Title: Novel clinical MEG/MSI approach to detect and localize the subtle and non-localizing epileptogenic events.

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Background: MEG is used in phase-1 evaluation of refractory epilepsy patients to delineate the epileptogenic foci. There are circumstances where identifying interictal epileptiform discharges (IEDs) in the raw data can be challenging, and or the standard single dipole fitting method may fall short in modeling some of these epileptogenic events. Here we propose a strategy to identify the interictal events and subsequently localize or map their source generators. **Methods:** We prospectively applied this strategy in 23 patients during our first clinical MEG meeting, when there was a concern or difficulty with the detection or localization using traditional equivalent current dipole fitting method. The effectiveness of this approach was evaluated on different levels, including Level I: Consistent agreement with the standard dipole fitting approach findings; Level II: Able to identify events that is not detectable in the raw data; Level III: inability of employing standardized methods to localize the source of non-localizing events. The recorded MEG data was analyzed with a unique strategy (Velmurugan et al 2022) by combining the spatial filter (minimum variance adaptive beamformer) and a blind source separation (independent component analysis-ICA). The resulting source components were then reviewed manually for the presence of IED on the basis of their electrophysiological characteristics and morphology. Presumed epileptogenic zone (EZ) was estimated for each patient based on their pre-surgical electrophysiological (EEG and video telemetry) and neuroimaging (MRI/PET/SPECT) studies. We evaluated the concordance between presumed EZ and the source localization results obtained using our approach. **Results:** MEG data was reviewed for distinct spikes, polyspikes, sharp waves, beta bursts, ictal-interictal continuum and rhythmic focal slowing amidst the background activity. The current approach detected additional interictal events that were not detected during the conventional MEG data review in 6 patients (26%) at the level 2. Non-localizing and subtle events identified during conventional clinical analysis were able to successfully localize in 11 patients (48%) at the level 3. In another 6 patients (26%), obtained results agreed to the conventional ECD modeling at the level 1 agreement. In 76% of the patients (n=19), more interictal episodes were detected utilizing our method than during the traditional review. The source localization results generated using the suggested technique demonstrated a substantial spatial concordance with the assumed EZ (Cohen's k =0.79). Our approach provided insight and assisted in the challenging clinical interpretation especially in the following EZ regions: mesial frontal and deep sources such as cingulate, insular,sulcal depth, mesial temporal sources, multifocal epilepsies and bitemporal epilepsies (Figure-1).**Conclusion:** This analytical strategy intends to enhance the IED detection and localization accuracy of the epileptogenic zone. Additionally, it minimizes the arbitrary bias of choosing interictal spikes and determining a time interval to simulate the dipole fit.

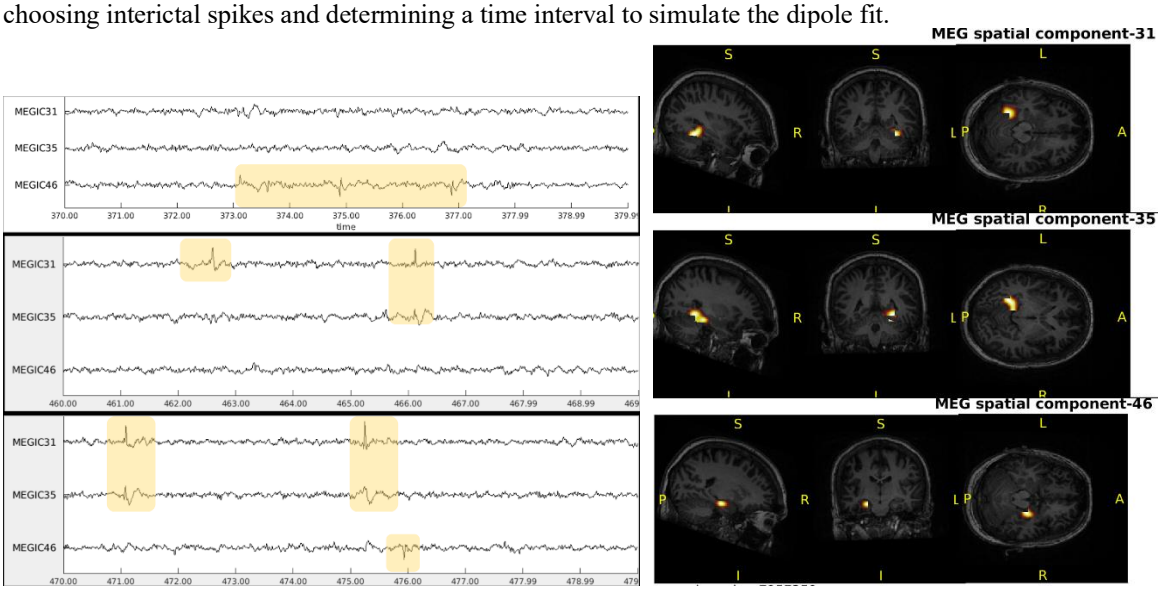

Figure-1: *This figure illustrates a patient with bi-temporal focal cortical dysplasia where routine EEG and MEG reading picked up only the left temporal spikes and sharp waves (MEG IC-31 and 35). However, with the proposed approach we were able to detect the asynchronous low amplitude spikes and sharp waves in the right mesial temporal lobe which is consistent with this patient's presumed epileptogenic zone.*