes—The scalp electrodes were located in the MRIs by a combination of two methods: surface fitting and fiducial point registration. On each occasion that the scalp recordings were obtained, 33 electrode locations and 11 fiducial points (nose tip, nasion, preauricular fossae, external auditory meati, external canthi, mastoids, and left cheek) were digitized three times using a Fastrak radiofrequency localizer (Polhemus, Inc. Colchester, VT), the stylus of which was placed at each electrode location marked on the scalp. The accuracy is less than the width of an electrode (Towle et al., 1993). One-hundred and fifty points on the scalp were also digitized along with the electrode locations and fiducial points to provide a patient-specific coordinate reference for registering the electrode locations with the MR images. A surface-matching algorithm was used to fit the digitized scalp to the MR images segmented scalp (Pelizzari et al., 1989;Towle et al., 2003).

2.2.6 Registration of subdural electrodes—The subdural SEP recordings were registered to the MR images using two procedures. The electrode arrays and radio-opaque markers placed on the contralateral scalp were determined from a 3-dimensional reconstruction of skull films (Metz and Fencil, 1989). They were then located on a hybrid skin/brain segmented surface for each patient using the surface-fitting algorithm (Towle et al., 2003). The fitting process was finalized by ensuring that the distances to the anterior and posterior poles and the inferior surface of the brain were proportional in the lateral skull film and the MR images. A second technique involved identifying the electrode locations in intraoperative photographs of the craniotomy and manually projecting their locations onto the 3-D-rendered cortical images. The grid location relative to the craniotomy and gyral patterns appeared identical in the two images. This required the extrapolation of electrode locations, which were not visible in the photographs. Neither technique appeared clearly superior to the other, so the results of the two strategies were averaged, yielding an error term for the grid registration process (Towle et al., 2003).

2.2.7 Identification of the central sulcus based on functional MRI—The functional MRI results for three patients and seven normal subjects were obtained from the motor task and sensory stimulation (Towle et al., 2003). The motor task was performed by a finger opposition movement. The sensory activation during the function MRI scan was elicited by the experimenter manually rubbing the subject's flaccid hand. In the normal subjects, the mean signal increase in the primary cluster was similar for the two functional tasks: 4.3% for the motor task and 3.9% for the sensory task. Using an identical threshold criterion for the two tasks, the volume of activation was approximately equal for the two activating conditions. The fMRI findings for the three patients were similar to that of the normal subjects. According to the motor task and sensory stimulation, the sensory and motor regions can be determined from the fMRI mappings. In addition, Yousry and co-worker (1997) suggested that the segment of the precentral gyrus contained motor hand function was a knob-like structure, which is shaped like an omega or epsilon in the axial plane and like a hook in the sagittal plane. In this study, the primary motor hand area and the primary sensory hand area, and the central sulcus were determined by the fMRI findings and gyral anatomy.

2.3 Analysis Protocol

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The protocol of the present data analysis is shown in Fig. 1. First, the scalp electrodes were located on MR images by co-registration. The BE head model was created from the MR images of each subject using Curry 5.0TM (Compumedics, Inc., El Paso, TX). Second, the motor area, sensory area and central sulcus were identified from fMRI mappings and gyral anatomy of structure MRI. Third, the subdural electrodes of patients were located on the BE model by coregistration of the MR and CT images. Fourth, Curry 5.0[™] was used to analyze SEP estimating CCD distributions in all subjects, using the MNLS, LORETA- L_p , sLORETA L_p -norm and L_1 -norm (linear programming) methods. For the LORETA method with L_p norm, the p value was set to 1, 1.5 and 2. Since the minimum L_p -norm (p=2) method is mathematically equivalent to the MNLS method, we choosed the MNLS method to replace the L_p -norm method with p being equal to 2. In the following, the L1, LP1, LP1, S, MN, LR1, LR1, S, LR2 and SLR refer to the L_1 -norm (linear programming), L_p -norm (p=1), L_p -norm (p=1.5), MNLS, LORETA- L_p (p=1), LORETA- L_p (p=1.5), LORETA- L_p (p=2) and sLORETA methods, respectively. Lastly, for the patients, the ECoG mappings provide a golden standard (in terms of locating the central sulcus and sensory and motor areas) to evaluate the CCD estimates using the various methods discussed above. In addition to the comparison of the CCD distributions and the sensory area as identified from ECoG mappings or fMRI, the locations of maximum CCD points from different inverse algorithms were converted into Talairach coordinates, and then evaluated based on their distance from the central sulcus.

In order to select the regularization parameter λ , different methods have been reported in the literature (Morozov, 1984;Colli Franzone et al., 1985;Hansen, 1990;Wahba, 1977;Johnston & Gulrajani, 1997;Lian & He, 2001), thus possibly leading to slightly different inverse solutions which are beyond the scope of the present study. In the present study, for the MN, LP_{1.5}, LP₁, LR₂, LR_{1.5}, LR₁, L₁ and SLR, the regularization parameter λ was selected by the χ^2 criterion method implemented in Curry 5.0TM (Wischmann et al., 1992). All CCD results using various algorithms are displayed with a threshold set at 70% of the maximum current density ($\mu A/mm^2$) or F-distribution value for SLR (Fuchs, 1999).

2.4 Evaluation Protocol

The accuracy of the inverse solution was quantitatively evaluated by means of distance *d. d* is the distance between the location with maximum value of CCD and the central sulcus of the cortex (top view of the cortex). Here, the maximum points of CCD and the central sulcus of the cortex were converted into the Talairach coordinates. In the present study, the central sulcus of all normal subjects was determined by the functional MRI results (Towle et al., 2003) and gyral anatomy (Yousry et al., 1995;1997). As an example, Fig. 2 illustrates the distance parameter, the central sulcus, and the location with maximum value of CCD. The central sulcus and the location with maximum value of CCD were first obtained in the original coordinates (Fig. 2a). These points were then converted into the Talairach coordinates as shown in Fig. 2b. The distance parameter d was subsequently calculated in the Talairach coordinates (Fig. 2b).

3 Results

3.1 Functional MRI

Fig. 3 shows the fMRI in a normal subject during motor task and sensory stimulation. The blurring segments on the axial MRI show the motor (a) and sensory (b) activities. Note that the overlap of two activities located on a sulcus. A knob-like structure shaped like an epsilon is also observed to be located on the right side of the green point and left side of the blurring region. The central sulcus is thus identified and marked by a green line.

3.2 CCD Imaging in Patients

Results of the five CCD algorithms for patient #1 are depicted in Fig. 4. A positive/negative dipolar pattern can be observed over the scalp (Fig. 4a) and the subdural surface (Fig. 4b), at 29.8 ms following right median nerve stimulation. According to the features of SEPs published in the previous literature, the negativity of the dipolar pattern corresponds to the motor area (the front of the central sulcus), and the positivity corresponds to the somatosensory area (behind the central sulcus) in Fig. 4b. Comparing the zero-potential line separating the negativity and positivity with the cortex's sulcus, the central sulcus, motor and sensory areas can be identified accordingly. The CCD results are shown in Fig. 4: (c) SLR; (d) LR₂; (e) LR_{1.5}; (f) LR₁; (g) L₁; (h) MN; (i) LP_{1.5}; and (j) LP₁; where all results are displayed with a threshold set at 70% of the maximum current density ($\mu A/mm^2$). The SLR method is a statistical value (F-distribution) and others are CCD ($\mu A/mm^2$). It is noted that the 'hot spot' (yellow area) of source activities, estimated by (c) SLR, (d) LR2, (e) LR1.5, (f) LR1, (g) L1, (h) MN, (i) $LP_{1,5}$ and (j) $LP_{1,5}$ are located on the primary sensory area. These results are consistent with the results published in the literature, suggesting that the sources of SEPs are located within the primary sensory cortex. The locations of the 'hot spots' of the source activities estimated by the five algorithms varied. The 'hot spots' obtained from (c) SLR, (d) LR_2 , (e) $LR_{1.5}$, (f) LR1, (h) MN, (i) LP15, (j) LP1 are located on similar areas of the sensory cortex. The 'hot spot' of (g) L₁ is located on another area of the sensory cortex. The 'hot spot' locations of (d) LR₂, (e) LR_{1.5}, (f) LR₁, (h) MN, (i) LP_{1.5}, (j) LP₁ were more posterior than (g) L₁. From Fig. 4b, the location of the subdural grid was more lower and anterior than the 'hot spot' of the estimated CCDs. The 'hot spot' of $(g) L_1$ was the closest to the positivity area of the direct cortical mapping as compared with others. The 'hot spot' of (c) SLR was located behind the sensory area. Also, for (d) LR₂, (e) LR_{1.5}, (f) LR₁ or (h) MN, (i) LP_{1.5}, (j) LP₁, the CCD distributions were sharper when the p value decreases. Comparing (d) LR₂, (e) LR_{1.5} and (f) LR₁ with (h) MN, (i) LP_{1.5} and (j) LP₁, the results in Fig. 4 indicate that the LORETA- L_p method provided a smoother CCD distribution than the L_p -norm method. Also note that the CCD distributions of (f) LR_1 and (i) LP_1 are slightly smoother than that of (g) L_1 , some source activities were located around the 'hot spot'.

Similar analyses were performed in patients #2 and #3. Fig. 5 shows the results obtained in patient #2 at 30 msec after the onset of left median nerve stimulation. In Fig. 5 (a, b), the positive/negative areas of the dipolar pattern can be observed from the scalp potential map and ECoG map, respectively. Comparing this pattern with cortex' sulcus, the central sulcus was identified on the surface of the cortex. All 'hot spots' of source activities estimated by (d) LR_2 , (e) $LR_{1.5}$, (f) LR_1 , (g) L_1 , (h) MN, (i) $LP_{1.5}$, and (j) LP_1 for patient #2 are also located on the sensory area except for (c) SLR. Results of (f) LR_1 , (g) L_1 and (j) LP_1 are more localized on the primary sensory area than others. The other features of CCD imaging results obtained in patient #2 are comparable with those in patient #1.

3.3 CCD Imaging in Normal Subjects

The same procedure of the SEP analysis was performed on the data from seven normal subjects. Figs. 6 show the results obtained from subject #4. Fig. 6a shows the scalp potential map at 30 ms after the onset of right median nerve stimuli. The central sulcus is identified according to the cortex structure and functional MRI of motor task and sensory stimulation in the subject. Figs. 6(b-j) display the hot spots (the locations of the maximum CCD points) returned by the CDR methods. The CCD images were shown on (c) SLR, (d) LR₂, (e) LR_{1.5}, (f) LR₁, (g) L₁, (h) MN, (i) LP_{1.5}, and (j) LP₁. Except for the hot spot obtained by (c) SLR, other hot spots are located on the primary sensory area of the cortex. The major features of the CCD results are consistent with those obtained in the patients. Firstly, the LORETA result is smoother than the MNLS result. Secondly, the CCD distributions given by the LORETA- L_p and L_p -norm

methods are also sharper when p value decreases. Thirdly, the results obtained by the L_1 -norm methods, e.g., (f) LR₁, (g) L₁ and (j) LP₁ are more localized than other methods.

3.4 Analysis of Maxima of CCD Images in Patients and Normal Subjects

Fig. 7 shows the locations of maximum CCD values in the Talairach coordinates, obtained by the eight techniques (a) MN; (b) $LP_{1.5}$, (c) LP_1 , (d) L_1 , (e) LR_2 , (f) $LR_{1.5}$, (g) LR_1 and (h) SLR, respectively. Fig. 7 indicates that the distributions of maximum CCD points given by (c) LP_1 , (d) L_1 and (g) LR_1 appear to be more concentrated than others. Generally speaking, the sensory region responding to the median nerve stimulation at the wrist is only a part of the sensory area and there can be some variation of the locations of this sensory region among subjects within the sensory area. The distribution in the R-L direction among the subjects was smaller when using (c) LP_1 , (d) L_1 and (g) LR_1 .

Using the procedure described in Section 2.4, d of three patients and seven normal subjects were estimated by the reconstruction algorithms. Fig. 8 shows scatterplot of the localization error for the eight techniques tested. Horizontal line indicates median localization error for each technique. The *d* distributions given by LP₁, L₁ and LR₁ were closer to the central sulcus than others. The relative ability of each algorithm to localize the hand sensory error was assessed using a Friedman 1-way nonparametric analysis of variance of *d*, which revealed a highly significant difference between the techniques using L1-norm and those using L1.5 or L2 norm ($\chi^2 = 26.22$, df = 7, p < .001). There was no significant difference between the L1, LP1 and LR1 techniques in their localization accuracy.

4 Discussion

Source imaging has generated considerable interest in the past decades with its promise of localizing and imaging neural sources from noninvasive electrical or magnetic measurements. A unique feature of source imaging is its need for an explicit source model, based on which inverse solutions are obtained. This is due to the general non-uniqueness of the inverse problem. On the other hand, numerous studies have demonstrated the merits of source imaging even though a source model has to be assumed, *a priori*.

Validation is of crucial importance in source imaging due to the need of assuming a source model. Frequently, computer simulations are used to evaluate a source imaging algorithm, in which all the parameters can be well controlled and the sensitivity of each parameter to the inverse solution delineated. However, source imaging involves multiple factors, such as measurement noise, head conductor modeling error, conductivity value error, and algorithm error. The sophisticated nature of the inverse problem necessitates the use of a biological system to validate a source imaging approach in an experimental condition, comparing them with either intracranial recordings or well defined physiological knowledge. Previous validation works include assessment of dipole source localization methods using an animal model (He et al., 1987) or in patients undergoing neurosurgery (Cohen et al., 1990), and comparison study of the quantitative dipole source localization approach with physician assessment in a clinical setting (Towle et al., 2003).

The aim of the present study is to experimentally validate the well adopted cortical current density (CCD) source model (Dale & Sereno, 1993), and assess several well adopted inverse algorithms in the context of CCD imaging, for a well defined and studied somatosensory experimental protocol. To our best knowledge, this is the first attempt to validate CCD imaging using intracranial recordings. The present experimental results in patients demonstrate the ability of CCD imaging to localize and image cortical sources evoked by somatosensory stimulation. The comparison among the numerical algorithms provided experimental evidence that L_1 -norm based algorithms provide the best performance for imaging localized neural

sources, as shown by the statistical analysis of the distance of the maximum in CCD distribution to the central sulcus.

Yao and Dewald (2005) compared several source reconstruction methods (moving dipoles, minimum L_p norm, and LORETA with L_p norm, p equal to 1, 1.5, and 2), using both computer simulations and data analysis of noninvasive scalp SEPs and upper limb motor-related potentials (MRPs) obtained in one human subject. Their study shows that the LROETA- L_p norm method with p equal to 1 has a better source localization ability than any of the other methods studied, and provides physiologically meaningful reconstruction results (Yao and Dewald, 2005). Grova et al. (2006) evaluated six localization methods (based on the L_2 norm): the minimum norm, the minimum norm weighted by the multivariate source prelocalization, cortical LORETA- L_2 with or without additional minimum norm regularization, and two derivations of the maximum entropy on the mean approach, in a computer simulation study with simulated interictal spikes. Grova et al.'s study suggested that LORETA- L_2 method and the maximum entropy on the mean approach can provide the best detection accuracy. And both methods should be compared with the maximum of activity detected using the multivariate source prelocalization (Grova et al., 2006).

Direct SEP recordings have been used to assess the source localization method (Towle et al., 2003) and the cortical potential image (CPI) technique (He et al., 2002a). Towle et al. (2003) compared expert judgment, functional MRI, and dipole localization for noninvasive identification of human central sulcus with direct cortical recordings. Their results suggested that the expert judgment was significantly more variable (less reliable) than the dipole location or functional MRI. They suggested that functional MRI and dipole localization studies were desirable for preoperative surgical planning, where a spherical head model was used for dipole source localization. He et al. (2002a) compared the cortical potential imaging results with the direct cortical recordings using a realistic geometry head model. Their analysis suggested clearly the feasibility of reconstructing cortical potentials from noninvasive scalp EEG recordings with the aid of anatomic information from MRI and an inverse estimation procedure. These previous studies indicate that direct cortical recording can be an effective approach to evaluate inverse estimation strategies from noninvasive recordings.

In the present study, we evaluated the performance of several well adopted algorithms, including the minimum norm least square solution (MNLS), low-resolution electromagnetic tomography (LORETA) with L_p -norm (p equal to 1, 1.5 and 2.), standardized LORETA (sLORETA), the minimum L_p -norm and L_1 -norm (the Linear programming) algorithms, in a group of 10 human subjects undergoing an experimental SEP protocol. For all subjects, fMRI was obtained during a motor task and sensory stimulation in order to provide an independent determination of the location of the hand primary sensory and motor areas. For the three patients undergoing neurosurgical evaluation, ECoG recordings were made to further confirm the location of central sulcus. The CCD inverse solutions were then estimated and compared based upon the physiological knowledge (activation of somatosensory cortex in responding to somatosensory stimulation). Figs. 4 and 5 show clearly the estimated cortical current density distribution in the context of the cortical structure using the above-mentioned co-registration strategy, and their relationship with the electrical potential field over the subdural surface. Similar analysis was also performed in 7 normal subjects who also underwent fMRI, and similar features of source reconstruction obtained as shown in Fig. 6.

The finding that the CCD distributions estimated by the L_p -norm and LORETA- L_p methods were smoother when p value increased is in accordance with previous reports (Matsuura and Okabe, 1995;Beucker and Schlitt, 1996;Uutela etal., 1999;Huang et al., 2006). Secondly, comparing the present results with other works about LORETA (Pascual-Marqui and Michel, 1994a;Fuchs et al., 1999;Pascual-Marqui, 2002), it further indicates that the LORETA based

on the L_1 norm is more suitable to use for imaging well localized sources than the LORETA- L_2 method. On the other hand, when the sources are not focal, LORETA- L_2 method may perform well, as shown in the simulation studies by Grova et al. (2006). Lastly, an analysis of the locations of maximum CCD was performed for all patient and normal subjects using d parameter (Figs. 7 and 8). These analysis results indicate that the sources estimated by the LP₁, L₁ and LR₁ algorithms are less variable and more accurate among the 10 subjects studied, as compared with other algorithms. Furthermore, the statistical analysis of the median distance from the CCD maxima to the central sulcus indicates that there is significant difference between the group of algorithms based on L_1 norm and the others. The results using the L_1 norm based CCD techniques are consistent with the previous literatures (Matsuura and Okaba, 1995; Uutela etal., 1999;Huang et al., 2006). This is also in agreement with previous suggestion derived from computer simulation studies and human studies using noninvasive SEP and MRP data (Yao & Dewald, 2005). In Yao and Dewald's study, they used the single dipole area with a fixed center and a variable radius ranging with 5mm to 10mm to generate the simulated EEG data. Their results indicate that the LORETA- L_1 method can provide the best location accuracy of single dipole localization with the averaged localization error of 15 mm by the comparison of several noninvasive methods. Towle et al. (2003) reported an averaged dipole localization error of 16-18mm by analyzing the N/P20 component of SEP in a group of human subjects using a spherical head model. This level of localization accuracy may be due to the conductivity misspecification and the simplified head model. Compared with the previous reports, the present study achieved an averaged localization accuracy of 4mm with standard deviation of 3 mm (using L₁ norm algorithm) among the ten human subjects studied, as judged from the distance from the maximum location in CCD distribution to the central sulcus. The present findings suggest that the L_1 norm based CCD techniques are superior in localization ability compared to a spherical-model-based dipole localization and expert judgments for localization of central sulcus (Towle et al., 2003).

In summary, we have conducted an experimental study in 10 human subjects to validate and compare inverse algorithms in the context of cortical current density imaging. The present results demonstrate that the L_I norm based algorithms perform better than others when imaging well-localized cortical sources such as neural generators of P30 component of SEP following median nerve electrical stimulation at wrist.

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Fig 1.

The procedure of the evolution of five CCD methods using the real EEG, ECoG recordings and fMRI results. The MNLS, LORETA- L_p , sLORETA, L_p -norm and L_1 -norm (linear programming) methods are used in this study. In the LORETA and L_p -norm methods, the p value was set to 1, 1.5 and 2. Since the L_p -norm method of the CurryTM 5.0 is based on the MNLS method, the MNLS- L_p (p=2) method is equivalent to the MNLS method in the mathematics. In this study, L_1 , LP_1 , $LP_{1.5}$, LR_1 , $LR_{1.5}$, LR_2 , SLR and MN expressed the L_1 -norm (linear programming), L_p -norm (p=1), L_p -norm (p=1.5), LORETA- L_p (p=1), LORETA- L_p (p=2), sLORETA and MNLS methods respectively.



Fig 2.

The evaluation procedure and method; d is the distance between the maximum point of CCD and central sulcus of cortex (Top view). (a) The maximum point of CCD and the central sulcus of cortex, (b) the maximum point of CCD and the central sulcus of cortex after converted into the Talairach coordinates. In the present study, d is calculated in the Talairach coordinates.



Fig 3.

Functional MRI activation obtained from one normal subject. (a) The motor task and (b) sensory stimulation. The right side of the green point is a knob-like structure, which is shaped like an epsilon in the axial plane. The central sulcus of the normal subject can be identified with functional MRI (a, b) and the gyrus structure.



Fig 4.

Results obtained using five CCD methods for patient #1. (a) The scalp potential mapping and the cortex; (b) the direct subdural ECoG recordings and the central sulcus; (c) SLR; (d) LR₂; (e) LR_{1.5}; (f) LR₁; (g) L₁; (h) MN; (i) LP_{1.5}; (j) LP₁. All CCD results are shown with a threshold set at 70% of the maximum current density ($\mu A/mm^2$) or F-distribution value for SLR. The sLORETA is a statistical value (F-distribution) and others are CCD ($\mu A/mm^2$).





Fig 5.

Results obtained using five CCD methods for patient 2#. (a) the scalp potential mapping and the cortex; (b) the direct subdural ECoG recordings and the central sulcus; (c) SLR; (d) LR₂; (e) LR_{1.5}; (f) LR₁; (g) L₁; (h) MN; (i) LP_{1.5}; (j) LP₁. All CCD results are shown with a threshold set at 70% of the maximum. The SLR is a statistical value (F-distribution) and others are CCD ($\mu A/mm^2$).



Fig 6.

Results obtained using five CCD methods for normal subject 1#. (a) the scalp potential mapping and the cortex; (b) the maximum CCD point of all methods; (c) SLR; (d) LR₂; (e) LR_{1.5}; (f) LR₁; (g) L₁; (h) MN; (i) LP_{1.5}; (j) LP₁. All CCD results are shown with a threshold set at 70% of the maximum. The SLR is a statistical value (F distribution) and others are CCD ($\mu A/mm^2$).



Fig 7.

Maximum CCD points in the Talairach coordinates, using the eight techniques from three patients and seven normal subjects. (a) MN; (b) $LP_{1.5}$; (c) LP_1 ; (d) L_1 ; (e) LR_2 ; (f) $LR_{1.5}$; (g) LR_1 ; (h) SLR. The physical units are mm. AC and PC are anterior commissure and posterior commissure, respectively



Fig 8.

Scatterplot of the localization error for the eight techniques tested. Horizontal line indicates median localization error for each technique.