Effective Connectivity in the Primary Somatosensory Network using Combined EEG and MEG

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***Abstract*— The primary somatosensory cortex remains one of the most investigated brain areas. However, there is still an absence of an integrated methodology to describe the early temporal alterations in the primary somatosensory network. Source analysis based on combined Electro-(EEG) and Magneto- (MEG) Encephalography (EMEG) has been recently shown to outperform the one's based on single modality EEG or MEG. The study and potential of combined EMEG form the goal of the current study, which investigates the time-variant connectivity of the primary somatosensory network. A subject-individualized pipeline combines a functional source separation approach with the effective connectivity analysis of different spatiotemporal source patterns using a realistic and skull-conductivity calibrated head model. Three-time windows are chosen for each modality EEG, MEG, and EMEG to highlight the thalamocortical and corticocortical interactions. The results show that EMEG is promising in suppressing a so-called connectivity 'leakage' effect when later components seem to influence earlier components, just due to too similar leadfields. Our current results support the notion that EMEG is superior in suppressing the spurious flows within a network of very rapid alterations.**

Keywords — primary somatosensory cortex, Electroencephalography, Magnetoencephalography, Functional Source Separation, Finite element modeling, Source Analysis, Connectivity Analysis

I. INTRODUCTION

Electro- (EEG) and magnetoencephalography (MEG) are measurement modalities that offer temporal resolution in the (sub-)millisecond range and thereby allow to non-invasively study network connectivity in the human brain. The primary somatosensory cortex (SI) is a well-investigated network that can offer high Signal-to-Noise Ratio (SNR) somatosensory evoked potentials (SEP) in EEG or fields (SEF) in MEG [1]. Most often, electrical stimulation at the median nerve is applied for eliciting SEP/SEF. The first component arrives at 14 ms post stimulus in the thalamic region, (P14). A first cortical component can be observed at 20 ms (P20/N20), localized in Brodmann area 3b in the primary somatosensory cortex (SI). A next component at 30 ms (N30/P30) has opposite polarity with regard to the P20/N20 and a third can be found at 45 ms (P45/N45) [1]. An emerging question is whether the combination of EEG and MEG can outperform single modality EEG or MEG in source and connectivity analysis of these early thalamocortical connections.

Due to the complementary character of EEG and MEG in theory [2] and in practice [3], a combination of both, EMEG, can enable more robust source reconstructions than the single modalities [3, 4]. While MEG source analysis is mainly not influenced by the inter-individual skull conductivity variations, the EEG is most sensitive to it [3, 4, 5]. In our work, in order to individualize the head volume conductor model and thereby enable a combined EEG and MEG analysis, we will use a calibration procedure, where individual skull conductivity is estimated within the source analysis of the SEP/SEF P20/N20 component [3, 4], and we will individually model white matter conductivity anisotropy using diffusion tensor Magnetic Resonance Imaging (DTI) data [6]. Thereby, we can exploit the complementary characteristics of EEG and MEG for investigating the time-variant alterations in the primary somatosensory network.

The early SEP/SEF responses are temporally close to each other, and a decomposition technique might be necessary before attempting to reconstruct the time-variant primary somatosensory network. Functional source separation (FSS) is a method that has been applied in SEP [7] and SEF [8] responses separately and has led to different yet statistically relevant functional sources – FS. In the present study, we will make use of the FSS algorithm for the distinction of primary somatosensory components from combined SEP/SEF as well as single modality SEP or SEF data. In terms of source reconstruction, we use the standardized LOw-Resolution brain Electromagnetic TomogrAphy – sLORETA, which was shown to not suffer from depth bias in single source reconstruction scenarios [9].

In this study, we will attempt to investigate network alterations in the primary somatosensory network. However, due to the close proximity of the sources in SI, we have to be aware of connectivity leakages between the reconstructed source nodes of the early transient components [10]. A leakage effect may lead to implausible connections within a network. The focus will thus be on testing the ability of EMEG in better suppressing leakage effects when compared to single modality EEG or MEG investigations. As a connectivity estimator, we employ the Generalized Orthogonalized Partial Directed Coherence – GOPDC, which can diminish the co-variability due to spatial smearing [11]. In combination with surrogate analysis, having the goal not to lose the most informative network connections [12], we compare side-by-side the derived networks from EEG, MEG, and EMEG.

In summary, the current study provides a subject-specific pipeline that builds a modular scheme based on advanced methods as follows: (1) FSS to isolate the functional components; (2) given the individually skull conductivity calibrated realistic head model of the participant, source analysis of the back-projected EEG, MEG and EMEG data is performed based on Finite Element Method (FEM) forward modeling and the sLORETA

inverse approach; (3) connectivity analysis is applied to the reconstructed source waveforms using time-varying GOPDC.

The description of methods and data is illustrated in Section II. The results of the study are presented in Section III, followed by a discussion and the outlook in Section IV.

II. Participant and Methods

A. Experimental setup and Preprocessing

A healthy volunteer (32 years old) underwent a median nerve stimulation at the right wrist. The stimulus strength was adjusted until a clear movement of the thumb was observed. The inter-stimulus interval (ISI) was 400 ms with a random deviation of 50 ms to avoid habituation. We used a pulse duration of 0.5 ms. The entire measurement session was ten minutes long and resulted in 1,198 trials. Simultaneous EEG/MEG was acquired with a sampling frequency of 1200 Hz. The EEG system consisted of 80 electrodes, and the MEG system (VMS MedTech Ltd) was comprised of 275 first order axial gradiometers. A 3 T MAGNETOM MRI (Siemens Medical Solutions) was used to measure T1w-, T2w- and diffusion-weighted MR images of 1 mm and 1.9 mm resolution, respectively.

The preprocessing was implemented with the high-level FieldTrip toolbox in MATLAB [13]. In particular, a band-pass filter of 20-250 Hz and a Notch filter suppressing the (harmonics of) power line noise of 50 Hz were applied. The window of each trial was defined as the time interval from -100 to 200 ms, with the stimulus trigger at 0 ms and the stimulus artifact peak at 5 ms.

B. Functional Source Separation and Source Analysis

The FSS isolates each component separately, starting each time from the observed data X and returns the functional source (FS) with the corresponding functional property [7, 8]. The cost function used by the algorithm is defined as $F = J + \lambda R_{FS}$, where J is the kurtosis being used in the independent component analysis (ICA), R_{FSk} is the a priori information and λ is chosen to maximize the influence of the R_{FS} while minimizing the computational time. The prior knowledge for the k^{th} component was computed as:

$$R_{FSk} = \sum_{t_k - \Delta 1 t_k}^{t_k + \Delta 2 t_k} |EA(t)| - \sum_{\alpha}^{\beta} |EA(t)| \qquad (1)$$

where the EA (i.e., the evoked activity) is determined by averaging signal trials of the corresponding source FSk (k = 14, 20, 30 and 45), t_k is the time point with the maximum activation, the $\Delta 1 t_k$ and $\Delta 2 t_k$ denoted the 50% of this maximum activation around t_k and the second term denoted the baseline (no response). The simulated annealing algorithm is employed to find the global optimum of the cost function F, starting from an initial random vector w_{in} until it is converged to an optimal w_{opt}. The parameters we use set as follows: λ is set at $1e5$ for EEG and $1e3$ for MEG; for SA the cooling factor is set to 0.8, the initial temperature at 1, stop temperature at $1e{-}16$ and max iteration at 300.

Source localization was performed on the back-projected FSs of each modality (EEG, MEG, and EMEG) for every time instant, using the sLORETA algorithm on a skull-conductivity calibrated and white-matter anisotropic realistic head model including six tissue compartments (scalp, skull compacta and spongiosa, cerebrospinal fluid (CSF), gray and white matter) [3, 4]. The source waveforms were produced by taking the average power of 100 samples in the source space with the maximum power. FEM forward simulations were applied through the SimBio toolbox (https://www.mrt.uni-jena.de/simbio/index.php/Main_Page). The conductivities were 0.43 S/m for the scalp, 0.0083 S/m for skull compacta, 0.031 S/m for skull spongiosa, 1.79 S/m for CSF and 0.33 for gray matter and anisotropic white matter conductivity was modeled based on the the dMRI data [6]. The source space followed the gray matter folding and the sources fulfilled the St. Venant condition [3]. The total number was 17618 source points.

C. Source Connectivity Analysis

We modeled the effective source connectivity between the components of the somatosensory network by using the time-varying generalized orthogonalized partial directed coherence (tv-GOPDC) [11]. The connectivity analysis was applied for the source waveforms of each modality. A window of 10 ms was selected and an overlap between the previous and the next window (sliding window) of less than 1 ms. Each window was fitted to a multivariable model in order to bring out the causalities between the signals in the coefficients matrix A, which was calculated using the ARfit toolbox [14]. The tv-GOPDC flows were calculated by computing the mean of frequency values, whose outcome was placed at the middle time point of the sliding window. Finally, we assessed the resulting flows through a statistical evaluation for the survival of the significant flows. An empirical distribution of 300 surrogate data was estimated from which a threshold was determined at 90% of the distribution. A flow was determined as significant if it was higher than the aforementioned statistical threshold.

III. Results

The averaged SEP/SEF across all trials are presented in Fig. 1 together with the topographies at the latencies of interest. Clear dipolar patterns occurred for the components P20/N20, N30/P30 and P45/N45 for both EEG and MEG while the P14 had a dipolar pattern with large distance between poles, pointing to the higher depth of the underlying source. When comparing the topographies between EEG and MEG, we observe that the EEG scalp topography is less focal and always perpendicular to the MEG one. Furthermore, the MEG is not able to detect the P14 component.

Fig. 2 illustrates the evoked activities for each modality together with the scalp topographies of the back-projected FS_k at the respective time peaks (dashed lines). We abbreviated it as EAk where k denotes the corresponding functional component of interest (P14, P20/N20, N30/P30 and P45/N45). Each EAk showed an enhancement around the peak of the FSk of interest (dashed lines) of the functional components.

A similar pattern was observed in the source waveforms (Fig. 3) after the application of source analysis for each modality (EEG, MEG and EMEG). Furthermore, the EMEG waveforms of the common components for EEG and MEG preserved higher power than the single modalities (EEG or MEG). In addition, the maximum power of the sLORETA reconstructions is shown on the T1-MRI for the Thalamic component and for the SI components, which were distributed in the area 3b of the primary somatosensory

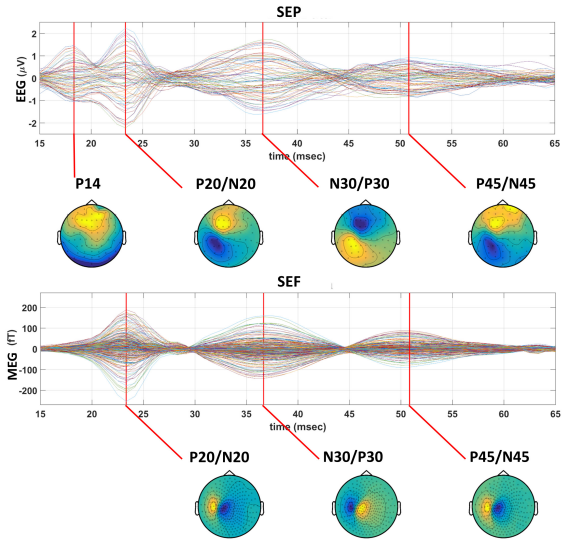

Fig. 1. The averaged SEP (upper row) and SEF (lower row) responses with the topographies of their functional components at the corresponding peaks. Red lines indicate the latency of every depicted scalp topography.

cortex. We could observe that EMEG was able to localize the P14 closer to the thalamus than EEG alone. All other components were localized in or close to area 3b for all modalities, with EEG localizations being slightly deeper.

The time-varying connectivity analysis was performed on the source waveforms, separately for each modality. Three time windows were selected to point out the effective connectivity of: $P14 \rightarrow 3b$, $3b \rightarrow P45/N45$ and $P45/N45 \rightarrow 3b$. The area 3b was reflected by the averaged activation across the P20 and N30 components with average peak at 30

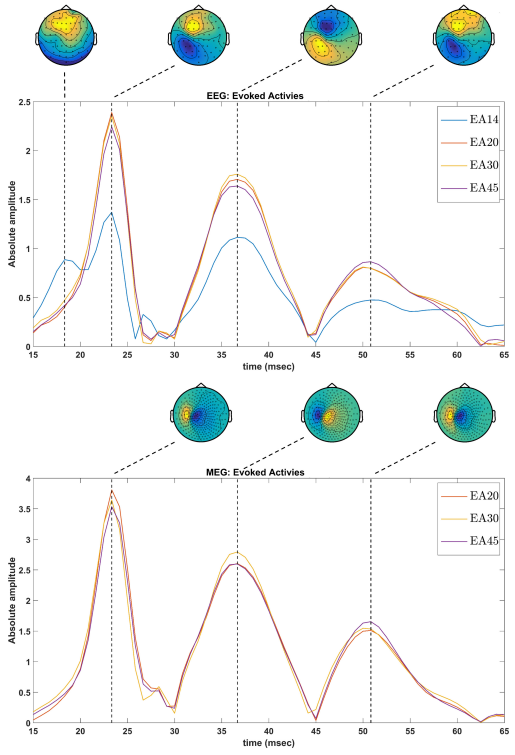

Fig. 2. The evoked activities for every functional component of EEG (upper row) and MEG (lower row). The topographies of the back-projected FS_k (k = 14, 20, 30 and 45) were illustrated at the corresponding peaks (dashed lines) of their functional components. The horizontal axis shows the time in ms and the vertical axis (note the different scaling) represents the absolute amplitude of the evoked activities.

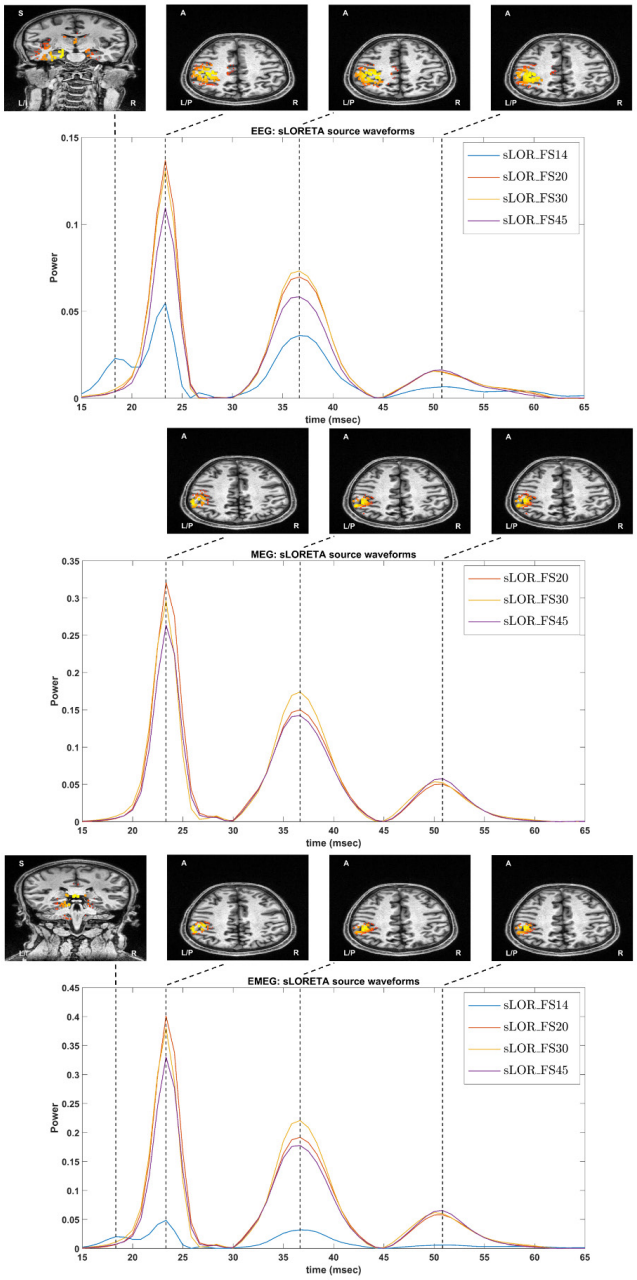

Fig. 3. The source waveforms for each modality EEG, MEG and EMEG with the maximum power of the sLORETA reconstructions visualized on the T1 MRI (coronal view for the Thalamic component and axial view for the SI components) with their specific time peaks (dashed lines). The horizontal axes show the time in ms and the vertical axes (note the different scalings) show the power of the source waveforms.

ms. These windows (Fig. 4) represented the maximum influence of the first component to the second one, around the peak of the former for a range of $\pm$ 5 ms. Quite similar patterns were highlighted among the three modalities for every time window. However, EMEG reduced the spurious flow from P45/N45 to 3b for the first time window (Fig. 4, first column) in comparison with EEG from 0.13 (EEG) down to 0.08 (EMEG). Furthermore, EMEG strengthened the possible flow in the later time-window (Fig.4, right column) from P45/N45 to 3b when compared to the EEG from 0.07 (EEG) to 0.12 (EMEG).

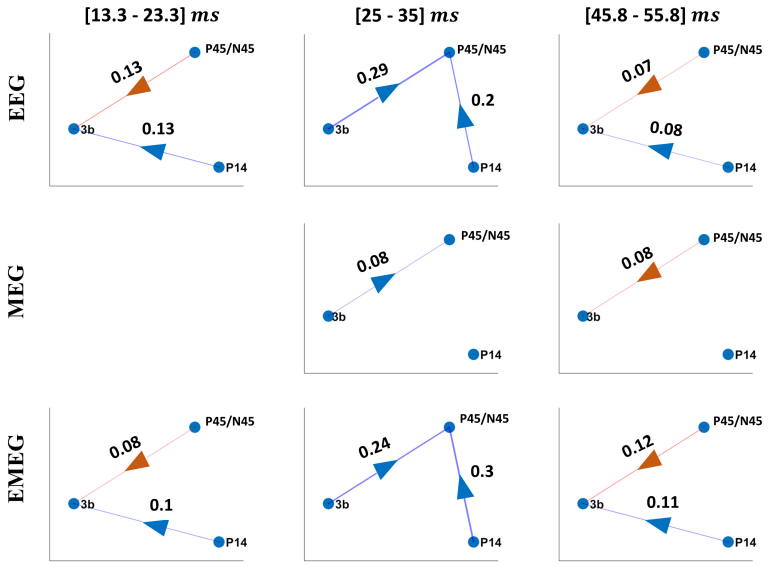

Fig. 4. The causality graphs of each modality for three specific time windows. For these windows, the maximum influence of the P14, 3b and P45/N45 was represented at a range of ± 5 *ms* around their peaks to the 3b, P45/N45 and 3b, respectively. The forward flow was represented with blue and the backward with red. Additionally, the MEG was not able to detect activities from P14. For this reason it was not interacting with the other components. Only the flows that survived the statistical evaluations were presented.

IV. Discussion and Outlook

In the present subject-specific study, we proposed a pipeline for connectivity analysis of early somatosensory evoked responses using a modular sequence of novel techniques, such as the functional source separation, the use of individual and calibrated head models and the combined EEG and MEG source analysis. We used the separation algorithm, FSS, to decompose the somatosensory evoked responses into functionally independent components. The realistic head model used in source localization comprised six compartments, involving skin, skull compacta, skull spongiosa, CSF, gray and white matter, including the brain anisotropy and calibrated skull conductivities. Our study indicates that, while the main problem of decomposing the single components with quite similar spatial topography is nearly identical in EMEG or single modality EEG or MEG, the combined EMEG uses the complementary information of both modalities and reduces the most probably spurious flow from the later cortical P45 component to the earlier 3b component in the early time-window of the most probably mainly thalamo-cortical flow. Thereby, the EMEG is considered superior in source analysis compared to the single EEG or MEG, see also [4]. Finally, the tv-GOPDC can detect a dynamic response of the brain in the somatosensory experiment even if the network has rapid alternations.

Our EMEG source network brought together the complementarity of EEG and MEG [2] for modeling the rapid alterations within the somatosensory network at very early time instants. Comparing with previous attempts, the authors in [8] achieved to enhance the somatosensory functional source responses by applying FSS on SEF responses. Later, study [7] utilized the FSS method for the decomposition of the early SEP components, but their source estimations were based on simplified head models of standard tissue conductivity and thereby, the proposed results might be influenced due to the vulnerability of the electric potentials to tissue conductivity changes [3, 4, 5]. In the present work, we showed that FSS was able to derive components for all types of measurement modalities. The source reconstructions were accurately estimated in Brodmann area 3b and near to the thalamus by using an individually calibrated realistic head volume conductor model.

With regard to the resulting causal networks, we could observe the directed connections between the investigated components. The present results show that EEG was able to detect also the deep thalamic source, while MEG was insensitive to it [3]. However, the EEG-only based network reconstructions contained a higher connectivity leakage [10] in the thalomocortical connections, which were alleviated when we combined SEP and SEF in the EMEG. The EMEG-based network reconstructions will additionally allow more precise source localizations, due to the MEG mm accurate localization properties for lateral and mainly tangentially-oriented SI sources and the therefore much lower sensitivity of the MEG SI source reconstructions to individual tissue conductivities [3, 4].

Due to the low number of subjects (single subject study), the present functional source separated components and the revealed source network results cannot be generalized to other subjects, we therefore would need to run a group-study, as planned in our future investigations. In [15], for example, it was shown that in 10 out of 12 subjects, the thalamus did not contribute to the peak of the P20 component, while in 2 out of 12, there was still an overlaid activity. Network connectivity might thus also have inter-individual differences.

To conclude, in this work we developed an integrated approach for the design of a novel pipeline that should improve the reconstruction of causalities in neural networks. Limitations are network components of nearly the same origin and nearly the same (or inverted) orientation. The advantages of the proposed pipeline can be seen in using the complementarity of EEG and MEG, focusing on specific subject characteristic and in better revealing close temporal causalities of components by suppressing spurious interaction activities. However, leakages on the connection

of nodes occurred in all modalities, they were reduced, but not eliminated, by the use of EMEG. Even though further experiments are needed as described above, our study supports the notion that network connectivity investigations can profit from the use of EMEG and source reconstructions that are based on individually skull-conductivity calibrated realistic FEM head models.

This study was based on the recently defended diploma thesis at the Technical University of Crete [16].

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