Realistic Spatial Sampling for MEG Beamformer Images

Gareth R. Barnes,* Arjan Hillebrand, Ian P. Fawcett, and Krish D. Singh

Neurosciences Research Institute, Aston University, Birmingham, United Kingdom

Abstract: The spatial resolution achievable using magnetoencephalography (MEG) beamformer techniques is inhomogeneous across the brain and is related directly to the amplitude of the underlying electrical sources [Barnes and Hillebrand, *Hum Brain Mapp* 2003;18:1–12; Gross et al., *Proc Natl Acad Sci USA* 2001;98:694–699; Van Veen et al., *IEEE Trans Biomed Eng* 1997;44:867–860; Vrba and Robinson, *Proc 12th Int Conf Biomagn* 2001]. We set out to examine what an adequate level of spatial sampling of the brain volume is in a realistic situation, and what implications these inhomogeneities have for region-of-interest analysis. As a basis for these calculations, we used a simple retinotopic mapping experiment where stimuli were 17-Hz reversing gratings presented in either left or right visual hemifield. Beamformer weights were calculated based on the covariance of the MEG data in a 0–80 Hz bandwidth. We then estimated volumetric full-width half-maximum (FWHM) maps at a range of sampling levels. We show that approximately 10% of the 1 mm cubic voxels in the occipital volume have a FWHM smoothness of <5 mm, and 80% <10 mm in three subjects. This was despite relatively low mean signal-to-noise ratios (SNR) values of 1.5. We demonstrate how visualization of these FWHM maps can be used to avoid some of the pitfalls implicit in beamformer region-of-interest analysis. *Hum Brain Mapp* 23:120–127, 2004.

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Key words: magnetoencephalography; synthetic aperture magnetometry; SAM; FWHM; spatial resolution; region-of-interest analysis

INTRODUCTION

Beamforming-based imaging algorithms [Gross et al., 2001; Robinson and Vrba, 1999; Sekihara et al., 2001; Van Veen et al., 1997] are proving to be a useful tool for magnetoencephalographic (MEG) brain imaging [Gaetz and Cheyne, 2003; Hashimoto et al., 2001; Hirata et al., 2002; Kato et al., 2003; Singh et al., 2002, 2003; Taniguchi et al., 1998, 2000].

Beamformer analysis [Gross et al., 2001; Robinson and Vrba, 1999; Van Veen et al., 1997] involves a direct transformation of MEG signal space into source space (the brain). The source space is then sampled to produce electrical activity estimates over time at each location, and changes in these estimates are used to produce statistical parametric maps (SPMs) [Barnes and Hillebrand, 2003; Gross et al., 2001]. However, this source space is not homogeneously smooth, with spatial resolution increasing monotonically (and potentially infinitely) in some regions with the strength of the underlying electrical source [Barnes and Hillebrand, 2003; Gross et al., 2001; Van Veen et al., 1997; Vrba and Robinson, 2001]. Previous studies have demonstrated how analytical expressions can be formed that predict spatial resolution from source strength and lead field sensitivity [Gross et al., 2003; Vrba and Robinson, 2001]. Such methods are computationally efficient but rely on the assumption that both the number of active sources and their contribution to the eigenvalue spectrum are known a priori.

We empirically examine what constitutes a realistic sampling of the beamformer source space, first in terms of the

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*Correspondence to: Dr. Gareth R. Barnes, The Wellcome Trust Laboratory for MEG Studies, Neurosciences Research Institute, Aston University, Birmingham B4 7 ET, United Kingdom.
E-mail: barnesgr@aston.ac.uk

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grid spacing to produce a whole-brain SPM, and secondly in terms of how this inhomogeneous spatial resolution impacts on region-of-interest (ROI) or virtual electrode [Kato et al., 2001; Singh et al., 2002] analysis. Intuitively, the SPM reconstruction grid spacing should be as fine as possible, but practically this has to be balanced against computing time (halving the grid spacing gives rise to an eightfold increase in processing time and memory requirements).

We use a brief simulation study to demonstrate what happens to full-width half-maximum (FWHM) estimates [Barnes and Hillebrand, 2003] across sampling levels for different source strengths. We then examine the distribution of FWHMs from three experimental datasets to obtain approximate sampling levels for real data. Lastly, we show how FWHM images can be critical in determining the placement of virtual electrodes.

In summary, we show that MEG beamformer implementations achieve very high spatial resolution (1–2 mm) for unexceptional datasets with relatively low signal-to-noise ratio (SNR) (~ 1.5). The results suggest that such images are currently being under-sampled, by as much as an order of magnitude, by the beamformer community.

MATERIALS AND METHODS

Beamformer-Based Imaging

We describe the beamformer implementation in two stages. The first stage involves computation of the weight vectors that map measurement channels to target voxels within the source space. The second stage involves computation of an SPM by looking at changes in the time series, at successive target voxels, which covary with stimulus presentation.

Beamformer weights

Weight vectors for each point in the source space were calculated using the minimum variance nonlinear beamformer methodology known as synthetic aperture magnetometry (SAM) [Robinson and Vrba, 1999]. SAM is a minimum variance beamformer in which the optimal source orientation at each point is chosen by a non-linear search. In brief, for each point (and orientation) θ in the source space a weight vector $\mathbf{W}_\theta$ (with N elements mapping to N measurement channels) is computed as

$$\mathbf{W}_\theta = (\mathbf{H}_\theta^T \mathbf{C}^{-1} \mathbf{H}_\theta)^{-1} \mathbf{H}_\theta^T \mathbf{C}^{-1} \quad (1)$$

where $\mathbf{C}$ is the data covariance matrix and $\mathbf{H}_\theta$ is the lead field vector of a dipolar source element, at location and orientation specified by θ . The data covariance $\mathbf{C}$ was estimated from the average of the covariance matrices of all individual epochs (and not from the covariance of the averaged data). The selection of the orientation of the source element (the non-linear stage) is chosen by maximizing the projected power at this location [Vrba and Robinson, 2001]:

$$P_{or(\theta)} = \max_{or(\theta)} \{ [\mathbf{H}_\theta^T \mathbf{C}^{-1} \mathbf{H}_\theta]^{-1} \} \quad (2)$$

where $or(\theta)$ is used to show that only the orientation and not the positional component of θ is subject to the maximization. This procedure is repeated at each grid point.

SPMs

In some beamformer implementations [e.g., Robinson and Vrba, 1999], equation (2) is used to calculate the power in active and control states, based on active and passive covariance matrices. We treat the computation of the weights (equation [1]) as a distinct stage from the calculation of a statistical difference image [see Barnes and Hillebrand, 2003 for a complete description]. For each element in the source space, an estimate of the electrical activity at that point or “virtual electrode” is constructed.

$$y(t) = \mathbf{W}_\theta^T \mathbf{m}(t) \quad (3)$$

where $\mathbf{m}(t)$ is the vector of N magnetic field measurements at time t .

Equation 3 gives a time-varying estimate of the electrical activity at a point in the source space. This data can be partitioned into active and passive blocks according to the experimental design, and a statistical measure of spectral change can be computed. In this study, we used a Mann–Whitney test to compare active and passive amplitudes (as obtained from the amplitude of the Hilbert transform) across all epochs (the Mann–Whitney U statistic tends to the z distribution for more than about 20 epochs). Plotting this statistic for all elements in the source space gives a statistical parametric map for the volume (which we refer to as an mw-SPM).

In the simulations, we looked for broad-band active-passive changes in the 0–140 Hz band, whereas for the empirical study, we used 32–36 Hz as the band of interest because the original study [Fawcett et al., 2004] found the greatest steady-state response at the second harmonic (34 Hz) of the stimulation frequency (17 Hz).

Smoothness measures

We used the FWHM of an equivalent Gaussian point spread function as a metric of smoothness across the volume. The local smoothness of a beamformer image can be assessed by looking at the relationship between weight vectors that map to neighboring virtual electrode locations [Barnes and Hillebrand, 2003]. For example, if adjacent weight vectors are identical then the same virtual electrode time series (equation [3]) will be projected to adjacent locations and this section of the resulting beamformer image will be smooth.

The method of calculating FWHM from the set of weight vectors is described in detail in Barnes and Hillebrand [2003]. Briefly, the method centers on the local computation of resolution elements or resels (inversely related to FWHM) as one moves through the source space [Friston et al., 1995];

Poline et al., 1995; Worsley et al., 1999]. For functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), resels are defined by how correlated the residual noise is at adjacent voxels [Kiebel et al., 1999]. Barnes and Hillebrand [2003] showed that in the beamformer formulation, the spatial structure of residual noise relies entirely on the weight vectors. They then described how resel counts could therefore be derived directly from the correlation between neighboring weight vectors.

Accurate FWHM estimates also depend on adequate spatial sampling [Friston et al., 1995]. That is, for spatial sampling at κ mm intervals, the smallest FWHM it is possible to estimate is 2κ mm. By analogy with the Nyquist sampling theorem, we refer to this as the Nyquist limit as any portions of the image less smooth than 2κ mm FWHM will be under-sampled.

Simulation

A single equivalent current dipole was simulated at a depth of 4 cm below the scalp surface. The dipole moment was sinusoidally modulated at 100 Hz for 100 ms at peak amplitudes ranging from 0.1–3.4 nAm. A single sphere model was used in the forward problem calculation (for a 151-channel Omega MEG system, third order gradiometer mode; CTF Systems Inc., Port Coquitlam, BC, Canada) and channel white noise was set to $7\text{fT}/\sqrt{\text{Hz}}$ over a 140-Hz bandwidth. One hundred epochs of data were simulated, each with a 100-ms prestimulus period that consisted of just channel white noise. Data covariance, and hence beamformer weight calculation (see below), was based on a 200-ms window that spanned both signal and noise periods. Minimum FWHM, within a cubic subvolume of side length 1.6 cm centered on the source, was computed for each signal level and over a range of grid spacings (1, 2, 4, and 8 mm).

Experimental Data

Stimuli

The stimulus was a square checkerboard pattern at 100% contrast subtending a visual angle of 2° at an eccentricity of 0.5° in either the left or right visual field. The checkerboard patterns were contrast reversed at a rate of 17 Hz and were presented in a pseudorandom, boxcar experimental design: on for 15 s followed by a 15-s period of fixation.

MEG data collection and preprocessing

The data were collected using a 151-channel Omega MEG system in a single epoch of acquisition, lasting 480 s at a sampling rate of 312 Hz and with anti-aliasing filters at 100 Hz. Data were comb-filtered to remove the 50 Hz power line and its harmonics. We used a surface-matching procedure [Kozinska et al., 2001] to co-register a digitized head surface in MEG coordinates with the subject's MRI-extracted scalp surface. This MRI scalp surface was also used to find best fitting local spheres (to be used in the lead field calculations) for each of the MEG sensor channels.

Data covariance was computed based on non-overlapping 30-sec segments of data spanning the whole recording period, bandpass filtered from 0–80 Hz. For each subject volumetric FWHM images, using 1-mm grid spacing, were made of the occipital lobe using the procedure described above. The experiment consisted of eight 15-s stimulation periods per visual field. The first 5 s of each stimulated (active) and fixation (passive) period were divided into five 1-sec epochs. Mann–Whitney SPMs were then computed based on the 40 active/passive epoch pairs per visual stimulus.

RESULTS

Simulation

We ran simulations using a single equivalent current dipole in a subvolume to examine the behavior of the FWHM measure for various levels of spatial sampling and signal strength. Figure 1A shows the FWHM estimate at the simulated source location as a function of sampling level at various dipole moments. As expected [Gross et al., 2001; Van Veen et al., 1997; Vrba and Robinson, 2001], increasing the dipole moment effectively increased the spatial resolution of the beamformer (or decreased the FWHM). In addition (but not shown here), the source location corresponded to the point of minimum FWHM in the subvolume [Barnes and Hillebrand, 2003]. For low amplitude signal (e.g., 0.2 and 0.6 nAm) the estimate of FWHM is independent of spatial sampling level, i.e., a coarse lattice is sufficient to describe the volume if it is smooth. Also plotted is a line showing the minimum smoothness (FWHM) that one could represent by sampling at this grid spacing (the Nyquist limit). For higher dipole moments (1.8 and 3.4 nAm) in conjunction with coarse sampling (4 and 8 mm), the FWHM estimate saturates at the Nyquist limit (solid line), indicating that the source space is possibly under-sampled. Increasing the spatial sampling rate further, however, shows that the estimated FWHM begins to diverge from the Nyquist limit, indicating adequate sampling. Figure 1B shows volumetric images of the beamformer estimates of power change (active divided by passive spectral power in the 0–140 Hz band) for different dipole moments. The first contour represents the true FWHM. The FWHM values observed in the volumetric images accord well with the estimates of FWHM from Figure 1A, even though these were made based only on the weight vectors corresponding to the central voxel and its immediate neighbors.

Experimental Data

Having established that the method of FWHM estimation was robust in the simulated case, we examined some recorded MEG data. Figure 2A shows four axial slices through the FWHM image of the occipital lobe of subject K.D.S. There is a tendency for the image to increase in smoothness with depth, as one would predict based on the lead-field sensitivity [Gross et al., 2003; Vrba and Robinson, 2001]. If the lead field sensitivity were the only issue, however, one

Figure 1.

A: Estimates of FWHM (broken lines) at the simulated source location are plotted against grid spacing for dipole moments of 0.2 (up triangles), 0.6 (diamonds), 1.2 (squares), 1.8 (down triangles) and 3.2 nAm (circles). The larger the dipole moment, the smaller the FWHM. For low dipole moments (0.2 and 0.6 nAm), the smoothness estimate is independent of spatial sampling as the source space is sampled adequately at all levels. As dipole moment increases (1.8 and 3.2 nAm), however, it is clear that the smoothness estimate saturates at the Nyquist limit (solid line) for coarse grid spacing (6 and 8 mm). Only when grid spacing is sufficiently fine does the smoothness estimate diverge from saturation to its true value. **B:** The beamformer estimate of spectral power change (active/baseline) in the 0–140 Hz band for different source amplitudes from three orthogonal views. The dark contour shows the measured FWHMs for these images. FWHM estimates from A (which are averages across all three dimensions) are based only on the weight vectors relating to the central voxel and its immediate neighbors; however, they accord well with those observed in the volumetric power change image.

would expect FWHM to be minimum at the scalp surface. This is not the case, and the example illustrates how the distribution of FWHM is rather complex, depending on the underlying sources as well as the system sensitivity. Another interesting observation is that FWHM changes faster tangentially to the scalp surface than it does radially. We speculate that this is due to the higher rate of change of lead fields in this direction [Cuffin and Cohen, 1979]. Histograms of occipital voxel FWHM values for subjects KDS and AS are shown in Figure 2B and 2C, respectively. In both subjects, the FWHM varies from 2 mm to 15–20 mm with an approximate median value of 8 mm. This information is re-presented in Figure 2D, where voxel FWHM for all three subjects is plotted as a fraction of total occipital volume. That is, for subject AW (blue, solid) approximately 10% of voxels within the volume have an intrinsic FWHM of less than 5 mm. In other words, a grid spacing of greater than 2.5 mm will lead to an under-sampling of 10% of the source space. The mean SNR (active power divided by baseline power in the 32–36

Hz band) per occipital channel was 1.4, 1.3, and 1.7 for KDS, AS, and AW, respectively (maximum occipital channel SNR values were 2.33, 2.4, and 6.9, respectively).

Figure 3A (lower panel) shows an axial occipital slice of the mw-SPM in the 32–36-Hz band for left visual field stimulation in subject A.S. There is clear contralateral visual cortex activation. The upper panel shows the corresponding FWHM image for this axial slice. Interestingly, the FWHM trough is at the edges and not the center of the estimated underlying activity, as was the case in the simulation (see below).

In Figure 3B (a magnified section of Fig. 3A), a line is shown marking a track of 20 virtual electrode locations at 1.4-mm spacing, extending from the SPM peak. Virtual electrodes locations at 0, 14, and 17 mm from the SPM peak are highlighted. Figure 3C shows the square of the Pearson correlation coefficient (i.e., the fraction of variance explained) between the weight vectors for virtual electrode 0 and all other virtual electrodes (red diamonds). It is clear that weight vectors at locations neighboring location 0 are

Figure 2.

A: FWHM estimates for four axial slices at 1.2-cm separation (z axis) through the occipital lobe of subject K.D.S. The calcarine sulcus extends medially from $x = -0.07$ on slice $z = 0.022$ up to $x = -0.04$ on slice $z = 0.034$. It can be seen that FWHM tends to increase toward the head center, reflecting the decrease in MEG system sensitivity to sources in this area. The smallest FWHM values, however, are not simply distributed at the scalp surface, as one would expect if FWHM were related directly to sensitivity

alone. Histograms of the per-voxel FWHM for subjects K.D.S. and A.S. are shown in **B** and **C**, respectively. In both cases the median FWHM is around 8 mm extending down to 2 mm (the minimum we could measure) and up to 20 mm. **D:** Cumulative FWHM counts for 3 subjects (K.D.S., crossed; A.S., dotted; A.W., solid) are shown. In this case, the FWHM count is shown as a fraction of total volume. For example, for subject K.D.S. (dotted), 20% of voxels have an FWHM below 6 mm, and 80% less than 10 mm.

intrinsically highly correlated and that this correlation falls off with distance. The square of the correlation between virtual electrode data time series for the same point pairs (blue circled line) falls off in a similar manner. The two curves (correlation between weight vectors and correlation between virtual electrode time series) would overlay if there were no underlying neuronal signal [Barnes and Hillebrand, 2003]. The third trace is the FWHM value at each voxel along

the line (note different scale); it is clear that as the line passes through regions of low FWHM, the weight vectors and corresponding time series estimates change markedly. This effect is illustrated in Figure 3D, where three spectra show the power in the virtual electrode at location 0 (a peak at 34 Hz), at 14 mm (clearly similar), and then at 17 mm, only 3 mm further away, yet where the stimulus related signal is completely absent.

Figure 3.

A: The upper panel shows a single axial slice ($z = 2.4$ cm) of the FWHM image for subject A.S. based on the covariance window of 0–80 Hz. The lower panel shows the 32–36 Hz mw-SPM for the same axial slice. The stimulus was in the right visual field and there is clear contralateral visual cortex activation. Comparing upper and lower panels, it seems that regions of low FWHM correspond to regions of high SPM gradient. The line on the SPM is for reference to **B**. **B:** Enlargement of **A** marked with a track of 20 virtual electrode locations extending from the SPM peak (location 0) and spaced at 1.4 mm. Highlighted locations are at 0, 14, and 17 mm from the peak. **C:** The square of the Pearson correlation coefficient (i.e., fraction of variance explained) between location 0

and all other locations is plotted for both weight vectors (diamonds) and virtual electrode time series (dotted, circles). FWHM estimate (see scale at right) at each voxel along the line is also plotted (solid, squares). Arrows mark distances 0, 14, and 17 mm from the peak. The trough in FWHM estimate corresponds to the sharp fall-off in the degree of relationship between virtual electrodes. **D:** Spectral power estimates at virtual electrode locations 0 (dotted, circles), 14 (dashed, green), and 17 mm (solid) are shown. The visual cortex is clearly being driven at 34 Hz by the 17-Hz reversing checkerboard. As the virtual electrode locations cross the low FWHM boundary, the signal rapidly (over the space of 3 mm) disappears.

DISCUSSION

We have demonstrated that in realistic recording situations MEG beamformer images approach very high resolution (Fig. 2). Approximately 10% of the source space has a point spread function of less than 5 mm and 50% less than 8 mm. These FWHM values were smaller than expected; al-

most all previous studies [e.g., Gross et al., 2001; Singh et al., 2002; Taniguchi et al., 2000] have assumed grid spacing of the order of 5–8 mm to be sufficient (but see Gaetz and Cheyne [2003], who used local high-density sampling). The results are based on measurements on a relatively superficial (<4 cm depth) and electrically active region of source space

(occipital lobe for visual stimulation) and are therefore perhaps an overestimate of spatial resolution across the entire brain volume. This said, no attempt was made to maximize spatial resolution, such as computing data covariance based on the time and frequency range over which the cortex was being stimulated.

The results are consistent across the occipital lobes of three subjects, yet the findings do not extrapolate well to the whole brain volume. If the mean voxel FWHM value were of the order of 10 mm, this would imply approximately 2,000 (assuming an 8-cm radius spherical head) degrees of freedom per volumetric beamformer image. As the FWHM estimates are based on the weight-vectors alone, the result implies that the linear transformation of the 151 measurement channels has an order of magnitude more degrees of freedom, which clearly cannot be the case. Taking into account the marked spatial inhomogeneity in FWHM (Fig. 2), however, and the fact that these results pertain to relatively superficial cortex (<4 cm), brings the volumetric and degrees of freedom estimates into closer correspondence. The empirical FWHM estimates reflect a single experiment and stimulus condition and are therefore not absolute but may serve to set some rule of thumb guidelines. Furthermore, at the heart of the beamformer formulation is the dipolar source model; the beamformer resolution will only equate to image smoothness in the case where there are no large, self-correlated, distributed sources.

Given the above caveats, our results are in broad agreement with those of Gross et al. [2003], in which theoretical estimates of FWHM across the brain volume dominated by values of less than 8 mm. It is also clear from the simulation results (Fig. 1) that for relatively conservative values of source dipole moment (e.g., 3 nAm) [Hillebrand and Barnes, 2002] and relatively deep (4 cm) sources, one would expect FWHM to be of the order of a few millimeters.

This work (Fig. 3) also highlights potential pitfalls implicit in MEG beamformer region-of-interest (or virtual electrode) analysis. In regions of low FWHM, the choice of virtual electrode location is critical; in the space of a few millimeters the estimate of neuronal activity will change considerably. For whole-brain analysis, this translates into a possibility of completely missing an image maximum due to spatial under-sampling. On the other hand, choosing a virtual electrode in a region where the FWHM is high will not be particularly anatomically specific. As a short-term solution, we have implemented a function that produces a volumetric map of FWHM, similar to Figure 3, around each chosen virtual electrode location. For each location, this gives an estimate of the effective size of the region of interest. Given the marked inhomogeneities in smoothness, our findings suggest that beamformer region of interest analysis based purely on anatomic priors, without reference to local FWHM information, is a precarious proposition.

The results also impact on group imaging studies with MEG [Singh et al., 2002, 2003]. For any group imaging study, the smoothness should be of the same order as the intersubject functional and anatomic variability [Steinmetz and Seitz,

1991; Xiong et al., 2000]. Even given that the subjects have identical functional anatomy, which is itself unlikely, typical MEG-MRI co-registration errors of a few millimeters [Adjamian et al., 2004; Singh et al., 1997] suggest that minimum FWHM should be of the order of 1 cm. This would imply that even though it is necessary to highly sample to accurately represent the source space, it will also be necessary to discard this high resolution (by smoothing) to do group imaging. An elegant alternative to resampling (and then smoothing) is to actively lower the intrinsic spatial resolution of the beamformer, as proposed by Gross et al. [2003], through the use of a regularization parameter in the weight calculation stage [Gross et al., 2001; Robinson and Vrba, 1999]. This parameter governs the trade-off between spatial resolution and the amount of projected sensor white noise at the virtual electrode. We used a value of zero, for which spatial resolution and projected white noise in the virtual electrode time series are the highest.

In the empirical data, the FWHM seemed to be at a minimum at the edges of the mw-SPM peak (Fig. 3A) and this contrasts with simulation results, where FWHM minimum and SPM peak are at the same location [Barnes and Hillebrand, 2003]. For perfect source reconstruction, the edges of the source are indeed where one would expect the FWHM minima to be. In simulation, it can be shown [Vrba, 2002] that the SAM reconstruction of an extended, self-correlated, area of activation appears as a single point source. Simulations in our lab have also shown that in this case (a 1-cm radius simulated disc) FWHM minima coincide with SAM peaks at the source center. Given the beamformer's very high sensitivity to source orientation [Hillebrand and Barnes, 2003], we believe that these empirically observed changes in FWHM may reflect underlying cortical curvature. Alternatively, these minima in FWHM correspond to cortical sources that do not covary with the experimental design.

In summary, in real experimental conditions the spatial resolution of MEG beamformer imaging is intrinsically very high (FWHM < 8 mm for 50% of the volume). We hope these findings will lead to the development of co-registration and experimental techniques that can be used to exploit this potential.

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