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The spatiotemporal hemodynamic response function for depth-dependent functional imaging of human cortex

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The spatiotemporal hemodynamic response function for depth-dependent functional imaging of human cortex

Abstract

The gray matter of human cortex is characterized by depth-dependent differences in neuronal activity and connections (Shipp, 2007) as well as in the associated vasculature (Duvernoy et al., 1981). The resolution limit of functional magnetic resonance imaging (fMRI) measurements is now below a millimeter, promising the non-invasive measurement of these properties in awake and behaving humans (Muckli et al., 2015; Olman et al., 2012; Ress et al., 2007). To advance this endeavor, we present a detailed spatiotemporal hemodynamic response function (HRF) reconstructed through the use of high-resolution, submillimeter fMRI. We decomposed the HRF into directions tangential and perpendicular to the cortical surface and found that key spatial properties of the HRF change significantly with depth from the cortical surface. Notably, we found that the spatial spread of the HRF increases linearly from 4.8mm at the gray/white matter boundary to 6.6mm near the cortical surface. Using a hemodynamic model, we posit that this effect can be explained by the depth profile of the cortical vasculature, and as such, must be taken into account to properly estimate the underlying neuronal responses at different cortical depths.

Keywords

functional, imaging, function, response, hemodynamic, depth, human, spatiotemporal, cortex, dependent

Disciplines

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Abstract

The gray matter of human cortex is characterized by depth-dependent differences in neuronal activity and connections (Ship, 2007) as well as in the associated vasculature (Duvernoy et al., 1981). The resolution limit of functional magnetic resonance imaging (fMRI) measurements is now below a millimeter, promising the non-invasive measurement of these properties in awake and behaving humans (Muckli et al., 2015; Olman et al., 2012; Ress et al., 2007). To advance this endeavor, we present a detailed spatiotemporal hemodynamic response function (HRF) reconstructed through the use of high-resolution, submillimeter fMRI. We decomposed the HRF into directions tangential and perpendicular to the cortical surface and found that key spatial properties of the HRF change significantly with depth from the cortical surface. Notably, we found that the spatial spread of the HRF increases linearly from 4.8 mm at the gray/white matter boundary to 6.6 mm near the cortical surface. Using a hemodynamic model, we posit that this effect can be explained by the depth profile of the cortical vasculature, and as such, must be taken into account to properly estimate the underlying neuronal responses at different cortical depths.

Keywords

High-resolution, fMRI, hemodynamic response, human, visual cortex, layers

1. Introduction

Advances in imaging hardware and analysis techniques have pushed the resolution limits of fMRI below a millimeter, allowing blood oxygenation level dependent (BOLD) responses to be resolved through the depth of cortical gray matter (Jin & Kim, 2008; Siero et al., 2011; Silva et al., 2000). In parallel with advances in modeling and deconvolution techniques (Aquino et al., 2014; Drysdale et al., 2010), this delivers the potential to infer depth-dependent neuronal activity and to thereby distinguish feedforward, feedback, and recurrent neuronal activity in cortical circuits (Bastos et al., 2012; Logothetis, 2008). However, this requires a characterization of the spatiotemporal structure present in the BOLD response and specifically how it changes through cortical depth.

A number of models have been used to describe the hemodynamic response that the BOLD signal represents, and these models have grown in complexity with our understanding of the response. Early on the HRF was described using models that only characterized the temporal dimension (Buxton et al., 1998; Friston et al., 1994). More recently, work has been done to incorporate both the temporal and spatial aspects of the BOLD response giving way to HRF models that describe the spatial aspect of the response tangential to the cortical surface, the temporal dimension, and how these two components relate (Aquino et al., 2012; Shmuel et al., 2007). Other work has described changes in various aspects of the HRF through the depth of cortex (Koopmans et al., 2010; Olman et al., 2012; Ress et al., 2007; Siero et al., 2015; Yu et al., 2012), and Heinzle et

al. (2016) have recently extended a commonly used hemodynamic model (Buxton et al., 1998; Friston et al., 2000; Stephan et al., 2007) to incorporate blood draining effects across cortical depth to explain some of these differences. To date, however, there is no characterization that features the complete spatiotemporal structure of the BOLD response, that is both tangential and perpendicular to the cortical surface.

Here we measure the HRF in primary visual cortex using high-resolution fMRI and quantify how the response changes in time and space, both tangential to the cortical surface and through the depth of cortex. This constitutes the first characterization of the spatiotemporal HRF that can be used for depth-dependent functional imaging of human cortex.

We also relate our empirical measurements to a recent physiologically-based model of the HRF (Drysdale et al., 2010) that approximates cortical tissue as a porous elastic medium enabling the hemodynamics to be explained in a continuous mean-field manner. An important finding from this work was that waves of hemodynamic activity were predicted and supported by results in primary visual cortex (Aquino et al., 2012). These waves couple space and time, supporting the notion that a complete description of the BOLD response requires a spatiotemporal model of hemodynamics (Biessman et al., 2012; Gardner et al., 2010; Kriegeskorte et al., 2010; Shmuel et al., 2007). The hemodynamic waves travel along the cortical sheet and are characterized by two parameters:

hemodynamic velocity and damping rate, both of which reflect basic properties of the underlying physiology (Aquino et al., 2012). Here we find further evidence of these waves and examine how their properties change as a function of cortical depth.

2. Materials and Methods

2.1 Overview

To measure the spatiotemporal structure of the HRF we combined sub-millimeter MRI with an experimental design to maximize the spatial and temporal resolution of our data (0.8 mm isotropic resolution, 500 ms effective sampling rate). Exploiting the organization of primary visual cortex (Schira et al., 2010) we used a visual stimulus (Fig. 1A) that elicits a thin line of cortical activation stretching across V1 (Fig. 1B). To investigate the spatiotemporal structure of the HRF tangential to the cortical surface we sampled the temporal fMRI response as a function of the distance from the center of activation (Fig. 1C). To quantify how the response varies perpendicular to the surface this was done at a series of different cortical depths. For these last two steps, we implemented a custom, surface-based sampling method.

Figure 1. Measuring the spatiotemporal HRF. A. The visual stimulus was a thin, black and white, flickering ring designed to stimulate isoeccentric responses in visual cortex. B. Medial view of a computationally inflated cortical surface mesh. Zoomed region shows primary visual cortex, V1. Distance from the center of activation elicited by the stimulus is color-coded. C. Spatiotemporal HRF plot illustrating the structure of the HRF parallel to the surface. x is the distance from the center of activation, where positive is toward the periphery and negative is toward the fovea. The color indicates BOLD signal amplitude (%).

2.2 Subjects

Six subjects (2 female; 22-35 years, mean 27 years) with normal or corrected-to-normal vision and no history of neurological or psychiatric diseases participated. The experiment was conducted with the written consent of each subject and was approved by the Human Ethics Committee at the University of Queensland in accordance with the Australian National Health and Medical Research Council's guidelines.

2.3 Magnetic resonance imaging data acquisition and preprocessing

MRI scanning was performed using a Siemens MAGNETOM Trio 3T MRI scanner with a 32-channel head coil at the Centre for Advanced Imaging at the University of Queensland. Multiple T1-weighted anatomical images were collected: (1) full brain MPRAGE with 0.75 mm^3 resolution using a TE of 2.7 ms, TR of 1900 ms, 9 degree flip angle, FOV of 240 mm, matrix size of 320 x 320, and 224 slices; (2) partial coverage MPRAGE focusing on the occipital pole with 0.50 mm^3 resolution using a TE of 5.0 ms, TR of 2410 ms, 9 degree flip angle, FOV 210 mm, matrix size of 416 x 416, and 256 slices; (3) partial coverage MP2RAGE focusing on the occipital pole with 0.54 mm^3 resolution using a TE of 3.0 ms, TR of 4000 ms, flip angles of 6 and 7 degrees, FOV 210 mm, matrix size of 390 x 390, and 256 slices. Each of the anatomical datasets were subsequently aligned through a rigid body transform with 6 degrees of freedom using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). All images were interpolated to 0.4 mm^3 and then averaged to construct a high quality, high-resolution anatomical image for each subject. The lower resolution sequence (0.75 mm^3) provided high SNR and coverage of the entire brain while the two different higher resolution protocols, although noisier, provided better definition of the gray/white boundary at the occipital pole. The high-resolution of this anatomy and hence surface reconstruction was particularly helpful with estimation of distances along the cortical surface.

All functional data were acquired using a gradient-echo sequence with a matrix

size of 240 x 240 and an FOV of 192 mm, resulting in an in-plane resolution of 0.8 mm x 0.8 mm. Within a TR of 4 s, 37 slices (0.8 mm thick) were acquired using a flip angle of 90 degrees, a TE of 38 ms, an echo spacing of 1.31 ms, an EPI factor of **60**, Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) (Griswold et al., 2002) with an acceleration factor of 3, an effective bandwidth of 768 kHz, and 6/8 partial Fourier sampling. This results in a readout length of 78.6 ms (60 x 1.31 ms), which increases the voxel size in the phase-encode direction by approximately 15-17% using a gray matter T2* of 40ms at 3T (Haacke et al., 1999). The acquisition slab was positioned at the edge of the at the occipital pole and extended anteriorly ensuring coverage of V1.

Functional data were slice time corrected using SPM8. Motion correction was performed using a two-step procedure in which head motion vectors were first estimated using SPM8. These vectors were then low-pass filtered (cut-off 45 seconds) and then applied to the EPI volume time series. This prevented strong BOLD signal modulations present in the high-resolution EPI data from affecting the motion correction (Schira et al., 2010). Using custom MATLAB scripts and the mrVista Toolbox (<http://white.stanford.edu/software/>), the data were aligned and interpolated (trilinear) to match the space defined by the anatomical data (see Inline Supplementary Fig. S1). The time series for each voxel was low-pass filtered using a third order Butterworth filter with a frequency cutoff at 0.1 Hz.

2.4 Visual paradigm

Visual stimulation was presented on a white screen using an LCD projector and viewed using a mirror mounted on the head coil. The display extended to 15° eccentricity. The stimulus was designed and presented using Psychtoolbox version 3 (Brainard, 1997; Pelli, 1997).

The stimulus used (Fig. 1A) consisted of a very thin (1 pixel), black and white flickering (250 ms contrast reversal) ring stimulus with a radius of 2 degrees ('ON' for 4 seconds) that alternated with a uniform gray field ('OFF' for 16.5 s). The stimulus timing was designed to elicit robust BOLD response while avoiding nonlinearities in the BOLD signal known to be elicited by very brief ON periods (less than 2-3 s in visual cortex) and OFF periods (less than 4 s) (Birn & Bandettini, 2005; Soltysik et al., 2004). The stimulus was designed to induce a discrete isoeccentric band of neural responses in visual cortex approximately 1 mm in width (Tootell et al., 1981; Vanduffel et al., 2002) and is similar to that used in our previous study (Aquino et al., 2012). Subjects performed a fixation color detection task at a central marker, and a fixation grid was overlaid on the stimulus to stabilize fixation throughout the entire run. Previous studies have demonstrated that with this stimulus setup, subjects typically fixate very accurately, within 10' of visual angle, probably better (Schira et al., 2007). This fixation jitter results in a spread of the representation of the ring of less than 0.54 mm on the cortical surface (Schira et al., 2010). The ON/OFF cycle (totaling 20.5 s) was repeated 8 times per run thereby allowing the evoked response to be

sampled with an effective temporal resolution higher than the scanner repetition time. This was achieved by the stimulus onset being dephased by 500 ms per cycle for 8 cycles, and then reordering the time-course to acquire a single response at an effective temporal resolution of 500ms. Each run was 3 minutes long and 18-25 runs were collected across two MRI sessions for each subject.

In addition to the thin ring stimuli, phase-encoded retinotopic mapping was performed to acquire polar angle maps for visual area identification. A rotating bowtie stimulus (two wedges opposite one another and meeting at fixation) was used (Schira et al., 2009). The aperture contained one of three colored texture patterns (checkers, expanding and contracting spirals, or rotating sinusoidal gratings) which changed randomly every 250 ms. Each retinotopic mapping run was 6 minutes in duration (15 cycles), and two runs were collected per subject. Subjects performed a fixation color detection task at a central marker, and a fixation grid was overlaid atop the stimuli.

2.5 Laminar surface reconstruction and data sampling

To characterize the functional data at different cortical depths, a surface-based sampling method was used. First, a detailed, manual gray/white matter segmentation of the average anatomical image was performed for each subject using the segmentation program ITK-Gray (Yushkevich et al., 2006). Based on this segmentation, high-resolution cortical surface meshes (approximately 0.4 mm between nodes) were constructed using the cortical surface analysis

package Caret, version 5.65 (Van Essen et al., 2001). Caret was chosen as it allows the construction of precise parallel surfaces shrunk (into white matter) or expanded (toward the pial surface) along the surface normals (i.e., in the direction that is perpendicular to the surface at each vertex). Note that this procedure ensures that all laminar surface meshes contain the same number of nodes and edges. In total, 6 surfaces were constructed for each subject located - 0.8, 0, 0.8, 1.6, 2.4, and 3.2 mm from the gray/white matter boundary (negative is into white matter, positive is towards the cortical surface). The volumetric fMRI data were then manually aligned to the anatomical data (using the mrVista software) and subsequently linearly interpolated onto each of these surfaces using MATLAB. Primary visual cortex is rather thin with a thickness of approximately 2.0 – 2.5 mm (Scholtens et al., 2015; Wagstyl et al., 2015); therefore, the surface constructed at 3.2 mm from the gray/white boundary will be primarily sampling data from the large surface vessels located outside the pial surface (vascular arachnoid).

2.6 Region of interest and distance measurements

The analysis was restricted to primary visual cortex, V1, as determined by the polar angle retinotopy data (DeYoe et al., 1996; Wandell & Winawer, 2011). The centerline of the activation elicited by the thin ring stimulus was identified as described previously (Figure 4 in Aquino et al., 2012). Briefly this is achieved by (i) identifying clusters of voxels that correlate to the task on a flattened representation of V1, (ii) fitting a polynomial to this cluster, and (ii) selecting

voxels close to this polynomial to represent the centerline. For each laminar surface, all further analyses were restricted to only those surface nodes within 15 mm of the centerline (in both directions). The geodesic distance of the shortest path between each surrounding mesh node and the centerline was calculated using a fast-marching algorithm (Sethian, 1999) implemented in MATLAB. By allowing the shortest path to cross mesh faces rather than being bound to the edges, the fast-marching algorithm avoids metrication error inherent in other techniques such as Dijkstra's algorithm (Bronstein et al., 2008). The distance measures were used to investigate how the hemodynamic response changes with distance from the source of activation, tangential to the cortical surface. The distances between surface nodes change with cortical depth; therefore, the distance measures were calculated for each laminar surface individually.

2.7 Spatiotemporal HRF profile

Spatiotemporal HRF responses were constructed by averaging time-course responses based on the distance of the responses from the centerline of activation, using a 1 mm bin size. Each surface node is approximately, but not exactly, 0.4 mm from one another. Hence using a 1mm bin size ensured the distance bin containing the centerline of activation was comprised of the centerline node and at least one surface node in each direction away from the centerline. These averaged responses were then used to compute a contour plot (Fig. 1C) that shows the structure of the HRF tangential to the cortical surface in which distance from the centerline is represented along the x-axis (negative

refers to distance towards the fovea, that is roughly towards the posterior of the brain and positive signifies distance toward the periphery of the retinotopic map, that is roughly anterior), time is represented along the y-axis, and color represents BOLD amplitude. Note that the information included in a typical, temporal HRF profile is represented in our spatiotemporal profile. Rather than represent time on the x-axis and amplitude on the y-axis, time is represented on the y-axis and amplitude as color (see Inline Supplementary Fig. S2). The spatial range (i.e., the x-axis limits) was chosen to exclude interference from other sources. Individual HRF profile plots were constructed for each laminar surface (e.g. Fig. 2, right). Group-averaged spatiotemporal HRF profile plots were constructed (Fig. 2, left) at each cortical depth by averaging the HRF profiles across all 12 hemispheres. The averaging was achieved by calculating the mean time-course within each distance bin across the profiles from the individual subjects.

To estimate the spatial spread and peak amplitude of the HRF, a Gaussian function was fitted to the spatial component, $s(x)$, of the peak response in each hemisphere with:

$$s(x) = A \exp \left[-\frac{(x-x_0)^2}{\Delta x^2 / (2\sqrt{\ln 2})} \right], \quad (1)$$

where A is the peak signal amplitude, x_0 is the spatial location of the peak of activation, and Δx is the full-width-at-half-maximum (FWHM) of the Gaussian

function. As the time to peak varied slightly across subjects, the response peaks between 5-6 s following stimulus onset were used. The parameters were fitted using the Trust-Region algorithm implemented in MATLAB's *fit* function.

2.8 Estimation of hemodynamic wave parameters

The hemodynamic response can be represented as a planar wave (i.e., a wave traveling through space x and time t):

$$S(x, t) = \text{Re}[e^{-ikx - t(\Gamma \pm ikv)}] \quad (4)$$

where S is the signal, k is the wave number, v is the wave velocity, and Γ is the wave damping parameter (Aquino et al., 2014). Note that the $\pm$ indicates waves traveling towards the positive and negative directions.

We calculated the wave parameters Γ and v for the group-averaged hemodynamic responses at different depths as previously described (Aquino et al., 2012). Briefly, to calculate v we fitted a line to the instantaneous signal phase fronts traveling from $x = 0$ outwards at the peak of the BOLD amplitude. As described in Aquino et al. (2014) the predicted hemodynamic response contains a local mode which is a temporal mode that is non-propagating, and a propagating mode which encompasses the propagation due to hemodynamic waves. Thus to ensure we capture the propagating mode only, we calculated these wave fronts outside 2 mm from the center (central core), which ensures

that the local mode is not contributing to the hemodynamic response. Additionally, we restricted the velocity calculation to before the edge to ensure we capture the waves and not additional sources. The instantaneous signal phase was calculated using a Hilbert transform. To calculate I , we measured the exponent of exponential signal decay along the signal wave front by linear regression.

There is some variation in the wave parameters left and right of the stimulus (towards and away from the fovea, respectively). It is likely that this arises from changes in vascular density that follow changes in neural density as a function of eccentricity. Here we have, however, restricted our analysis to the the average between these two quantities as additional data is required to properly investigate this variation.

2.9 Statistical analyses

Two levels of statistics were implemented in IBM SPSS Statistics 19.0. First, two separate repeated measures ANOVA tests were performed to test for statistically significant differences across cortical depth for both the spatial spread and peak amplitude measurements. These were performed using the measurements acquired from the Gaussian fitting procedure in each individual hemisphere ($n = 12$). Mauchly's test revealed that the assumption of sphericity underlying both repeated measures ANOVAs was violated so Greenhouse-Geisser corrections were used. Because both the spatial spread and the amplitude of the HRF were

found to vary significantly with depth [$F(1.86, 20.5) = 5.61, p = 0.013$ and $F(1.22, 13.4) = 9.75, p = 0.006$ respectively], a second level of statistics was performed to investigate the relationships between each dependent variable (spatial spread and amplitude) and cortical depth using linear regression. The uncertainty values ($\pm$) associated with the reported parameter estimates (coefficients) indicate standard error.

3. Results

Surface reconstruction of the BOLD response yielded a spatiotemporal HRF, describing the response across (1) time, (2) space tangential to the cortical surface, and (3) space perpendicular to the cortical surface, through cortical depth. The response displays a number of notable properties that depend on cortical depth (Fig. 2). As expected, there is very little response modulation at $z = -0.8$ mm (that is 0.8 mm below the gray/white boundary; Fig. 2, bottom panel). At more superficial depths (increasing z) the response is stronger and broader. Moreover, at all depths much of the response propagates as a traveling wave, evident as increasingly delayed BOLD changes away from the central response. Note that in Figure 2 the spatiotemporal HRF is illustrated by a series of plots showing the response tangential to the surface vs. time with each plot in the series representing data at a different cortical depth. The same data is provided in an alternate video format showing the response tangential to the surface vs. space orthogonal to the surface with each video frame representing the response at a different time point (see Supplementary Material, S3 and S4).

Figure 2. Group-averaged (left) and single subject (right) spatiotemporal HRF plots vs. cortical depth relative to the gray/white boundary, z (middle). Each plot represents a slice through the HRF at a different cortical depth and illustrates the structure of the HRF tangential to the surface at that depth. Color indicates the percent modulation of BOLD.

3.1 Characterizing depth-dependent HRF properties

The spatiotemporal hemodynamic response thus varies through the depth of gray matter. We quantified the spatial spread Δx and the peak amplitude A of the spatiotemporal HRF as a function of z by fitting a Gaussian to each individual spatial profile at the peak time point 5-6 seconds following the onset of the BOLD response (Fig. 3, top). This analysis confirmed that both Δx and A vary significantly with z ($p < 0.05$), quantifying the visually apparent effect. Moreover, the variations in Δx and A are well described by linear regression (both $p \leq 0.001$) with

$$\Delta x = (0.6 \pm 0.2) * z + (4.8 \pm 0.4) \text{ mm} \quad R^2 = 0.2,$$

and

$$A = [(0.30 \pm 0.07) \% \text{ mm}^{-1}] * z + (0.5 \pm 0.1) \% \quad R^2 = 0.2.$$

376

377 **Figure 3.** HRF properties vs. z . Top: Variation in the spatial spread Δx and peak
 378 amplitude A of the HRF vs. z . Depth at $z = 0$ corresponds to the gray/white
 379 boundary. Increasing z moves towards the pial surface. Error bars correspond to
 380 standard error (across 12 hemispheres). Solid gray lines show the linear
 381 regression fits. Bottom: Wave parameter estimates v and Γ calculated for the
 382 group-averaged hemodynamic response as a function of z . The points indicate
 383 the average of each parameter calculated for the wave fronts towards the fovea
 384 and towards the periphery. Error bars indicate the standard error across profiles,
 385 and the solid gray lines show the linear regression fits.

386

387 **3.2 Hemodynamic traveling waves and the underlying physiology**

388 The spatiotemporal HRF plots in Figure 2 show clear evidence of traveling waves
389 at all depths, consistent with the predictions of our recent, physiologically-derived
390 model (Aquino et al., 2012). This is not only true for the average response (Fig.
391 2, left) but can also be seen in the responses of individual subjects (cf. Fig. 2,
392 right). The hemodynamic waves can be characterized by two key parameters:
393 the hemodynamic velocity v , which corresponds to the speed of the response
394 propagation, and the wave damping Γ , which describes the signal decay. In the
395 hemodynamic model, these parameters reflect basic properties of the physiology.
396 The velocity v depends on the average stiffness of cortical vasculature, while
397 damping Γ is attributed to blood viscosity and blood outflow. Note that in the
398 mean field, these are averaged quantities and the velocity parameter also
399 depends on the mean resistance of vessels as encapsulated by the dependence
400 on resting pressure.

401

402 We estimated v and Γ at each cortical depth (Fig. 3, bottom) using a linear fit and
403 found that velocity v shows a trend level increase with z ($p = 0.07$ F-test, using a
404 linear model vs a constant model) while damping Γ is uniform vs. z ($p = 0.77$ F-
405 test, using a linear model vs a constant model). The results were restricted to $z >$
406 0 ($z = -0.8$ mm was high in signal noise) and are shown in Figure 3 (bottom). The
407 regression equation for v is given by,

408

$$v = [(0.3 \pm 0.1) \text{ s}^{-1}]^* z + (0.9 \pm 0.2) \text{ mm s}^{-1} \quad R^2 = 0.7,$$

410

411 and for Γ ,

412

$$\Gamma = [(0.01 \pm 0.03) \text{ mm}^{-1} \text{ s}^{-1}]^* z + (0.50 \pm 0.06) \text{ s}^{-1} \quad R^2 = 0.03,$$

414

415 where the uncertainty values ($\pm$) indicate standard error of the estimated
416 parameters.

417

418 **4. Discussion**

419 We found that the amplitude A and spatial spread Δx of the HRF decrease with
420 depth (i.e., smaller values of z), and this can be approximated as a simple linear
421 decrease for both amplitude and spatial spread. We also found that the
422 hemodynamic wave velocity v increases towards the surface while damping Γ
423 remains uniform through cortical depth. In wave theory these parameters
424 determine the spatial extent of the hemodynamic waves, estimated by the
425 characteristic range R (Aquino et al., 2012) given by

426

$$R = v/\Gamma$$

428

429 and taking the approximation that Γ is roughly constant, the characteristic range
430 for the hemodynamic waves is

$$R \sim (0.6 \pm 0.2) z + (1.8 \pm 0.4) \text{ mm},$$

431

where it is noted that these waves are in addition to the central core of activation. Therefore, our finding that R increases with z suggests that the observed increase in the spatial spread of the HRF (Δx) toward the surface reflects depth-dependent differences in vascular properties. Specifically, v is dependent on the linear elasticity coefficient of cortical vessels; hence the observed changes imply an increase in the linear elasticity coefficient as a function of z . This finding is consistent with prior knowledge that vessels closer to the pia have more elastic tissue (Iadecola, 2004; Zhang et al., 1990). In particular, recent work in optical imaging and modeling found that the dilatatory expressions of cortical vessels increase from the gray/white boundary to the surface owing to the corresponding increases in the Virchow-Robin space (Gao et al., 2015).

In agreement with our findings, it has been shown by a number of groups that the amplitude of the BOLD response increases toward the cortical surface (Chen et al., 2013; Koopmans et al., 2010; Ress et al., 2007). In addition to the increase in amplitude, Polimeni et al. (2010) demonstrated a loss in spatial specificity of the BOLD response towards the surface. Importantly, our experimental design permitted to describe, quantify, and explain this in terms of depth-dependent changes in the spatial spread of the HRF. In combination with our physiological model this suggests that the loss of specificity is not the result of large surface vessels alone, but rather reflects a more gradual change in vascular elasticity that appears to occur monotonically with depth.

4.1 Implications for depth-dependent fMRI

It has long been acknowledged that neuronal modulation does not only change the BOLD signal in the immediate voxel surrounding the response, but that the modulation extends in space to neighboring voxels (Engel et al., 1997). Despite this, the HRF is typically characterized only in the temporal dimension, with some analyses completely ignoring the spatial component of the response (Boynton et al., 2012). Furthermore, analysis methods that do consider both the temporal and spatial aspects of the HRF regard the HRF as the product of a spatial and temporal component. This implicitly enforces the approximation that the spatial and temporal dynamics of the hemodynamic response are uncoupled.

Due to the range of these effects, traditional fMRI studies (e.g. region based-studies with resolution $\geq 3\text{mm}$) are less affected; however, the assumption that the spatial and temporal dynamics of the hemodynamic response are uncoupled is untenable in the face of high spatial resolution fMRI. We have previously shown that this approximation is unphysical as there is an intrinsic spatiotemporal coupling in the hemodynamic response tangential to the cortical surface (Aquino et al., 2012). This introduces interdependence in the BOLD response among neighboring voxels in a time-dependent manner (Biessmann et al., 2012; Kriegeskorte et al., 2010; Shmuel et al., 2007). We have also shown that accounting for this interdependence using a spatiotemporal HRF model and an integrated spatial and temporal deconvolution results in improved estimation of the underlying neuronal responses compared to a more conventional analysis

using a space-time separable HRF (Aquino et al., 2014), even for medium resolution data (such as 1.5 mm^3 voxels).

In order to apply spatiotemporal deconvolution to estimate depth-dependent neuronal responses, it is vital to determine the hemodynamic changes at different cortical depths. Here, we extend our previous work by examining the spatiotemporal structure of the hemodynamic response perpendicular to the cortical surface, quantifying key changes in the HRF with cortical depth. The magnitudes of these changes are such that they must be accounted for in order to properly interpret depth-dependent BOLD measurements. For example, the spatial spread of the hemodynamic response tangential to the surface varies by nearly 2 mm (equivalent to 2.5 voxels at the resolution employed here) through the thickness of the cortical sheet.

Our present observations coupled with our past work therefore demonstrate the necessity and enable the use of a spatiotemporal HRF model for depth-dependent fMRI of human cortex. The empirically derived velocity, damping, and amplitude estimates (Fig. 3) in combination with the theoretically derived framework of the poroelastic model of hemodynamics (Aquino et al 2014; Drysdale et al., 2010) provide such a spatiotemporal HRF model (Fig. 4). Moreover, we suggest that just as deconvolution is now standard for diffusion (Tournier et al., 2004) and susceptibility imaging (Li et al., 2012), its use (with a spatiotemporal HRF model) should become standard for fMRI.

Figure 4. Modeled spatiotemporal HRF plots vs. cortical depth relative to the gray/white boundary, z . These plots were constructed using the empirically derived velocity, damping, and amplitude estimates (Fig. 3) and the theoretically derived framework of the poroelastic model of hemodynamics (Aquino et al 2014).

4.2 Implications for hemodynamic modeling

The spatiotemporal dynamics found in this study are consistent with a poroelastic model of hemodynamics (Drysdales et al., 2010). In particular, hemodynamic waves were observed and could be characterized with velocity and damping coefficients which are within predicted ranges (Aquino et al. 2014). Although the poroelastic model averages cortical vascular anatomy in a continuous mean field, key dynamics are accurately represented and related to physiology thus enabling it to be used to deconvolve BOLD signals to estimate the underlying neuronal responses that drive the hemodynamic response.

The variation of the hemodynamic parameters versus cortical depth we show provides insights and constraints into extending hemodynamic modeling into the depth dimension. As indicated by previous vascular physiology, an important consideration is to account for changes in cortical elasticity as a function of depth. Including this in the poroelastic model can be accomplished by adding heterogeneities in the model equations thus changing the dynamics as a function of depth, namely the hemodynamic velocity. While the depth-dependent changes in velocity observed here are consistent with known changes in vascular elasticity, it is important to note that other vascular properties known to change across cortical depth may also contribute, such as vascular density (Tsai et al., 2009).

4.3 Limitations and considerations

Previous work has shown that the temporal properties of the HRF vary across a number of factors such as cortical region (Handwerker et al., 2004; Puckett et al., 2014; Soltysik et al., 2004). Since our model parameters were found by measuring the response in primary visual cortex it remains unknown how generalizable these parameters are to other cortical regions. Moreover, some aspects of the HRF may depend on MRI acquisition parameters such as field strength and sequence type (Davis et al., 1998; Obata et al., 2006; Siero et al., 2013). It is important to note, however, that the technique we employ (gradient echo at 3T) is the most commonly used today, and hence the data provided is positioned to inform a large body of work.

At present there is still significant debate about the general feasibility of using fMRI to infer depth-dependent neuronal activity. While in principle effects of vessels from deeper cortical layers such as layer 4, passing through higher cortical layers can be disentangled (Heinzle et al., 2016), the spatial spread of vascular responses is unclear. Our study here addresses spatial spread tangential to the cortical surface and how it changes with cortical depth, but we cannot characterize spatial spread orthogonal to the cortical surface, through the depth of cortical layers. As such, the across depth variation in the spatiotemporal HRF is currently modeled in a stratified fashion, using a set of independent HRF profiles describing the structure of the response tangential to the surface at

different depths, z (Fig. 4). Future work is required to connect these profiles by incorporating across layer dynamics into the model.

Using the HRF data provided here to estimate the underlying neuronal responses also requires an assumption regarding the neural response profile elicited by our stimulus. A uniform neural response profile across depth is the simplest assumption, and the linear changes in the HRF we report are well explained through a linear change in vascular properties, with no contribution from laminar changes in neuronal activity. It has been shown in macaque that a simple visual stimulus elicits uniform multi-unit spike activity across cortical depth (Xing et al., 2012) suggesting this may be a reasonable assumption. However, the same study revealed that local field potential activity showed a non-uniform response profile across depth suggesting that some of the HRF variation we observe may reflect non-uniformity in neuronal responses as suggested previously (Koopmans et al., 2010).

Another important issue is the challenge of defining laminar surfaces using MRI data, with two main automatic techniques in the literature: (i) equidistant models, i.e. sampling layers by fraction of the cortical thickness (Muckli et al., 2015; Olman et al., 2012; Polimeni et al., 2010) and (ii) equivolume techniques, i.e., sampling using Bok's principle (Waehnert et al., 2014). These methods take into account the variation of thickness and curvature and normalize the surface sampling methods. For our study we employed an absolute sampling method

that ignores this variation. We note, however, that because the responses reported here are from a single eccentricity in V1 and that the curvature and thickness are uniform in most of V1 (Fischl & Dale, 2000; Hinds et al., 2008) the methods should yield equivalent results. It is also important to reiterate that the most superficial laminar surface ($z = 3.2$ mm) is likely in the vascular arachnoid, outside of the cortical sheet. Although sampling outside of cortex, the BOLD response measured here still reflects changes in neuronal activity as blood vessels that feed/drain the responses within cortex exist in this range. These responses are also important to consider as they are likely to further inform mechanisms of spatial spreading (Gao et al., 2015; Kim et al., 2013). We currently model this response (Fig. 4, $z = 3.2$ mm) using the same poroelastic model derived for responses within the cortical sheet. In the context of the model, the vessels in the arachnoid are connected to the pores within the cortical sheet. This appears to yield a reasonable approximation of the empirical response (cf. Fig. 2); however, future work will be needed to take into account differences in the underlying physiology that exists between the vascular arachnoid and the cortical sheet

4.4 Conclusion

The spatiotemporal BOLD response to a simple visual stimulus propagates from its source (i.e., the neuronal drive) through the surrounding vasculature. We report how fundamental properties of the response vary as a function of cortical depth. By quantifying spatiotemporal properties of the HRF tangential and

599 perpendicular to the cortical surface, we provide a characterization of an HRF
600 able to capture this variation, finding that the temporal and spatial responses are
601 fundamentally inseparable. Together with spatiotemporal deconvolution this lays
602 the foundation to infer depth-dependent neuronal activity, which importantly can
603 be related to cortical layers either through previous knowledge or careful co-
604 registration with high-resolution structural MRI data.

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Supplementary Material:

Figure S1: Example showing co-registration between the mean EPI image (gray) and the anatomical image (red). The anatomical image has been thresholded to emphasize white matter. Images are from a single subject and 8 slices are displayed.

Figure S2: Illustration of the relationship between the spatiotemporal HRF profile (left) and a temporal HRF profile (right). The relationship may best be understood by considering the response only at the centerline (white rectangle, $x = 0.0$ mm). If this response is plotted such that time is on the x-axis (rather than the y-axis) and amplitude is represented along the y-axis (rather than by color), then a temporal HRF profile is retrieved. The data used here were taken from the group-averaged response at $z = 1.6$ mm. The relationship between our spatiotemporal

HRF and the temporal HRF is outlined mathematically and discussed in detail in previous publications (Aquino et al., 2012; Drysdale et al., 2010).

Video S3: Group-averaged spatiotemporal HRF video showing the structure tangential to the surface (x) vs. space orthogonal to the surface (z) with each frame representing the response at a different time point. Color indicates the percent modulation of BOLD.

Video S4: Single subject spatiotemporal HRF video showing the structure tangential to the surface (x) vs. space orthogonal to the surface (z) with each frame representing the response at a different time point. Color indicates the percent modulation of BOLD