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COMMENTARY

Intracerebral Sources Reconstructed on the Basis of High-Resolution Scalp EEG and MEG

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This question discussed in two recent papers published in *Nature Communications* (Pizzo et al. 2019; Seeber et al. 2019), has been an important matter of debate in Electroencephalography (EEG)/Magnetoencephalography (MEG) for a long time. The crucial question is whether subcortical Local Field Potentials (LFPs) can reach the scalp EEG by volume conduction? This question may be formulated in a similar way: can "high resolution EEG scalp recordings, or MEG signals, be used to estimate corresponding sources localized in deep subcortical brain areas?"

The Nature of Local Field Potentials

In order to be able to validate such estimates it is necessary to have independent measures of the intracerebral LFPs comparable with the estimated local field potentials directly recorded in the same subcortical areas. A fundamental question is: what are these intracerebral sources? In this context, we have to realize that many intracranial sources of LFPs form "closed fields" according to the nomenclature introduced by Lorente de Nó, in a classic study (Lorente de Nó 1947). He called those electrical fields generated by neurons with dendritic arborizations radially distributed about the soma "closed fields". This may be interpreted as implying that under these circumstances, not only the tangential but also the radial components of the currents would cancel in the far field. But it should be realized that the real situation is rather more complex. The amplitude of extracellular field depends on how well the centers of gravity of the sink and the source are separated, and also on the resistance of the extracellular medium. In short, in a polarized (pyramidal) neuron this would resemble the field of a dipole. Many intracerebral Local Field sources are constituted by these kinds of configurations, most field potentials are composed of the linear superposition of currents generated by a large number of neurons, their "synchrony" (overlap in time) constitutes an important issue; experimental evidence indicates that synchronous action potentials can still contribute substantially to high-frequency components of the EEG signal, for example when neurons are synchronized through gap junctions (Einevoll et al. 2013). Thus, a local field may represent low-frequency activities originating from postsynaptic currents (< 250 Hz), but also high-frequency components (> 250 Hz) often indicated as high-frequency oscillations, such as ripples and fast ripples associated with spiking activity (Wadman and Lopes da Silva 2018). The main question discussed in the papers referred above is whether these Local Field Potential intracerebral configurations can be estimated based on scalp recordings.

Different Analytical Methods

It is most interesting to note that those two papers used different analytical approaches. In the latter study (Seeber et al. 2019) the analytical tool used consisted of correlation analysis; the assumption was that the time course of a cortical signal should correlate with the time course of source-estimated signals proximal to the intracranial electrode, if the scalp EEG indeed would detect subcortical neuronal activity through volume conduction. The same should also apply to the MEG. According to this approach EEG source dynamics were reconstructed using distributed source modeling (Michel et al. 2004; Grave de Peralta et al. 2004; Michel and Murray 2012; Michel and He 2017) based on realistic head models (Birot et al. 2014; Michel and Brunet

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2019) derived from the individual MRI scans. EEG source imaging results were compared with the positions of actual intracerebral electrode, identified using computer tomography (CT), that were we spatially aligned using data from different modalities.

This investigation shows that alpha envelopes recorded from intracranial electrodes correlated with EEG source reconstructed signals, located to subcortical regions in close proximity to the actual electrode sites of intracranial recordings, obtained using bipolar recalculated recordings, while the scalp EEG recordings were recalculated offline against the average reference. These recordings were performed in Gilles de Tourette Syndrome (GTS) and in obsessive–compulsive disorder (OCD) patients undergoing electrode implantation in order to realize deep brain stimulation (DBS) therapy.

In the former study (Pizzo et al. 2019) the analytical approach consisted of independent component analysis (ICA). This enabled activity arising from large neocortical networks to be disentangled from that of deeper structures, the amplitude of which at the cortical surface was small, although significant. In this way the authors were able to measure non-invasively hippocampal and amygdala brain activity. Consequently, these authors identified different networks: namely, mesial (M) networks, confined to mesial temporal structures (i.e. amygdala or hippocampus), lateral (L) networks involving only lateral neocortical structures, and mesio-lateral (ML) networks involving mesial and lateral structures. Furthermore the authors classified as extended limbic (eL) those networks that correlated with structures of the limbic circuitry outside the temporal lobe, such as the thalamus, the insula and the orbitofrontal cortex. It should be noted that not in all patients the same networks could be identified. Each ICA component could be seen as the surface representation of the brain structure/s (SEEG signals) with which it is correlated.

Main Results According to the Latter Study: Seeber et al. 2019

The finding that scalp EEG can detect subcortical sources, in the case of alpha rhythms, shows that EEG contains both, cortical and subcortical signals and non-significant ESI correlation. The absence of a well-pronounced alpha peak at the right hemispheric electrode in one patient is concomitant with no significant cross-correlation between hemispheres, and it indicates that a clear signal must be present in subcortical recordings in order to locate that signal with scalp EEG (Krishnaswamy et al. 2017).

The finding that EEG alpha waves contain thalamic activity, does not imply that thalamocortical interactions might be the only alpha source (Lopes da Silva et al. 1980). EEG source imaging considers solely volume conduction, no active processing in cortical structures. Because in this study intracranial recordings were used as a covariate in the source reconstruction analyses to isolate thalamic signals, the EEG source images intentionally show the reconstructed counterpart of these signals, not the cortical activity driven by thalamic interactions.

In earlier experimental work in animal (Lopes da Silva et al. 1973), alpha-rhythms with the same peak frequency were recorded from both cortical and thalamic areas at the same time, but the coherences between related cortical areas were consistently larger than the thalamo-cortical coherences. This is in line with the fact observed in this investigation that that correlation analysis of intracranial and scalp EEG leads to correct identification of the subcortical sources and is not contaminated by scalp alpha activity but loosely related to subcortical signals, although appearing at the same time.

Main Results According to the Former Study: Pizzo et al

In this paper the authors report the possibility of recording activities generated in specific mesial temporal lobe structures including the amygdala and the hippocampus using MEG, in patients with focal drug-resistant epilepsy. The results are based on simultaneous MEG and SEEG recordings (Dubarry et al. 2014; Badier et al. 2017). This approach enables assessments on exactly the same signals. Importantly, the independent component analysis (ICA) is powerful as a way to disentangle networks in which activities are mixed at the sensor level. Furthermore, the authors were also able to obtain evidence of MEG detectability of other deep brain structures outside the temporal lobe, such as the thalamus. Most important the authors demonstrate that ICA could automatically separate the different mesial temporal activities, also including pure hippocampal activity. To avoid capturing a source not visible by SEEG, the authors introduced also a series of strict tests to the correlation analysis, including zero-lag analysis, across both temporal and trial dimensions.

Interestingly the authors achieved the conclusion that current methods of source localization are not fully adapted for the localization of mesial structures (Attal et al. 2009; Meyer et al. 2017). This may due to the "depth of the generators, their geometry, the low signal to noise ratio and the difficulty in obtaining noise covariance matrix for ICA topographies all hamper the current techniques." Furthermore, the orientation of the dipolar source should also be considered, an important issue.

They recommend that future studies should be done to optimize source localization methodology to improve detection of mesial structures. Nonetheless the authors show that an overall sensitivity of 0.81 for source localization of mesial ICA components was found, what can be considered a relatively high score. Furthermore, an important additional finding is the observation that besides the relevance of the hippocampus and amygdala, also other subcortical structures participate in subcortical epileptic networks, namely the thalamus, putamen, orbitofrontal cortex and insula.

Some General Conclusions

The two papers are remarkable because they address an important question that has been a focus of attention and controversies in the EEG/MEG literature. The two papers discussed here adopted further but related approaches: correlation analysis (Seeber et al. 2019) and a decomposition by Independent Component Analysis (Pizzo et al. 2019). These approaches are based on two main assumptions: (1) the summation of potentials arising from the different parts of the brain and the body is linear at the electrodes (superposition principle) and (2) diffusion delays from the sources to the electrodes are negligible (instantaneous diffusion due to volume conduction).

In this way signals can be decomposed in separate linear decomposition of various contributions of sources (for example, cortical EEG or MEG and subcortical signals) to the mixed signal collected at the level of scalp electrodes. This approach belongs to the so-called "Blind Source separation (BSS)" family of methods where "blind" refers to the fact that the separation relies only on statistical assumptions on the source process, whereas no information or hypothesis is required about the biophysical or physiological aspects of the sources and volume conductor. The superposition principle and instantaneous diffusion makes it possible to relate linearly of the source process.

A popular member of the BSS family is independent component analysis. In this case, the only assumption is that the sources are statistically independent. As a consequence, at most one of them may be Gaussian, which is the main limitation of this method. The application of ICA-based methods in the EEG field has been extensively developed over the past decade. The measured observations are multiplied by the pseudo-inverse (Moore–Penrose matrix inverse) of the estimated mixing matrix, namely the "un-mixing" matrix B, in order to identify the source processes adequately (Malinowska et al. 2014; Wendling et al. 2018).

In the context of cortical—thalamic relationships Roux et al. (2013), based on MEG data, used TE (Temporal Entropy, a method derived from the concept of Mutual Information) to analyze the coupling between gamma and alpha oscillations in cortical and thalamic sources; in this way these authors estimated time delays between thalamic and cortical sources that are compatible with independent neurophysiological findings obtained in animals. Thus, we can see that the analytical approach used in both papers discussed here, is closely related with these theoretical concepts. This highlights the importance of the criteria's choice that was made by the authors of both papers.

In addition to the importance of these papers concerning analytical methodology, it is also very relevant to emphasize the importance of the main neuroscientific findings. The `Seeber et al.'-paper showed clearly that EEG/MEG alpha waves contain thalamic activity, and thus that the latter can be recorded at the level of the cortex using appropriate analytical methods. The 'Pizzo et al.'-paper reports the important finding that besides the relevance of the hippocampus and amygdala in patients with mesiotemporal epilepsy, also other subcortical structures participate in subcortical epileptic networks, namely the thalamus, putamen, orbitofrontal cortex and insula.

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