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Strain differences of the effect of enucleation and anophthalmia on the size and growth of sensory cortices in mice

Ian O. Massé[a], *Sonia Guillemette*[a], *Marie-Eve Laramée*[a,1], *Gilles Bronchti*[a], *Denis Boire*[a,b,*]

[a]*Département d'anatomie, Université du Québec à Trois-Rivières, Québec, Canada G9A 5H7*
[b]*École d'optométrie, Université de Montréal, Québec, Canada H3C 3J7*

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ABSTRACT

Anophthalmia is a condition in which the eye does not develop from the early embryonic period. Early blindness induces cross-modal plastic modifications in the brain such as auditory and haptic activations of the visual cortex and also leads to a greater solicitation of the somatosensory and auditory cortices. The visual cortex is activated by auditory stimuli in anophthalmic mice and activity is known to alter the growth pattern of the cerebral cortex. The size of the primary visual, auditory and somatosensory cortices and of the corresponding specific sensory thalamic nuclei were measured in intact and enucleated C57Bl/6J mice and in ZRDCT anophthalmic mice (ZRDCT/An) to evaluate the contribution of cross-modal activity on the growth of the cerebral cortex. In addition, the size of these structures were compared in intact, enucleated and anophthalmic fourth generation backcrossed hybrid C57Bl/6J × ZRDCT/An mice to parse out the effects of mouse strains and of the different visual deprivations. The visual cortex was smaller in the anophthalmic ZRDCT/An than in the intact and enucleated C57Bl/6J mice. Also the auditory cortex was larger and the somatosensory cortex smaller in the ZRDCT/An than in the intact and enucleated C57Bl/6J mice. The size differences of sensory cortices between the enucleated and anophthalmic mice were no longer present in the hybrid mice, showing specific genetic differences between C57Bl/6J and ZRDCT mice. The post natal size increase of the visual cortex was less in the enucleated than in the anophthalmic and intact hybrid mice. This suggests differences in the activity of the visual cortex between enucleated and anophthalmic mice and that early in-utero spontaneous neural activity in the visual system contributes to the shaping of functional properties of cortical networks.

*Correspondence to: Département d'anatomie Université du Québec à Trois-Rivières, 3351, boulevard des Forges, C.P. 500 Trois-Rivières, Québec, Canada G9A 5H7. Fax: +1 819 376 5084.
E-mail addresses: ian.masse@uqtr.ca (I.O. Massé), sonia.guillemette@uqtr.ca (S. Guillemette), marieeve.laramee@bio.kuleuven.be (M.-E. Laramée), gilles.bronchti@uqtr.ca (G. Bronchti), denis.boire@uqtr.ca (D. Boire).
[1]Present address: Department of Biology, KU Leuven, Belgium.

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1. Introduction

Anophthalmia is a condition in which the eyes fail to develop from early embryonic stages. The incidence of anophthalmia in the general population has been estimated at 1.8 in 100,000 (Shaw et al., 2005). Little is known about the neurobiological consequences of anophthalmia in humans (Bock et al., 2013; Bridge et al., 2009; Watkins et al., 2012). A reduced optic tract and lateral geniculate nucleus, no size reduction of the optic radiation and only a slight reduction of the gray matter volume in a small area of the primary visual cortex were reported in a sample of anophthalmic humans (Bridge et al., 2009). Because activity plays an important role in brain growth, the preserved structure and connectivity of the occipital cortex of anophthalmic subjects has been explained by possible cross-modal rewiring of the visual cortex (Bridge et al., 2009).

There are two aspects of cross-modal interactions to be considered; firstly, the cross-modal activation in the visual cortex and secondly, the altered development and physiology of the non-deprived sensory pathways following the loss of one sensory channel. For example, in early blind subjects (loss of sight from multiple peripheral causes; in most subjects ˂age of 2 years), the white matter associated with the somatosensory cortex is increased (Noppeney et al., 2005). There are also reports of an expanded representation of the Braille reading fingers in the somatosensory cortex (Pascual-Leone and Torres, 1993; Sterr et al., 1998) and expanded auditory cortex (Elbert et al., 2002). Such intermodal interactions have not been observed in anophthalmic subjects (Bridge et al., 2009). However, there are several examples of such interactions in animal models of early blindness. Neonatal enucleation in mice causes an enlargement (Bronchti et al., 1992; Rauschecker et al., 1992; Zheng and Purves, 1995) and increased blood vessel density (Zheng and Purves, 1995) of the cortical barrel field and enlargement of the auditory cortex (Gyllensten et al., 1966). Early enucleated rats perform better than intact animals in navigation tasks and have altered electrophysiological responses of the somatosensory cortex (Toldi et al., 1994a).

During normal development, regional differences in electrical activity and metabolism are correlated with regional differences in cortical growth (Riddle et al., 1993; Zheng and Purves, 1995). Cross-modal activations of sensory cortices following various regimens of early visual deprivations would provide abnormal activity levels and patterns that could contribute to altered growth patterns of sensory cortices.

To test whether prenatal activity levels contribute to the subsequent development of the visual cortex, the size and postnatal size increase of primary sensory areas were studied in congenital anophthalmic, neonatally enucleated and intact mice.

In mice enucleated at birth there is a brief prenatal exposure of cortical subplate neurons to afferent spontaneous retinal activity that is not present in anophthalmic mice. In the mouse, thalamic projections reach the subplate on E14 (Auladell et al., 2000; del Rio et al., 2000; Deng and Elberger, 2001) where they establish synaptic contacts on E15 (del Rio et al., 2000). Furthermore, waves of spontaneous retinal activity are present as early as E17 in rats (Galli and Maffei, 1988), which correspond to E15 in mice (Clancy et al., 2001). Therefore, patterned spontaneous activity generated at the retina can be transmitted to the lateral geniculate and to the cortical subplate to influence further cortical development prior to the day of birth. However, as geniculate axons only reach cortical layer IV on PND2 (21 days post-conception) (Clancy et al., 2001) in mice, spontaneous retinal activity never reaches the cortical plate layer IV throughout the prenatal period.

Anophthalmic mice of the ZRDCT strain (ZRDCT Rax^{ey1}/ChUmdJ) (named here ZRDCT/An for conciseness) (Chase, 1942, 1944, 1945; Harch et al., 1978; Tucker et al., 2001) were used in several studies of the neurobiological consequences of visual deprivations. Their visual cortex is altered in several ways. There is a decreased density of spines on layer V neurons of the primary visual cortex (V1) (Kaiserman-Abramof, 1979). The callosal projections of V1 and the surrounding extrastriate cortices are more severely altered in anophthalmic mice compared to early enucleated mice (Olavarria and van Sluyters, 1984; Rhoades et al., 1984). The thalamocortical projections from the lateral geniculate nucleus appear quite normal, although V1 of ZRDCT/An mice also receives extrageniculate projections from the lateral posterior and laterodorsal thalamic nuclei (Godement et al., 1979; Kaiserman-Abramof et al., 1980). Conversely, the subcortical projections to the superior colliculus appear quite normal (Rhoades et al., 1985). There is also evidence for cross-modal plasticity in that the visual cortex is activated by auditory stimuli in ZRDCT/An mice (Chabot et al., 2007). This auditory activity could originate from a projection from the inferior colliculus to the lateral geniculate nucleus (Chabot et al., 2008) and from direct cortical connections between the auditory and visual cortex (Charbonneau et al., 2012).

In most studies, ZRDCT/An mice are compared to enucleated or intact mice of other strains, often C57Bl/6J. Therefore differences between experimental groups might result from strain differences rather than exclusively from the absence of afferent activity. In order to parse out the strain differences in the consequences of early enucleation and anophthalmia, the size of the primary, visual, auditory and somatosensory cortices as well as the volume of their respective specific thalamic relays were measured and compared between intact, enucleated C57Bl/6J mice and anophthalmic ZRDCT/An mice. In addition, the size and growth of these sensory cortices were compared between intact, enucleated and anophthalmic fourth generation hybrid mice resulting from backcrossing heterozygous hybrid mice with normal eyes and ZRDCT/An mice. The volume of the whole neocortex was also measured in these mice to see whether size differences between sensory cortices are the result of a general effect on the cortex, or specific to each sensory modality.

2. Results

The effect of early loss of vision on the development of sensory cortices and their related thalamic nuclei was evaluated by comparing their size in anophthalmic, enucleated and sighted adult mice. In order to parse the effects of anophthalmia and early enucleation, the size of these structures was compared in intact, enucleated and anophthalmic fourth generation hybrid