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

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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.

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.

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 than localized and

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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.

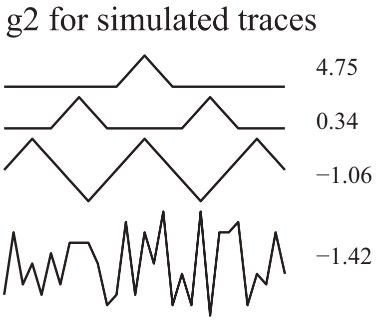

Fig. 1. g_2 values for simulated traces. Excess kurtosis (g_2) is high for channels with an outlier event. A single spike (first trace from the top) yielded a higher g_2 value compared with two spikes (second trace). The oscillating (third trace) and random noise channels (bottom trace) yielded negative g_2 values. Note that the central limit for g_2 is zero for an infinite length Gaussian random time series.