The missing link: analogous human and primate cortical gamma oscillations

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Recent animal studies highlighting the relationship between functional imaging signals and the underlying neuronal activity have revealed the potential capabilities of non-invasive methods. However, the valuable exchange of information between animal and human studies remains restricted by the limited evidence of direct physiological links between species. In this study we used magnetoencephalography (MEG) to investigate the occurrence of 30–70 Hz (gamma) oscillations in human visual cortex, induced by the presentation of visual stimuli of varying contrast. These oscillations, well described in the animal literature, were observed in retinotopically concordant locations of visual cortex and show striking similarity to those found in primate visual cortex using surgically implanted electrodes. The amplitude of the gamma oscillations increases linearly with stimulus contrast in strong correlation with the gamma oscillations found in the local field potential (LFP) of the macaque. We demonstrate that non-invasive magnetic field measurements of gamma oscillations in human visual cortex concur with invasive measures of activation in primate visual cortex, suggesting both a direct representation of underlying neuronal activity and a concurrence between human and primate cortical activity.

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Introduction

Research in both animals and humans is crucial to our continued understanding in the field of neuroscience. However, despite the long established anatomical comparisons between various animal species and the human, the animal and human research literatures remain relatively isolated. The impracticality of invasive research in healthy humans and the disparities associated with pathological models suggests that a non-invasive human equivalent would be the most constructive solution. Gamma (30–70 Hz) oscillatory activity in visual cortex is a widely studied phenomenon in both animals (Fries et al., 1997; Gail et al., 2000; Gray and McCormick, 1996; Kreiter and Singer, 1996; Logothetis et al., 2001; Rols et al., 2001; Siegel and Konig, 2003) and humans (Keil et al., 1999; Tallon-Baudry et al., 1998).

A recent primate study using surgically implanted electrodes to measure local field potentials (LFP) and multi unit activity (MUA) observed gamma activity in primary visual cortex, which increased linearly in amplitude with stimulus contrast (Logothetis et al., 2001). Here we investigate the occurrence of gamma activity in human visual cortex in response to visual stimulation, recorded using magnetoencephalography (MEG) and analysed using the synthetic aperture magnetometry (SAM) beamforming method (Vrba and Robinson, 2001). This method has high spatial and temporal resolution and a demonstrable spatial coincidence with the MRI BOLD response (Singh et al., 2002, 2003). A number of groups have recently used SAM as a method of MEG signal analysis (Fawcett et al., 2004; Furlong et al., 2004; Gaetz and Cheyne, 2003; Hall et al., 2004; Hirata et al., 2004; Ihara et al., 2003; Ishii et al., 1999, 2003; Singh et al., 2002, 2003; Taniguchi et al., 2000; Ukai et al., 2002; Vrba and Robinson, 2001; Xiang et al., 2001). Additionally, a spatially selective reconstruction of neuronal activity derived from the SAM beamformer implementation, called a ‘virtual electrode’ (VE) (Barnes and Hillebrand, 2003; Fawcett et al., 2004; Hall et al., 2004; Hillebrand et al., in press; Singh et al., 2002), was used to observe spatially discrete gamma activity and identify changes in amplitude as a function of stimulus contrast.

In this study we use SAM and VEs to describe how gamma oscillations in human primary visual cortex co-vary with stimulus contrast and compare these data with similar studies on the macaque visual cortex (Logothetis et al., 2001).
Materials and methods

Recording

Data were recorded using a 151 channel whole head MEG system (CTF Systems Inc., Port Coquitlam, Canada) at a sample rate of 625 Hz and collected over a single trial lasting 12.5 min, using a third order gradiometer configuration with a 50-Hz comb filter and 200-Hz anti-aliasing filter. Subjects (n = 9) passively viewed a stimulus monitor reflected through a window in the scanner room by a front silvered mirror at a distance of 2 m.

Stimuli consisted of horizontally oriented, stationary sinusoidal gratings of three cycles per degree (cpd) presented for a 2-s ‘on’ period followed by a 2-s ‘off’ period. We chose a spatial frequency of 3 cpd as gamma oscillations in human primary visual cortex seem to be maximal at this spatial frequency (Adjamian et al., 2004).

The gratings were presented at six different contrast levels in a randomised order, each of the contrast levels were presented a total of 25 times. The stimulus cycle, duration and random presentation were chosen in order to avoid adaptation, masking and attentional effects. Stimuli were presented in the lower left quadrant of visual field and subtended 3° × 3° of visual angle at an eccentricity of 0.5° from both horizontal and vertical meridians. A single quadrant was used in order to avoid cancellation effects from sources on opposing banks of the calcarine sulcus (Taniguchi et al., 2000).

The stimuli were displayed at six Michelson contrast (C_m) levels defined as:

\[ C_m = \frac{L_{\text{max}} - L_{\text{min}}}{L_{\text{max}} + L_{\text{min}}} \times 100 \]  

where \( L_{\text{max}} \) and \( L_{\text{min}} \) represent the maximum and minimum luminance, respectively.

The stimuli were generated on a VSG 3/2 graphics card, presented on a gamma corrected Eizo Flexscan T562-T monitor with a refresh rate of 85 Hz. Following data collection, a 3-D digitiser (Polhemus Isotrak, Kaiser Aerospace Inc.) was used to digitise the subject’s scalp surface, which was then coregistered with the individual subject’s anatomical MRI scan using surface matching software.

Analysis

Synthetic aperture magnetometry (SAM)

Linearly constrained minimum variance (LCMV) beamformer algorithms (van Veen et al., 1997) make an estimate of the electrical activity in each part of a pre-defined source space through a weighted sum of the sensor channels. A separate set of weights, or spatial filter, is computed for each source location based on the minimisation of the output power of the spatial filter, with the constraint that the filter has unity gain at this location (also used to define a so-called ‘virtual electrode’ (VE)). These constraints effectively make the beamformer a special case of the generalised linear inverse (or Wiener) solution (Eq. (2)) in which the underlying source current covariance matrix is diagonal and the amplitude of its elements is estimated from the data (and not based on the sensor-source space geometry as is the case for weighted minimum norm solutions; for details, see Hillebrand et al., in press; Mosher et al., 2003).

Formally, the generalised linear inverse which gives the estimate of the distribution of underlying neuronal currents, \( \hat{J} \), is given by:

\[ \hat{J} = C L^T C_D^{-1} b \]  

with \( b \) the measured field vector (1 × N), \( C_D \) the data covariance matrix (N × N), \( C_i \) the source current covariance matrix (M × M), \( L \) the lead field matrix (N × M), N the number of channels and M the number of elements in the source space. In the beamformer formulation, the source current covariance matrix \( C_i \) is assumed to be diagonal (no linear correlations between sources) and the variance component \( \sigma_i^2 \) corresponding to source space element \( i \) with lead field \( l_i \) is estimated from:

\[ \sigma_i^2 = \left( l_i^T C_D^{-1} l_i \right)^{-1} \]  

Various parameters can be computed based on the beamformer output (Eq. (2)) for a target location, for example the Neural Activity Index (van Veen et al., 1997) or the pseudo-Z statistic. A volumetric spatial image of brain activity can be formed by estimating such an index of neuronal activity sequentially. Additionally, one can define active and passive experimental states for each target voxel and statistically compare the neuronal activation in these states, forming the so-called statistical parametric maps that highlight brain regions that were activated to a different extent in the active and passive states (Barnes and Hillebrand, 2003; Gross et al., 2003; Singh et al., 2002, 2003).

Analysis protocol

SAM analysis was conducted on the active versus passive periods in the gamma (30–70 Hz) frequency range for all 150 stimulus presentations. The peak of activity in the SAM image localised to the primary visual cortex in all subjects. This was used to determine the coordinate basis for virtual electrode location and subsequent time frequency analysis. Additionally, the SAM images were spatially normalised and a random effects analysis used to generate a group SAM rfx image (Fig. 1a) (Singh et al., 2002, 2003).

Subsequently, Morlet–Wavelet time frequency and virtual electrode plots at peak loci were used to illustrate the envelope of gamma activity (Figs. 1b and c) in the individual participants. Gamma amplitude increase was determined by Mann–Whitney comparison of active and passive time windows. To account for the non-stationary nature of the signal, we computed the peak amplitude increase in the 30–70 Hz frequency band over the time window of interest and corrected for the influence of noise by subtracting the peak value for the 0% vs. 0% contrast case. The values for each of the stimulus contrast levels were subsequently normalised to the maximal value in each individual. The group means of these values were then used to plot the contrast response functions of the peak virtual electrode loci (visual area VI) in the gamma frequency range (Fig. 2).

Results

Results showed strong gamma activity in the upper right bank of the calcarine sulcus (Fig. 1a) in all subjects (group
SAM: $t = 4.24, P < 0.01$), retinotopically concordant with the lower left visual presentation. The mean contrast response curve in the gamma band was subsequently computed for this location in the visual cortex (Fig. 2). There was a linear increase in gamma amplitude with stimulus contrast ($r = 0.994, P < 0.01$), strongly correlated with LFP ($r = 0.997, P < 0.01$) and MUA ($r = 0.996, P < 0.01$) responses obtained by Logothetis et al. (2001) using surgically implanted electrodes in macaque visual cortex (Fig. 2).

**Discussion**

We show that measures of gamma oscillatory activity recorded non-invasively in human primary visual cortex using MEG (Fig. 1) have similar spatial, temporal and functional properties to those studied using invasive LFP recordings in the primate (Logothetis et al., 2001) (Fig. 2).

The principle findings of our study are that non-invasive MEG measurement in humans reveal gamma frequency oscillations of...
remarkable similarity to those found using invasively recorded gamma oscillations in the macaque monkey (Figs. 1b and 1d) (Logothetis et al., 2001).

In addition, these gamma oscillations increase in amplitude linearly with the contrast of the stimulus. This linear increase in amplitude correlates strongly with the linear gamma contrast response function observed in the macaque visual cortex (Logothetis et al., 2001).

The results obtained imply that invasive observations of LFP and MUA, which represent activity measured at the micron and millimeter levels, respectively (Legatt et al., 1980; Mitzdorf, 1987), are robustly represented in MEG activity obtained from the wider neuronal population (Figs. 1b and d). Furthermore, the results demonstrate the ability of MEG to non-invasively resolve the underlying neuronal activity observed by invasive procedures, thus adding MEG to the list of functional imaging studies able to draw such comparisons (Heeger et al., 2000; Logothetis et al., 2001), yet affording the additional attribute of millisecond temporal resolution.

It should be noted that our experimental design is by no means identical to that of Logothetis et al. (2001). For example, we used a single quadrant grating stimulus, rather than a polar checkerboard (see methods). As the beamformer focuses on regions of high source power (Barnes and Hillebrand, 2003; van Veen et al., 1997) and given that temporal modulation produces a large evoked cortical signature (Fawcett et al., 2004), we presented our stimuli without temporal modulation in order to highlight induced rather than evoked phenomena.

This said, the spatially focal and (implicitly) locally coherent gamma oscillations we observed have been observed in a number of invasive primate studies (Gail et al., 2000; Rols et al., 2001) in addition to the Logothetis study. Our results are also consistent with the primate studies of Rols et al. (2001), who demonstrate intra-cortically recorded gamma oscillations at loci that are retinotopically concordant with the stimulus presentation. Consequently, our results appear to demonstrate a remarkable consistency between the oscillatory phenomena in humans and primates in response to visual stimuli.

In summary, we show that current non-invasive human neuroimaging methods are beginning to acquire spatial and temporal resolution, previously achievable only in invasive animal techniques.

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