Vision Research 114 (2015) 48–55

Contents lists available at ScienceDirect

Vision Research

journal homepage: www.elsevier.com/locate/visres

Altered white matter in early visual pathways of humans with amblyopia

Brian Allen [a], Daniel P. Spiegel [c,d], Benjamin Thompson [c,e], Franco Pestilli [b,1], Bas Rokers [a,*,1]

[a] Department of Psychology, University of Wisconsin-Madison, Madison, WI, United States
[b] Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, United States
[c] Optometry and Vision Science, University of Auckland, Auckland, New Zealand
[d] McGill Vision Research, Department of Ophthalmology, McGill University, Montreal, Canada
[e] Optometry and Vision Science, University of Waterloo, Canada

ARTICLE INFO

Article history:
Received 8 September 2014
Received in revised form 16 December 2014
Available online 20 January 2015

Keywords:
Amblyopia
White matter
Tractography
Diffusion-MRI

ABSTRACT

Amblyopia is a visual disorder caused by poorly coordinated binocular input during development. Little is known about the impact of amblyopia on the white matter within the visual system. We studied the properties of six major visual white-matter pathways in a group of adults with amblyopia ($n = 10$) and matched controls ($n = 10$) using diffusion weighted imaging (DWI) and fiber tractography. While we did not find significant differences in diffusion properties in cortico-cortical pathways, patients with amblyopia exhibited increased mean diffusivity in thalamo-cortical visual pathways. These findings suggest that amblyopia may systematically alter the white matter properties of early visual pathways.

1. Introduction

Amblyopia is a developmental disorder that occurs when the visual input from the two eyes is poorly correlated during early development. Such poor correlation may be due to a chronically blurred image in one eye (anisometropia), a turned eye (strabismus), or deprivation of one or both eyes. Since visual input is atypical in amblyopia, it is of interest not only as a clinical disorder, but also as a human model of the interplay between sensory input and neural development. Accordingly, amblyopia has been widely studied both neurophysiologically (Hubel & Wiesel, 1970) and psychophysically (Asper, Crewther, & Sheila, 2000).

Amblyopia is associated with impairments in both monocular and binocular vision (McKee, Levi, & Movshon, 2003). Monocular deficits are apparent when patients use only their amblyopic eye, and include impaired spatial acuity (Holmes & Clarke, 2006; Levi & Klein, 1982), reduced contrast sensitivity (Hess & Howell, 1977; Levi & Harwerth, 1978) and impaired performance on tasks requiring the integration of form or motion (for a recent review see Hamm et al., 2014). Binocular visual dysfunction is also common in patients with amblyopia, often resulting in severely degraded or absent sensitivity to binocular disparity (Holmes & Clarke, 2006; Li et al., 2011).

The neuro-anatomical consequences of amblyopia in humans are less established than the functional deficits. There is evidence for reduced grey matter in the lateral geniculate nucleus (LGN) (Barnes et al., 2010; von Noorden, Crawford, & Levacy, 1983), and the primary and extrastriate visual cortex (Chan et al., 2004; Mendola et al., 2005). Whether these structural changes are restricted to grey matter or affect the white matter is an open question, although some evidence for abnormal development of the prechiasmatic pathways (Gümüstas et al., 2013; Pineles & Demer, 2009) and optic radiations has been reported in children with amblyopia (Ming-xia et al., 2007; Song et al., 2010; Xie et al., 2007).

Recent developments in MRI-based diffusion weighted imaging (DWI) and tract-estimating algorithms (called "tractography") provide means to identify the anatomy, location and structural properties of white matter pathways. The ability to identify the general characteristics of these pathways in humans *in vivo* is a crucial step in understanding how visual networks develop. Accordingly, we used a novel DWI protocol that is able to track multiple, potentially intersecting tracts within the visual system, and assessed whether the structural properties of white matter within the visual system differed between controls and participants with amblyopia.

We selected a number of white matter pathways, that connect visual areas known to be affected by amblyopia (LGN, V1 & hMT+). The first pathway of interest was the optic radiation, a

* Corresponding author at: Department of Psychology, University of Wisconsin-Madison, 1202 W Johnson St., Madison, WI 53706, United States. Fax: +1 (608) 262 4029.
E-mail address: rokers@wisc.edu (B. Rokers).
[1] These authors contributed equally to this work and share senior authorship.

http://dx.doi.org/10.1016/j.visres.2014.12.021
0042-6989/

primary thalamo-cortical pathway projecting from the lateral geniculate nucleus to the primary visual cortex. Functional (Hess et al., 2009, 2010; Levi & Harwerth, 1978; Lv et al., 2008; Miki et al., 2003; Mizoguchi et al., 2005) and structural (von Noorden, Crawford, & Levacy, 1983; Movson et al., 1987; Barnes et al., 2010; Chan et al., 2004; Lv et al., 2008; Mendola et al., 2005) abnormalities have been reported in the LGN and V1 in adults with amblyopia. From V1, we focused on the dorsal white matter projection to area hMT+. This area has a well-established role in the integration of motion information, and is sensitive to binocular disparity (Born & Bradley, 2005; Felleman & Van Essen, 1991; Lewis & Van Essen, 2000; Zeki et al., 1991), functions that are affected by amblyopia (Li et al., 2011; McKee, Levi, & Movshon, 2003; Simmers et al., 2003). Furthermore, functional abnormalities of MT/hMT+ have been reported in both human and non-human primates with amblyopia (Bonhomme et al., 2006; Ho & Giaschi, 2009; El-Shamayleh et al., 2010; Secen et al., 2011; Thompson et al., 2012).

The cortical pathway from V1 to hMT+ is central to conscious perception of visual motion (Cowey, 2010; Rodman, Gross, & Albright, 1989; Schoenfeld, Heinze, & Woldorff, 2002). However, temporary (or even permanent) disruption of V1 activity does not abolish the direction-specific responses to motion in area hMT+ (Cowey, 2010; Cowey & Stoerig, 1991; Zeki & Ffytche, 1998) or MT-MST in macaques (Rodman, Gross, & Albright, 1989, 1990). The fact that visual motion information can still be processed when V1 is lesioned indicates that area hMT+ must receive some input that does not relay through the primary visual cortex.

Indeed, subsequent human and non-human investigations have identified two additional direct thalamic projections to hMT+, which bypass V1 entirely. First, a "subcortical" pathway projects from predominantly koniocellular layers in LGN directly to hMT+ (Sincich et al., 2004). To date, the functional role of this pathway and its role in development and behavior in health and disease has not been determined. A second subcortical pathway connects area hMT+ and the inferior pulvinar nucleus (PLN). Activity in this subcortical visual pathway has been associated with the control of eye movements (Chalupa, Coyle, & Lindsley, 1976; Robinson & McClurkin, 1989), and motion perception (Berman & Wurtz, 2010; Berman & Wurtz, 2011; Casanova et al., 2001; Shipp, 2001). Work in humans suggests that this pathway mediates residual motion perception in blindsight (Cowey, 2010; Intriligator, Xie, & Barton, 2002; Lanyon et al., 2009; Leh et al., 2010; Poppel, Held, & Frost, 1973; Rodman, Gross, & Albright, 1989, 1990; Stoerig & Cowey, 1997), and may underlie Riddoch's phenomenon when conscious motion perception is spared (e.g., Zeki & Ffytche, 1998).

In addition to the thalamo-cortical pathways described above, we also investigated the interhemispheric pathways connecting the left and right hMT+ and V1. These pathways pass through the posterior aspect of the corpus callosum and have been linked to the processing of horizontal motion and anchoring percepts of bistable motion stimuli (Genç et al., 2011).

In the first part of our study, we used DWI and probabilistic tractography to identify the location and diffusion properties of these six early visual pathways in 10 normally sighted participants. By modifying standard techniques for analyzing DWI data, we were able to successfully identify previously difficult to isolate white matter tracts, including the optic radiations and the two subcortical projections to hMT+ that bypass V1 described above. The methodological improvements our protocol offers over traditional DWI tractography methods are considered in the discussion.

We then identified the same six pathways in 10 participants with strabismic, anisometropic or mixed amblyopia. We found significant increases in mean diffusivity within thalamic projections in patients with amblyopia relative to controls. In contrast, no differences were found in cortico-cortical pathways. These results suggest that amblyopia may affect the structural properties of early visual pathways originating in the thalamus.

2. Methods

2.1. Participants

2.1.1. Controls

Ten normally sighted individuals (6 males), aged between 26 and 66 years (mean = 37.3, SD = 13.8), participated as age-matched controls in the study. One participant (male, aged 66 years), whose data contained consistent outliers likely due to excessive head motion, was excluded from the analyses. The next oldest control participant was 65 years old. These participants had normal or corrected-to-normal vision and reported no history of visual disorders.

2.1.2. Participants with amblyopia

Ten individuals (6 males) with amblyopia, aged between 19 and 67 years (mean = 40.6, SD = 14.7), participated in the study. Three had strabismic amblyopia, five anisometropic amblyopia and two mixed amblyopia (both strabismus and anisometropia). Anisometropia was defined as a $\geqslant$1D spherical equivalent difference between the two eyes. Visual acuity was measured using an ETDRS chart viewed from 6 m and stereopsis was measured using the Randot Stereo test (see Table 1 for details). Informed consent was obtained in accordance to the requirements of the IRB review board committee of the University of Auckland. All work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

3. Magnetic resonance imaging

Scans were conducted with a Philips Achieva, 3-T magnetic resonance scanner at Trinity MRI, Auckland, New Zealand equipped with a Phillips 8 Channel head coil. The scanning session included a T1-weighted anatomical scan (2.7 ms TE; 5.8 ms TR; 8° flip angle, 1 mm^3 voxel size) followed by a diffusion-weighted scan (single-shot spin echo EPI, parallel imaging (55 slices)) with 32 measured diffusion directions. Diffusion scans were measured with transverse orientation; AP fold-over direction; TE: 72 ms; TR: 7.139 s; flip angle: 90°; isotropic 2.5 × 2.5 × 2.5 mm^3 resolution; FOV: LR 240 mm × AP 240 mm × FH 137.5 mm; acquisition matrix MxP: 96 × 94; reconstruction matrix 96 × 96; *B* value = 1000; total scan time: 4:02.9 min. We used partial k-space acquisition (SENSE = 2).

4. Data processing

Fig. 1 shows the steps involved in the preprocessing and analysis of the diffusion data.

4.1. Pre-processing & tensor fitting

First, the mean $b = 0$ was computed for the diffusion weighted images, followed by an eddy current correction (with resampling). The corrected DWI data was then aligned to the T1 image. In order to characterize the local properties of the white matter, tensors were fit using the "least-squares" tensor estimation (bootstrapped 500 times; Basser, Mattiello, & LeBihan, 1994). Diffusion imaging pre-processing was performed using vistasoft (Stanford University, Stanford, CA, github.com/vistalab/vistasoft/mrDiffusion). See Fig. 1 panel 1a for an axial view of a representative participant's diffusion weighted imaging data. Tractography visualizations in Fig. 2, panels 4 & 5 were generated with the Matlab Brain Anatomy (MBA)