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Binocular eyelid closure promotes anatomical but not behavioral recovery from monocular deprivation

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A B S T R A C T

Deprivation of patterned vision of frontal eyed mammals early in postnatal life alters structural and functional attributes of neurones in the central visual pathways, and can produce severe impairments of the vision of the deprived eye that resemble the visual loss observed in human amblyopia. A traditional approach to treatment of amblyopia has been the occlusion of the stronger fellow eye in order to force use of the weaker eye and thereby strengthen its connections in the visual cortex. Although this monocular treatment strategy can be effective at promoting recovery of visual acuity of the amblyopic eye, such binocular visual functions as stereoscopic vision often remain impaired due in part to the lack of concordant vision during the period of unilateral occlusion. The recent development of binocular approaches for treatment of amblyopia that improve the possibility for binocular interaction have achieved success in promoting visual recovery. The full and rapid recovery of visual acuity observed in amblyopic kittens placed in complete darkness is an example of a binocular treatment whose success may in part derive from a restored balance of visually-driven neural activity. In the current study we examined as an alternative to dark rearing the efficacy of binocular lid suture (BLS) to stimulate anatomical and visual recovery from a preceding amblyogenic period of monocular deprivation. In the dorsal lateral geniculate nucleus (dLGN) of monocularly deprived kittens, darkness or BLS for 10 days produced a complete recovery of neurone soma size within initially deprived layers. The growth of neurone somata within initially deprived dLGN layers after darkness or BLS was accompanied by an increase in neurotrophin-4/5 labeling within these layers. Although anatomical recovery was observed in both recovery conditions, BLS failed to promote any improvement of the visual acuity of the deprived eye no matter whether it followed immediately or was delayed with respect to the prior period of monocular deprivation. Notwithstanding the lack of visual recovery with BLS, all animals in the BLS condition that were subsequently placed in darkness exhibited a substantial recovery of visual acuity in the amblyopic eye. We conclude that the balanced binocular visual input provided by BLS does not stimulate the collection of neural events necessary to support recovery from amblyopia. The complete absence of visually-driven activity that occurs with dark rearing evidently plays an important role in the recovery process.

1. Introduction

There is growing awareness of the beneficial outcomes associated with binocular approaches to treatment of amblyopia, a visual impairment that develops from unequal visual experience between the two eyes early in postnatal life (Birch, 2013; Hess, Thompson, & Baker, 2014; Mitchell & Duffy, 2014). The success of binocular-based amblyopia treatments may be rooted in the visual system's inherent preference during postnatal development for concordant binocular input (Mitchell, Kennie, & Duffy, 2011). Disruption of normal binocular input in mammals by such extreme manipulations as monocular deprivation early in development has profound negative consequences for the structure and function of neurones as early in the visual pathway as the thalamus. In the dLGN of monocularly deprived kittens, the somata of neurones that receive their exclusive ocular input from the deprived eye are smaller relative to their counterparts that receive innervation from the non-deprived eye (Wiesel & Hubel, 1963a). The geniculocortical afferents from the deprived eye have less complex axon terminal fields (Antonini & Stryker, 1993), and the dendrites of deprived neurones can be rendered thin and tortuous (Friedlander, Stanford, & Sherman, 1982). Electrophysiological recordings from single neurones in primary visual cortex of monocularly deprived kittens

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reveal significant and rapid alterations that include a shift in ocular dominance that substantially reduces the number of neurones that can be excited by monocular stimulation of the deprived eye, and which leaves a virtual absence of binocularly responsive cells (Freeman & Olson, 1979; Wiesel & Hubel, 1963b). Although methods that employ binocular visual stimulation reveal residual influences from the deprived eye, the responses are grossly abnormal in both monocularly deprived cats (Freeman & Ohzawa, 1988) and monkeys (Smith et al., 1997). In kittens, severe impairment of the vision of the deprived eye is also readily apparent (Dews & Wiesel, 1970; Giffin & Mitchell, 1978), and presumably originates from the deprivation-induced changes to neuron structure and function at various levels in the visual pathway.

Some anatomical, physiological, and behavioral recovery from the effects of monocular deprivation in kittens can occur provided that early in development the deprivation is relieved to either restore normal visual input to both eyes, or if there is a reversal of the initial deprivation (reverse occlusion) so that at the time visual input is restored to the deprived eye, the fellow eye is occluded (Blakemore & Van Sluyters, 1974; Olson & Freeman, 1978; Mitchell, Cynader, & Movshon, 1977). Greater eventual recovery of the visual acuity of the initially deprived eye is observed when the deprivation is reversed than when the deprived eye is simply opened to provide binocular visual input (Mitchell, Cynader, & Movshon, 1977; Mitchell, 1988); however, recovery in both conditions is rather slow, and neither condition promotes the restoration of normal binocular interaction (Mitchell, Cynader, & Movshon, 1977; Olson & Freeman, 1978). Interestingly in monkeys, restoration of simultaneous visual input to both eyes subsequent to monocular deprivation (binocular recovery) is not sufficient to promote physiological recovery in the primary visual cortex, while forced usage of the deprived eye through reverse occlusion yields similar physiological recovery in the visual cortex to that observed in kittens but likewise precludes development of normal binocularity (Blakemore, Garey, & Vital-Durrand, 1978; Blakemore, Vital-Durand, & Garey, 1981). The benefits of treatments for amblyopia that improve the visual acuity of the amblyopic eye by means of procedures that encourage binocular interactions have recently been reviewed in relation to the results of conventional methods of treatment that in many but not all cases involve periods of penalization of the visual input to the fellow eye (Birch, 2013; Hess et al., 2014; Mitchell & Duffy, 2014). Among these potential treatments for amblyopia is the use of periods of complete darkness, which has been shown to promote recovery of visual acuity in adult rats and kittens (Duffy & Mitchell, 2013; He, Ray, Dennis, & Quinlan, 2007). In kittens monocularly deprived for seven days, the soma size of deprived dLGN neurones recovers in complete darkness to the extent that following 8 days in darkness deprived neurones grew to match the size of non-deprived counterparts (O'Leary, Kutcher, Mitchell, & Duffy, 2012). Kittens that had developed a significant and stable amblyopia from a week of monocular deprivation showed rapid and complete recovery of visual acuity in the deprived eye following 10 days spent in complete darkness (Duffy & Mitchell, 2013). The remarkable visual recovery precipitated in amblyopic kittens following immersion in darkness raises the intriguing possibility that this approach could be translated to treatment of human amblyopia. The practical and infrastructural demands of implementation of darkness as a treatment for human amblyopia has led us to examine in kittens the potential of alternative treatment regimes that are also based on the maintenance of binocular visual balance. In the current study we examined the efficacy of binocular eyelid closure to mimic translucent binocular bandaging as a more practical alternative to immersion in complete darkness.

The use of binocular deprivation by either dark rearing or binocular lid closure has enriched our understanding of the contribution of early visual experience to the development of the visual system (Daw, 2006; Mitchell & Timney, 1984). However, it is important to recognize that the consequences of these two forms of binocular deprivation on neural development are not equal (Blais et al., 2008; Mower, Berry, Burchfiel, & Duffy, 1981), and the differences derive from the kind of visual deprivation that each provides. Whereas darkness results in the complete deprivation of all visual stimulation, binocular eyelid suture allows transmission of some light (Crawford & Marc, 1976) and low spatial frequency form information that can both support brightness discrimination as well as permit cortical neurones to respond to the diffuse light that passes through the eyelids with visual stimulation (Loop & Sherman, 1977; Spear, Tong, & Langsetmo, 1978). Because binocular eyelid suture results in an equally degraded signal for each eye (Blais et al., 2008), it could be argued that both deprivation conditions provide balanced geniculocortical activity from the two eyes through either balanced impoverished visual stimulation (for binocular eyelid closure), or the complete lack of any visually-driven neural activity (for dark rearing). Here we present results in which the effectiveness of binocular eyelid suture is examined as an alternative recovery strategy to darkness for deprivation amblyopia in kittens. Our data indicate that while binocular lid suture and dark rearing both promote recovery of dLGN soma size in monocularly deprived kittens, only complete elimination of visual experience by dark rearing produces a recovery of the visual acuity of the amblyopic eye.

2. Methods

2.1. Animals and conditions

Anatomical and behavioral experiments were conducted on 24 male and female kittens that were born and raised in a closed laboratory colony at Dalhousie University. All experiments followed protocols approved by the University Committee on Laboratory Animals in accordance with policies established by the Canadian Council on Animal Care, which were in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Anatomical studies were performed on 16 animals separated into four groups: normal kittens raised to postnatal day (PND) 37–40 ($n = 4$); kittens monocularly deprived for 7 days at PND 30 ($n = 4$); kittens monocularly deprived at PND 30 for 7 days that were then placed in complete darkness for 10 days ($n = 4$); and kittens monocularly deprived at PND 30 for 7 days that then received BLS for 10 days ($n = 4$).

Behavioral experiments were conducted on 8 kittens that were monocularly deprived by eyelid suture for 7 days at about PND 30 (29–31), the peak of the critical period for ocular dominance plasticity (Olson & Freeman, 1980). The 8 animals were divided into two groups of 4 that differed in the age at which BLS occurred with respect to the prior period of monocular deprivation (MD). For the 4 kittens in the Immediate BLS (IBLS) Group, the two periods of deprivation were contiguous while for the other, the Delayed BLS (DBLS) Group, the period of BLS occurred 8 weeks after the period of MD. For animals in the IBLS group, the eyelids of the non-deprived eye were sutured closed at the end of the period of MD for 10 days at which time the eyelids of both eyes were opened to allow simultaneous vision during which time longitudinal measurements of the visual acuity of each eye were made to document the extent of visual recovery. By contrast, for animals assigned to the DBLS group, eyelids of the deprived eye were opened after the period of MD to allow for an 8-week period of simultaneous binocular exposure. Longitudinal measurements of the visual acuity of each eye were measured throughout this period so as to doc-