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Fully automated quality assurance and localization of volumetric MEG for single-subject mapping

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HIGHLIGHTS

- Automated quality assurance and thresholding for volumetric MEG maps were demonstrated.
- This method produces a previously lacking QA metric that parallels goodness of fit used in dipole models.
- Automated thresholding produces strong co-localization with dipole mapping in simple paradigms.
- Our method is ideally suited for single-subject MEG mapping including when complex activation is expected.

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ABSTRACT

Background: Robust and reproducible source mapping with magnetoencephalography is particularly challenging at the individual level. We evaluated a receiver-operating characteristic reliability (ROC-r) method for automated production of volumetric MEG maps in single-subjects. ROC-r provides quality assurance comparable to that offered by goodness-of-fit (GoF) and confidence volume (CV) for equivalent current dipole (ECD) modeling.

New method: ROC-r utilizes within-session reproducibility for quality assurance, latency identification, and thresholding of volumetric source maps. We tested ROC-r on simulated and real MEG with a strongly focal source, using somatosensory evoked fields (SEFs) elicited by bilateral median nerve stimulation (MNS). For quality assurance, the ROC-r reliable fraction (F_R) was compared to the ECD GoF and CV. Peak beamformer locations and latencies identified by ROC-r were compared to the ECD for co-localization accuracy.

Results: The predominant component of the SEF response occurred around 35 ms, contralateral to the MNS.

Comparison with existing methods: F_R and 1/CV were more strongly correlated (mean Pearson's correlation: 0.76; 95% CI 0.60–0.87) than F_R and GoF (0.65; 95% CI 0.32–0.85). There was no difference in the latency of the peak GoF (35.0+/−0.6 ms), CV (34.8+/−0.7 ms) and F_R (35.5+/−0.8 ms). The ECD fits and ROC-r peaks co-localized to within a mean (median) distance of 8.3+/−5.9 mm (6.2 mm).

Conclusion: ROC-r volumetric mapping co-localized closely with the standard ECD approach. This analysis can be added to any whole-brain MEG source imaging protocol, and is especially useful for single-subject mapping. Additionally, the development of F_R as an analogue to GoF or CV for volumetric mapping is a critical improvement for clinical applications.

1. Introduction

Magnetoencephalography (MEG) localizes functional neuroanatomy based on relatively direct measurements of cortical electrical activity. Most localization studies use the equivalent current dipole (ECD) model (Kanno et al., 2004; Lin et al., 2005; Huttunen et al., 2006), which has been validated in a number of pre-

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surgical mapping studies (Sutherling et al., 1988; Inoue et al., 1999; Oishi et al., 2003; Korvenoja et al., 2006; Niranjan et al., 2013). The ECD model is attractive because of its simplicity, and well-defined goodness-of-fit (GoF) and confidence volume (CV) parameters for quality assurance. It is common to see GoF as a criterion for selecting dipoles in pre-surgical mapping with ECD (Oishi et al., 2003). However, the validity of the ECD model is suspect for distributed cortical activity or multiple cortical sources, with more complicated evoked fields. Models using multiple dipoles are available, but require *a priori* specification of the number of dipoles. This makes them challenging for clinical practice due mainly to poor inter-rater reliability.

More recently, studies have used volumetric source models to overcome limitations of the ECD model and have clinically validated the accuracy of volumetric source models (in this case, the beamformer spatial filter) in pre-surgical mapping applications (Cheyne et al., 2007; Nagarajan et al., 2008; Pang et al., 2008; Tarapore et al., 2012). Volumetric source models generate whole-brain source maps capable of describing multiple or distributed cortical sources, alleviating the need to specify the number of dipoles. Despite increasing use in pre-surgical mapping, there is no established method for quality assurance of volumetric source models. Additionally, thresholding of single-subject maps is often based on *a priori* expectations for the clinically relevant activation patterns, undermining improvements in inter-rater reliability achieved by moving away from ECD models. A method to assess the quality of volumetric source maps and determine appropriate threshold levels is needed.

We have thus developed methods for quality assurance and automated thresholding of volumetric MEG source maps to improve the reproducibility of the source modeling process. Our approach uses a receiver–operator curve reliability (ROC-r) framework previously demonstrated for fMRI mapping (Stevens et al., 2013). The advantages of ROC-r are two-fold. Firstly, ROC-r provides quantitative measures of source map reliability, increasing confidence in localization results. Secondly, ROC-r identifies optimal data-driven thresholds, facilitating push-button processing of volumetric source maps. This reduces the reliance on *ad hoc* thresholding and decreases inter-rater variability. Thus the addition of ROC-r analysis to whole-brain MEG mapping enhances the detection of MEG activity in single subjects, notably for clinical applications like pre-surgical mapping.

In this study, we aim to validate the ROC-r method for quality assurance and thresholding of volumetric MEG maps by comparison with the ECD quality measures (GoF, CV) and localization. While the greatest benefit of volumetric MEG source mapping over ECD localization is for distributed source configurations, our validation is performed first with simulated MEG data, and followed with real MEG data, with a single, focal source to provide ideal conditions for ECD modeling. The most robust MEG localizations are typically realized with somatosensory evoked field (SEF) mapping (Sutherling et al., 1988), for which the most ubiquitous paradigms are median nerve stimulation (MNS: Inoue et al., 1999; Korvenoja et al., 2006), vibrotactile stimulation (Bardouille and Ross, 2008), and pneumatic stimulation (Castillo et al., 2004), all of which elicit sensory evoked fields (SEF) from the contralateral primary somatosensory cortex.

MNS is a particularly suitable choice for validation of ROC-r quality assurance, as it is also used intra-operatively to map the central sulcus *via* phase reversal of surface electrocorticography (Inoue et al., 1999), and generally provides robust localization of the early SEF response in single subjects. In particular, the MNS SEF has been shown to contain three distinct peaks at 20, 35, and 60 ms (Huttunen et al., 2006). Most clinical studies have focussed on the 20 ms response (Inoue et al., 1999; Oishi et al., 2003; Korvenoja et al., 2006), however the 35 and 60 ms evoked fields are typically stronger, easier to detect, and originate from the same cortical gyrus (Lin et al., 2005; Huttunen et al., 2006). In this work, following the validation with simulated data, we will thus use the 35 ms component of the MNS SEF as a robust test case to demonstrate the utility of ROC-r analysis for single-subject volumetric MEG mapping.

We will show that ROC-r provides quality assurance metrics for whole-brain MEG mapping analogous to the GoF and CV of the ECD model. Furthermore, we will show that ROC-r automated thresholds identify brain areas well-matched to those determined using ECD in both simulated and real MEG data. These findings establish the utility of ROC-r for future application to pre-surgical MEG mapping, by introducing quantitative measures of data quality and automated methods for detecting significant areas of activity. Although we demonstrate the application of ROC-r to a predominantly dipolar evoked field, this technique could be applied to a variety of paradigms, and can be readily extended to the case of volumetric mapping of multiple dipoles.

2. Methods

2.1. Data collection

Eighteen healthy volunteers participated in this study (10 females; age 19–29, mean 24 years). The study was approved by the local ethics board, and subjects provided informed consent. Each participant completed an MEG session during which the somatosensory cortices were localized using bilateral MNS, as part of a larger study. Head position indicator coils placed on both the left and right temples and mastoids monitored head position throughout the MEG scan. The nasion, left/right pre-auriculars, and scalp surface were digitized for source modeling. Electrooculargraphy (EOG) electrodes were placed above and below the left eye and lateral to each eye for the removal of artifacts. MEG and EOG data were collected at 1000 Hz sampling frequency, with an in-line 0.1–330 Hz filter using a whole-head 306 channel Neuromag system (Elekta AB, Stockholm, SE).

2.2. MNS paradigm

Both primary somatosensory cortices were mapped using bilateral electrical MNS. Motor thresholds were determined by applying supra-threshold stimulation, and reducing the stimulation strength until thumb twitches were no longer discernible. Sub-threshold stimulation was delivered in single 0.5 ms pulses 1–2 s apart. Eighty to one-hundred stimuli were applied to each side in random order to localize the P35m component of the SEF. Clinically, somatosensory mapping uses the N20m, which requires approximately 200 to 500 stimuli per side. However, only P35 m localization was necessary for the larger study. Like the N20m, the P35 m component of the SEF has a focal distribution and localizes to the post-central gyrus. As such, we considered the P35 m component to be sufficient for testing our single subject localization method.

2.3. Data pre-processing

MEG data were pre-processed to create the SEF responses to left and right MNS. Following environmental noise reduction with temporal signal space separation (Taulu and Simola, 2006), a low-pass filter was applied (70 Hz), and data were down-sampled to 250 Hz. Independent component analysis was performed to remove components correlated with the EOG signals. The data was segmented into epochs relative to the left or right MNS onset ($-200 < t < 200$ ms), and baseline corrected for the -100 to 0 ms period. The epoched MEG data were averaged for left and right MNS separately to generate SEF responses.