Predicting Stimulus-Rate Sensitivity of Human Somatosensory fMRI Signals With MEG

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Abstract: With increasing stimulus rate (SR), cortical EEG and MEG responses typically decrease in amplitude whereas BOLD fMRI signals increase. To address this discrepancy, we predicted BOLD responses with squared MEG waveforms using a recently proposed energy-density model. Tactile stimuli were delivered to finger tips at SRs of 1, 4, or 10 Hz in successive 25-s blocks, and brain signals were detected from area 3b of the primary somatosensory cortex of nine healthy adults using a 306-channel whole-scalp neuromagnetometer and a 3-T fMRI magnet. The main MEG deflections decreased in amplitude as a function of SR, whereas the BOLD signals increased from 1- to 4-Hz SR, with no further change at 10 Hz. MEG energy densities, obtained over the whole stimulus train and convolved with different hemodynamic response functions, predicted both the shape and amplitude of the BOLD signals well, and incorporation of nonlinear terms into the model did not offer any further advantage. Thus, squared MEG waveforms obtained over the entire stimulus train provided an appropriate estimate of area 3b neuronal activity associated with the BOLD signal. *Hum Brain Mapp* 30:1824–1832, 2009. © 2009 Wiley-Liss, Inc.

Key words: energy density; human; modeling; primary somatosensory cortex

INTRODUCTION

Elucidating the underlying neuronal activity from the blood-oxygenation-level-dependent (BOLD) signal—itsself an outcome of neuronal, metabolic and hemodynamic

changes—is one of the key aims of functional magnetic resonance imaging (fMRI). Currently, the best noninvasive and direct measures of neuronal activity in the human brain derive from electrophysiological signals that provide temporal information on the order of milliseconds. Curiously, however, the electroencephalographic (EEG) and magnetoencephalographic (MEG) responses behave differently than the fMRI signals as a function of stimulus rate (SR). For example, the peak amplitudes of the 30-ms (electrical stimulation) and 50-ms (tactile stimulation) evoked responses of the primary somatosensory cortex (SI) decrease with increasing SR [Delberghe et al., 1990; Forss et al., 1995; Mauguire et al., 1997; Tiihonen et al., 1989], whereas the amplitude of the BOLD fMRI signal increases [Ferretti et al., 2007; Iramina et al., 2001; Kampe et al., 2000].

In humans, MEG is a useful tool to detect neuronal activity from cortical areas located in walls of cortical

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fissures, such as area 3b in the SI cortex. To date, few models integrating MEG and fMRI signals have been proposed. The integrated MEG/fMRI model of Babajani et al. [2005] was recently tested using data obtained from human auditory cortex [Babajani-Feremi et al., 2008]. The total energy consumed by the post-synaptic potentials (PSPs), estimated from the MEG signals, served as input to the extended Balloon model [Friston et al., 2000] to predict the BOLD signal. The predictions visually matched the measured BOLD signals. A recent, more straightforward model [Nangini et al., 2008] used the MEG energy density, that is the squared MEG waveforms, to successfully predict BOLD signals in human SI in response to short-duration (≤ 1 s) stimuli by convolving the MEG energy density with a hemodynamic response function. The model was developed to link the energy contained in the magnetic field with the metabolic energy associated with the BOLD signal. Both these MEG/fMRI models rely on integrative measures of neuronal activity rather than on peak amplitudes of evoked responses.

In this study, we compared the SR dependencies of the evoked MEG signals and BOLD amplitudes from human SI in response to long-duration (25 s) stimuli. We also tested whether the MEG energy-density model could account for the SR-sensitivity of BOLD fMRI signals, in both amplitude and waveform.

MATERIALS AND METHODS

Subjects

Nine healthy right-handed young adults (six males, three females, aged 23–33 years, mean 29 years), reporting no history of neurological disorders, participated in MEG and fMRI experiments. Both the MEG and fMRI recordings were approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District. The study was undertaken with the informed consent of the volunteers. Some results of the fMRI experiments have been previously reported by Hlushchuk and Hari [2006].

Recordings

Cortical signals were recorded with 3-T fMRI (Signa VH/i, General Electric, Milwaukee, WI) with a standard GE quadrature receiver/transmitter head coil, and 306-channel whole-scalp MEG (Neuromag; currently Elekta Neuromag Oy, Finland). MEG signals were bandpass filtered at 0.03–200 Hz and sampled at 600 Hz. Recordings were obtained in two identical sessions less than 10-min apart.

Before MEG recording, four head-position indicator (HPI) coils were attached to the head and their positions were digitized (Isotrak 3S10002; Polhemus Navigation Sciences, Colchester, VT) to determine the coil locations relative to three anatomical landmarks (left and right pre-

auricular points, and nasion). These points served to align the MEG data with the coordinate system of each subject's anatomical MR images. During MEG recordings, vertical electro-oculograms (EOGs) were also recorded, and epochs coinciding with EOG signals exceeding 300 μ V were excluded from the analysis.

Stimuli

Pneumotactile stimuli, produced by balloon diaphragms driven by compressed air, were delivered to one of three digits of the right hand at SRs of 1, 4, or 10 Hz in successive 25-s blocks that were separated by 25-s (fMRI) or 5-s (MEG) rest periods. The stimulation of the separate fingers was randomized with the constraint that the same finger was never stimulated twice in succession. The order of the stimulation blocks was counterbalanced once and then coded into the stimulation sequence, which was the same across subjects. While the fMRI sequence comprised five stimulation blocks of each SR, the two MEG sessions comprised 10 (blocks) $\times$ 2 (sessions) at 1-Hz SR, 4 $\times$ 2 at 4-Hz SR, and 3 $\times$ 2 at 10-Hz SR. We used an increasing number of stimuli for progressively higher SRs in the MEG recordings to compensate for the decrease in evoked-response amplitude at higher SR and thereby boost the signal-to-noise ratio. Due to artifacts, only 17, seven, and five traces for Subject 1 and 14, six, and four traces for Subject 6 were available for each SR, respectively.

MEG Analysis

The single MEG responses were averaged in two different ways. To obtain conventional somatosensory evoked fields (SEFs), the single evoked responses were online-averaged across all stimuli from -100 to 400 ms with respect to stimulus onset, separately for each SR; the first three stimuli within each block were excluded. Source waveforms corresponding to current dipoles that best explained the responses for the 1-Hz SR were determined for each subject; these 1-Hz dipoles were then used to obtain source waveforms for the 4- and 10-Hz SRs. The peak amplitudes of the source waveforms within a time window of 30–100 ms were calculated for each SR, normalized to the peak for 1-Hz SR, and then averaged across subjects.

SEFs were also averaged block-wise ("block-SEFs"), separately for each SR, after the application of a temporal signal-space separation (tSSS) algorithm for artifact elimination [Taulu and Simola, 2006]. The time-window started 500 ms before the block onset and ended 100 ms after the block offset. All amplitudes were measured with respect to the 500-ms prestimulus baseline. Because the differences in head position between both sessions were less than 5 mm in all three directions for all subjects, blocks corresponding to the same SR (1, 4, or 10 Hz) were averaged

across sessions. The average block-SEFs were bandpass filtered (0.1–140 Hz).

Two separate approaches were then used on the block SEFs to obtain the energy density: one based on single-channel responses and the other on source strengths, as outlined below.

Single-channel data

For each subject, the block-SEFs calculated above were extracted from a single sensor picking up the largest MEG response from the SI cortex. Since each sensor consists of two orthogonal planar gradiometers (grad_x and grad_y), the squared vector sum from the average block-SEFs, separately for all three SRs, was calculated according to the formula $vsum^2 = \text{grad}_x^2 + \text{grad}_y^2$. This quantity was assumed to represent the energy density of the signal, based on arguments outlined previously by Nangini et al. [2008].

The squared vector sums for the three SRs were individually normalized by the peak amplitude of the 1-Hz $vsum^2$ waveform within a time window of 36–75 ms, centred around 50 ms (corresponding to the mean latency of the first major deflection of the response). No clear deflections were found within this time window for Subject 8 who was therefore excluded from further analysis. The normalized $vsum^2$ waveforms were then averaged across subjects for the three SRs.

Source waveforms

In the second approach, least-squares fitting was applied to search for an equivalent current dipole (ECD) best explaining the field pattern during the peak of the 50-ms response of each block-SEF; the computation was based on signals from 14 to 20 planar gradiometers above the contralateral SI area. The current dipoles associated with the source waveforms were all located in the SI hand area, as confirmed by overlaying them onto individual anatomical MR images (not shown). In each subject, the 1-Hz dipole was subsequently used to explain responses to the 4- and 10-Hz SRs. Subject 1 was excluded from analysis since no current dipole was found at this latency.

The ECD waveforms obtained for each SR were squared (ECD^2) to estimate the energy density of the block-SEFs, and averaged across subjects for each SR. No normalization was applied here since source waveforms are independent of the subject's head position relative to the MEG sensors.

Time-frequency spectra

The time-frequency spectra of the $vsum^2$ and ECD^2 waveforms were calculated for the 0–80 Hz range in frequency steps of 0.5 Hz. Additionally, the total power at each frequency step was collapsed across time.

Both the $vsum^2$ and ECD^2 waveforms, averaged across subjects and representing the energy density contained in a full stimulus block, were then used to predict the mean fMRI data of the whole group of subjects (see *Modeling of BOLD Signals*).

MRI Scanning and fMRI Data Analysis

Functional MR images were acquired with echo-planar imaging (EPI) pulse sequence (field-of-view (FOV) = 20 cm, matrix = 64×64 , echo time (TE) = 32 ms, repetition rate (TR) = 2,500 ms, flip angle (θ) = 90° , axial slice thickness = 4 mm, 314 time points). Sagittal anatomical images with high spatial resolution were obtained using conventional 3D fast spoiled-gradient (SPGR) imaging (FOV = $24 \times 26 \text{ cm}^2$, matrix = 256×256 , TE/TR/ θ = 1.9 ms/9 ms/ 15° , axial slice thickness = 1.3 or 1.4 mm).

fMRI data were analyzed with BrainVoyager QXTM; (BV QX) software (Brain Innovation B.V., Maastricht, Netherlands). The fMRI signals were corrected for motion, slice acquisition time, and linear trends, and then spatially smoothed using a Gaussian filter (FWHM = 6 mm). Both functional and anatomical images were normalized into Talairach space [Talairach and Tournoux, 1988].

We first used the SR contrast [10 Hz + 4 Hz + 1 Hz] > baseline, thresholded at false discovery rate (FDR) < 0.05 [Genovese et al., 2002], to delineate contralateral SI at group level (random-effects analysis). Within the SI cluster, we then applied the SR-sensitive contrast ([4 Hz – 1 Hz] + [10 Hz – 1 Hz] > 0; $P_{\text{FDR}} < 0.05$) to search for voxels whose responses at 4- and 10-Hz SRs were larger than at 1-Hz SR. This contrast was chosen because previous literature (see Introduction) indicates the major increase in SI BOLD response to occur from 1- to 5-Hz SRs, and we thus expected to see a marked difference in BOLD response at 1-Hz SR vs. 4- and 10-Hz SR. The SR-sensitive contrast revealed a sub-cluster in the rostral bank of the postcentral gyrus that corresponded to area 3b [Geyer et al., 2000]. The SEFs we obtained likely originated from area 3b [Hari and Forss, 1999], and we therefore modeled BOLD signals from this sub-cluster using our MEG data. The BOLD signals associated with each of the three SRs were extracted from the SR-sensitive sub-cluster and averaged across subjects, then subsequently used as signals to be predicted in the modeling (see below).

Modeling of BOLD Signals

The BOLD signals were modeled using a Volterra series [Friston et al., 1998]. The general form, containing linear (first sum) and nonlinear (second sum) terms, is given by

$$y(t) = c^0 + \sum c^1 x_i(t) + \sum c^2_{ij} x_i(t) \cdot x_j(t) \quad (1)$$

The output $y(t)$ represents the predicted BOLD signal, the coefficients c^n are scaling factors, and $x_i(t) = b_i(t) \otimes u(t)$, where b_i are basis functions representing the

Figure 1.

Basis functions used in least-squares fitting. Left: canonical IRF (solid line) and γ -variate IRF (dotted line), used in the linear convolution model. Right: γ -variate IRF and its derivative (smaller curve), used in the nonlinear convolution model.

hemodynamic impulse response function (IRF), $\otimes$ is the convolution operator, and u is an input function that is typically given by the stimulus boxcar function. In the energy-density model, however, u represents the MEG energy density. The functions b_i were pre-assigned, and the coefficients c'' were obtained by calculating a least-squares fit between $y(t)$ and the measured BOLD signals in order to minimize χ^2 . The minimization was performed for all three SRs simultaneously; that is, predictions $y(t)$ for each SR were calculated using the corresponding energy-density function $u(t)$ and simultaneously least-squares fit to the measured BOLD signals. Reduced χ^2 values, defined as $\chi_r^2 = \chi^2/\nu$, were computed to evaluate the goodness-of-fit, where $\nu = N-p-1$, for N time points and p model parameters; for a good fit, χ_r^2 approaches ν , such that $\chi_r^2 \approx 1$ [McClave and Dietrich, 1982]. For statistical comparison of different models, we calculated a quantity s^2 , that is, the sum of squares of the residuals divided by $N-1$, and conducted F -tests on the ratio $s_{\text{model1A}}^2/s_{\text{model1B}}^2$.

Determining the Basis Functions b_i

Figure 1 shows the IRFs used in Eq. (1): a canonical IRF obtained from the AFNI waver program [Cox, 1996] (linear model), and a γ -variate IRF with one (linear model) or two (nonlinear model) basis functions. The parameters for the canonical IRF (peak = 4 s, full-width-at-half-maximum = 11 s, return to baseline = 17 s) were based on parameter values within the reported range [e.g., Friston et al., 1998; e.g., Glover, 1999]. Parameters for the γ -variate IRF were obtained from Cohen [1997]. In the full non-linear expansion of Eq. (1), a γ -variate function and its first derivative were chosen as basis functions [see Friston et al., 1998].

RESULTS

Figure 2 (left) shows the mean $\pm$ SEM peak amplitudes (across all nine subjects) of the source waveforms for each SR, normalized to the value at 1 Hz. The responses at 4- and 10-Hz SRs were $\sim 38\%$ ($P < 0.001$; 2-tailed t -test) and

$\sim 71\%$ ($P < 0.0001$) weaker than at 1 Hz, respectively. The inserted examples of SEF waveforms for a representative subject (S2) display a distinct transient evoked response at 1 Hz, whereas at 4 Hz the responses merge together, and at 10 Hz a sinusoidal (steady-state) response is seen.

Figure 2 (right) shows the mean $\pm$ SEM BOLD amplitudes (computed from 7.5 to 27.5 s) corresponding to each SR. In clear contrast to the SEF source strengths (Fig. 2, left), the mean BOLD amplitude *increased* from 1 to 4 Hz by $\sim 28\%$ ($P < 0.02$), with no further increase at 10 Hz ($p > 0.7$).

Figure 3 shows the MEG energy density waveforms for all three SRs, based on the block-wise averaged signals. The main features of the $vsum^2$ (left) and ECD^2 (right) waveforms are very similar. At 1-Hz SR, evoked responses at each stimulus event are clearly discerned, although the first response is the largest. The waveforms for 4- and 10-Hz SR are also characterized by a transient response that is larger than at later time points, especially for the ECD^2 waveforms. The peak amplitudes of the onset transients were ~ 4 ($vsum^2$) and ~ 7 (ECD^2) times larger than the mean amplitudes of responses occurring afterwards at 4- and 10-Hz SRs, respectively.

Figure 4 shows the time-frequency spectra for the ECD^2 waveforms, plotted in 0.5-Hz steps from 0 to 80 Hz, along with the mean activity for each frequency step collapsed across time (right-hand side of each spectrum). The line plots on the right clearly show an increase in power for 4- and 10-Hz SR with respect to 1-Hz SR, especially in the 0–40 Hz band. The results for the $vsum^2$ waveforms (not shown) were similar.

Figure 5 shows the results of the least-squares fits for all three models. The measured BOLD signals (black lines showing the mean $\pm$ SEM values) are superimposed on predictions based on $vsum^2$ and ECD^2 waveforms (red and blue lines, respectively). Visual inspection shows that the

Figure 2.

Left: Mean $\pm$ SEM amplitudes of source strengths (open circles) as a function of stimulus rate. The inserts show somatosensory evoked fields for a representative subject (S2), averaged over sequential stimuli. Right: Mean $\pm$ SEM BOLD signal amplitudes as a function of stimulus rate.

Figure 3.

Energy density estimates, averaged across $N = 8$ subjects, based on $vsum^2$ (left) and ECD^2 (right) waveforms for each stimulus rate. Units in vertical scales are arbitrary for $vsum^2$ data since signals were normalized with respect to the early-latency (36–75 ms) peak amplitude of the 1-Hz $vsum^2$ waveform; the ECD^2 units are in $(nAm)^2$, obtained by directly squaring ECD waveforms.

predictions from the linear model qualitatively fit the measured BOLD signals well, both with the canonical IRF (top row) and γ -variate IRF (middle row). The same was also true for the predictions of the nonlinear model that used two γ -variate basis functions (bottom row). Goodness-of-fit estimates, represented by χ_r^2 values, ranged from 0.96 to 1.3 (see Table I); according to F -tests, the models were not statistically different ($S_{canonical}^2/S_{\gamma\text{-variate}}^2$: $F(58,49) = 1.18$ ($vsum^2$) and 1.19 (ECD^2), $P > 0.05$; $S_{canonical}^2/S_{nonlinear}^2$: $F(49,54) = 1.60$ ($vsum^2$) and 1.14 (ECD^2), $P > 0.05$; $S_{\gamma\text{-variate}}^2/S_{nonlinear}^2$: $F(58,54) = 1.56$ ($vsum^2$) and 1.36 (ECD^2), $P > 0.05$).

We note that the energy density model predictions obtained using fMRI data from the *whole* SI cluster (which did not exhibit SR-sensitivity) were significantly (F -test, $P < 0.05$) inferior to the predictions of area 3b data (not shown). Specifically, the predicted amplitude was smaller at 1-Hz SR and larger at 10-Hz SR than the corresponding measured amplitudes.

Figure 6 shows the mean $\pm$ SEM BOLD amplitudes (squares), along with the predictions of the linear model (canonical IRF) based on the $vsum^2$ (red line) and ECD^2 (blue line) waveforms. The predictions obtained from the other two models (based on both $vsum^2$ and ECD^2) produced similar results (not shown). The predicted BOLD amplitudes fell within the SEM error bars of the measured BOLD amplitudes, consistent with the χ_r^2 values that indicated good fits. Predictions based on the other models similarly matched the measured BOLD amplitudes (data not shown).

DISCUSSION

We predicted the SR-dependence of BOLD signals in area 3b of the human SI cortex using the energy density of

the evoked somatosensory MEG signal, derived from the time courses of both single-channel signals ($vsum^2$) and the source strengths (ECD^2). Despite the opposite SR dependences of the peak MEG responses and the mean amplitudes of the BOLD responses, the models predicted the fMRI data well. This rather straightforward result is interesting because the spontaneous EEG/MEG oscillations can have quite different relationships with the BOLD signal, depending on the frequency band. For example, the convolution of the parietal 8–12 Hz EEG power revealed a negative correlation with the fMRI signal [Laufs et al., 2003], whereas BOLD amplitudes positively correlated with the power of γ -band EEG in cat visual cortex [Niessing et al., 2005], γ -band MEG in human visual cortex [Muthukumaraswamy and Singh, 2008], as well as the power of intracranial γ -band EEG in reading-related areas in epileptic patients performing a reading task [Lachaux et al., 2007]. Spontaneous BOLD fluctuations also correlated with spontaneous fluctuations in the power of intracortical γ -band activity (24–90 Hz) and of higher frequencies (at 130–300 Hz and at 300–2,500 Hz) in monkey visual cortex [Shmuel and Leopold, 2008].

Apparent Discrepancy Between SR Effects on MEG and fMRI Signals

In agreement with the literature, our results showed that the peak SEF amplitudes decreased with increasing SR, whereas BOLD amplitudes increased from 1- to 4-Hz SR, with no further increase at 10 Hz. Although this apparent discrepancy is confusing at first sight, our results add to the growing number of studies indicating that this electrophysiological-hemodynamic discrepancy is largely illusory. Specifically, by modeling the whole time course of the

Figure 4.

Legend: Time-frequency spectra (0–80 Hz in 0.5 Hz steps) of the ECD^2 energy density waveforms shown in Figure 3. The mean activity at each frequency step, collapsed across time, is plotted as a curve on the right-hand side of each spectrum.

BOLD signal, the relationship between neural and hemodynamic activity can be better clarified.

Many previous studies have only considered how peak amplitudes of evoked responses correlate with intensity changes of hemodynamic signals. For example, positive correlation between somatosensory evoked potentials (SEPs) and cerebral blood flow (CBF) and BOLD response has been found when both the SR and the stimulus duration are kept fixed but the stimulus intensity is varied [Arthurs et al., 2000 (SEP and BOLD, human SI); Nielsen and Lauritzen, 2001 (SEP and CBF, rat SI); Arthurs et al., 2007 (SEP and BOLD, human SI)]. However, when SR is varied but stimulus duration and intensity are fixed, the changes in the mean or peak BOLD signal are better predicted by an *integrative* measure of neuronal activity than simply by the peak amplitude of the evoked response. For example, the cumulative sum of peak amplitudes of intra-

cortical SEPs across stimulus trains (ΣSEP_{peak}) correlated, in rat SI, with peak BOLD responses [Huttunen et al., 2008] and with peak cerebral blood flow and volume (CBF, CBV) [Martin et al., 2006]. Similarly, ΣSEP_{peak} values obtained from subcutaneous scalp recordings, also in rat SI, correlated with the intensity change of the peak BOLD signal [Van Camp et al., 2006] and with the mean regional blood flow [Ngai et al., 1999]. In a comprehensive rat experiment [Franceschini et al., 2008], the duration, SR, and amplitude of stimulus trains were varied to investigate the relationship between SEPs and the total amount of haemoglobin (HbT), related to the blood flow supplied to SI. The ΣSEP_{area}^2 , defined as the sum of the squared area of the response under the P1-N1-P2 deflections (which peaked at ~17 ms, ~31 ms, and ~66 ms, respectively) correlated with HbT (as did the ΣSEP_{area} values, but to a lesser extent for variable SRs and train amplitudes).

Although integrative measures of neuronal activity, such as those discussed above, show good correlation to mean or peak amplitudes of hemodynamic signals, the next level of investigation is to predict the *whole time course* based on an appropriate neuronal correlate and integrative model. In monkeys, the power of the electrophysiological signal, obtained as a function of time and in different frequency bands (i.e., high-frequency MUA, and lower-frequency LFPs) has, in the linear convolution model, successfully predicted both positive [Logothetis et al., 2001; Shmuel et al., 2006] and negative [Shmuel et al., 2006] BOLD signals in response to visual stimulation.

The Energy-Density Model

In predicting BOLD signals, the simplest approximation is to use the stimulus boxcar itself in the linear convolution model, as is done in conventional fMRI analysis. However, a simulation study using experimental SI BOLD data for different stimulus train durations (2–20 s) showed that the boxcar approximation is inferior to other, more neurophysiologically plausible neuronal waveforms [Nangini et al., 2005]. As a further improvement to the boxcar approach, the energy-density model, proposed by Nangini et al. [2008], uses the square of measured MEG signals, representing the energy contained in the neuromagnetic field. According to the model, the energy density is related to the metabolic energy expended in BOLD signal generation since the postsynaptic current is proportional to both the metabolic energy required to restore membrane potentials following neuronal signaling [Attwell and Laughlin, 2001] and the strength of the source of the neuromagnetic field [Hämäläinen et al., 1993]. Indeed, spectral analysis of the energy density waveforms in the current study showed that more energy is contained in the responses elicited at the 10- or 4-Hz SRs than at the 1-Hz SR (see Fig. 4), consistent with the SR-dependence of the BOLD signal amplitude.

Figure 5.

Measured and predicted BOLD signals for stimulus rates of 1, 4, and 10 Hz, separately for canonical impulse response function (IRF; top row; linear model), γ -variate IRF (middle row; linear model), and 2 γ -variate IRFs (bottom row; nonlinear model). The black lines depict the mean $\pm$ SEM measured signals, and

the predictions based on $vsum^2$ and ECD^2 waveforms are shown in red and blue, respectively. In the last row, the stimulus duration is indicated by shaded boxes, and the window used to calculate mean amplitudes is shown by the horizontal bars.

Our predicted BOLD waveforms, based on the energy density model which considers only signals time-locked to the stimulus blocks, explained a large fraction of the variance in the measured signals, as indicated by the goodness-of-fit measures, but it did not capture detailed features, such as the prominent onset transient in the response elicited at 10-Hz SR. A better fit might be obtained if the induced responses, in addition to the evoked responses, would be included as well, although such an integrative model has not yet been formulated.

Energy Density Estimates: $vsum^2$ vs. ECD^2

We used two different estimates of the MEG energy density. The $vsum^2$ prediction was applied as a proof-of-principle because the $vsum^2$ signal, although filtered with the same passband as the source waveforms, could have contained contributions from currents outside the SI hand area. In the ECD^2 method, the source waveforms were

estimated for a current dipole in the SI cortex. For our data, both estimates adequately predicted the BOLD signals. However, without the ECD^2 analysis, it would not

TABLE I. Reduced χ^2 values (χ_r^2) for the linear and nonlinear convolution models based on $vsum^2$ and ECD^2 energy density estimates

Model	IRF	Energy density waveform	χ_r^2
Linear	Canonical	$vsum^2$	1.2
		ECD^2	1.2
Linear	Gamma-variate	$vsum^2$	1.1
		ECD^2	1.1
Nonlinear	2 Gamma-variates	$vsum^2$	0.78
		ECD^2	0.93

Goodness-of-fit estimates for each model.

Figure 6.

The measured (open squares) and predicted (long dashed line, $vsum^2$; short dashed line, ECD^2) BOLD signal amplitudes as a function of stimulus rate.

have been possible to ascertain if the model predictions produced from $vsum^2$ energy densities were the result of SI activity.

Model Robustness

Our linear models were insensitive to the particular class of impulse response function used (canonical vs. γ -variate IRF), as was indicated by the F -test comparisons. The nonlinear approach was included to investigate whether the shape of the predicted responses for the 10-Hz SR could improve with a better combination of basis functions. However, visual inspection showed that this was not the case, and no statistical advantage over the linear models was found. It should be noted, however, that the small number of time points (60) in this study precludes the use of too many model parameters in the least-squares fitting. With more time points, and with a much better signal-to-noise ratio for the BOLD signals, an optimal IRF might be found, for example by allowing optimizable IRF parameters (ours were fixed based on *a priori* information) and/or more basis functions, and the need for nonlinear terms could be investigated further.

CONCLUSIONS

We predicted the waveforms and amplitudes of the SR-sensitive SI BOLD signals in response to long-duration tactile stimuli using the energy-density model based on the whole time courses of the MEG signals. Our results support the notion that an integrative measure of evoked activity, rather than e.g., peak amplitudes of evoked responses, is an appropriate estimate of the neuronal activ-

ity underlying the BOLD signal. However, the signal-to-noise ratio of our fMRI data prevents us from concluding that the energy density waveforms are sufficient to model BOLD signals in general. Moreover, the generalizability of the energy density model should in future be tested using MEG/fMRI signals originating from brain areas beyond the SI cortex.

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