Published in final edited form as:

J Clin Neurophysiol. 2016 October ; 33(5): 414–420. doi:10.1097/WNP.0000000000000255.

Localization of interictal epileptic spikes with MEG: optimization of an automated beamformer screening method (SAMepi) in a diverse epilepsy population

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Abstract

OBJECTIVE—To describe and optimize an automated beamforming technique followed by identification of locations with excess kurtosis (g_2) for efficient detection and localization of interictal spikes in medically refractory epilepsy patients.

METHODS—Synthetic Aperture Magnetometry with g_2 averaged over a sliding time window (SAMepi) was performed in 7 focal epilepsy patients and 5 healthy volunteers. The effect of varied window lengths on detection of spiking activity was evaluated.

RESULTS—Sliding window lengths of 0.5–10 seconds performed similarly, with 0.5 and 1 second windows detecting spiking activity in one of the 3 virtual sensor locations with highest kurtosis. These locations were concordant with the region of eventual surgical resection in these 7 patients who remained seizure free at one year. Average g_2 values increased with increasing sliding window length in all subjects. In healthy volunteers kurtosis values stabilized in datasets longer than two minutes.

CONCLUSIONS—SAMepi using g_2 averaged over 1 second sliding time windows in datasets of at least 2 minutes duration reliably identified interictal spiking and the presumed seizure focus in these 7 patients. Screening the 5 locations with highest kurtosis values for spiking activity is an efficient and accurate technique for localizing interictal activity using MEG.

SIGNIFICANCE—SAMepi should be applied using the parameter values and procedure described for optimal detection and localization of interictal spikes. Use of this screening procedure could significantly improve the efficiency of MEG analysis if clinically validated.

Keywords

Magnetoencephalography; source localization; epilepsy; beamforming; kurtosis

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Conflicts of Interest:

Authors report no conflicts of interest.

Magnetic source imaging (MSI) is a noninvasive imaging technique frequently used in the pre-surgical evaluation of patients with medically refractory focal epilepsy (Ebersole, 1997; Stufflebeam et al., 2009). Identification and subsequent localization of interictal epileptiform activity using magnetoencephalography (MEG) can help direct placement of intracranial electrodes and resective surgery (Jung et al., 2013; Knowlton et al., 1997; Sutherling et al., 2008). The current clinical gold standard for MEG interictal spike localization is the Equivalent Current Dipole (ECD) method. Synthetic Aperture Magnetometry with excess kurtosis (SAM(g2)) is an alternate approach that has been used in studies by multiple MEG centers. Harpaz et al. (2014) recently described an adaptation of this approach (SAMEpi), that may be more sensitive to frequent interictal epileptiform activity than SAM(g2). In this study, we seek to describe the clinical implementation of SAMEpi and optimize its parameters for use in clinical populations.

As described previously, SAM applies a linearly constrained minimum variance beamformer to MEG sensor data to estimate neural activity at pre-specified locations within the brain (Vrba and Robinson, 2001). For each location, a Virtual Sensor (VS) time series is created that estimates the amplitude of the neural source activity at that specific location. Interictal spikes are assumed to produce higher excess kurtosis (g2) than normal brain activity (Vrba and Robinson, 2001), so VS with kurtosis above a certain threshold are selected for further evaluation. VS with interictal spikes must then be identified, either by an automated spike detection algorithm or by visual inspection, because sharply contoured normal brain activity or artifacts, such as eye blinks or muscle, can also generate high kurtosis values. Kirsch et al. (2006) provide a detailed description of the equations used by SAM(g2) as well as an excellent description of the proper use of the technique (Kirsch et al., 2006).

SAM(g2) and now SAMEpi have a number of advantages when compared to the ECD method. SAM(g2) was initially developed as a screening tool to simplify visual detection of spikes due to the decreased number of channels to review. Most current MEGs produce 250+ sensor time series, and a well-trained reader is required to identify interictal spikes. Visual identification of spikes is influenced by frequency of occurrence, morphology, noise in the recording, and montage selection. Once spikes are identified, single or multiple dipoles must be fit to each single or averaged spike and the results assessed for clustering and reliability. This process is time consuming and labor intensive. When using SAM(g2), a reader simply has to identify which sensors contain activity of interest, as the location of the activity is already defined. In a recent survey, MEG centers reported taking on average 9 days to produce an MEG report, with some centers taking much longer (Bagi, 2011). Therefore, alternate automated or semiautomated methods for spike detection and localization such as SAM(g2) and SAMEpi are of significant clinical interest.

Multiple centers have experience using SAM(g2), although there appears to be some variability in the actual implementation. Various groups have reported successful detection of interictal spikes (Kirsch et al., 2006) and good agreement with localization of interictal activity using ECD, distributed source modeling, and intracranial EEG (Robinson et al., 2004; Kirsch et al., 2006; Ishii et al., 2008; Rose et al., 2013; de Gooijer-van de Groep et al., 2013; Agirre-Arrizubieta et al., 2014; Tenney et al., 2014). Concordance with area of

resection and surgical outcome has also been demonstrated (Zhang et al., 2011; Rose et al., 2013; Tenney et al., 2014).

Although quite effective, SAM(g2) is susceptible to emphasizing brain regions generating rare over frequent spikes. This was described in detail by Harpaz et al. (2014), who suggest that this limitation can be corrected by calculating g2 over a sliding time window selected such that each window contains no more than one spike, and summing the g2 values for each window over the length of the dataset (SAMepi). This procedure was tested on simulated data and in two subjects with differing but very frequent spiking (2–3 spikes per second). Since patients have variable spiking frequencies, we seek to optimize the SAMepi procedure described by Harpaz et al. for general use in epilepsy patients. We explore the effect of sliding window length on the detection of interictal spikes in a diverse group of epilepsy patients. We also examine the effect of dataset length on g2 values for healthy controls. Finally we suggest a thresholding procedure to determine which VS should be visually inspected for interictal spikes.

Methods

Patient Information and Data Acquisition

Resting state MEG recordings with simultaneous EEG were retrospectively assembled from MEG recordings of medically refractory epilepsy patients at the National Institutes of Health Clinical Center. Inclusion criteria were a MEG study unobscured by artifact, positive dipole findings on MEG, an accompanying structural MRI with fiducial markers, resective surgery following the MEG, and seizure freedom at 12 months. Data from 5 normal controls were also recorded. This study was approved by the NIH Combined Neurosciences Institutional Review Board and all patients and volunteers provided written informed consent.

Data for all subjects were recorded using a CTF 275-channel whole-head MEG system with 3rd gradient noise cancellation (VSM MedTech Ltd/CTF Systems, Port Coquitlam, BC) in 6 to 30 minute runs. All runs with acceptable head movement and without excessive artifact were included in the analysis. Continuous head localization was not available for all subjects. For subjects missing continuous head localization, the head location before and after each run was recorded. Movement of more than 5mm was considered excessive and the run was not analyzed. 12 runs in 7 patients met these criteria. Data from normal controls included at least one 6 minute run with eyes open and one 6 minute run with eyes closed. Patient data were recorded at a sampling rate of 600 Hz. Data from normal controls were recorded at a sampling rate of 1200 Hz and resampled to 600 Hz prior to analysis. T1-weighted Magnetic Resonance Images (MRIs) were obtained for all subjects in the NIH Clinical Center. Fiducial markers at the nasion and the two pre-auricular points were placed for coregistration of the MRI with the MEG.

Noise Rejection and Preparation of Dataset

All data were visually inspected for artifact. Runs including artifacts that persisted throughout the recording (such as breathing or metal artifacts) were not analyzed. Muscle artifact was identified by visual inspection and the portion of data including the artifact was

removed prior to analysis. One run included a seizure. Data from 10 seconds before the seizure through the end of the run were discarded due to movement during the event.

MRI Preparation and Head Model

Fiducials were marked in Analysis of Functional NeuroImages (AFNI; NIMH, NIH, Bethesda, MD) software and the MEG and MRI datasets were then processed using AFNI and software developed by the National Institutes of Mental Health MEG Core Facility. This software coregistered the MEG to the MRI, created a 3D brain mask, and generated a realistic head model for computation of the forward solution using the Nolte method (Nolte, 2003).

SAMepi MEG Data Processing

MEG data were preprocessed using CTF software (<http://www.ctf.com/>) in an automated pipeline. The initial processing steps are identical to those described for SAM(g2), and subsequent steps are as described in Harpaz et al (2014). Briefly, a 20–70Hz bandpass filter was applied to the sensor level MEG data in order to optimize detection of interictal spikes. SAM beamforming was computed on an evenly spaced grid (5mm) inside of the brain mask and a virtual sensor (VS) was created for each location. For each VS, excess kurtosis was calculated over successive sliding windows of various lengths with 50% overlap. Windows with negative g2 were discarded.

A 3D map of g2 values was created using the average from all windows with positive excess kurtosis at each grid location. Averaging was used instead of the sum method described by Harpaz et al. so that runs of different lengths could be compared. The 10 locations with the highest average kurtosis values were then selected and the beamformer was reapplied for a frequency band of 1 to 70Hz to generate virtual sensor traces appropriate for visual inspection.

The 10 virtual sensor time series for all runs were visually inspected for interictal spike activity using CTF software. Spikes were defined as sharp waveforms that disrupt the background and have a correlate in the filtered MEG or EEG tracings (Figure 1). VS located more than 5 mm outside of the brain (one grid spacing) were excluded from further analysis. These were often located in the orbits and included clear eye blink artifacts. VS localizing to the cerebellum were also excluded as they often corresponded with EKG activity (Figure 2). Remaining VS were divided into four categories: (1) clear spikes with the highest kurtosis in each sublobar region (information containing), (2) clear spikes with lower kurtosis in the same sublobar region, likely representing field or spread from (1), (3) possible spikes, defined as non-artifact sharp waveforms that disrupt the background with no MEG or EEG correlate, or (4) no spikes.

Effect of Window Length on Spike Detection

All runs were analyzed with sliding time windows of 0.5, 1, 2, 5, and 10 seconds, and 2 minutes. The first six values were selected based on the results reported by Harpaz et al (2014). The 2 minute window length was selected to estimate results from SAM(g2), which

is typically implemented for datasets 1 to 2 minutes in length (Robinson et al., 2004; Kirsch et al., 2006; Zhang et al., 2011).

Effect of Dataset Length on Kurtosis

SAMepi analysis using a 1 second window was completed on subdivided portions of runs for five normal volunteers to assess the effect of dataset length on g2. One eyes-closed run for each subject was subdivided into consecutive 30 second, 1, 2, 3, 4, 5, and 6 minute segments. Similar analysis was not conducted for patients because spike frequencies and other abnormal brain activity (such as high amplitude slowing) varied significantly within runs.

Results

Patient Data and SAMepi Concordance with Area of Resection

MEG data were analyzed from seven patients who met our inclusion criteria. Included patients had a wide range of interictal spike frequencies, ages, resection locations, and spike patterns (Table 1). All had identifiable MEG spikes and were seizure free at one year following surgical resection. Our optimized SAMepi procedure identified spiking locations in every run of this highly selected series, and the localizations were concordant with sublobar resection location in each run. For one subject (Patient 5), one of two SAMepi localizations was not resected, in all others there was complete agreement between sublobar SAMepi and resection locations (Table 1).

Effect of Window Length on Spike Detection

Sliding window lengths of 0.5, 1 and 2 seconds identified VS with spiking activity in all 12 runs. The 1 second time window was the only window for which the highest kurtosis VS from all runs included spikes. It performed significantly better than a sliding window of two minutes, which detected spikes in the top ranked VS in 7/12 runs (58%; $p < 0.04$). This longer window length approximates that used in previous g2 studies. There were no other significant differences in spike detection between sliding time windows (Figure 3A). All subsequent results were generated using SAMepi with a 1 second window length.

It was also observed that average g2 values increase with window length for both patients and healthy volunteers (Figure 3B). This has implications when considering threshold selection, as a g2 cutoff for one time window will not apply to any other time window.

Effect of Dataset Length on Kurtosis

Excess kurtosis values were quite variable for 30 second and 1 minute datasets in healthy volunteers. Kurtosis values stabilized at 2 minutes and remained consistent for longer runs (assessed up to 6 minutes in length) (Figure 4). This confirms that averaging the non-negative g2 values from each time window makes SAMepi relatively insensitive to dataset length, and allows comparison across runs with different length datasets, at least in the case where no spiking is present.

Thresholding

All information containing VS ranked in the top 3 VS for a run when ranked by kurtosis value (Figure 5). To allow for increased sensitivity in larger data sets, we recommend that the top 5 VS be visually inspected for spikes. In Figure 5, for comparison, VS in healthy volunteers have a median kurtosis value of 0.575 when using a 1 second window length. This is quite similar to the g_2 value of an information-containing channel in one patient, although none were lower (Figure 5). We therefore do not recommend an absolute value kurtosis threshold. These criteria removed 64.7% (46/71) of the category 3 or 4 VS (possible or no spikes) in our dataset and 21% (7/33) of channels in category 2 (non-information containing spikes).

Discussion

The current study strives to optimize the SAMepi procedure for identification of interictal epileptiform activity in a diverse clinical epilepsy population. In comparison to SAM(g_2), SAMepi looks for excess kurtosis using a sliding window in order to identify both frequent and infrequent spike generators. In practice, a large variety of spiking rates are seen, including some patients with more than one focus. Clinically, identification of all potential spiking areas is desirable when planning a surgical strategy. Therefore, we aim to identify any sublobar regions with independent spiking activity regardless of spike frequency.

Using these criteria to evaluate performance, applying SAMepi with a sliding window of 1 second on datasets greater than 2 minutes in length provided the best sensitivity for detection of interictal spikes in our patient population. A window length of 0.5 seconds was equally sensitive, but the spiking channel no longer had the maximum kurtosis value in all runs. The only other study using a similar method showed similar results, with maximum g_2 values for frequent spikes with a window of 0.5s and for less frequent spikes with a window of 1s (Harpaz et al., 2014). It is important to note that the VS with “infrequent” spikes from the above study had a spike frequency higher than any found in this study. Based on their simulations, Harpaz et al (2014) concluded that 0.25–0.5 second windows should be more reliable, as longer windows fail when spike rates are high. However, window lengths that are too short may fail in the setting of spike bursts or polyspikes, as quiet data should be included in each segment to produce high g_2 values. Therefore, based on the combination of our observations and their simulations, a 1 second window length seems optimal.

We also found that g_2 values produced by SAMepi remain stable for datasets longer than 2 minutes. The primary implication of this finding is that once bad epochs have been removed, SAMepi can be run on the entire MEG dataset without regard to data set length or the need to select active portions of the study. This is likely due to the fact that windows with negative or zero kurtosis do not contribute to the average kurtosis calculated by SAMepi, so there is no penalty for including periods without interictal activity. In this study, using SAMepi with a 1 second time window provided good results for runs up to 30 minutes in length including spike-free periods of up to 10 minutes. This is in contrast to SAM(g_2), where longer runs would strongly favor very infrequent events and neglect frequent spiking.

Because SAMEpi is a screening tool for detecting locations with spiking activity, a conservative thresholding process is useful to further limit the number of channels being considered. In our data, we found that selecting the top five VS allows for 100% sensitivity while substantially improving specificity. While a hard or scaled kurtosis cutoff was relatively effective in the data used for this study, rank is expected to be more consistent across datasets with varying maximal g_2 values. This could be further evaluated in a larger study.

In reviewing the literature, some centers do not describe visually inspecting the SAM(g_2) VS. Figure 2 provides an example as to why this could be problematic. V4 in Figure 2B met all of our criteria for a spiking channel. If just inspecting the map in Figure 2D, V4 would likely be called a positive localization at the right temporal tip. However, as soon as the VS is inspected along with a frontal EEG electrode, it becomes clear that the activity producing high g_2 values at that location is actually eye blinks. This emphasizes that virtual sensors must always be visually inspected, and that activity on the VS should be compared to EEG, MEG, and EKG channels to ensure sharp activity is not due to artifact.

Should SAMEpi be clinically validated, it could improve the efficiency of many MEG centers. On average, it takes MEG centers 9 days to produce an MEG report, with some centers taking much longer (Bagi, 2011). In our center, review of SAMEpi VS takes approximately an hour for all subjects, while ECD analysis time is highly variable but takes approximately 4 hours per subject. Further, SAMEpi can be used to mark interictal spikes for subsequent inspection using other source modeling techniques, including ECD, without reviewing the entire MEG recording of 250+ channels. These benefits of SAMEpi could decrease the time of analysis and thus time to report in many MEG centers, especially those with few expert magnetoencephalographers.

The most notable limitation of this study is a small patient population. This study was designed to allow optimization of the SAMEpi algorithm for clinical use, and should not be interpreted as a clinical validation of the technique. We preselected patients with clear spikes on MEG and who were seizure free one year following surgery in order to be confident in the clinical validity of the results. Though the results are promising, it is unknown how SAMEpi will perform on datasets with multifocal or more ambiguous spiking activity. A larger study focusing on the clinical validity of SAMEpi localizations with respect to surgical outcome is currently in progress and includes comparison to ECD and SAM(g_2) localizations.

Acknowledgments

This work was supported by the Intramural Research Program of the NIH, NINDS. The authors would like to acknowledge technologists Michael Duran and Jackie Greenfield who assisted with data collection. The authors also acknowledge Dr. William Theodore, Irene Dustin, and the clinical fellows of the Clinical Epilepsy Section for their support of this work.

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Figure 1.
 Example output of SAMepi. A. Kurtosis map showing high kurtosis values in the right occipital lobe. B. Virtual Sensor (VS) tracings for locations within the right occipital lobe. The crosshairs in A indicate the location of the V1 VS. C. MEG tracings from right occipital channels. Red arrows indicate spikes present in both the VS and MEG tracings.

Figure 2.

Examples of artifacts commonly detected as high kurtosis locations by SAMEpi. A. An EKG channel displayed with two SAMEpi Virtual Sensors (VS) that contain EKG artifact. B. Frontal EEG channels showing clear eye blink artifacts displayed with a SAMEpi VS that contains the same artifacts. C. The location of V1 from A. D. The location of the VS from B.

Figure 3.

Effect of time window length on g_2 and the sensitivity of SAMepi. A. Number of runs for which SAMepi detected locations with spikes in the top VS compared to number of runs where spikes were found in the top SAMepi channel (* represents $p < 0.05$, Fisher's exact). B. g_2 values by time window for individual patients (gray) and healthy volunteers (light blue) as well as population means for patients (black) and healthy volunteers (dark blue) (* represents $p < 0.05$, ** represents $p < 0.01$, two sided T Test for populations with unequal variance).

Figure 4.
Effect of dataset length on g2 value. Each shade of marker represents a single healthy volunteer. Mean (black line) and mean $\pm$ standard deviation (gray lines) are shown.

Figure 5.

Kurtosis Levels and VS category for all subjects. Information containing VS are those with clear spikes with the top g_2 value in a subbar region. Field (Spread) VS contain clear spikes within the same subbar region as an information containing VS. Possible VS are those containing sharp waveforms that disrupt the background, but have no MEG or EEG correlate. Other VS are those with no spikes or those excluded due to artifact. The dashed line represents the median of g_2 values for VS from healthy volunteers.

Table 1

Description of patient data used in this study

Run	Age	Duration (min)	Spike Frequency	Max Spike Frequency	Max g2 Value*	Resection Location(s)	SAMepi Localization(s)
Patient 1 Run 1	21	12	5/min	11/min	1.479	Right Lateral Frontal	Right Lateral Frontal and Right Fronto-temporal
Patient 1 Run 2		10.6	14.5/min	27/min	1.502		
Patient 2 Run 1	4	30	4/min	16/min	1.976	Right Occipital	Right Occipital
Patient 2 Run 2		15.25	6.2/min	18/min	4.177		
Patient 3 Run 1	17	20	7.8/min	16/min	1.351	Right Temporal	Right Anterior Temporal
Patient 3 Run 2		20	4.25/min	8/min	0.927		
Patient 4 Run 1	17	14.5	7.6/min	12/min	1.139	Left Frontal	Left Lateral Frontal
Patient 5 Run 1	23	20	7.4/min	13/min	3.158	Left Anterior Temporal	Left Orbito-frontal and Anterior Temporal
Patient 5 Run 2		10	7.9/min	12/min	3.545		
Patient 6 Run 1	25	6	1.17/min	2/min	1.032	Left Anterior Temporal	Left Anterior Temporal
Patient 7 Run 1	51	20	3.76/min	14/min	0.625	Right Orbitofrontal and Anterior Temporal	Right Orbitofrontal and Anterior Temporal
Patient 7 Run 2		8	4.83/min	12/min	0.95		

* Max g2 Value for the 1 second sliding time window reported.