Comparison of imaging modalities and source-localization algorithms in locating the induced activity during deep brain stimulation of the STN*

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***Abstract*— One of the most commonly used therapy to treat patients with Parkinson's disease (PD) is deep brain stimulation (DBS) of the subthalamic nucleus (STN). Identifying the most optimal target area for the placement of the DBS electrodes have become one of the intensive research area. In this study, the first aim is to investigate the capabilities of different source-analysis techniques in detecting deep sources located at the sub-cortical level and validating it using the a-priori information about the location of the source, that is, the STN. Secondly, we aim at an investigation of whether EEG or MEG is best suited in mapping the DBS-induced brain activity. To do this, simultaneous EEG and MEG measurement were used to record the DBS-induced electromagnetic potentials and fields. The boundary-element method (BEM) have been used to solve the forward problem. The position of the DBS electrodes was then estimated using the dipole (moving, rotating, and fixed MUSIC), and current-density-reconstruction (CDR) (minimum-norm and sLORETA) approaches. The source-localization results from the dipole approaches demonstrated that the fixed MUSIC algorithm best localizes deep focal sources, whereas the moving dipole detects not only the region of interest but also neighboring regions that are affected by stimulating the STN. The results from the CDR approaches validated the capability of sLORETA in detecting the STN compared to minimum-norm. Moreover, the source-localization results using the EEG modality outperformed that of the MEG by locating the DBS-induced activity in the STN.**

I. INTRODUCTION

Deep brain stimulation (DBS) is a neurosurgical procedure used in the treatment of movement disorders like Parkinson's disease (PD). It is an invasive therapeutic technique, whereby small electrodes are implanted to deliver electric stimulus (pulses) to the intracerebral nuclei through a subcutaneously implanted pulse generator (IPG). The IPG is programmed to send continuous electrical pulses with a low-voltage and/or current in the range of 1-4 mV and/or mA at a repetition frequency of 130-180 Hz having a short pulse width of 60 µs. These constant electrical stimulation influences the brain circuits by slowing the cellular activity of the targeted nucleus and thereby regulating the disease-related abnormal network activity of the brain. In PD, the neurons at a cortical level are firing synchronously in the Parkinsonian state and they get desynchronized when stimulated in the most important target area, the subthalamic nucleus (STN) [1]. From a clinical point of view identifying the exact target area within the brain is still not yet precisely defined. Thus, pinpointing the exact target area plays an important role in obtaining optimal clinical results.

DBS is also one of the clinical paradigms used as a source validation in localizing the STN from scalp recordings, using different source-localization algorithms. Electroencephalography (EEG) and magnetoencephalography (MEG) are the best imaging modalities that are used to map DBS-induced (after implanting the DBS electrodes) brain activity compared to scanning methods like MRI, as the strong magnetic fields involved in MRI can cause over heating or movement of the implanted electrodes or the associated IPG. This leads to a comparison of the two modalities and an investigation whether EEG or MEG are best suited for studying patients with high-frequency settings, as the significant increase in electromagnetic energy generated at high-frequency DBS will interfere with the EEG and/or MEG electrodes and/or sensors, respectively.

Thus, the aim of this study is to detect and validate the position of the implanted electrodes in the STN by applying different source-analysis techniques on the induced potentials and fields, basically the artifacts generated by the DBS electrodes. The capabilities of the source-analysis to detect the DBS electrodes in the STN are tested and compared between the two modalities (EEG vs MEG) and the two source-localization approaches (dipole vs current-density-reconstruction (CDR)).

II. DATA ACQUISITION

Five PD patients having bilaterally implanted stimulating electrodes in the STN participated in this study. All patients were tested with the DBS-on condition using unipolar stimulation delivering rectangular pulses of width 60 µs with an amplitude of 1.5 V at a frequency of 130 Hz. The recording lasted for 2 min and the study was approved by the local

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Ethics Committee, Medical Faculty, University of Kiel and all patients gave their informed consent.

The induced electromagnetic potentials and fields, caused by stimulating the STN, were recorded using simultaneous EEG and MEG imaging modalities, respectively. The recording was done using the Elekta Neuromag whole-head system placed in a magnetically shielded room. The EEG data were recorded using 60 electrodes and the MEG data using 306 sensors arranged in an array of 102 different locations, each with two orthogonal focally sensitive planar gradiometers and one widespread sensitive magnetometer. Both the EEG and MEG data were sampled at 2500 Hz. Moreover, the data were band-pass filtered (125-135 Hz) to capture the stimulation frequency, that is, 130 Hz.

III. METHODS

Forward modeling and inverse problem constitute together the source level of signal analysis. The forward model is useful in evaluating the electric potentials or magnetic fields which occur due to the presence of current sources deep inside the brain. On the other hand, the inverse model uses the EEG and MEG signals obtained from external sensors or electrodes positioned on the surface of the scalp to locate the current sources present within the brain. All the analyses were performed using CURRY software (from Neuroscan).

A. Forward Modeling

Forward modeling relies on a head model that describes the geometrical and electrical properties of the tissue in the head. To achieve an accurate approximate of the human brain, realistically shaped head model is constructed based on the boundary-element method (BEM) using a description of the individual electrode locations and magnetic resonance imaging (MRI) from each patient [2]. The realistic head model is an arbitrary non-spherical shape that resembles the human head, consisting of multiple compartments (tissues). The tissues required for the computation of the forward problem are the brain, skull, and skin obtained from the individual MRIs using a segmentation technique by setting a threshold value for each tissue such that they do not overlap. These tissues are assumed to be isotropic and homogeneous with conductivity values 0.33, 0.0042, and 0.33 S/m for the brain, skull, and skin, respectively. The surface between these tissue types is described with boundaries using reasonable number of triangular meshes to keep it computationally feasible. The resulting forward solution is then used to solve the inverse problem.

B. Inverse Problem

To localize the location of the DBS electrodes, two source-localization algorithms were used, namely, dipole (moving, rotating, and fixed MUSIC) and CDR (minimum-norm and sLORETA).

1) Dipole Analysis: Parametric approaches also referred as spatio-temporal dipole-fit models require an explicit a-priori assumption about the cerebral current sources. Localizing a current dipole in the brain implies estimation of the 6 unknown source parameters: 3 for location, 2 for orientation, and 1 for strength. Therefore, all dipole-fit algorithms need to restrict the number of parameters to solve the ill-posed problem and also need an a-priori assumption about the number of sources (dipoles). Thus, different dipole-fit algorithms can be found by varying the degrees of freedom of the source parameters. Moving, rotating, and fixed dipoles are the most common source models that are used as an a-priori constraints [3].

1) Moving dipole: Each time point, from a selected time interval, is treated with a separate model, that is, the locations, orientations, and dipole strengths are calculated for each dipole, independent of all other time points. This results in free dipole locations and free dipole orientations, which are well suited to model propagating sources.
2) Rotating dipole: These models restrict the location of the dipoles to be fixed throughout the selected time interval but allow variation in the orientation and strength. Thus, the dipole strengths and orientations are calculated for each dipole, at each time point, independent of all other time points.
3) Fixed dipole: These models assume that each dipole represents a fixed neuroanatomical structure and also it assumes that physiologically its orientation should not rotate. Thus, only the strength for each dipole is calculated at each time point, independent of all other time points throughout the selected time interval.

The estimation of the unknown parameters is based on the least-squares technique which attempts to find the set of parameter values that minimize the square of the difference (error) between the model and the measured data. The optimal source model, Y_{model}, is determined given the measured data, Y_{meas}, by minimizing the sum of squares (cost function), over n electrodes and/or sensors, given the source model parameters as:

$$\min_{a,b,c} \left\{ \sum_{i=1}^{n} \left[Y_{meas,i} - Y_{model,i}(a,b,c) \right]^2 \right\} \tag{1}$$

The measured data depends on the location of the electrodes and/or sensors, whereas the source model depends not only on the location but also on the source model parameters denoted as a, b, and c corresponding to location, orientation, and strength. When the data is too noisy, the least-squares algorithm can yield physiologically unexplainable dipole strength results which are caused by over-estimation (over-fitting) of the number of active sources. This problem can be solved using the dipole-fit regularization methods such as multiple signal classification (MUSIC) algorithm. The MUSIC cost function, CF, to be minimized is given as [3-4]:

$$\mathrm{CF} = \frac{\left\| (\mathbf{I} - \mathbf{U_s}\mathbf{U_s}^T)\mathbf{L} \right\|_2^2}{\|\mathbf{L}\|_2^2} = \frac{\|\mathbf{U_n}\mathbf{L}\|_2^2}{\|\mathbf{L}\|_2^2}, \tag{2}$$

where $\mathbf{U}_s$ spans the signal subspace while $\mathbf{U}_n$ spans the orthogonal counterpart of the signal subspace, that is, the noise subspace. $\mathbf{I}$ is the identity matrix and $\mathbf{L}$ is the lead-field matrix obtained from the BEM solution.

2) Current-density-reconstruction: CDR computes the simultaneous activity of all the sources confined in a given source space, either a 3D grid or a surface [5]. Unlike the dipole analysis which estimate point dipoles here the distributed activity throughout the brain volume is computed which is discretized as a dense 3D grid where several dipolar sources are located on each grid point. Thus, at each element of these grids (voxels) the strength of the dipole, $\mathbf{Q}$, is estimated. To compensate the non-uniqueness of the solution, an additional constraint for the sources that measures the closeness to a given source model, known as the model term, shown in equation (3), is added to that of the data term, which measures the closeness of the obtained solution to the data.

$$\Delta(\mathbf{Q}) = data(\mathbf{Q}) + \lambda \cdot model(\mathbf{Q}) \stackrel{!}{=} \min \tag{3}$$

Mathematically, this is expressed as:

$$\Delta(\mathbf{Q}) = \min_{\mathbf{Q}} \|\mathbf{Y} - \mathbf{LQ}\|_p + \lambda \|\mathbf{WQ}\|_p \,, \tag{4}$$

where $\mathbf{Y}$ is the potential or field of the dipole and $\mathbf{W}$ is the diagonal source-depth weighting matrix. The dipole distribution should be minimal with respect to a specific norm p, $1 \leq p \leq 2$. The data and model terms are linked using a regularization parameter λ. The common regularization scheme in the field of electrical source imaging is the constrained minimum-norm [6].

1) Minimum-norm: The best known minimum norm method is the minimum-least-squares (MNLS, L2-norm), which is basically minimizing the sum of the squares of the differences between the target value and the estimated value. It searches for the solution with minimum power and leads to a smooth current distribution. The MNLS adopts the formulation of Tikhonov's regulariztion to find the best approximate solution, $\hat{\mathbf{q}}$, that minimizes equation (4) [7]. Here the source-depth weighting matrix is not taken into account in the source model. The explicit solution to the minimization of the function is obtained by taking its derivative with respect to $\mathbf{Q}$ yielding:

$$\hat{\mathbf{q}} = \mathbf{L}^T \left(\mathbf{LL}^T + \lambda\mathbf{I}\right)^{-1} \mathbf{Y} \tag{5}$$

   Minimum-norm tends to favor superficial brain regions and underestimate contributions from deeper source areas. However, modifications to minimum-norm solution can result in a better localization of deep sources. This gives rise to another method known as low-resolution electromagnetic tomography which produces a low-resolution tomography of the electromagnetic activity at every instant of time conserving the location of maximal activity.

2) Standardized low-resolution electromagnetic tomography (sLORETA): This is a tomographic method which applies a modification to the basic minimum-norm estimator in which the localization inference is based on images of standardized current density [8]. Thus, this method provides not the current density but a statistical measure, that is, the current strength for each location is divided by its error (variance) yielding F-scores of activation. Thus, the estimate of the standardized current density is given as:

$$\hat{\mathbf{q}}_v^T \quad [\nu_{\hat{\mathbf{q}}}]_{vv}\}^{-1} \hat{\mathbf{q}}_v, \tag{6}$$

   where $\hat{\mathbf{q}}_v$ is the current density estimate at the vth voxel obtained from the minimum-norm and $[\nu_{\hat{\mathbf{q}}}]_{vv}$ is the vth diagonal block of the resolution matrix (variance of the estimated current density).

IV. RESULTS

Prior to source-localization, the epochs-of-interest (trials containing the induced potentials and fields) from the recorded EEG and MEG data were extracted based on the stimuli, that is, the time instance after the DBS is turned on. Thus, epochs containing group of pulses within (0-500 ms) duration were extracted and averaged. The two source-localization approaches (dipole and CDR) were then applied on these averaged epochs. The source-localization results from the dipole and CDR approaches depicted that the EEG modality localizes the induced activity in the deeper slice of the STN better than the MEG modality, validating the a-priori information about the position of the DBS electrodes as shown in Fig. 1 and 2, respectively, for one of the representative patients.

As it can be seen from the EEG modality, the moving dipole algorithm detected not only the STN but also different regions of the brain that are activated due to the stimulation of the STN having varying dipole-moment intensity indicated by the different colors. Moreover, the rotating dipole and fixed MUSIC algorithms were able to localize the source in the deeper slice of the STN. This result was supported by calculating the euclidean distance between the reference (x,y,z) coordinate, mid-line of the STN separating the two hemispheres, to that of the estimated coordinate obtained from the source analysis for each patient separately (mean±std: rotating = fixed MUSIC = 20.36±8.62 mm). However, it can be seen that for the MEG modality the dipole analysis localize the induced activity in the top-most slice of the brain (parietal region), which is not the region of interest (mean±std: rotating = fixed MUSIC = 55.47±26.34 mm). In the CDR analysis, the minimum-norm algorithm showed a weak intensity of current over the STN region for the EEG modality, whereas it failed to localize the induced activity in the region of interest for the MEG modality. However, the results from the sLORETA algorithm for the EEG modality showed the extent of the current distribution with the highest activity being in the STN along with weak distributions in its neighboring brain regions. This result

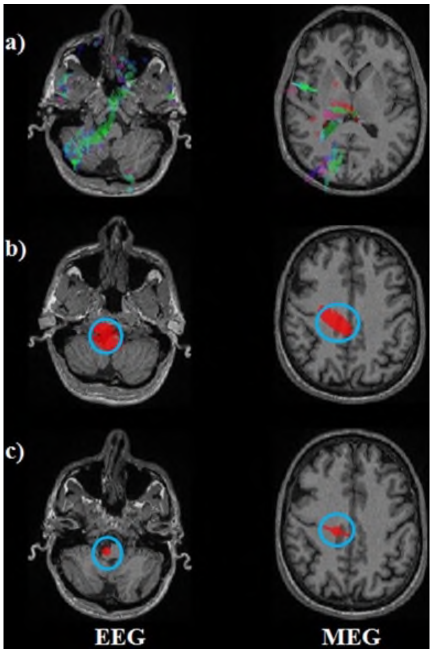

Fig. 1. Dipole-based source-localization results on a single-slice plot of the individual MRI from one of the representative patients using (a) moving, (b) rotating, and (c) fixed MUSIC algorithms. The first and second columns show the results for the EEG and MEG modality, respectively. The location of the induced activity is indicated inside the circle.

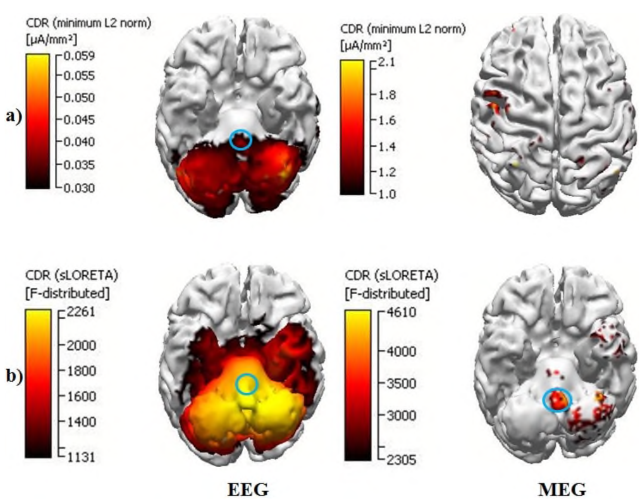

Fig. 2. CDR-based source-localization results on the cortical surface from one of the representative patients using (a) minimum-norm and (b) sLORETA algorithms. The first and second columns show the results for the EEG and MEG modality, respectively. The location of the STN is indicated inside the circle. The color bar indicates the intensity levels of the current density and F-distribution from the lowest (black) to the highest (yellow) level.

was also supported by calculating the euclidean distance to that of the coordinate with the highest distribution for each patient separately (mean±std: sLORETA = 18.45±2.46 mm). However, in MEG it showed less distribution in the STN (mean±std: sLORETA = 61.56±25.07 mm).

V. CONCLUSIONS

In this study, we have used the clinical data obtained form PD patients as a source validation to localize the DBS-induced activity using different source-localization algorithms having STN as an a-priori information about the location of the source. In addition to comparing different source-localization algorithms, differences between the two modalities (EEG vs MEG) were compared. From the dipole approaches we have used moving, rotating, and fixed MUSIC algorithms and found out in all the patients that the fixed MUSIC is best in localizing deep focal sources, whereas moving dipole helps in detecting propagating sources, that is, in this case regions of the brain that are affected by stimulating the STN. From the CDR approaches, we have used minimum-norm and sLORETA algorithms and found out in all the patients that sLORETA outperformed minimum-norm in detecting deeper regions of the brain validating the fact that minimum-norm tends to favor superficial brain regions and underestimate contributions from deeper regions of the brain. Moreover, comparing the modalities, we found out that the source-localization using the EEG modality outperforms that of the MEG validating the hypothesis that MEG is weak in detecting deeper sources as they generate weak magnetic fields. The other time-domain beamforming approaches like the synthetic aperture magnetometry (SAM) and linear constrained minimum-variance (LCMV) could be tested to compare the localization accuracy of these methods in locating the STN DBS electrodes.

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