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Improving the excess kurtosis (g_2) method for localizing epileptic sources in magnetoencephalographic recordings

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Abstract

Objective: To suggest ways to apply the excess kurtosis estimator g_2 , in the detection of epileptic activity with magnetoencephalography, while avoiding its bias towards detecting high-amplitude, infrequent events.

Methods: Synthetic aperture magnetometry (SAM), combined with g_2 , was applied using window lengths ranging from 0.125 s to 32 s and with sum and maximum metrics on simulated data and recordings of two focal epilepsy patients.

Results: Comparing sources with different spike rates (two per second and one per 2 s), the sum metric was most efficient when using a window of 0.25 s. Simulations showed that the sum metric is insensitive to spike frequency when the window includes more than one spike. SAM(g_2) images from long segments with maximum metric resulted in misleading images, showing the strongest activity away from the lesions.

Conclusions: Using a sliding window and the sum metric is beneficial when imaging interictal spikes and status epilepticus. Windows should be short enough not to include more than one interictal event. For continuous events such as electrographic seizures windows should contain baseline data and the epileptic event.

Significance: The sliding window and metric should be set according to the suggested guidelines when using SAM(g_2) for presurgical evaluation.

Keywords

Epilepsy; Beamforming; Kurtosis; Spike; Source localization

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Conflict of interest

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1. Introduction

Magnetoencephalography (MEG) has been used as a non-invasive method for localizing epileptogenic brain regions as a part of pre-surgical evaluation of non-lesional cases (Barkley and Baumgartner, 2003; Ebersole, 1997; Knake et al., 2006; RamachandranNair et al., 2007). The identification and localization of interictal and ictal epileptiform brainwaves is valuable to surgeons when choosing the region to be resected or to be investigated by invasive methods such as intracranial grids. Typically, the MEG traces are reviewed visually for epileptic spike waveforms. The locations of the spike generators are then localized and superposed with an MRI image of the patient's brain. The resulting image indicates the existence of one or more sources of epileptogenic activity and shows their locations and extent.

SAM(g_2) is a method for imaging epileptic activity as measured by magnetoencephalography. It was initially developed by CTF Systems Inc. as a screening method for long MEG data recordings in order to eliminate the need to manually identify spikes prior to localization. Subsequently, the efficacy of SAM(g_2) has been demonstrated in clinical settings (Canuet et al., 2008a,b; Guggisberg et al., 2008; Ishii et al., 2008; Kirsch et al., 2006; Robinson et al., 2004; Rose et al., 2013; Schwartz et al., 2008; Sugiyama et al., 2009; Ukai et al., 2004; Zhang et al., 2011). The current work explores two parameters that are critical, in our opinion, for reliable identification of epileptic sources: the effects of time-window length and metric.

1.1. SAM(g_2)

The SAM(g_2) method combines a linearly constrained minimum variance beamformer with a measure of excess kurtosis (Kirsch et al., 2006). Synthetic aperture magnetometry (SAM) is applied to the multi-sensor MEG signal in order to estimate the neural source activity at specified locations in the brain on a regular grid. Then, for each location (voxel in the resulting image) a virtual sensor (VS) trace is constructed, which is a time series describing the estimated amplitude of neural source activity. Since for each location the beamformer minimizes the magnetic signal originating from all other sources, the resulting VS usually has greater signal-to-noise ratio compared to that of the MEG sensors. The excess kurtosis is then computed for each voxel's VS time series. Excess kurtosis is a measure testing whether there is an outlier in a distribution. For epilepsy tests it is useful for emphasizing source locations that generate spikes compared to sources that generate normal brainwaves, because the spike is detected as an outlier. g_2 is an unbiased estimator of excess kurtosis, based on Fisher's g statistics for population moments (Fisher, 1925; see Kirsch et al. (2006) for the equations applied by SAM(g_2)). The SAM(g_2) method yields a 3D image of putative epileptic foci and is very useful when trying to identify candidate regions for neurosurgery. In clinical practice, the VS waveforms for locations having high g_2 values are subsequently reviewed by an epileptologist in order to assure that they are not benign cortical activity or artifacts. Whereas the VSs maintain information about time and space, SAM(g_2) reduces the time dimension and results in a single static image of spike generators.

Losing the time dimension at the first stage of exploring the data is desirable because of the abundance of data. Ideally, the traces of the VSs should be viewed along with MEG

sensor level data in order to verify the sources responsible for the epileptic MEG waveforms. However, source localization with, for example, 5 mm spatial resolution can yield about 10,000 traces of VSs within an average brain. Considering the fact that data acquisition may take an hour or two it is practically impossible to manually inspect all the traces for the entire acquisition duration in search of epileptic activity and compare it to the sensor level traces. For practical purposes, therefore, the time courses of only a few selected regions of interest are displayed for inspection. It is at this selection phase that excess kurtosis (g_2) is useful, pointing to the locations for which visual inspection should be applied. For an example of using the method in this manner (observing VS traces after the imaging) see Rose et al. (2013).

Although g_2 has been used mainly with SAM beamforming, it is possible to apply it to other methods of source estimation of EEG and MEG such as different beamformers, or minimum norm estimates. In this work we will describe properties of g_2 and examine the optimal manner of its use, focusing on SAM beamforming. However, these recommendations apply to other source estimation methods as well.

1.2. Factors affecting g_2 images for identification of epileptic activity

A few factors must be considered before computing g_2 for identification of epileptic activity. We assume here that the data for which the VSs were created is relatively free of artifacts. The SAM beamformer intrinsically attenuates most artifacts. However, muscle artifacts may appear like epileptic activity under some circumstances. We also assume that the grid used for computing the VSs is dense. Since the spatial resolution of SAM depends on the amplitude of the sources, we recommend computing the VSs at intervals of 5 mm or smaller, since a high amplitude source of spikes may be missed when using coarser resolution.

1.2.1. Filter—In order to improve the contrast of epileptic activity from normal brain activity, a band-pass filter should be used. Generally speaking, for most epileptic activity a 20–70 Hz band-pass filter is sufficient (Kirsch et al., 2006; Schwartz et al., 2008). However, one can optimize the filter for each patient by measuring the increase of power for an epileptic compared to a normative segment of data. A filter can be applied at two different stages of the analysis: on the raw data before creating the VSs or on the VSs themselves. By default the second stage filter should be avoided. It is useful mainly when computing the spatial filter for a large range of frequencies (first-stage filter) and then creating images for narrower bands (second stage). However, a thorough examination of filter effects on the resulting images is beyond the scope of the current work.

1.2.2. Window length—Excess kurtosis (g_2) is computed after estimation of the band-limited VS waveforms. Here one should consider the length of the data segment used for g_2 computation. The largest g_2 values occur when there is a rare high amplitude transient event when compared with background activity. To illustrate this, we simulated a V-shaped spike padded with zeros, a similar trace containing two spikes, an oscillating channel (triangular waveform to resemble alpha rhythm) and a noisy channel (Fig. 1). As can be seen in the figure, the highest g_2 value was the one computed for the single spike whereas for oscillation and random noise g_2 was negative. Therefore, when sparse interictal spikes are present in

the data, g_2 calculated for the whole length of the data is expected to distinguish between channels containing spikes from those that do not.

Introducing a second spike in the simulation (Fig. 1b) reduced g_2 from 4.7 to 0.34. This effect demonstrates that g_2 is biased toward rare events, an issue which will be further discussed below (Sections 1.2.3 and 1.2.4). Multiple spikes in one trace can still, however, yield a high g_2 value, depending on the amount of spike-free data it contains. Although it is possible to produce images based on 1 h long segments to examine the consistency of the epileptic activity, a better strategy would be to segment the data into shorter epochs (presuming there is at least one spike in every segment) and produce g_2 images for every epoch.

An example of real MEG data is presented in Fig. 2. Here the sensor level data was band-pass filtered (20–70 Hz) and g_2 was calculated for a single 10 s segment. The frontal VS is of a source that generated one epileptic spike (within this time window) and had a higher g_2 value (2.15) compared to the parietal VS (0.55). This demonstrates that the increase of g_2 occurs for a real interictal spike, and not only for simulated data.

Although SAM(g_2) was developed to find interictal spikes it can also be useful for localizing ictal events (Canuet et al., 2008b) or electrographic seizures (magnetographic in this context) which are events of continuous, usually high frequency epileptic activity, lasting for seconds or minutes. When computing g_2 for such events it is important to include spike-free baseline data in addition to the epileptic event. Fig. 3 shows the frontal VS of Fig. 2 but for an extended time window of about 60 s following the initial spike (marked with the letter 'S'). After the spike there is an epileptic event of about 10 s followed by relatively quiet activity. The g_2 value calculated for the magnetographic seizure only (10 s, $g_2 = 8.83$) is lower than for a larger segment that included the subsequent quiet epoch (70 s, $g_2 = 40.50$). Therefore, g_2 images with a window length large enough to include epileptic free data accentuate regions of continuous epileptic activity. Note, however, that including the whole length of an epileptic event is not recommended for localizing the seizure origin, since such events tend to propagate to distant regions (Zhang et al., 2011). For pre-surgical evaluation it may be more sensible to compute g_2 for the period preceding the ictal (or magnetographic) event while including only the beginning of the long event in the analysis. Another reason for analyzing ictal events in this manner is that, following ictal onset they are sometimes contaminated by muscle and head movement artifacts.

When imaging electrical status epilepticus of sleep, Landau–Kleffner syndrome or other traces with frequent spikes, it is often difficult to get a sufficient baseline. Since VSs for such data may contain many spikes, sometimes more than one per second, their g_2 values are expected to be small when computed for large segments of data. g_2 will only reflect the strength of the signal for such frequent spike generators when computed for short segments, ideally with one spike per segment. One can therefore segment the data to epochs of about 0.5 s and make hundreds of SAM(g_2) images, one per segment. A more economic approach however is to use a sliding window to compute the g_2 values for each segment and integrating these values over all segments to generate a single image as will be shown below.

1.2.3. Sliding window—The sliding window method allows us to identify locations containing frequent spikes, by collapsing multi-segment g_2 values into a single measurement per voxel. If we take, for example, a source with ten spikes in ten seconds, we can set the window length to 1 s and compute g_2 for overlapping epochs of 1 s beginning in times 0 s, 0.5 s, 1 s and so on, up to the segment beginning at 9.5 s (50% overlap), resulting in 19 g_2 values – one per segment. In order to test for spikiness, one could use either their maximum or their sum as a metric. If the maximum value is used (for the sum metric see the next item), the functional image intensity value will be largest for locations generating larger spikes. The use of the maximum metric in combination with a sliding window allows the detection of large and frequent spikes, which might be missed if large segments were used.

A sliding window can be used for examining not only continuous epileptic waveforms but also any data containing multiple spikes. Since g_2 is biased to rare events, an image based on the whole, unsegmented trace will make infrequent spike generators more salient than frequent ones (keeping their amplitude constant). This may explain the poor performance of $\text{SAM}(g_2)$ for some patients (de Gooijer-van de Groep et al., 2013) where g_2 was computed for traces 100 s long or longer.

1.2.4. Metric—Although the sliding window eliminates the bias for rare spikes, for some patients with multiple sources the images that were produced appeared misleading. In some cases, the aim is to find generators of frequent spikes of smaller amplitude, compared to other, less frequent spikes. For these cases, the cancellation of the bias for infrequent spikes (by using a sliding window and the maximum metric) is not sufficient, and a metric that makes frequent spikes more salient than infrequent ones is desired. One possibility is to sum the g_2 values per VS, thus integrating spike amplitude relative to background activity and spike rate. The sum is larger for larger spike generators because they yield a greater g_2 value per segment compared to smaller spike generators. The sum is also larger for frequent spikes because their g_2 values will add up to a larger sum compared to infrequent spikes. The main aim of the current work was therefore to test the effect of the metric (either sum or maximum g_2 for multiple segments) and window size on g_2 images for different signals.

In order to test the effect of the metric and window length we started by computing g_2 for two VSs that had spikes with different amplitude and rate (Fig. 4), using various window lengths and different metrics. We then ran a simulation focused on the sum method in order to find general rules for choosing window length as a function of spike rate. Finally, two $\text{SAM}(g_2)$ images were produced from real patient data to demonstrate that for some patients using sum of g_2 instead of g_2 for large segments of 100 s or more can help avoid emphasizing less important spike generators.

2. Methods

2.1. Comparing sum, maximum and large segment methods

MEG recordings were conducted with a whole-head, 248-channel magnetometer array (4-D Neuroimaging, Magnes 3600 WH) in a magnetically shielded room. The data were digitized with a sample rate of 678.17 Hz and an online 1–200 Hz band-pass filter. SAM beamforming was computed at a spatial sampling grid of 5 mm. A 20–70 Hz bandpass filter

was applied on the sensor level data before calculating the VSs, and also applied to the VSs prior to computing g_2 .

Two VSs (Fig. 4) with durations of 100 s were selected for the analysis because of their differences in spike rate and spike amplitude (Fig. 4). The source on the left had a spike rate of about once in 2 s while that on the right, closest to a lesion, had a spike rate of about two per second. Note that for this comparison the spikes on the left VS are referred to as rare, not because of they were absolutely rare but because they were less frequent than the right source spikes. The maximum left spike amplitude was 1.73 times larger than that of the right while noise levels were similar for the two channels.

g_2 was calculated for each VS nineteen times. Once for the whole segment to test the large segment method, and 2 (maximum and sum methods) by 9 times (window sizes 0.125–32 s; see Fig. 5) to test the effect of overlapping window size. For each window length n , the data was segmented with an overlap such that every segment started $n/2$ samples after the beginning of the previous one. This was done in order not to miss high g_2 values for spikes starting in one segment and continuing in the next one. g_2 was then calculated for every segment. The maximum of all the g_2 values per VS was taken as metric for the maximum method. The metric for the sum method was the sum of all non-negative g_2 values. The process was repeated for every window length separately, yielding 19 g_2 values per VS.

2.2. Window size and spike rate simulation

In order to simulate a VS with spikes a vector was created, 67,817 samples long (100 s) of Gaussian random values between -0.5 and 0.5 . The traces were designed to simulate data with the same sampling rate as the real data we collected (678.17 Hz, Sections 2.1 and 2.3). A spike was created as a separate vector, 33 samples long (49 ms). Its values delineated an upside down V-shape with a peak amplitude of 8.0 relative to a zero baseline. For every spike rate (1/4, 1/8, 1/16 and 1/32 spikes per second) a new VS was created, adding the values of the spike vector to the random noise in regular intervals (of 4–32 s). g_2 was then computed for each spike rate using the sum method and sliding windows of 0.125, 0.25, 0.5, 1, 2, 4, 8, 16 and 32 s.

2.3. SAM(g_2) images for real data

MEG data from two patients were obtained for presurgical evaluation, for which they gave informed consent. The use of their data for research purposes was approved by the institutional review board of Bar-Ilan University and the ethics committee of Tel-Aviv Sourasky Medical Center (0375-12-TLV).

Both patients had MRI-visible lesions and a high spike rate (between 2 and 3 spikes per second, judged by counting spikes for the whole sensor array). For both patients SAM(g_2) using the large segment and maximum methods yielded images with high g_2 values that were distant from the lesions.

SAM(g_2) images were produced twice for each patient, once using the large segment method (SAMepi v2.5) for 100 s long segments (Canuet et al., 2008a,b; de Gooijer-van de Groep et al., 2013; Ishii et al., 2008; Kirsch et al., 2006; Robinson et al., 2004; Schwartz et al., 2008;

Sugiyama et al., 2009; Ukai et al., 2004) and once with the sum method (SAMEpi v3.0) and a sliding window of 0.5 s. The spatial resolution was set at 0.5 cm. The head-model for computing the forward solution was a multiple spheres model based on the scalp shape. Dipole orientation for each location was estimated using a 3D vector, thus not ignoring the radial component. Although the radial component of sources, as compared to tangential components, is harder to detect and to localize using MEG, it has been shown (Prendergast et al., 2013), that a beamformer can be made more accurate and more robust if the analysis is not restricted to the tangential plane. The images were rendered using AFNI software (Cox, 1996).

3. Results

3.1. Comparing sum, maximum and large segment methods

g_2 values computed over 100 s of data, without segmentation, were 5.55 for the right source (near the lesion) and 16.90 for the left source. This was expected because the left source produced larger and less frequent spikes. Using sliding windows and the maximum metric still yielded greater g_2 values for the left, compared to the right, source, and for all window lengths (Fig. 5A). The sum method results (Fig. 5B) show that, up to a window length of 2 s, g_2 sums are greater for the more frequent, right source than for the left. The ratio between g_2 values (frequent g_2 /rare g_2) peaked for the 0.25 s window (2.06).

In order to observe the sensitivity of the sliding window procedure a 10 s-long VS segment is charted (Fig. 6), showing spikes at irregular intervals near the lesion. The spikes were identified by a clinical reviewer who compared the occurrences of epileptic events on the virtual sensors against the unfiltered MEG data. Please note that no attempt was made to distinguish between spikes, spike and wave complexes or related abnormal activity, and all epileptic events are generally marked as spikes (Fig. 6). The g_2 for 0.25 s windows are displayed over their respective data segments. Note that, since there is a 50% overlap, each spike contributes to the g_2 of two adjacent windows. In windows without spikes, such as from 6 to 7.5 s, g_2 values are negative and are excluded from the sum. Also note that larger spikes (grayed) yield larger g_2 values. We can observe that the sensitivity of the sum metric to epileptic spikes is satisfactory because all spikes contribute to the sum metric according to their size. We can also see that the specificity, at least for the current data, is high, because segments with no spikes yield negative g_2 values and do not contribute to the sum (only positive values are summed).

3.2. Window size and spike rate simulation

In order to test whether a certain window length allows discrimination between more and less frequent spike generators, we calculated the increase of g_2 values against increase in spike rates. For example, using a 1 s sliding window and spikes at intervals of 4, 8, 16, and 32 s resulted in g_2 sums of 1325, 651, 309 and 140, correspondingly. The ratios between adjacent rates in this example are 2.04 (for 1325/651), 2.11 and 2.21. From this it is seen that when spikes are twice as frequent they yield a sum of g_2 about two times greater. This means that for 1 s window length the sum method performed well, yielding greater g_2 for more frequent spikes regardless of the inter-spike interval. Fig. 7 shows the ratio between g_2

values for each interval (of the intervals 8, 16 and 32) and the interval below it against the window length. The ratio between the g_2 values dropped to about one when there were more than one frequent spike per window. For example, the g_2 ratios for spikes with intervals of 4 and 8 s (solid line) were below 1.0 for window durations greater than 8 s.

3.3. SAM(g_2) images for real data

For both subjects the frequent spike imaging using the sum method localized the sources of the epilepsy near the lesion while the large segment method localized it away from the lesion (Fig. 8). Subject A (Fig. 8, top) had a lesion in the left prefrontal cortex. The large segment method yielded one distinct source of spikes in the left parietal lobe, close to the central gyrus (Fig. 8, top left). This parietal source was also visible in the sum g_2 image but another source bordering the lower part of the lesion became evident (Fig. 8, top right). The large segment method for subject B also showed left parietal epileptic activity (Fig. 8, bottom left) although the lesion was located in the right hemisphere. In contrast, the sum method revealed three epileptiform sources localized in the right hemisphere, close to the lesion.

In order to trace the cause for the success of the sum method to detect spikes in the lesions, two time-courses per patient were plotted, delineating the change in g_2 from segment to segment using 0.5 and 10 s windows (Fig. 9). Generally, the g_2 traces corresponded well to the manual spike detection. Time windows containing spikes yielded relatively high g_2 values. As mentioned above (Section 3.1), for single instances g_2 reflected mainly spike size. Therefore, summing g_2 over time yields a measure that integrates spike size and spike frequency.

Regarding window size effect on g_2 metrics, it can be seen that for both patients, the distant spikes (gray dots) yielded higher g_2 values (solid and dashed gray traces) compared to spikes originating in the lesion (black dots). Hence, maximum g_2 value was greater for the distant VS (gray traces) compared to the in-lesion VS (black traces) for both patients. This implies that the maximum metric would fail detecting frequent spikes generators for these subjects, regardless of window length. The sum for 10 s windows also yielded larger g_2 values for the distant VSs (354 for subject A and 161 for subject B) compared to the in-lesion VSs (88 and 61). This was mainly due to lower spike rates, and occasionally to larger spikes, for the distant VSs. At 0.5 s windows however, the distant VSs yielded *lower* sums (571 and 264) compared to the in-lesion VSs (692 and 351). Note that for subject B a large spike at 61 s in the distant location yielded a high g_2 , even for 0.5 s window (34). However, the sum of the smaller g_2 values in the lesion, from preceding and succeeding time windows eventually surpassed the sum of the distant location.

4. Discussion

The current work aimed at finding guidelines for the utilization of g_2 when imaging epileptic MEG activity. Previous works have applied SAM(g_2) in a way that biases the images towards generators of infrequent spikes. Here we described a method that makes frequent spike generators more salient. The comparison of the sum, maximum and large segment methods for two virtual sensors (Section 3.1), a sliding window 0.25 s long and the sum

metric were optimal for biasing the results toward frequent spikes. For windows larger than 2 s, the advantage for the frequent spike was diminished and even reversed because the frequent spike VS had more spikes per segment compared to the infrequent spikes. This computation, based on real data, confirms that the maximum window length to use when imaging frequent spike generators should not be larger than $1/(\text{spike rate})$, leaving about one spike per window.

Although the short time windows were advantageous for spike rates of about one and two per second, it remained unclear whether a window length smaller than 2 s is sufficient to distinguish between two sources with sparser spike rates. However, the simulation results (Section 3.2) demonstrated that a 0.25 s window can be efficient for spikes as sparse as once in 32 s (Fig. 6, dotted line). It can be concluded therefore that the smaller windows (0.25–0.5 s) are more reliable because they perform well for various spike rates while larger windows fail when spike rate is high. It has to be noted, however, that a 0.25 window may be too small for different patterns of epileptic activity such as poly-spikes, where, like in the analysis of electrographic events, quiet data should be included in each segment to yield high g_2 values.

SAM(g_2) localized epileptic sources near the lesions of the two patients only when using the sum method. The large segment method localized the epileptic activity in another lobe (subject A) or in the opposite hemisphere (subject B). The source of large (but rare) spikes for subject B, evident using the large segment method, was below display threshold for the sum metric (Fig. 7). This made only the source in the lesion visible. For subject A the sum method yielded similar magnitude for both sources, allowing both of them to be seen. Relaxing the display threshold can make other sources visible, although the color would still make same sources salient: large spikes generators for the maximum method and frequent spikes generators for the sum method.

When diagnosing patients with known anatomical lesions it is usually assumed that the source of the epilepsy is in the area of the lesion and the MEG scan is performed to determine which part of the lesion generates the epileptic activity. In those cases, the use of the large segment method images might not yield the expected results. This is not because no spikes are generated at the highlighted locations, but because these spike generators are implausible causes of the clinical situation. The sum g_2 images in the above examples were biased to frequent spikes and did display sources of epilepsy close to the lesions. This makes them much more informative for the clinician when considering dissection of a part (or parts) of the lesion.

Other patients with no visible lesions can theoretically have similar spike patterns but without anatomical landmarks to help validating their results. It is therefore, in our opinion, important not to rely only on spike size imaging (using the large segments or maximum method) but to use the sum method as well. In fact, since the sum method integrates spike size and spike rate (Section 1.2.4) it can be preferred and be conducted instead of the other methods.

SAM(g_2) can be used to localize continuous epileptic events, such as electrographic seizures, using the large segment method as long as there is baseline, quiet data recorded along with the epileptic event. Imaging frequent interictal spike generators can also be performed using SAM(g_2) and can be an important contribution to clinical work and research. In this case, SAM(g_2) can be applied using a 20–70 Hz filter and a sliding window small enough not to include many spikes per segment per location. However, since it is impossible to tell in advance the spike rate of each location, a crude assessment of the sensor level data is recommended. If a spike is visible 3 times per second or less, a 0.25 s window is recommended. This would cover most of the MEG recordings of interictal spikes and status epilepticus. For more frequent spikes a shorter window is recommended.

The different methods of g_2 processing do not change the VS waveform but only help us select the ones that are most meaningful. After choosing locations, their VSs must be visually inspected in order to confirm that the morphology indicates epileptic activity and not benign brain activity or artifacts. When signal-to-noise ratio is sufficient, the VSs should also correlate well with the physical sensor level data.

Prendergast et al. (2013) suggested to improve SAM(g_2) by computing g_2 at an earlier stage, before the creation of virtual sensors, at the stage of determining dipole orientation. However, they used the common, long segment method. It is therefore plausible that using the sum method at this stage should allow even greater sensitivity than that achieved in the current and previous works. This can be tested in a future study.

Another approach that might prove useful in a future study is computing g_2 images after manual selection of spikes. Guggisberg et al. (2008) claim that the SpiFi method might be preferred by neurologists who are used to detecting spikes in the physical sensor data before performing source localization (such as dipole fit). However, one can use SAM(g_2) for manually selected time windows instead of using an overlapping window. Using SAM in this way would allow the clinician to keep the same order of work as used in dipole fitting (when signal-to-noise is sufficient), while benefiting from the advantage of the sum metric for visualizing frequent spike generators.

Although g_2 imaging is an automated method that does not rely on visual inspection of single events it is important to look at the data as a whole in order to understand whether the default filter, sliding window and metric are expected to perform well. Keeping these parameters in mind is necessary for the production of informative images and for a more reliable clinical assessment.

We conclude by emphasizing the importance of detecting frequent-spikes generators, since for some patients they can be more informative than large-spikes generators. For that purpose, the sum metric should be used on windows short enough not to allow two spikes per window.

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HIGHLIGHTS

- MEG signals of frequent interictal brain activity carry information to localize epileptic foci.
- $SAM(g_2)$ applied to short time windows of MEG signals and summed across windows, is sensitive to frequent interictal brain activity arising from a specific brain region.
- The time window should be short enough to only include one interictal event.

g_2 for simulated traces

Fig. 1.

g_2 values for simulated traces. Excess kurtosis (g_2) is high for channels with an outlier event. A single spike (first trace from the top) yielded a higher g_2 value compared with two spikes (second trace). The oscillating (third trace) and random noise channels (bottom trace) yielded negative g_2 values. Note that the central limit for g_2 is zero for an infinite length Gaussian random time series.

Fig. 2.

g_2 values for virtual sensors derived from measured MEG data. The figure shows traces of one physical MEG sensor (A22, located over the frontal lobe, left of the midline) and two SAM-derived virtual sensors. The frontal virtual sensor had a spike corresponding to the MEG sensor spike. Its g_2 was high compared with a parietal virtual sensor where no spike was observable.

Fig. 3.
 g_2 for a virtual sensor during an ictal event. We observe that g_2 is higher when a baseline period is included after the event. The letter 'S' marks the spike which was displayed in Fig. 2.

Fig. 4.

Two virtual sensors based on real data. The top virtual sensor is located near a lesion and has more frequent but smaller spikes compared to the bottom virtual sensor, which was located in the opposite hemisphere. The experiment tests which sliding window lengths yield greater g_2 values for the top, frequent virtual sensor.

Fig. 5.

Window length effect on g_2 for virtual sensors based on real data. Maximum g_2 is higher for the rare spike, regardless of window size, because it has higher amplitude. The sum g_2 values over multiple time windows (length 2 s and less) was larger for the frequent spikes despite their lower amplitude.

Fig. 6. g_2 values per window. A 10 s long virtual sensor containing interictal spikes (marked as dots) is displayed at the bottom panel, along with g_2 values at the top panel. g_2 was computed using a sliding window of 0.25 s and an overlap of 50%. A large spike at 2.16 s yielded a g_2 of 5.18 for the grayed segment, and 3.77 for the following segment. Segments without spikes (e.g., from 6 to 7.5 s) yielded negative g_2 and were not summed up.

Fig. 7.

Window length and spike rate effects on g_2 for simulated spikes. The lines represent the ratio of g_2 values for traces with frequent spikes (e.g., a spike every 16 s) and less frequent spikes (e.g., a spike every 32 s, dotted line). For small windows the g_2 ratio was about two, meaning that the measure was biased to frequent spikes, as expected. When the window was large enough to allow two infrequent spikes to be present in it (e.g., 8 s window for the solid line) the ratio was close to one and did not reflect spike frequency.

Fig. 8. SAM(g_2) images for two patients with lesions. Top (A) and bottom (B) are subjects with a frontal lesion and a right hemisphere lesion, correspondingly. For both subjects the large segment method (left) yielded the highest g_2 values at a source distant from the lesion. The sum method (right), however, revealed epileptic sources that were within or close to the lesions. The images are oriented using the radiological convention (left = right).

Fig. 9.

g_2 values per subject by location and window size. The dots under each plot represent occurrences of spikes in the lesion (black) and away from it (gray). For both subjects and for 0.5 as well as for 10 s windows, maximum g_2 values were in the location distant from the lesion. This resulted from more frequent, but smaller spikes in the lesion, compared to the remote location. Using the sum metric with 10 s windows still yielded larger g_2 for

the remote regions, because there were less spikes per window, compared to the lesion. However, summing g_2 for 0.5 s windows yielded greater g_2 for the lesions.