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MEG language lateralization in partial epilepsy using dSPM of auditory event-related fields

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ABSTRACT

Objective: Methods employed to determine hemispheric language dominance using magnetoencephalography (MEG) have differed significantly across studies in the choice of language-task, the nature of the physiological response studied, recording hardware, and source modeling methods. Our goal was to determine whether an analysis based on distributed source modeling can replicate the results of prior studies that have used dipole-modeling of event-related fields (ERFs) generated by an auditory word-recognition task to determine language dominance in patients with epilepsy.

Methods: We analyzed data from 45 adult patients with drug-resistant partial epilepsy who performed an auditory word-recognition task during MEG recording and also completed a language fMRI study as part of their evaluation for epilepsy surgery. Source imaging of auditory ERFs was performed using dynamic statistical parametric mapping (dSPM). Language laterality indices (LIs) were calculated for four regions of interest (ROIs) by counting above-threshold activations within a 300–600 ms time window after stimulus onset. Language laterality (LL) classifications based on these LIs were compared to the results from fMRI.

Results: The most lateralized MEG responses to language stimuli were observed in a parietal region that included the angular and supramarginal gyri (*AngSmg*). In this region, using a half-maximal threshold, source activations were left dominant in 32 (71%) patients, right dominant in 8 (18%), and symmetric in 5 patients (11%). The best agreement between MEG and fMRI on the ternary classification of regional language dominance into left, right, or symmetric groups was also found at the *AngSmg* ROI (69%). This was followed by the *whole-hemisphere* and *temporal* ROIs (both 62%). The *frontal* ROI showed the least agreement with fMRI (51%). Gross discordances between MEG and FMRI findings were disproportionately of the type where MEG favored atypical right-hemispheric language in a patient with right-hemispheric seizure origin ($p < 0.05$ at three of the four ROIs).

Significance: In a parietal region that includes the angular and supramarginal gyri, language laterality estimates based on dSPM of ERFs during auditory word-recognition shows a degree of MEG-fMRI concordance that is comparable to previously published estimates for MEG-Wada concordance using dipole counting methods and the same task. Our data also suggest that MEG language laterality estimates based on this task may be influenced by the laterality of epileptic networks in some patients. This has not been reported previously and deserves further study.

1. Introduction

Determining hemispheric language dominance is an important step in the presurgical evaluation of patients with drug resistant epilepsy. For over 50 years the Wada test has been the gold standard to determine language laterality (LL) in patients being evaluated for neurosurgical procedures [1]. The procedure, however, has drawbacks: it is invasive, is susceptible to invalid studies from both excessive and inadequate anesthetization of a hemisphere, and is associated with a small but significant procedure-related morbidity [2,3]. Over the past couple of decades, noninvasive methods to assess hemispheric language dominance have been developed by several groups.

Although MEG is increasingly utilized in presurgical evaluations to localize epileptic dysfunction in the cortex [4], it has yet to find wide use across epilepsy centers for lateralizing language dominance. The feasibility of determining hemispheric language dominance with MEG has however been demonstrated using several different methods [5–14]. These methods differ from each other on several key dimensions: (1) language tasks (the sensory modality used for stimulus delivery

Abbreviations: MEG, magnetoencephalography; ERF, event-related field; dSPM, dynamic statistical parametric mapping; ROI, Region of Interest; LI, laterality index; LL, language laterality; ECD, equivalent current dipole; CRM, Continuous Recognition Memory.

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and cognitive processes engaged), (2) MEG sensor type (gradiometers versus magnetometers or both), (3) physiological response studied (event-related fields versus oscillatory power changes in the beta and gamma bands), and (4) the nature of the source modeling method employed (single dipole modeling versus source imaging methods) [15]. There is no consensus yet on optimal MEG methodologies for lateralizing language dominance in clinical applications.

Of the many language tasks that have been employed in clinical MEG studies, a simple word-recognition task (often referred to as a *Continuous Recognition Memory*, or CRM task) [8,13,16–18] has been extensively studied in epilepsy patients using both auditory and visual stimuli. The most comprehensive of these studies compared MEG language lateralization (LL) based on dipole modeling of event-related fields (ERFs) generated by an auditory CRM task against the Wada test in 100 consecutive patients with drug resistant epilepsy. The authors found a high degree of concordance (87%) between the two methods in the 85 patients where satisfactory ERFs were elicited [8]. A more recent study of 35 epilepsy and brain-tumor patients by an independent group using the same task and methods found a concordance rate of 69% between the Wada test and MEG [18] for the ternary classification of LL into left, right, or "bilateral" (i.e., symmetric). A Spanish version of the task has also been studied in a small series of patients [19], and was found to yield a high concordance with the Wada test in determining LL. The same task and analysis methods have been shown to successfully lateralize language in children with epilepsy, both with and without sedation during stimulus presentation [17,20]. In all of these studies equivalent current dipole (ECD) models were estimated separately over each hemisphere at fixed intervals of time during the late portions of the auditory ERFs, and language laterality (LL) indices were calculated from the number of dipoles in each hemisphere that met acceptance criteria.

While point-dipolar sources are typically satisfactory for modeling focal cortical activity such as epileptic spikes or evoked responses from primary sensory cortices, they may be suboptimal for modeling cortical activity that is spatially extensive, such as those during language processing. For instance, two separate areas of strong cortical activation within a region would yield a poorly fitting single dipole. This could potentially undermine laterality estimates based on counting dipoles that meet acceptance criteria [15]. The dipole counting method also requires estimation of ECD models using separate sensor groups for each hemisphere. Together with differences in hardware and analysis software between MEG systems, this can pose significant challenges in reproducible implementation across centers. Distributed source modeling techniques [21] provide alternative approaches to explore the spatial topography of task-related cortical activation.

We wanted to determine if an analysis based on distributed source modeling of ERFs during auditory word-recognition yields language lateralization results in patients with epilepsy that are comparable to those previously reported using dipole-counting methods [8,16–18,20]. We compared our MEG results to those from a well characterized fMRI language protocol that the patients underwent as part of their clinical evaluation [22] in much the same way that prior MEG studies in clinical populations have compared their results to those from the Wada test.

2. Materials and methods

2.1. Patients

Study subjects were recruited retrospectively from among patients evaluated at the Adult Comprehensive Epilepsy Program at the Medical College of Wisconsin for epilepsy surgery. All patients had completed a clinical MEG study during which an auditory word-recognition task was performed, and also completed an fMRI study of language as part of their presurgical evaluation. We enrolled a consecutive series of 45 adult patients who provided written informed consent for research use of MEG recordings, fMRI data, and relevant clinical variables under a protocol approved by the Institutional Review Board of the Medical College of Wisconsin.

2.2. MEG recording

All MEG data were collected at Froedtert Hospital (Milwaukee, WI, USA) using a 306-channel (204 planar gradiometers and 102 magnetometers) whole-head biomagnetometer system (Vectorview, Elekta Neuromag Ltd., Helsinki, Finland) located in a magnetically shielded room (ETS-Lindgren, Eura, Finland). Data were recorded with a 0.03 Hz high-pass filter. The sampling rate for the recordings was 1000 Hz (with a 330 Hz low-pass filter) in all but nine of the earliest studies in this series, where the sampling rate was 1500 Hz (with a 495 Hz, low-pass filter). EOG and EKG tracings were also acquired simultaneously for off-line artifact removal. All patients underwent simultaneous EEG recording using 22 scalp silver/silver-chloride EEG electrodes (Ambu® Neuroline Cup electrodes, Ambu Inc., Maryland, USA). An empty-room recording of at least 3 min was performed before acquiring data from each patient. Patients were screened for the presence of metallic artifacts such as dental work using a metal detector (Garrett Model 1165190, Garland, Texas, USA). As standard protocol for all MEG recordings, the presence of magnetic interference is routinely screened for using a brief MEG recording prior to acquisition of clinical data. The language task was performed in a supine position in seven of the earliest studies in our series; patients were seated in an upright position in subsequent studies.

Since our language tasks were performed during MEG studies that were part of evaluations for epilepsy surgery, patients were sleep deprived the night before to increase the yield of epileptic spikes. They were encouraged to sleep during the initial portion of the MEG recording. They were woken up after a minimum of at least 40 min of satisfactory MEG recording and allowed a break before task-related MEG recordings were performed. Patients were monitored during task-performance by the MEG technologist to make sure they remained alert, continued to maintain fixation on a target presented on a screen, and responded to target trials. However false-negative or false-positive responses were not recorded to permit assessment of accuracy.

2.3. Language task

Our language task was similar to the version of the auditory CRM task described by Rezaie et al. [20]. The stimuli consisted of 5 target words and 40 distractor words, which were read by a native English speaker digitized at a sampling rate of 44,100 Hz with 16-bit amplitude resolution. Mean stimulus duration was 586 ms (range 395–925 ms). Three blocks of the word stimuli were created, each mixing the 45 words in random order. The auditory stimuli were presented using E-Prime 1.2 software (Psychology Software Tools, Pittsburgh, PA) and delivered binaurally to the patient using Tubal Insert Earphones (TIP-300, Nicolet Biomedical, Madison, WI). Prior to the start of the MEG recording, the 5 target words were presented to the patient several times. During the language task patients kept their eyes open and maintained visual fixation on a small square presented on a screen while listening to the words. Patients were instructed to lift an index finger when they recognized a target word. During the language task, the three blocks of stimuli were presented once, one word at a time. A variable inter-stimulus interval of 400 to1100 ms separated the presentation of each word. Starting from patient #5 in this series, in each of the three blocks of stimuli, we also presented 45 randomly interleaved noise stimuli. The noise-stimuli were designed to mimic the low-level acoustic properties of the word stimuli, and were generated from the 45 word sounds to match their spectral characteristics and duration.