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Increased cortical surface area and gyrification following long-term survival from early monocular enucleation

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ABSTRACT

Purpose: Retinoblastoma is typically diagnosed before 5 years of age and is often treated by enucleation (surgical removal) of the cancerous eye. Here, we sought to characterize morphological changes of the cortex following long-term survival from early monocular enucleation.
Methods: Nine adults with early right-eye enucleation (≤48 months of age) due to retinoblastoma were compared to 18 binocularly intact controls. Surface area, cortical thickness, and gyrification estimates were obtained from T_1 weighted images and group differences were examined.
Results: Early monocular enucleation was associated with increased surface area and/or gyrification in visual (i.e., V1, inferior temporal), auditory (i.e., supramarginal), and multisensory (i.e., superior temporal, inferior parietal, superior parietal) cortices compared with controls. Visual cortex increases were restricted to the right hemisphere contralateral to the remaining eye, consistent with previous subcortical data showing asymmetrical lateral geniculate nucleus volume following early monocular enucleation.
Conclusions: Altered morphological development of visual, auditory, and multisensory regions occurs subsequent to long-time survival from early eye loss.

1. Introduction

Although some morphological and physiological aspects of the visual system are established prenatally, this system is far from mature and continues to develop into adolescence (e.g., Garey and de Courten, 1983; Huttenlocher and De Courten, 1987; for review see Daw, 2006). Studies on animals with postnatal monocular deprivation from lid suture and humans with congenital cataracts or strabismus show adverse effects during postnatal development on visual behaviour (e.g., Wiesel and Hubel, 1965; Ellemberg et al., 2000). Monocular deprivation from strabismus and anisometropia also leads to changes in the morphology of the human visual system, including reductions in grey matter concentration in lateral geniculate nuclei (LGN) (Barnes et al., 2010) and grey matter volume in visual cortex (Mendola et al., 2005). These findings suggest that it is imperative for the developing visual system to receive balanced binocular input for typical postnatal maturation. Although these forms of deprivation provide an excellent model for studying monocular deprivation, the brain nonetheless receives anomalous visual input from the deprived eye.

Here, we investigated morphological development of the cortex in adults who have experienced a more complete form of early monocular deprivation, surgical removal of one eye (monocular enucleation), due to retinoblastoma (cancer of the retina). Although retinoblastoma is rare, it accounts for 6% of all childhood cancers and generally occurs before 5 years of age (Broaddus et al., 2009a, b). Unilateral retinoblastoma has a high survival rate, and eye enucleation is the most frequent and effective treatment due to the aggressive nature of the tumour. Monocular enucleation at such a young age is likely to alter visual system development since half of the visual inputs are deafferented at a time when the brain is not fully mature.

Behavioural studies show that early-enucleated adults exhibit impairments in motion perception including motion-defined letter recognition and speed discrimination, and different patterns of oculomotor function compared to binocularly intact controls (Reed et al., 1991; Steeves et al., 2002; Kelly et al., 2013b). These data indicate a critical period for receiving balanced binocular input for the development of these visual abilities. However, unlike other forms of monocular deprivation such as strabismus or amblyopia, spatial form visual abilities such as contrast sensitivity/discrimination and global shape discrimination remains intact or is enhanced following early monocular enucleation (Nicholas et al., 1996; Steeves et al., 2004; Kelly et al., 2013b). Intact/enhanced spatial form vision suggests that altered development occurs in

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visual cortex in response to the loss of one eye early in life (reviewed in Kelly et al., 2013a; Steeves et al., 2008).

While behavioural visual development is well-documented following early eye enucleation, less is understood regarding the long-term consequences on the morphological development of the visual system in adult humans. Subcortically, non-primate models of enucleation show increased crossed retinal projections from the remaining eye in mice and rabbits (Grigonis et al., 1986; Godement et al., 1987), and rabbits exhibit a 50% reduction in volume of the deafferented LGN (Grigonis et al., 1986). Cortically, early eye-enucleated mice display an expansion and accelerated refinement of retinotopic primary visual cortex (V1) (Faguet et al., 2009), as well as decreased neuronal density and metabolic activity in visual cortex contralateral to the enucleated eye (Heumann and Rabinowicz, 1982; Chow et al., 2011). In monkeys, postnatal monocular enucleation is associated with cell degeneration, and a reduction in or lack of LGN layers and ocular dominance columns in V1 associated with the enucleated eye (Rakic, 1981; Sloper et al., 1987; Horton and Hocking, 1998).

Limited research has been conducted on the effects of eye enucleation on the morphology of the human visual system. The majority of these studies consist of post-mortem brains of adults who lost an eye during adulthood when the critical period for development has long been surpassed (Beatty et al., 1982; Horton, 1997; Adams et al., 2007). A handful of studies have assessed early enucleation in children and found results similar to monkey models of enucleation (Rakic, 1981; Sloper et al., 1987; Horton and Hocking, 1998); yet, these studies were conducted post-mortem on children whose visual system had not yet reached maturity. For example, one study showed that enucleation at 6 years of age resulted in degenerated LGN layers (Hickey and Guillery, 1979). Another study found a lack of ocular dominance columns in two children enucleated in infancy due to retinoblastoma (Horton & Hocking, 1998). One child had tumors in the remaining eye, resulting in decreased acuity, and both children died from brain tumors that may have affected cortical development independent of the enucleated eye. Physiologically, children who have been enucleated early in life have stronger functional activity in V1 contralateral to the remaining eye (Barb et al., 2011). These data suggest that the lack of binocular competition for space within visual cortex alters the development of primary visual cortex.

Previous studies of enucleation fail to address whether the changes observed in childhood persist throughout adulthood, or whether the visual system continues to change past the age of maturity. To answer this question, we have previously conducted a study assessing subcortical development following early monocular enucleation in adults (Kelly et al., 2014a). Using structural magnetic resonance imaging (MRI), we examined optic nerve and optic tract widths, and optic chiasm and LGN volumes. We found that the early enucleation group exhibited general decreases in the structures observed compared with binocularly intact controls. A surprising finding, however, was that decreases in optic tract width and LGN volume were less severe contralateral to the remaining eye. This asymmetry points to a relative sparing of geniculate cells contralateral to the remaining eye, which may be attributed to recruitment of deafferented cells by crossing retinal fibres and/or feedback from ipsilateral V1 with early eye enucleation. This notion is supported by rabbit and monkey models of enucleation showing that aberrant connections are formed between the remaining intact eye and deafferented geniculate cells (Rakic, 1981; Grigonis et al., 1986).

The goal of the present study was to expand on the subcortical data found in our laboratory and to determine how the visual cortex develops morphologically following long-term survival from early eye enucleation. We used structural MRI to assess surface area, thickness, and gyrification of the cortical grey matter in a group of individuals who experienced early monocular enucleation due to retinoblastoma and compared their results to binocularly intact controls. These morphological measures have been previously used to assess developmental disorders affecting vision, such as congenital anophthalmia (Bridge et al., 2009) and congenital blindness (Jiang et al., 2009; Park et al., 2009). We conducted: 1) whole brain analyses to examine regional differences across the entire cortical surface, 2) region-of-interest (ROI) analyses to examine differences in early visual regions known to process spatial form vision (V1, V2) (e.g., Hubel and Livingstone, 1987; Tootell et al., 1988), and 3) correlations with age at enucleation to examine the effect of timing of deprivation on these measures. Since cortical changes have been observed in non-primate and non-human primate models of early enucleation, and in human studies examining other forms of early visual deprivation (i.e., strabismus, amblyopia), we expect to observe altered morphological development of the visual cortex in the adult human brain following long-term survival from early monocular enucleation. In particular, we predict that enucleation will be associated with morphological changes in early visual areas V1 and V2. We also expect to observe hemisphere asymmetries in early visual cortices, similar to the contralateral biases found for LGN volume (Kelly et al., 2014a) and cortical activity in V1 of early-enucleated children (Barb et al., 2011). Findings from this study will help elucidate the effects of early monocular enucleation on long-term, morphological visual development, and will provide insight into the requirements for typical visual system maturation.

2. Methods

2.1. Participants

2.1.1. Early monocular enucleation (ME) group

We tested a rare group of 9 adults (5 males) who were former patients at The Hospital for Sick Children in Toronto, and had their right eye enucleated early in life due to retinoblastoma. Mean age (±SD) was 26 ± 14 years (range = 17–54 years) and mean age at enucleation (AAE) (±SD) was 20 ± 13 months (range = 4–48 months). Based on the size and position of the tumour under retinal examination, it is estimated that the average tumour would have disrupted vision approximately 6 months prior to enucleation. All participants had normal or corrected-to-normal acuity as assessed by an EDTRS eye chart (Precision Vision™, La Salle, IL). Patients are regularly seen by their ophthalmologist, and no known neurological or ocular abnormalities in the remaining eye were reported (Table 1 lists individual patient histories). Based on our previous study showing an LGN asymmetry in early enucleation (Kelly et al., 2014a), and the fact that we were unable to recruit a sufficient number of left-eye enucleated participants due to the rarity of these patients, we restricted our analyses to right eye-enucleated participants only.

2.1.2. Control group

Eighteen binocularly intact controls (10 males) were tested who were approximately age- and sex-matched to the early ME group. Mean age (±SD) was 28 ± 12 years (range = 18–57 years). Participants had normal or corrected-to-normal acuity (Precision Vision™,

Table 1
Patient histories for ME participants including age, sex, Snellen acuity, enucleated eye, and age at enucleation (AAE).

Patient	Age (years)	Sex	Acuity	Enucleated Eye	AAE (months)
ME01	54	Male	20/16 − 1	Right	24
ME02	43	Female	20/12.5 + 2	Right	18
ME03	21	Male	20/20	Right	23
ME04	18	Female	20/20	Right	48
ME05	18	Male	20/20 + 4	Right	13
ME06	17	Male	20/20 + 2	Right	9
ME07	28	Male	20/16	Right	4
ME08	18	Female	20/16 + 3	Right	17
ME09	17	Female	20/12.5 + 1	Right	26