Hemifield columns co-opt ocular dominance column structure in human achiasma

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A B S T R A C T

In the absence of an optic chiasm, visual input to the right eye is represented in primary visual cortex (V1) in the right hemisphere, while visual input to the left eye activates V1 in the left hemisphere. Retinotopic mapping in V1 reveals that in each hemisphere left and right visual hemifield representations are overlaid (Hoffmann et al., 2012). To explain how overlapping hemifield representations in V1 do not impair vision, we tested the hypothesis that visual projections from nasal and temporal retina create interdigitated left and right visual hemifield representations in V1, similar to the ocular dominance columns observed in neurotypical subjects (Victor et al., 2000). We used high-resolution fMRI at 7 T to measure the spatial distribution of responses to left- and right-hemifield stimulation in one achiasmic subject. T2-weighted 2D Spin Echo images were acquired at 0.8 mm isotropic resolution. The left eye was occluded. To the right eye, a presentation of flickering checkerboards alternated between the left and right visual fields in a blocked stimulus design. The participant performed a demanding orientation-discrimination task at fixation. A general linear model was used to estimate the preference of voxels in V1 to left- and right-hemifield stimulation. The spatial distribution of voxels with significant preference for each hemifield showed interdigitated clusters which densely packed V1 in the right hemisphere. The spatial distribution of hemifield-preference voxels in the achiasmic subject was stable between two days of testing and comparable in scale to that of human ocular dominance columns. These results are the first in vivo evidence showing that visual hemifield representations interdigitate in achiasmic V1 following a similar developmental course to that of ocular dominance columns in V1 with intact optic chiasm.

Introduction

A congenital condition known as achiasma or non-decussating retinal-fugal fiber syndrome results in a failure of axons from retinal ganglion cells on the nasal side of the retina to cross to the contralateral side of the brain (Apkarian et al., 1994, 1995). The result is the absence of an optic chiasm, with all projections from the right eye following a path through the right lateral geniculate nucleus (LGN) to the right primary visual cortex (V1), and all projections from the left eye going to left V1 (Victor et al., 2000; Williams et al., 1994). Functional mapping studies show that these projections are functional, and the entire visual field (all information being received from each eye) is represented in each hemisphere (Davies-Thompson et al., 2013; Hoffmann et al., 2012; Kaule et al., 2014). Crucially, retinotopic mapping studies reveal that representations of the two halves of the visual field, which are separated between the two hemispheres in the neurotypical visual system, are superimposed on each other in the visual cortex of an achiasmic individual (Hoffmann et al., 2012) but functionally independent (Bao et al., 2015).

The fact that achiasmic individuals have functional vision and can readily discriminate objects in mirror-symmetric locations in the visual field indicates that left and right visual field representations are not confused in visual cortex, in spite of their complete overlap. The most likely explanation is that the left and right visual field representations are interdigitated in primary visual cortex, co-opting the mechanisms that typically guide left and right eye projections to cortex. In achiasmic
Belgian sheep dogs, Williams et al. (1994) found that axons from nasal retina that should have crossed at the optic chiasm are targeted to different layers in the LGN than axons from temporal retina (so left- and right-hemifield layers replace ipsi- and contra-lateral eye layers in the LGN). In a study of achiasma in humans, Víctor et al. (2000) hypothesized that if axons from separate layers in the LGN follow typical developmental markers then they should segregate in the input layers of V1.

To examine this hypothesis that inputs from left- and right-hemifield locations are segregated in the primary visual cortex of an achiasmic individual, we performed T2-weighted functional MRI with weighted anatomical images and retinotopic mapping data. The prediction under our hypothesis is that the functional imaging would reveal alternating stripes of left- and right-hemifield dominance in V1 that were observed in the same cortical location on separate days.

**Methods**

**Participants**

One participant with achiasma (male, age 31) and two control participants (one male, age 26, and one female, age 43) each participated in two separate scanning sessions after providing written informed consent. The experimental protocol was approved by the University of Minnesota Institutional Review Board. The participants had previously participated in other scanning sessions to acquire T1-weighted and T2-weighted images as baseline for functional imaging.

**Visual stimulus and task for achiasmic participant**

Visual stimuli consisted of black and white flickering checkerboards (spatial frequency: 0.5 cycles/degree; temporal frequency: 2 Hz) presented via an Avotec Silent Vision Fiber Optic Glasses (Avotec Inc., Stuart FL) to the participant’s right eye. The left eye was covered with a patch for comfort, so the participant could relax both eyes during the scanning session.

Each scan consisted of 8 checkerboard presentation blocks, 4 in the left visual field and 4 in the right visual field. Total visual field subtense was 24°(w)×18°(h). Each presentation block lasted 12 s and was followed by 12 s of rest. Including an additional rest block at the beginning of the scan, every scan was 208 s long. Stimulus presentation order was not randomized, and always alternated between hemifields, starting with the left in each scan. A total of 12 scans were conducted in “Day 1”, and were repeated in “Day 2”.

During each scan, the participant’s attention was engaged by a demanding orientation discrimination task on the fixation mark in the center of the screen. At random intervals uniformly distributed between 2 and 6 s, the fixation mark randomly changed from ‘+’ to ‘-’ for about 400 ms before returning to ‘+’.

**Functional Imaging**

Functional MRI data were collected at the University of Minnesota’s Center for Magnetic Resonance Research on a Siemens 7 T scanner equipped with the AC-84 head-gradient insert, which has a maximum strength of 80 mT/m and a slew rate of 333 T/m/s. A custom-made radio frequency head coil (4-channel transmit, 9-channel receive; Adriany et al., 2012) was used for T2-weighted (spin echo) echo-planar imaging (EPI) in the achiasmic participant and the first of the two control participants. Images were acquired with a coronal field of view (FOV) in 24 slices (0.8 mm thick) positioned near the occipital pole (Fig. 1). Nominal image resolution was 0.8 mm isotropic (field of view: 152×114 mm; matrix size: 192×144); data were acquired with an in-plane parallel imaging acceleration factor (R) of 2 and a right-left phase-encode direction (6/8 Partial Fourier, echo-spacing: 0.8 ms). The repetition time (TR) was 2.0 s. At the end of each scanning session, a 30-volume EPI series was acquired with a left-right phase-encode direction (reversed from the phase-encode direction of the functional data acquisition) to assist in distortion compensation during data analyses.
processing. Scanning parameters were identical for the second control participant, except the scanner was equipped with an SC72 body gradient, so echo spacing was 1 ms and a newly available 4-channel transmit, 32-channel receive coil was used, enabling greater acceleration (R=3) to combat distortion, albeit at the cost of signal-to-noise ratio.

**Anatomical data processing**

Cortical surfaces (gray matter/white matter boundary, and pial surface) were determined from a standard 1-mm isotropic T1-weighted MP-RAGE reference anatomy using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). No manual editing was done to adjust the surfaces. Visual inspection confirmed that the gray matter (GM) delineation was reasonable in the region of the calcarine sulcus.

**Data pre-processing**

Functional data were analyzed using tools provided by AFNI (https://afni.nimh.nih.gov/afni). Functional data were preprocessed in three steps: motion compensation (6-parameter affine transformation), distortion compensation (non-linear transformation), and non-linear warping to the reference anatomy. Transformation matrices or warping maps were saved from each step and then combined to resample the original data to a regular grid with spacing of 0.5 mm using Python (scipy.interpolate.griddata).

Data visualization

To create flattened representations of the cortical surface for visualization of data, patches of the inflated cortical surface containing just the calcarine sulcus were manually cut in FreeSurfer’s tksurfer tool and flattened using FreeSurfer’s mris_flatten tool. The mean distance between neighboring vertices on the flattened cortical surface was 0.6 mm. For each vertex contained in the calcarine sulcus patch, values of significance, selectivity and sensitivity were then assigned to an appropriate location in the three-dimensional space defined by the flattened patch and the depth-dependent volume sampling done by 3dVol2Surf. For visualization, the data at each depth were re-gridded to a regular grid with spacing of 0.5 mm using Python (scipy.interpolate.griddata).

**Results**

One achiasmatic individual participated in two days of scanning sessions, each session consisting of 12 3 ½-min scans during which checkerboard stimuli were presented in alternating 12-s blocks (with rest in between) to the left and right visual field of the right eye. Our slice prescription covered a portion of the calcarine sulcus; slice
prescription on the two days was close to identical in the anterior-posterior dimension (i.e., coverage was almost identical, Fig. 2). Maps of regions showing significant modulation across the 12 scans and throughout the cortical depth \((F_{2,1199} > 4.609, p < 0.01\) at the single-voxel level) revealed a region on the upper bank of the calcarine sulcus where visual responses were strong and registration between functional and anatomical data was excellent on both days. Further analyses were focused on this region (white boxes, Fig. 2). Both inclusion criteria (functional activation strength and EPI/T1 registration) contributed to the exclusion of data on the lower bank of the calcarine sulcus from further analysis. This is due in large part to the fact that this particular individual’s right-hemisphere calcarine sulcus is very close to the ventral surface of the cortex, where field perturbations by the sagittal and transverse sinuses and bone-tissue interfaces are greatest. Two control participants also completed two scanning sessions each, and their data were processed in the same way as the achiasmic participant’s data. Results from these participants are provided as Supplementary figures.

To confirm that the T2-weighted data acquisition was minimizing contributions to the signal from large surface veins, known to degrade resolution, we computed sensitivity profiles through the cortical depth in the regions where significant modulation throughout the cortical depth indicated good registration between functional and anatomical data. The sensitivity profiles in Fig. 3, left panel, show the expected peak response amplitude near the top of the parenchyma (De Martino et al., 2013; Goense and Logothetis, 2006; Koopmans et al., 2010). The selectivity of the signal for left vs. right hemifield (or eye, in the case of the control participants) is flat through the cortical depth (Fig. 3, right panel). Selectivity is expected to be maximal in the middle of the parenchyma, for all participants because spatial selectivity is best for the small vessels in the middle of the gray matter and for normally-sighted individuals because segregation of LGN inputs in neurotypical human is greatest in middle layers. While our nominal imaging resolution was 0.8 mm, blurring due to brain motion, head motion, and \(T2^*\) blurring due to the relatively long read-out time of the functional data acquisition decreased the resolution of this experiment. Therefore, our true resolution is likely 1 mm or above, and inadequate for detecting signals unique to middle layers.

Distribution of preference for left versus right visual hemifield stimulation across the V1 cortical surface is visualized at multiple sampling depths in Fig. 4. On both days, regions were observed where stripes of left-hemifield preference alternated with stripes of right-hemifield preference. These stripes were close to 1 mm wide (average width of one full left/right cycle was 2.5 mm), which is comparable to the widths of ocular dominance columns observed in humans (Cheng et al., 2001; Goodyear and Menon, 2001; Nasr et al., 2016; Yacoub et al., 2007). Importantly, the stripes were observed in the same locations on each day. In the top panels of Fig. 5, data sampled from the middle of the cortical depth on each day are shown side by side with fiducial marks (black lines) in the same location on the cortical surface to illustrate the consistency of the locations of left-hemisphere-dominated responses.

In spite of careful work to compensate for distortion in the EPI data and maximize accuracy of the image registration in the calcarine sulcus, residual errors in alignment are apparent in the fact that the most striking alternation between left- and right-hemifield dominance was observed at slightly different depths across the region of V1 selected for analysis. This is understandable, since the region being analyzed spans several centimeters across the cortical surface, including sections of high positive curvature on the bank of the calcarine sulcus and regions of strong negative curvature, so very small residual
distortions in errors in image registration result in an apparent change in the depth of functional data.

To facilitate visualization, a composite image was created by selecting regions of the data from each depth showing strong structure at 2–3 cycles/mm (the expected alternation frequency of ocular or hemifield dominance columns) across the cortical surface and then merging them into a single visualization. To accomplish this, a roving window (~1 cm²) was used to assign each cortical location a value representing the power in the 2–3 cycles/mm band (a donut, in Fourier space) relative to the entire power spectrum of the selectivity data in Fig. 4.
the 1 cm² window centered on that location. The power map at each depth was then raised to the 8th power and used as a weighting function for combining the images shown in Fig. 4 to create the composite images shown in the bottom panels of Fig. 5. No image filtering was done. Stripes at this scale were already prominent in different depth samples before the data were aggregated (Fig. 4); spatial frequency content was simply used as a weighting function to determine the relative weight of the selectivity patterns at each depth for each location, to aid visualization.

Comparable figures for the control participants (single-depth ocular dominance maps and through-depth composite images) are included in the Supplemental material. Because of the low selectivity for eye-of-origin in the control participants, the maps were not nearly as clear as for the achiasmic participant. Where visible, the alternating-eye structure had the same spatial scale (1 cycle every 2–3 mm) as observed for hemifield alternation in the achiasmic participant.

Discussion

We found that the cortical representation of the left and right visual hemifield of an achiasmic human participant are interdigitated in V1 in the form of hemifield dominance columns, co-opting the structure of ocular dominance in neurotypical V1. This finding, while unprecedented, is broadly anticipated. Prior to our current finding, it has been observed that both hemifields from each eye of achiasmic humans are fully represented in the brain hemisphere ipsilateral to the eye (Bao et al., 2015; Davies-Thompson et al.; Hoffmann et al., 2012; Kaule et al., 2014; Victor et al., 2000; Williams et al. 1994). Detailed retinotopic mappings (Bao et al., 2015; Hoffmann et al., 2012; Kaule et al., 2014) further revealed that visual field locations symmetrically positioned across the vertical meridian are represented by the same cortical locations in the retinotopically defined visual areas at a coarse resolution resolvable with 2–3 mm isotropic voxels. Despite the apparent retinotopic overlap, a broad range of psychophysical and physiological measurements have failed to show any interaction between the left and right visual fields (Bao et al., 2015; Victor et al., 2000). Williams et al. (1994) found in achiasmic Belgian sheep dog that inputs from the two visual fields stay segregated in the LGN, with layers for inputs from the contralateral eyes reassigned to inputs from the ipsilateral visual field, although the same study did not investigate any down-stream structures. These observations have led several authors to hypothesize that the ocular dominance columns in neurotypical V1 may be co-opted to form hemifield dominance columns in achiasma and albinism. (Albinism results in a complimentary condition associated with over-decussating fibers (Bao et al., 2015; Davies-Thompson et al., 2013; Guillery et al., 1984; Hoffmann and Dumoulin, 2015; Victor et al., 2000)). Our finding is the first empirical confirmation of this hypothesis in human.

Bao et al. (2015) had hypothesized that hemifield dominance is maintained downstream from V1 but its spatial organization becomes finely intermingled. They argued that those neurons that would have binocularity in a neurotypical visual system become monocular and unilateral in achiasma by randomly suppressing and pruning one of the inputs, because inputs from the two visual hemifields do not correlate. Since the pruning is random, the resulting spatial distribution of hemifield dominance becomes spatially intermingled downstream from Layer 4 of V1, which receives the segregated inputs from LGN. This hypothesis is consistent with the observation that hemifield dominance structure was most reliably observed in the middle of the cortical depth, although the resolution of this study was insufficient to verify that selectivity is greatest in the middle layers.

This study is exciting because it demonstrates that recent advances in imaging technology have made it possible to measure millimeter-scale structures in a wide range of participants, including clinical populations. Historically, studies of ocular dominance columns were done with anisotropic sampling resolution, focusing on a flat section of cortex through which a relatively thick slice could be placed to sample across the cortical surface with sub-millimeter in-plane resolution but poor resolution through the gray matter thickness (Cheng et al., 2001; Yacoub et al., 2007). Studying only planar regions of gray matter fails to show any interaction between the left and right visual fields (Bao et al., 2015; Victor et al., 2000). Williams et al. (1994) found in achiasmic Belgian sheep dog that inputs from the two visual fields stay segregated in the LGN, with layers for inputs from the contralateral eyes reassigned to inputs from the ipsilateral visual field, although the same study did not investigate any down-stream structures. These observations have led several authors to hypothesize that the ocular dominance columns in neurotypical V1 may be co-opted to form hemifield dominance columns in achiasma and albinism. (Albinism results in a complimentary condition associated with over-decussating fibers (Bao et al., 2015; Davies-Thompson et al., 2013; Guillery et al., 1984; Hoffmann and Dumoulin, 2015; Victor et al., 2000)). Our finding is the first empirical confirmation of this hypothesis in human.
arrays with small loops provides the signal-to-noise ratio (SNR) needed for small voxel volumes, and parallel imaging permits single-shot acquisition of large image matrices, thereby enabling multi-slice acquisition with reasonable SNR and temporal resolution.

As isotropic coverage of cortex increases, so does difficulty in registration between functional (EPI) and anatomical (MP-RAGE) data. Distortion compensation techniques, based either on fieldmaps (e.g., FSL’s FUGUE) or comparison of EPI acquisitions with opposite phase-encode directions (e.g., FSL’s TOPUP or AFNI’s 3dQwarp), do mitigate the problem. However, these techniques are not perfect, and even if they were, gradient non-linearities mean that anatomical and EPI scans often have different, sometimes unknown distortions. In the present work, we found that the residual disagreements between EPI and MP-RAGE structure existed on a smaller scale than could be explained by gradient or scanner non-linearities, so we adopted the pragmatic approach of using image-based non-linear warping of the EPI image to match the anatomical image, constraining the unwarping process with a weighting function that emphasized peri-calcarine regions. This additional step improved the image registration 20%, using the ratio of visually modulated voxels aligned with anatomical GM vs WM masks as a metric. The result was adequate for visualization of ocular dominance columns, but inadequate for assessing depth-dependent responses over a significant area of cortex. In the past, we have addressed this problem by restricting our analyses to very limited regions of cortex in which EPI/MP-RAGE registration could be visually verified (Olman et al., 2012). In the future, improved techniques that rely on GM/WM contrast in the EPI data (Kok et al., 2016) will be required to ensure that isotropic sampling resolution translates to reliable estimates of responses across the cortical surface and through the GM depth.

The selectivity index we used to assess hemifield dominance in each voxel or at each surface node was typically 10–20% in regions where hemifield dominance patterns were visible. Given our underlying model that inputs are entirely segregated according to hemifield of origin, a 10–20% advantage in the fMRI response is on the low end of expectations. However, the experiment used a single-condition design. In general, studies performed at ultra-high resolution seek to maximize contrast between conditions by adopting a differential design, directly contrasting Condition A and Condition B with no rest in between. Differential designs all but eliminate contributions from large vessels (Olman et al., 2007) and maximize the selectivity of the resulting stimulus. We instead chose a more conservative approach of allowing rest between blocks. This ensured that we were measuring the full hemodynamic response to each hemifield, and not artificially creating contrast between the left- and right-field stimuli. We used a T$_2$-weighted acquisition to minimize contamination of the signal from the largest veins on the pial surface (Olman and Yacoub, 2011). However, intracortical venules with intermediate diameters (~100 μm) that drain cortical territories comparable to the size of an ocular or hemifield dominance column contribute significantly to the T$_2$-weighted signal. Therefore, blurring by the vascular tree likely diminished the selectivity of the signal measured in each voxel. Participant motion and brain pulsatility should also blur the signal and reduce voxel selectivity due to partial volume effects. Data smoothness was estimated for the processed functional data (after motion and distortion compensation, as well as warping to anatomy) using AFNI’s 3dFWHMx routine. Consistent with previous work (Kemper et al., 2015), smoothness was greatest in the phase-encode direction (σ=0.9 mm) and least in the through-slice direction (σ=0.5 mm for through-slice direction, and 0.6 mm for read-out direction). Thus, in spite of our nominal 0.8 mm isotropic resolution, our sampling was blurred in the right/left direction. Lastly, part of the BOLD signal may not be stimulus specific but instead driven by anticipatory responses induced by the blocked timing of the stimulus (Sirotin and Das, 2009). All of these factors likely contributed to selectivity values that were typically 10–20% even for voxels or vertices centered on hemifield dominance columns in the middle of the cortical depth.

While spatial distortions caused by field inhomogeneity and gradient non-linearities remain the key challenges for imaging fine functional structures at 7 T, we were able to reveal columnar structures in the striate cortex of a single individual who does not have a favorably shaped calcarine sulcus. This individual was born without the optic chiasm. Our results constitute the first direct in vivo evidence showing that in human achiasma, the representations of the left and right visual hemifield interdigitate in the striate cortex, co-opting the ocular dominance column in a neurotypical V1.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2016.12.063.

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