Feedback to distal dendrites links fMRI signals to neural receptive fields in a spiking network model of the visual cortex

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Heikkinen H, Sharifian F, Vigario R, Vanni S. Feedback to distal dendrites links fMRI signals to neural receptive fields in a spiking network model of the visual cortex. J Neurophysiol 114: 57–69, 2015. First published April 29, 2015; doi:10.1152/jn.00169.2015.—The blood oxygen level-dependent (BOLD) response has been strongly associated with neuronal activity in the brain. However, some neuronal tuning properties are consistently different from the BOLD response. We studied the spatial extent of neural and hemodynamic responses in the primary visual cortex, where the BOLD responses spread and interact over much longer distances than the small receptive fields of individual neurons would predict. Our model shows that a feedforward-feedback loop between V1 and a higher visual area can dissociate by stimulus protocols or response temporal dynamics (Bartolo et al. 2011; Goense and Logothetis 2008; Logothetis et al. 2001; Rauch et al. 2008; Rees et al. 2000), it provides a blood oxygen level-dependent (BOLD) signal that is based on local hemodynamic responses triggered by the mean activity of thousands of neurons. Thus fMRI cannot be directly linked to local neural circuitry and function, and interpretation of the underlying neural events relies on accurate model of the measured signal.

The BOLD signal has been reported to correlate better with local field potentials than spiking activity, when the two can be dissociated by stimulus protocols or response temporal dynamics (Bartolo et al. 2011; Goense and Logothetis 2008; Logothetis et al. 2001; Nir et al. 2008; see, however, Lima et al. 2014 for an opposing view), suggesting that it reflects more the synaptic input of the neurons than their output. Subsequently, astrocytes have been identified as key mediators of the neurovascular coupling (Attwell et al. 2010; Gurden et al. 2006; Iadecola and Nedergaard 2007; Koehler et al. 2009; Petzold et al. 2010), and intracellular recordings have revealed different input efficiency depending on position of the synapse in the dendritic tree (Williams and Stuart 2002). Thus, the exact relationship between the measured BOLD response and single neuron responses would be expected to be stimulus or task specific, depending on the distribution of the specific input in the dendritic tree and resulting sensitivity of the spike output.

The difference between synaptic input and action potential output may underlie the observed differences, e.g., in sensory tuning functions between human fMRI (Henriksson et al. 2008) and monkey single cell responses (Foster et al. 1985), as well as the different responses these two measures provide for various cognitive tasks (Boytont 2011). We studied the spatial profiles of fMRI signals and neuronal spiking response in the primary visual cortex (V1), where the BOLD response spreads and interacts over significant distances (Sharifian et al. 2013; Zuidemaan et al. 2012), far beyond what could be expected based on the small receptive fields of the V1 neurons (Cavanaugh et al. 2002) but commensurable with the modulatory interactions in this area mediated via extensive lateral and interareal connections (Angelucci and Bressloff 2006; Ange lucci et al. 2002a; Binzegger et al. 2004). The role of various afferent connections as either “driving” or “modulating” may depend on the number of synapses (Binzegger et al. 2004) but also on anisotropic mapping of various inputs into the dendritic trees of the pyramidal neurons (Petreanu et al. 2009; Spruston 2008). Recognizing that the signal transformation by the individual neurons may play a key role in reconciling the differences between BOLD and spiking activity, we sought to implement a spiking network model that could examine the
role of the intracellular transformation in bridging these two measures.

First, we quantified the spatial spread of neural activation with two methods: with BOLD response in V1 and the estimated mean action potential output of the V1 neurons in response to a wedge-shaped grating input. We then implemented a two-dimensional spiking network model of the visual cortex, in which we sought to relate these two complementary activity measures. We explicitly monitored the glutamatergic input of the model V1 neurons when the network was presented with the wedge stimulus and compared it to the spiking output of the network. We wanted to study whether the distinct features of the BOLD response and mean spiking activity could arise from strong modulatory afferents landing on the dendritic tree, whose contribution remains subthreshold in the absence of driving input close to soma.

**METHODS**

*fMRI experiment.* Sixteen subjects (age 26–48 yr, 11 men) with normal or corrected-to-normal vision attended the experiment after written informed consent. Each subject participated in one recording session, consisting of 16 runs. First, three multifocal localizer runs were performed, to enable precise retinotopic mapping. A T1-weighted volume with $1 \times 1 \times 1$ mm resolution allowed for the segmentation of the gray matter. The final 12 runs comprised the main experiment, in which a wedge-shaped sinusoidal pattern (Fig. 1A) was presented, in a block design, with two different contrasts and spatial frequencies, and varying phase of the grating. The study was approved by the ethics committee of the Aalto University.

fMRI data were acquired with a 3 T MAGNETOM Skyra scanner (Siemens, Erlangen, Germany) with a 32-channel head coil modified for good binocular view. The functional volumes were acquired with a spin echo (SE) echo planar imaging sequence, which emphasizes the parenchymal signal in favor of the superficial veins and thus provides superior resolution compared with the gradient echo sequence (Parkes 2016).
consisting of black (4 cd/m$^2$) and white (200 cd/m$^2$) flickering (SR Research, Mississauga, Ontario, Canada). The timing of each stimulus was added as effects of interest after convolution with the canonical hemodynamic response model, and high-pass filtering (128 s cut-off) and temporal autoregressive noise model were applied to both the data and the model regressors. Head motion parameters were included as nuisance covariates. The relative BOLD signal changes were calculated for each voxel, by dividing the coefficient for the effect of interest by the voxel’s mean coefficient. The anatomical images were segmented, and signals were visualized on the inflated cortical surface using the Freesurfer software (Dale et al. 2005). The acquisition parameters were: repetition time 2.1 s, echo time 70 ms, field of view 18 cm, imaging matrix 64 $\times$ 64 resulting in 2.8 mm in-plane resolution, and a volume contained 20 slices with slice thickness of 2.8 mm.

Data were analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) Matlab (Mathworks, Natick, MA) toolbox. Images were converted to NIFTI format, followed by slice time correction, realignment, and reslicing (Friston et al. 2007). No spatial smoothing was applied, to avoid compromising spatial resolution. The relative hemodynamic response to each stimulus category was estimated, with the general linear model implemented in SPM8. Visual stimuli were generated with Matlab, and their timing and positioning were controlled with Presentation software (Neurobehavioral Systems, Albany, NY). The subject viewed the visual stimuli at 43 cm distance on a back projection screen, to which they were projected with a 3-micromirror Christie C3 data projector (Christie Digital System, Kitchener, Ontario, Canada). Dim photopic ambient light was on during the measurements. Subjects were instructed to fixate on a cross at the center of the screen and not pay attention to the stimuli. During the main experiment they were engaged in an attention control task at the center of fixation (Larsson et al. 2006). The quality of fixation was monitored with the EyeLink 1000 eye tracking system (SR Research, Mississauga, Ontario, Canada).

Multifocal localizers (Henriksen et al. 2012; Vanni et al. 2005), consisting of black (4 cd/m$^2$) and white (200 cd/m$^2$) flickering checkerboard patches (Fig. 1B), were presented in three runs. Two runs, each containing 42 complementary regions, were combined into an 84-point localizer for thorough sampling of the V1. The third multifocal run was redundant with the 84-point localizer and was not analyzed further. The positions of the localizer patches followed the increase in summation field size in monkey V1, as a function of eccentricity (Cavanaugh et al. 2002), and their sizes were optimized to minimize overlap while approximately following human M-scaling. Visual field coordinates were assigned to voxels showing a suprathreshold (T > 4.7) response to a localizer stimulus, in a cluster of at least three voxels within V1. Each voxel comprised a linear average of localizer stimulus visual field coordinates (complex valued $z$, expressed in visual field degrees), weighted by the respective BOLD signal change. The cortical location of each data point of the individual subjects was thus mapped to the visual space, and these locations were in turn converted to the V1 model cortex coordinates (complex valued $w$, measured in mm of cortex) via the log-polar Schwartz transform (Duncan and Boynton 2003; Schwartz 1994).

$$w = 17 \cdot \log(\frac{z + 1}{2}) \tag{1}$$

The individual subjects’ V1 labels contained on average 117 mapped voxels on the two hemispheres, ranging from 54 to 224 (median 105). The data from the two hemispheres were combined, and the continuously distributed individual coordinates were down-sampled to a regular $2 \times 2$ mm grid on the model V1. Grid squares with suprathreshold data from more than five subjects were included into the analysis.

The visual stimulus of the main experiment was a horizontal wedge-shaped sinusoidal pattern (Fig. 1A), expanding symmetrically from the fixation point at the center. BOLD signal changes in the V1 were measured in four different stimulus conditions with a balanced block design: the contrast of the stimulus was either 80 or 10%, and the spatial frequency of the sinusoidal pattern was either 0.5 or 2 cycles per degree. The two contrasts were analyzed independently, but the spatial frequency data were combined. The BOLD signal changes of the main experiment were used for the voxels previously labeled with visual field coordinates, without further thresholding.

**Deriving the neural activity estimate from the BOLD signal.** The measured change in the MRI signal is nonlinearly related to the stimulus-induced changes in the blood flow and, thus, to the underlying neural activity. This is due to changes in the blood inflow, which result in alterations in the blood volume, and in particular the deoxy-hemoglobin content of the intravascular space. The balloon model (Buxton et al. 1998) accounts for this nonlinearity and allows for the derivation of the BOLD signal as a function of changes in the cerebral blood flow (CBF). The amplitude of which we assumed linearly related to the underlying neural response. We used the average values of the model parameters based on the experimental data by Mildner et al. (2001) to calculate a relation between blood flow and the BOLD signal change at 3T for our stimulus blocks. We then fitted the canonical hemodynamic response function to the calculated responses to essentially replicate the analysis of our experimental data and thus obtain signal changes corresponding to the experimentally determined values. A 3rd-degree polynomial was fitted to the obtained BOLD signal change vs CBF relation (Fig. 1C) and subsequently used to convert the measured BOLD signal changes into the estimated change in cerebral blood flow (CBFe).

**Spike response: the area summation model.** Area summation function (Fig. 2A) describes the response of most primate V1 neurons as a function of stimulus diameter when circular grating stimuli of optimal orientation (Cavanaugh et al. 2002) are presented centered on the receptive field. When the stimulus diameter is increased, the neural firing rate response first increases and then decreases before reaching an asymptote. We modeled this area summation property for the V1 neurons to produce an estimate for the spike output pattern to our stimuli.

Cavanaugh and colleagues (Cavanaugh et al. 2002, their Eqs. 8 and 9) modeled the area summation response, $F(x)$, of V1 neurons to a circular grating stimulus with diameter $x$, as a scaled ratio of a positive and a negative two-dimensional Gaussian envelopes:

$$F(x) = \frac{k_c L_c(x)}{1 + k_s L_s(x)}$$

$$L_c(x) = \left( \frac{2}{\sqrt{\pi}} \int_0^x e^{-y^2} dy \right)^2$$

$$L_s(x) = \left( \frac{2}{\sqrt{\pi}} \int_0^x e^{-y^2} dy \right)^2$$

Parameters $k_c$, $k_s$, and $w_c$, $w_s$, are the gain, $k$, and spatial extent, $w$, parameters of the excitatory center and suppressive surround components, respectively. Summation and surround field sizes and summation indices for 551 macaque V1 neurons were kindly provided to us by J. R. Cavanaugh, Wyeth Bair, and J. Anthony Movshon. We estimated population averages of these parameters from the data as a function of eccentricity by linear regression (Fig. 2B). We then fitted Eq. 2 to the population data, to determine $w_c$, $w_s$, $k_c$, and $k_s$ as a function of eccentricity (Fig. 2, C and D). The obtained values for $k_c$ and $k_s$ were scaled for different stimulus contrasts based on their contrast dependence, as depicted in Fig. 9 of Cavanaugh et al. 2002. The contrast dependence of the response was based solely on the relative weighting of the excitatory and suppressive components, as indicated by $k_c$ and $k_s$ in Eq. 2.

The area summation response function $F(x)$ has been derived for circular stimuli. We constructed the response to a generic stimulus shape by summing linearly differential elements of $F(x)$. Each of these elements represents the contribution from a subregion of visual field at visual field distance $r$ (in degrees) from the neuron. The contribution $f(u,v)$ from each location $(u,v)$ consists of a nonlinear combination
The neurons’ receptive field centers spanned the visual space on one stimulus eccentricity. excitatory and suppressive envelopes as a function of \( D \) to the area summation parameters of single neurons. eccentricity by fitting the ratio of Gaussians model (Eq. 2) to the area summation parameters of single neurons. the weighting coefficients \( k_1 \) and \( k_2 \) (Eq. 2) of the excitatory and suppressive envelopes as a function of stimulus eccentricity.

of the excitatory and suppressive influences at corresponding distance \( r \) from the receptive field center. In a homogenous sampling of the visual field, \( f(u,v) \) can be derived analytically from \( F(x) \):

\[
f(u,v) = F'(2r) / \pi r = \frac{k_1 L_1'(x) - k_1 L_2'(x) k(L_1(x))}{[1 + k(L_1(x))]^2}
\]

\[
L_1'(x) = \frac{8}{\pi} e^{-(x/w_1)^2} \int_0^x e^{-(y/w_1)^2} dy
\]

\[
L_2'(x) = \frac{8}{\pi} e^{-(x/w_2)^2} \int_0^x e^{-(y/w_2)^2} dy
\]  

(3)

Here, following the formulation of the original model, \( x = 2r \). To obtain the expected spike response, we treated the wedge pattern as an optimally oriented ideal stimulus and weighed each \( f(u,v) \) at locations within the pattern equally, while contributions of locations outside the pattern were considered zero. \( f(u,v) \) was integrated over a region surrounding each neuron up to 7 degrees, a distance exceeding the asymptote of the spatial integration at all eccentricities. Finally, the obtained spike response patterns for the two stimulus contrasts were normalized by the amplitude and baseline activity of the response to the high contrast stimulus.

The predicted spiking responses of the V1 neurons to the high-contrast stimulus are shown in Fig. 3, A and D. at the full resolution, together with the fMRI recorded data (squares). For further analysis, and a comparison to the spiking network model output, the spike responses were downsampled to the same 2 × 2 mm grid as the BOLD data (squares in Fig. 3, A and D).

**Spiking neural network model: the neurons.** We constructed a two-dimensional spiking network model of the visual cortex on the Brian simulator platform (Goodman and Brette 2008). The spatial extent of the model connections (Fig. 4A) followed the architecture of a previously published rate-based model of spatial interactions on V1 (Schwabe et al. 2006) and anatomical studies of the primate visual cortex (Angelucci et al. 2002b). The V1 was modeled as a single-layered 2D network of excitatory (EV1) and inhibitory (IV1) neurons. The neurons’ receptive field centers spanned the visual space on one hemisphere between 0.5 and 28 degrees eccentricity, well beyond the region stimulated in the fMRI experiment (17.7 degrees along the horizontal meridian) to diminish border effects. The 42,849 EV1 neurons were evenly spaced on the model cortex, with 0.23 mm distance between neurons, corresponding to ~0.1 degrees in the visual field at 5–6 degrees eccentricity (Eq. 1). The ratio between inhibitory and excitatory neurons in V1 was 1:4, and the inhibitory neurons were also evenly spaced on the model cortex. The extrastriate cortex was modeled with 10,719 excitatory and inhibitory neurons, their receptive field centers in visual space corresponding to those of the V1 inhibitory neurons.

The membrane voltage in the soma of the model neurons, \( V_s \), followed the exponential integrate-and-fire (EIF) model (Fourcaud-Trocme et al. 2003):

\[
dV_s / dt = g_L(V_L - V_s) + \sum I_{syn}(t) + \Delta_T \exp \left( \frac{V_s - V_r}{\Delta_T} \right)
\]

(4)

where \( C \) is the membrane capacitance, and the leak conductance, \( g_L \), and its equilibrium potential, \( V_L \), determine the membrane potential at rest. \( \sum I_{syn}(t) \) is the sum of currents from individual synapses (see below). The spiking current, \( \phi(V) \), makes the equation unstable at membrane potentials depolarized to near or over threshold \( V_T \), enabling spike generation. \( \Delta_T \) is the voltage factor, determines the voltage dependence of the spiking current. Conceptually, a spike is triggered when the voltage equation diverges toward infinity. In practice, the spike event was recorded upon reaching a criterion potential, \( V_{cut} \), after which the membrane potential was reset to \( V_{reset} \) and integration was resumed again after a refractory period. The parameters for each neuron type are listed in Table 1.

The V1 pyramidal neurons comprised six compartments (Fig. 4C): soma, one isopotential compartment representing the basal dendrites, and four isopotential compartments connected in series, representing the apical dendrite. The soma served as an integrator of the synaptic input currents flowing in from the dendrites and obeyed Eq. 4, while the dendritic compartments were passive targets of the synaptic conductances, i.e., \( \phi(V) = 0 \). The areas of the compartments and the
intercompartmental resistances were tuned to reproduce a realistic dendritic decay of layer 5 pyramidal neurons (Williams and Stuart 2002) (Fig. 4C). When the synaptic inputs were connected to the dendritic compartments, the membrane voltage in the soma was governed by equation

$$C \frac{dV}{dt} = g_L(V_L - V) + \psi(V) + \sum I_{\text{dendrites}}(t)$$  \hspace{1cm} (5)

where $I_{\text{dendrites}}$ represents ohmic currents flowing into the dendritic compartments.

The compartmental V1 excitatory neurons (Ev1), which represented generic “pyramidal” or “regular spiking” (RS) cells (McCormick et al. 1985) were implemented with generic passive parameters (Table 1), with small total and somatic membrane area and time constant typical to V1 neurons, as well as high input resistance and firing rates (Amatrudo et al. 2012). For simplicity, the parameters for the extrastriate excitatory neurons (Ex) were tuned to approximately match the electrophysiological response properties of the Ev1 neurons to somatic current input. The inhibitory interneurons represented the “fast spiking” interneurons and were distinguished from the excitatory ones mainly by their shorter membrane time constant, as well as by their shorter refractory period, which enabled higher spike rates (McCormick et al. 1985).

Excitatory (AMPA) and inhibitory (GABAA) conductance inputs were modeled as fixed amplitude, exponentially decaying impulse changes in the membrane conductance of the compartments. The current through an individual synapse was given by

$$I_{\text{syn}}(t) = g_{\text{syn}}(t) \ast (E_{\text{rev}} - V_m)$$  \hspace{1cm} (6)

The total synaptic current in any compartment, $\sum I_{\text{syn}}(t)$, was calculated as the linear sum of all individual synaptic currents.

Spiking neural network model: connectivity. The excitatory neurons in V1 (Ev1) received feedforward input from spatially narrow “classical” receptive fields and horizontal excitatory and inhibitory input from their local surround. They also received excitatory input feedback from an extrastriate area, to which they also provided feedforward input. The extrastriate region was inspired by the area MT, in which neurons have large receptive fields and send strong recurrent feedback to V1 (Angelucci et al. 2002a). However, in our model this region effectively served as a relay station mediating long-distance modulatory interactions and did not attempt to further address signal processing at the higher-level visual cortices. The spatial distribution of each input was adapted from the primate anatomical studies (Angelucci et al. 2002a) at cortical location representing 5 degrees visual field eccentricity. In our 2D model, the spatial profile of connections was maintained constant throughout the cortex. This resulted in an invariant cortical point image, in line with physiology (Harvey and Dumoulin 2011; Palmer et al. 2012).

The lateral geniculate nucleus (LGN) cells produced Poisson distributed spike output, with high firing probability at stimulus location Fig. 3. cBFe and spiking responses spread differently in V1. A: the CBFe response (squares) and spiking output (background colors) in the model V1 in response to the high contrast stimulus. Dashed line, stimulus borders. B: normalized amplitudes of the CBFe and spike response samples in region 1, as indicated in the inset and Fig. 1C, as a function of visual field distance from the stimulus border. Curves approximate the data with 3 Gaussian functions. C: as D, for regions 2 and 3. E, F: as above, for the low-contrast stimulus.
in the fMRI experiment and lower basal rate elsewhere. The combined feedforward Poisson inputs at stimulus location corresponded to mean current of \(-0.1\) nA to a pyramidal neuron. The probability of a synaptic contact between a V1 neuron and an input layer neuron (LGN \(\rightarrow\) EV1), with receptive field centers at distance \(r\) from each other was calculated from (Schwabe et al. 2006):

\[
P = A \exp \left[ -\left( \frac{r}{\sqrt{2}\sigma} \right)^2 \right] \tag{7}
\]

Thus the total number of connections integrated over the two-dimensional space followed a Gaussian distribution as a function of distance \(r\).

For all the other connections between neuron groups, the synapses between groups \(i\) and \(j\) were generated stochastically based on probability distribution \(P_{ij}\), with the total number of synapses decayed exponentially as a function of the cortical distance (Schwabe et al. 2006):

\[
P_{ij} = B_{ij} \exp \left[ -\left( \frac{r}{\lambda_{ij}} \right) \right] \tag{8}
\]

In addition, each V1 excitatory neuron connected recursively to itself (EV1 \(\rightarrow\) EV1.self), representing local excitatory connections.

The overall number of synapses to each neuron, originating from different sources was thus determined through two factors: the parameters governing the distance dependence of synapse formation and the constants \(A\) and \(B_{ij}\) in Eqs. 7 and 8.

**Simulation.** The model network was run for 100 ms to achieve a stable baseline before stimulation. The stimulus was then presented for 400 ms. The input activity of each V1 excitatory neuron was calculated as the mean glutamatergic conductance \(g_{\text{exc}}\) during stimulation minus the mean \(g_{\text{exc}}\) during the baseline. The spiking activity was calculated as the mean spike count during stimulation.

The time step for the simulation was 0.1 ms.

**Fitting model output to the data: data and error measure.** Two measures of neural activity from the V1 spiking network model were compared with experimental data: the spike response of EV1 neurons was compared with the estimated spiking output of V1 neurons (derived from the V1 area summation model (Cavanaugh et al. 2002)), and their excitatory synaptic conductance estimated from our own fMRI data. We calculated the mean squared error (MSE) over the \(N\) samples in the \(2 \times 2\) mm grid and summed up the errors for the two activity measures:

\[
\text{MSE}_{\text{tot}} = \sum_i \left( R_{\text{spk,model,i}} - R_{\text{spk,target,i}} \right)^2 / N + \sum_i \left( R_{\text{ge,model,i}} - R_{\text{CBF,target,i}} \right)^2 / N \tag{9}
\]

\(R_{\text{spk,model,i}}\) represents the normalized mean spike count in sample \(i\). The response \(R_{\text{ge,model,i}}\) refers to the mean change in the excitatory conductance for the EV1 neurons in sample \(i\) during the 400 ms simulation. The respective targets, i.e., the expected spike activity pattern and the measured BOLD response, were constructed as described above and normalized to their maxima. Most of the information about differences between the spiking and BOLD data was found...
from the decaying part of the response outside the primary stimulus representation and thus significantly smaller than the maximum response. We thus reduced the contribution of noise by taking the logarithm of the normalized original responses, \( r_{data,source,i} \), before MSE calculation. The data contained significant negative values in regions outside stimulated area. Thus the data were offset by a constant value to avoid singularity of the logarithmic transform at regions outside stimulated area. Thus the data were offset by a constant value to avoid singularity of the logarithmic transform at zero, i.e.,

\[
R_{data,source,i} = \ln(r_{data,source,i} + 0.25).
\]

The error measures were calculated separately for the low and high stimulus contrasts and were evaluated independently.

**Fitting model output to the data: parameter search.** After initial parameter screening, parameter combinations with reasonably good output and dynamic range were selected as starting points for parameter optimization.

Two parameters were varied independently: 1) number of connections to and from the extrastriate cortex, including excitatory feedback to V1 (\( B_{FB} \)), i.e., connections \( E_{V1} \rightarrow EX \), \( E_X \rightarrow E_{V1} \) and \( E_X \rightarrow I_{V1} \); and 2) number of lateral connections on V1 to and from the inhibitory cells (\( B_{inh} \)), i.e., connections \( E_{V1} \rightarrow I_{V1} \) and \( I_{V1} \rightarrow E_{V1} \). The ratios of \( B_{inh} \) within a group were chosen to yield an approximately equal number of feedforward and feedback connections. The coefficients \( B_{inh} \) (Eq. 8) of reciprocal connections were always scaled together, and the common scaling factor was considered as the independent variable. Thus an \( N \)-fold change in \( B_{inh} \) or \( B_{FB} \) implied that all \( B_{inh} \) for connections belonging to the same group, were scaled by the same amount. Additionally, the extrastriate feedback to inhibitory neurons was tied to the strength of feedback to the excitatory neurons, so that \( \sim 10\% \) of the feedback synapses were to inhibitory neurons (Schwabe et al. 2010). MSE\(_{tot}\) was evaluated as a function of \( B_{FB} \) and \( B_{inh} \), in an exhaustive search of the two-dimensional parameter space and minima detected as the best fits to the data (Fig. 5, D and E). The results were essentially replicated when connection weights for the synapses were scaled, instead of changing the number of synapses (data not shown).

The model was evaluated in two configurations. In the first configuration all inhibitory and excitatory synapses were connected to the soma of \( \text{E}_{V1} \) neurons (“SOMA model,” corresponding to the point-like neuron model). In the second configuration (“DENDRITE model”), the synapses were connected to the dendritic compartments. This allowed for an evaluation of nonisotropic connectivity patterns for the different inputs of the \( \text{E}_{V1} \) neurons. The default connectivity of the feedforward and local connections was to the proximal dendritic compartments (Petreanu et al. 2009), whereas the interareal feedback connections were varied among three discretized distributions: sharp distribution of feedback synapses to the distal compartments (“distal”), flat distribution to all apical compartments with mean in the middle (“middle”), and as a sharp distribution of synapses to the proximal compartments (“proximal1” for inputs landing to the proximal compartment of the apical dendrite and “proximal2” for inputs shared equally by the proximal apical compartment and the basal compartment). Thus the configuration with the dendritic compartments led essentially to a cube search with the distribution of synapses as the third independent variable. After finding the model optima for the aforementioned independent parameters, we also tested how sensitive the obtained solutions were to perturbations in a number of individual parameters.

**RESULTS**

We quantified the spatial spread of the BOLD response in the V1 of 16 human subjects by measuring the response to a
wedge-shaped grating stimulus. The BOLD signal change in response to the stimulus formed a distinct pattern on V1 (outlined on the right hemisphere of a representative subject in Fig. 1A), with widespread representation of the parafoveal region and less cortical space dedicated to locations more distal from the center of fixation. We mapped the fMRI data of the individual subjects into visual field coordinates according to retinotopic localizer data (Henriksson et al. 2012) (Fig. 1B). The visual field locations were then transformed to a canonical model cortex (Fig. 1C). Finally, the BOLD responses were converted CBFe, following the balloon model (Buxton et al. 1998) and averaged over subjects. The neural data consisted of a canonical spiking response of primate V1 neurons (Fig. 2) to the same stimulus. It was constructed from eccentricity-dependent area summation function parameters of primate V1 neurons (Cavanaugh et al. 2002), which are similar to respective parameters found in human perception (Nurminen et al. 2009). The positive CBFe activation (squares in Figs. 1C and 3) spreads smoothly outside the primary retinotopic representation of the stimulus, systematically reaching negative values further away. Similar spread has been observed in earlier fMRI studies (Henriksson et al. 2012) (Fig. 1B). The visual field locations were then transformed to a canonical model cortex (Fig. 1C). Finally, the BOLD responses were converted CBFe, following the balloon model (Buxton et al. 1998) and averaged over subjects. The neural data consisted of a canonical spiking response of primate V1 neurons (Fig. 2) to the same stimulus. It was constructed from eccentricity-dependent area summation function parameters of primate V1 neurons (Cavanaugh et al. 2002), which are similar to respective parameters found in human perception (Nurminen et al. 2009). The positive CBFe activation (squares in Figs. 1C and 3) spreads smoothly outside the primary retinotopic representation of the stimulus, systematically reaching negative values further away. Similar spread has been observed in earlier fMRI studies (Sharifian et al. 2013; Zuiderbaan et al. 2012), according to the eccentricity along the horizontal meridian. The profile of the CBFe response to high contrast stimuli was well described with a sum of three Gaussians, both for the mean population data ($R^2 = 0.89$) and individual subjects (mean $R^2 = 0.87$): the response decayed sharply ($\sigma$ ranging from 0.2 to 0.5°, mean amplitude 0.8) near the edge of the stimulus but contained a smoothly decaying positive component ($\sigma$ ranging from 2.2 to 3.7°, mean amplitude 0.4). The positive CBFe was flanked by a small but consistent negative component, extending peripherally with respect to the stimulus.

The spike response, estimated from the widely adopted area summation model of visual receptive fields (Cavanaugh et al. 2002) is portrayed in Fig. 3, A and D, as smooth pattern behind the sampled CBFe data. It was much more localized than the CBFe response and lacked the smoothly spreading components (Fig. 3, B and C). The qualitative difference between the two neural activation patterns was similar in the responses to 80% (Fig. 3, A–C) and 10% (Fig. 3, D–F) stimulus contrasts. However, the relative amplitude of the smoothly decaying CBFe component was higher in the low contrast response and it extended further on the cortex. Only the high-contrast stimulus elicited a consistently negative CBFe component.

To understand how the different BOLD and spiking responses emerge, we constructed a two-dimensional hierarchical spiking network model of the visual cortex (Fig. 4A). Presenting the network with the wedge-shaped stimulus, we monitored separately the synaptic excitatory conductance ($g_{exc}$) of the V1 excitatory neurons and their spike count. Sampled similarly to the neural activation data, $g_{exc}$ served as
a proxy for the CBFe response while the spike count was compared with the predicted spiking pattern. The network covered a visual hemifield from 0.5 up to 28° eccentricity, with excitatory neurons (EV1) at 0.23 mm intervals in the two dimensions. The spatial reach of connections in the network was commensurate with anatomical feedforward, lateral, and feedback connectivity patterns of macaque V1 (Angelucci et al. 2002a,b). Thus the V1 neurons received narrowly tuned feedforward input from LGN, while the lateral connections integrated inputs from a wider region and the extrastriate feedforward and feedback connections were widely tuned, comprising large receptive fields (Fig. 4B). Similar mesoscopic approach and model architecture has previously successfully accounted for spatial interactions in neuronal firing rates of primate V1 neurons (Schwabe et al. 2006). The relative number of synapses to the EV1 neurons from various input sources were selected as independent variables in the model, while the cellular parameters and the anatomical reach of connections were fixed (Table 1). Initial values were selected based on maintaining a dynamic range in the network. Since varying the numbers of reciprocal connections independently is ambiguous, the relative numbers of synapses in reciprocal connections were fixed. Thus the inputs were lumped into three groups, in which the connections were scaled together: local excitatory connections in V1 (EV1 → EV1), excitatory-inhibitory connections in V1 (EV1 → I, and I → EV1), and the interareal connections (V1 to extrastriate area and back). In preliminary screenings of various model configurations, the first connection group was not found to have explanatory power regarding the distinction of BOLD and spike signals. Thus the numbers of inhibitory (B_inh) and interareal feedback-related (B_FB) connections were selected as independent variables when evaluating the model. The MSE was calculated separately for the two activity measures (spikes estimated from monkey single cell data vs. spikes from our model, and CBFe vs. model g_exc) but were summed into a single error measure MSE_tot to evaluate the overall goodness of the model.

The spiking network model was constructed in two configurations. In the first configuration, all the synapses to the excitatory V1 neurons were connected to an isopotential soma (SOMA model). This corresponds to a computationally efficient approach that has been widely adopted for cortical network models, even though the complexity of dendritic signal transformations as well as the potential for information processing within the dendritic tree of a neuron is well established (London and Hausser 2005; Spratling 2002). Figure 5A shows the spiking pattern (left) and the excitatory synaptic activity g_exc (right) on the model V1 with the minimal MSE_tot. In contrast to data, separating CBFe response and spiking activity profiles, this model configuration produced similar g_exc and spiking profiles (Fig. 5C, top). The spread of g_exc was also quite limited compared with the CBFe data (σ_model = 0.6 σ_CBFe for the smooth positive component), and the negative response was missing. Notably, the best solutions were limited to those with very little or no feedback from higher visual areas (Fig. 5, C–E).

As we could not capture the difference between the input and output of the neurons with the SOMA model to the extent suggested by the data, we sought further for a biologically feasible neural mechanism to account for the spread of the BOLD response. The majority of excitatory neurons in cerebral cortex are pyramidal neurons, which have extensive dendritic trees. The local regions of the dendritic trees sum excitatory synaptic input nonlinearly (Behabadi et al. 2012; Polsky et al. 2004) and may be sensitive to different aspects of the input space, receiving a larger range of subthreshold inputs than reflected by the often narrowly tuned action potential output (Jia et al. 2010). This is in line with electrophysiology data, where contextual modulation does not change the action potential count without a driving input at the center of the receptive field (Cavanaugh et al. 2002). In the second model configuration, we thus modeled V1 pyramidal neurons with four apical and one basal dendritic compartments, with realistic decay (Williams and Stuart 2002) of passive signals (Fig. 4C). This enabled us to treat the distribution of synapses from different sources to the dendritic compartments as independent variables. As the specific pattern of how inputs from different sources land on the dendritic tree of a neuron is not known, we studied different configurations. The data were best explained by widely tuned feedback from the extrastriate cortex arriving to the distal dendrites (Figs. 5, 6). This model captured the discrepancy between the positive CBFe and the spiking pattern, as well as the prominent features of the CBFe response both for the high-contrast (Fig. 5B) and the low-contrast stimuli (Fig. 6, Table 2).

The MSE_tot obtained by the DENDRITE model with distal feedback was 40% lower than in the SOMA model. Figure 5, D and E, illustrates the full MSE_tot landscapes for both stimulus contrasts as a function of the number of synapses in the feedback and inhibition pathways, from zero to near saturation. The SOMA model was more sensitive to perturbations in the parameters, and the transition to unstable state (red, high MSE_tot) was very sharp. Moreover, the parameter space corresponding to minimum MSE_tot was much wider in the DENDRITE model with distal feedback, indicating better tolerance to perturbations. This result was very robust and not sensitive to adjustments in the neuron parameters, such as 40% reduction in the dendritic decay function (data not shown). The goodness of fit, quantified by increasing MSE_tot, decreased sharply when the distribution of feedback synapses was varied from distal towards proximal compartments and finally to the SOMA model. It also decreased upon shifting the distribution of other inputs to the more distal parts of the dendrite, although it was less sensitive to variations in the lateral connections within V1 (Fig. 7). The results were not affected by perturbations in individual network connection weights, distances, or parameters governing distribution of synapses (data not shown).

DISCUSSION

Single neuron studies and macroscopic brain imaging have largely evolved as separate disciplines, calling for unifying approaches. In this study we bridged single cell responses to fMRI data with a biophysically and anatomically plausible neural network model of the visual cortex. We assumed that BOLD response represents the input rather than output of the V1 neurons (Attwell et al. 2010; Iadecola and Nedergaard 2007; Koehler et al. 2009; Petzold and Murthy 2011) and that connection distances (Angelucci et al. 2002a,b) and receptive field properties (Nurminen et al. 2009; Shushruth et al. 2013) on human V1 are comparable to those from the macaque.
From these assumptions, we found that the anisotropic landing of inputs to a compartmental neuron, with feedback concentrated in the distal dendritic compartments (Markov et al. 2014; Petreanu et al. 2009) provides the best fit between the data and the model. Our data show that compartmental units are able to reflect the substantial subthreshold EPSPs without passing their contribution directly into firing rate of a model neuron. Thus, compartmental units may significantly help cerebral cortex modeling, as they can have different tuning functions at the input and output of the neuron. Furthermore, they can functionally segregate synaptic inputs representing different aspects of the input space. Using computationally more efficient point-like units may seriously limit the applicability of large scale brain models.

In the present study, we modeled the neuronal dendrites with six isopotential compartments with realistic passive decay (Williams and Stuart 2002) between distal compartments and the soma, but neglecting the wealth of local nonlinear integration performed by dendrites of cortical neurons (Grienberger et al. 2015). This approach allowed different integration of inputs from functionally different regions within the neuron with minimal number of parameters affecting the model behavior.

fMRI is the tool of choice for investigating complex activation patterns in the human brain at millimeter resolution. Detailed functional maps correspond qualitatively with optical imaging data at submillimeter resolution (Moon et al. 2007; Yacoub et al. 2008). Furthermore, the spread of our CBFe data coincides with the measured point spread function (PSF) with voltage-sensitive dyes on monkey cortex (Grinvald et al. 1994; Palmer et al. 2012), for which the full-width half-maximum (FWHM) ranges from 3.3 to 4.5 mm depending on stimulus configuration. Previously quantified Gaussian PSF for BOLD signal with 3T SE sequence indicates that the BOLD response decays with FWHM 3.4 mm distance on V1 (Parkes et al. 2005), in accordance with the earlier estimation of 3.5 mm by (Engel et al. 1997). Simple fit of Gaussian decay to our data yields 3.5 ± 0.5 mm FWHM for the signal decay on the model cortex (data not shown). The more commonly used gradient echo (GE) sequence provides better signal-to-noise ratio (SNR) than SE sequence, but the GE sequence has a stronger contribution from the superficial draining veins (Parkes et al. 2005; Zhao et al. 2006). Thus activation may spread to individual voxels downstream from the site of neural activation at least in part of the voxels, leading into nonspecific spread of the signals. Exact quantitative comparison of the spread determined with different protocols may be also affected by the different stimuli used in the experiments, as our results indicate that the spread may be stimulus specific. However, in direct comparison of the two sequences at 3T (Parkes et al. 2005), the FWHM of 3.9 mm determined with GE sequence on human V1 was significantly higher than the FWHM obtained with SE, possibly reflecting this nonneural spread of the signal in the latter protocol. The previous studies on SE BOLD spread have not addressed the negative component of the response. However, the amplitude and approximate extent of the negative BOLD response in our data correspond to the negative envelope of the population receptive fields measured on V1 (Zuidervaan et al. 2012) even though our data do not warrant for a more precise quantitative comparison. The negative BOLD component has been shown to correlate with decreases in neuronal activity (Shmuel et al. 2006).

The BOLD response has been strongly associated with the synaptic activity in the cortex, first through its correspondence with various electrophysiological measures and later
glutamate release (Gurden et al. 2006). Thus adopting the glutamatergic transmission as the sole proxy for the BOLD response is a simplifying assumption.

The spiking network model comprises a simple visual system that was implemented for studying the spatial tuning of neuronal responses in V1. While it successfully bridges the imaging data to the activation at the single neuron level, its applicability in simulating cortical information processing is still very limited. The main simplification is the single layered structure of the model network, which necessarily omits the majority of local cortical computations. For the present work, simplified local connections were implemented on the single layer network, but they carry no capacity for complex information processing, which are expected at the cortical network level. Furthermore, the neurons’ receptive fields are defined only in terms of their spatial envelope. This is sufficient for the simple grating stimulus, as it can conveniently be approximated as a spatially constant optimal stimulus to the cortical neurons. However, for further studies on processing more complex stimuli, other aspects of neuronal receptive fields, such as orientation selectivity, need to be implemented also, preferentially through learning from the natural stimulus statistics. Future work will also benefit from explicit modeling of the variance in cellular parameters (Fig. 2B). Selecting the population mean by linear regression to the single neuron area summation data overemphasizes the largest parameter values, especially at small eccentricities. Thus the population behavior in our model rather exaggerates the receptive fields than underestimates the expected spread of the spike response.

The model fits the neural and imaging data well for the high-contrast stimulus but is less optimal for the low-stimulus contrast, although the results agree qualitatively with the high-contrast data. The lower SNR of the BOLD response to the low-contrast stimulus naturally contributes to the less optimal fit. However, our model does not fully capture the larger spreading of BOLD signal at low contrast. The stronger signal spreading of the low-contrast response is in line with enhanced spatial integration of the visual system in low contrasts and previous works on contrast-dependent functional connectivity (Nauhaus et al. 2009).

In summary, we have sought for correspondence between the fine structure of the BOLD response profile (Fig. 3) and changes in neural activity on V1. Our model bridges the gap between the very large spread of BOLD signals and the narrowly tuned action potentials, without needing to assume noise or unspecific hemodynamic effects. Instead, we suggest that the fundamental differences in BOLD and electrophysiological measures is not straightforward, as the local field potentials reflecting the synaptic input and the spike activity are generally also correlated so the causal relationship is difficult to decipher from the data. However, dissociation of the local field potential and spikes, either during sustained stimulation (Logothetis et al. 2001) or through suitable stimulus protocols (Bartolo et al. 2011), has strengthened the association of BOLD with the input of the neurons. Yet there is evidence supporting a direct causal link between neuronal input and imaging signals coming from recent literature on the role of neurotransmitter-mediated signaling to blood vessels. Therein, glutamatergic input to the pyramidal cells appears as the main driver of an astrocytic pathway to regulating blood flow via glutamate receptors in the astrocytic endfeet surrounding the synaptic terminals (Attwell et al. 2010; Gurden et al. 2006; Iadecola and Nedergaard 2007; Koehler et al. 2009; Petzold and Murthy 2011). Also NO, released by the postsynaptic neurons in response to glutamatergic input through an NMDA-receptor mediated pathway, contributes to the activity-dependent vasodilatation, potentially through a regulatory mechanism of the astrocytic signaling (reviewed e.g., by Attwell et al. 2010). The role of other neurotransmitters is less well established. The astrocytic end-feet selectively contact dendritic spines and have not been reported to surround the synapses to GABAergic neurons. GABAergic activity appears to have a role in BOLD amplitude (Muthukumara-swamy et al. 2009), but this may happen through decreased local spiking and thus local excitatory synaptic activity or by the more direct regulatory effect of GABA to the presynaptic via the established role of astrocytes and glutamate in generating the hemodynamic response. The analysis of correlation with electrophysiological measures is not straightforward, as the local field potentials reflecting the synaptic input and the spike activity are generally also correlated so the causal relationship is difficult to decipher from the data. However, dissociation of the local field potential and spikes, either during sustained stimulation (Logothetis et al. 2001) or through suitable stimulus protocols (Bartolo et al. 2011), has strengthened the association of BOLD with the input of the neurons. Yet there is evidence supporting a direct causal link between neuronal input and imaging signals coming from recent literature on the role of neurotransmitter-mediated signaling to blood vessels. Therein, glutamatergic input to the pyramidal cells appears as the main driver of an astrocytic pathway to regulating blood flow via glutamate receptors in the astrocytic endfeet surrounding the synaptic terminals (Attwell et al. 2010; Gurden et al. 2006; Iadecola and Nedergaard 2007; Koehler et al. 2009; Petzold and Murthy 2011). Also NO, released by the postsynaptic neurons in response to glutamatergic input through an NMDA-receptor mediated pathway, contributes to the activity-dependent vasodilatation, potentially through a regulatory mechanism of the astrocytic signaling (reviewed e.g., by Attwell et al. 2010). The role of other neurotransmitters is less well established. The astrocytic end-feet selectively contact dendritic spines and have not been reported to surround the synapses to GABAergic neurons. GABAergic activity appears to have a role in BOLD amplitude (Muthukumara-swamy et al. 2009), but this may happen through decreased local spiking and thus local excitatory synaptic activity or by the more direct regulatory effect of GABA to the presynaptic.
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Author Contributions

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