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Visual callosal topography in the absence of retinal input

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ABSTRACT

Using probabilistic diffusion tractography, we examined the retinotopic organization of splenial callosal connections within early blind, anophthalmic, and control subjects. Early blind subjects experienced prenatal retinal "waves" of spontaneous activity similar to those of sighted subjects, and only lack postnatal visual experience. In anophthalmia, the eye is either absent or arrested at an early prenatal stage, depriving these subjects of both pre- and postnatal visual input. Therefore, comparing these two groups provides a way of separating the influence of pre- and postnatal retinal input on the organization of visual connections across hemispheres. We found that retinotopic mapping within the splenium was not measurably disrupted in early blind or anophthalmic subjects compared to visually normal controls. No significant differences in splenial volume were observed across groups. No significant differences in diffusivity were found between early blind subjects and sighted controls, though some differences in diffusivity were noted between anophthalmic subjects and controls. These results suggest that neither prenatal retinal activity nor postnatal visual experience plays a role in the large-scale topographic organization of visual callosal connections within the splenium.

Introduction

Visual deprivation is a classic paradigm for studying organization and plasticity in the central nervous system within both animals and humans (Wiesel and Hubel, 1965a,b). The visual system is relatively well-understood and at least a fifth of the brain is normally devoted to visual processing, thereby offering the opportunity to study large-scale reorganization during development. Here we use blindness to examine the role of pre- and postnatal neural activity on the large scale organization of fibers within the corpus callosum in humans.

In many species (including humans), the right visual cortex represents the left side of the visual field and the left visual cortex represents the right visual field. These two halves are interconnected via axonal projections that pass through the splenium at the posterior end of the corpus callosum (Clarke and Miklossy, 1990; de Lacoste et al., 1985; Pandya et al., 1971; Rockland and Lund, 1983) allowing for coverage of the visual field across the vertical meridian. Although organization within the callosum is difficult to systematically map using electrophysiology techniques, studies in the cat (Hubel and Wiesel, 1967) and monkey (Rockland and Pandya, 1986) have found some evidence for topographic organization of visual fibers within the splenium itself. In humans, Dougherty et al. (2005) found dorsal-to-ventral organization within splenial fibers projecting from early visual areas (V1/V2, V3, V3A/B, V4 and V7). More recently, Saenz and Fine (2010) further demonstrated organization based on eccentricity. Visual inspection of the maps suggested that fibers connecting dorsal visual areas were clustered in the superior-caudal region of the splenium, while fibers connecting ventral visual areas were clustered in the inferior-rostral corner of the splenium. In the case of eccentricity, projections from foveal-to-peripheral V1 subregions appeared to map from the superior-rostral to the inferior-caudal direction within the splenium: orthogonal to the dorsal-to-ventral mapping.

While input from the retina influences the organization of cortical connections at the level of cortex (Goodman and Shatz, 1993; Katz and Crowley, 2002; Katz and Shatz, 1996; Lopez-Bendito and Molnar, 2003; Price et al., 2006; Sur and Rubenstein, 2005), it is less clear the degree to which retinal input affects the development and/or maintenance of fibers within the cortical white matter fiber tracts themselves. Some studies (Lepore et al., 2010; Levin et al., 2010) suggest that early postnatal blindness leads to a reduction in splenial white matter volume, however, Bridge et al. (2009) did not find any structural differences within the splenium between anophthalmic subjects and their matched control subjects. Similarly, one of the first studies to use diffusion-weighted imaging to investigate the developmental effects of sensory deprivation by Shimony et al. (2006) found a reduction in fractional anisotropy between early blind subjects and sighted

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controls (interestingly, Bridge et al. (2009) found somewhat different results using a smaller group of anophthalmic subjects).

Here, using T1- and diffusion-weighted imaging combined with diffusion based probabilistic tractography, we examined the volume, diffusivity, and topographic organization of visual callosal connections within normally-sighted, early blind, and anophthalmic subjects. Early blind subjects, who lost vision from birth to the first 5 years of life, experienced prenatal retinal "waves" of spontaneous activity prior to losing sight, and only lack postnatal visual experience. In anophthalmia, the input from the optic nerves to the thalamus and midbrain never exists (or only exists temporarily, early in development before the embryonic eyes degenerate (Stevenson, 2006)). As a result, anophthalmic subjects not only lack postnatal visual experience, but also do not experience (or have much reduced) prenatal retinal "waves" of spontaneous activity as compared to sighted and early blind humans. Comparing these groups offers a way of at least partially separating the influence of pre- and postnatal retinal input on the retinotopic organization of visual connections across hemispheres, and provides an important addition to literature investigating the influence of neuronal activity on the development and maintenance of retinotopic connections between visual hemispheres that has thus far been entirely confined to animal models (Chalupa, 2009; Graven, 2004; Huberman et al., 2005).

Several studies have examined the effect of visual deprivation on callosal connections, with somewhat inconsistent findings (Bridge et al., 2009; Lepore et al., 2010; Levin et al., 2010; Shimony et al., 2006), as described below. Our study is unique in examining the effect of blindness on the retinotopic organization of splenial connections. We find that visual callosal fibers are retinotopically organized in sighted controls, as shown previously (Dougherty et al., 2005; Saenz and Fine, 2010), and that this organization is preserved in both early blind and anophthalmic subjects. These results suggest that the gross retinotopic organization of visual fibers within the splenium develops and is maintained independently from any pre- or postnatal retinal input, and that changes as a result of blindness in this pathway may occur as white matter connections innervate cortex, rather than within the tracts themselves.

Materials and methods

Subjects

Six anophthalmic subjects (two females, mean age 24.2 +/− 5.2), six early blind subjects (three females, mean age 49.5 +/− 13.4) (see Table 1), and 15 normally-sighted control subjects (eight females, mean age 27.7 +/− 4.6) participated. Note that the average age of early blind subjects is larger than for the other two groups. However a 2-way ANOVA (subject group × diffusivity measure: FA, MD, L1, L23, see below) performed on the Fisher's r to z transform of the correlation between age and diffusivity measures found no interaction between age and diffusivity values. All sighted subjects had normal or corrected-to-normal vision. All subjects provided informed written consent, and all procedures involved were approved by either the Oxfordshire NHS Research Ethics Committee (07/Q1605/20) or the Institutional Review Board at the University of Washington.

Data collection and analysis

Imaging of six control and all anophthalmic subjects was performed at the Oxford Centre for Clinical Magnetic Resonance using a Siemens 3T Trio scanner with a 12-channel head coil. Imaging of the remaining nine control and all early blind subjects was performed at the UW Medical Center using a Philips 3T scanner with an 8-channel head coil. Some of the data and results (though using slightly different analysis methods) obtained from the six control and anophthalmic subjects whose data were collected at Oxford have been previously reported (Bridge et al., 2009), as specified below.

Table 1
Brief subject descriptions.

Subject	Gender	Age	Clinical description
EB1	F	61	Right eye ruptured at 2 months, detached retina at 5 years; no light perception
EB2	F	51	Retinopathy of prematurity; low light perception until retina detached at 25 years; 2 months premature
EB3	M	59	Retinopathy of prematurity; no light perception; 2 months premature
EB4	M	60	Retinopathy of prematurity; no light perception; 2 months premature
EB5	F	36	Retinopathy of prematurity; low light perception until 14 years; 2 months premature
EB6	M	30	Leber's congenital amaurosis; low light perception
Ano1	M	28	Bilateral anophthalmia associated with OTX2 mutation; mother carrier; delayed speech and motor development
Ano2	F	31	Isolated bilateral anophthalmia; family history of microphthalmia
Ano3	M	18	Isolated bilateral anophthalmia associated with dysplastic kidneys and mild systolic murmur; no family history
Ano4	F	20	Isolated bilateral anophthalmia, right with orbital cyst; no family history
Ano5	M	23	Isolated bilateral anophthalmia; no family history
Ano6	M	25	Isolated bilateral anophthalmia; no family history

Age is at time of scan.

At both centers high-resolution anatomical images were acquired using a standard 1 mm^3 T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) sequence. Diffusion-weighted images were acquired axially using echoplanar imaging, with isotropic voxels of 2 mm^3. The diffusion weighting was isotropically distributed through space (Jones et al., 1999) along 60 directions using a b-value of 1000 s/mm^2. For 1 early blind subject, diffusion weighting was distributed along 32 directions. The total acquisition time for both structural and diffusion data was ~30 min. All subsequent analysis of the data was conducted on the same workstation running Ubuntu 12.04. Analysis consisted of the following steps.

Definition of occipital ROIs on the cortical surface

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer v5.1.0 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Briefly, this processing includes skull-stripping (Segonne et al., 2004), subcortical segmentation (Fischl et al., 2002, 2004), intensity normalization (Sled et al., 1998), surface generation (Dale and Sereno, 1993; Dale et al., 1999; Fischl and Dale, 2000), topology correction (Fischl et al., 2001; Segonne et al., 2007), surface inflation (Fischl et al., 1999a), registration to a spherical atlas (Fischl et al., 1999b) and thickness calculation (Fischl and Dale, 2000).

Three sets of ROIs were then defined on the cortical surface:

Occipital lobe ROI

This ROI was chosen to include all early visual areas on the Freesurfer cortical surface using the Destrieux surface based atlas (Destrieux et al., 2010).

V1/V2 ROI

A surface-based estimate of the location of primary visual cortex (V1) from cortical folds was obtained using Freesurfer (Hinds et al., 2008, 2009). As callosal connections in primate visual cortex are found at the highest density within a narrow zone straddling the V1/V2 border (Clarke and Miklossy, 1990; Kennedy et al., 1986; Van Essen et al., 1982), a V1/V2 ROI (larger than the V1 ROI used by Saenz and Fine, 2010) was drawn by expanding the border of V1 to the fundi of the lingual sulcus and the neighboring paracalcarine sulcus to ensure the inclusion of visual callosal connections on the V1/V2 border. As the exact width of the