Vision Research 114 (2015) 79–86

Contents lists available at ScienceDirect

Vision Research

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

A new model of strabismic amblyopia: Loss of spatial acuity due to increased temporal dispersion of geniculate X-cell afferents on to cortical neurons

D.P. Crewther [a,c,*], S.G. Crewther [b,c]

[a] Centre for Human Psychopharmacology, Swinburne University, Hawthorn, Australia
[b] School of Psychological Science, La Trobe University, Bundoora, Australia
[c] School of Optometry, University of New South Wales, Kensington, Australia

ARTICLE INFO

Article history:
Received 29 September 2014
Received in revised form 5 April 2015
Available online 20 April 2015

Keywords:
Lateral geniculate
Lagged cell
Strabismus
Amblyopia
Temporal dispersion

ABSTRACT

Although the neural locus of strabismic amblyopia has been shown to lie at the first site of binocular integration, first in cat and then in primate, an adequate mechanism is still lacking. Here we hypothesise that increased temporal dispersion of LGN X-cell afferents driven by the deviating eye onto single cortical neurons may provide a neural mechanism for strabismic amblyopia. This idea was investigated via single cell extracellular recordings of 93 X and 50 Y type LGN neurons from strabismic and normal cats. Both X and Y neurons driven by the non-deviating eye showed shorter latencies than those driven by either the strabismic or normal eyes. Also the mean latency difference between X and Y neurons was much greater for the strabismic cells compared with the other two groups. The incidence of lagged X-cells driven by the deviating eye of the strabismic cats was higher than that of LGN X-cells from normal animals. Remarkably, none of the cells recorded from the laminae driven by the non-deviating eye were of the lagged class. A simple computational model was constructed in which a mixture of lagged and non-lagged afferents converge on to single cortical neurons. Model cut-off spatial frequencies to a moving grating stimulus were sensitive to the temporal dispersion of the geniculate afferents. Thus strabismic amblyopia could be viewed as a lack of developmental tuning of geniculate lags for neurons driven by the amblyopic eye. Monocular control of fixation by the non-deviating eye is associated with reduced incidence of lagged neurons, suggesting that in normal vision, lagged neurons might play a role in maintaining binocular connections for cortical neurons.

1. Introduction

Strabismic amblyopia, a loss a visual acuity associated with a deviating or "turned" eye, currently has no well-accepted neural mechanism. This is despite knowledge of amblyopia since the 9th century (Von Noorden, 1996), with George-Louis Leclerc, Conte de Buffon, credited in the 18th C with proposing the forced penalization of the eye with good acuity to treat the loss of acuity in the amblyopic eye. Animal models of amblyopia, in both cat and monkey, have also been investigated for over 50 years in terms of mechanisms of neural plasticity and manipulations such as form deprivation (Blakemore & Eggers, 1978; Blakemore & Van Sluyters, 1974; Hubel & Wiesel, 1964, 1970). Such models have instantiated ideas of binocular competition and critical periods of plasticity into the literature. However, the loss of spatial acuity found for the deviating eye in strabismic amblyopia is not very well fit by the theories based on visual competition. Indeed, strabismus created in the early post-natal period of kittens by simple disinsertion (tenotomy) of the lateral rectus muscle (resulting in an esotropia) is characterized by:

(i) No loss of acuity in retinal ganglion cells (Cleland et al., 1982) nor in cells of the lateral geniculate nucleus (LGN) (Gillard-Crewther & Crewther, 1988), nor cellular shrinkage in LGN neurons driven by the strabismic amblyopic eye (Cleland et al., 1982);
(ii) A cortical ocular dominance distribution that is relatively well balanced between the non-deviating and amblyopic (deviating) eye with a reduction of binocularly driven neurons in primary visual cortex (Crewther & Crewther, 1990; Freeman & Tsumoto, 1983; Hubel & Wiesel, 1965);

* Corresponding author at: Centre for Human Psychopharmacology, Swinburne University, Hawthorn, VIC 3122, Australia.
E-mail address: dcrewther@swin.edu.au (D.P. Crewther).

http://dx.doi.org/10.1016/j.visres.2015.04.005
0042-6989/

(iii) An initial locus of primary visual cortex, (Crewther & Crewther, 1990), with an average acuity loss of one octave;
(iv) The small population of binocularly driven neurons in primary visual cortex in strabismic cat show different acuities through stimulation of the two eyes (Crewther & Crewther, 1990, 1993);
(v) Observation that the receptive field (RF) sizes of neurons driven through the amblyopic eye are not significantly larger than those through the non-amblyopic fellow eye (Crewther & Crewther, 1990; Freeman & Tsumoto, 1983).

The literature contains other models of strabismus in cat. For example, surgical myectomy of the muscle mass of the lateral rectus results in physiological amblyopia in both LGN (Ikeda & Wright, 1976) and retinal ganglion cells (Crewther, Crewther, & Cleland, 1985; Ikeda & Tremain, 1979) as well as LGN cell shrinkage (Tremain & Ikeda, 1982) in laminae driven by the strabismic eye. Another preparation involves suturing to hold the misalignment in place (essentially recession), however, it is not clear whether the procedure involves some paralysis with unintended consequences.

Also, optical misalignment produced in cat (Van Sluyters & Levitt, 1979, 1980) and monkey (Smith et al., 1997) results in loss of binocularity but without creation of an amblyopic state.

In primate, many of the findings in strabismic monkeys are similar (Kiorpes & Movshon, 1996; Sengpiel & Blakemore, 1996), once the obvious differences in primary visual cortex between cat and monkey in terms of neural type and binocularity differences have been taken into account. Human studies of amblyopia have begun to take advantage of modern neuroimaging techniques. These demonstrate that the progression from the amblyopic eye towards higher processing levels in cortex is associated with successive impairment of information quality (Muckli et al., 2006).

1.1. Theories of amblyopia

Leading theories of amblyopia have invoked properties such as suppression (Li et al., 2011), spatial jitter (Kozma & Kiorpes, 2003), undersampling or shifts in spatial scale (Levi, 1988) and impairment in global form (Hess et al., 1999) and global motion processing (Kiorpes, 2006; Simmers et al., 2003) to explain the loss of spatial acuity. In connectivity studies, activity of a small group of amblyopes (mixed strabismic, anisometropic and form deprived) showed generally less BOLD derived signal in both feedforward and feedback modes through the amblyopia eye compared with the fellow eye (Li et al., 2011). This promising technique needs to be repeated for a sample of strabismic amblyopes as animal models of form deprivation would suggest an underconnectivity of LGN with all afferent projections. Under-sampling (Levi, 1988) certainly is a valid theoretical cause of amblyopia and has high relevance to deprivation amblyopia and any amblyopias in which the ocular dominance of visual cortex is dominated by the non amblyopic eye. However, with respect to the cat model of strabismic amblyopia being implemented in this paper has to deal with normal LGN acuities (Gillard-Crewther & Crewther, 1988) as well as balanced cortical ocular dominance distributions (Crewther & Crewther, 1990). The impairment in global perceptual function (Hess et al., 1999; Kiorpes, 2006; Simmers et al., 2003) represents most likely the involvement of a feedback from higher cortical regions.

In addition, the interocular suppression that accompanies strabismic amblyopia, with input from the strabismic eye habitually suppressed by that from the non-deviating eye has been suggested as a source of lasting alterations in the neural representations derived from the strabismic eye. This could form a further basis for amblyopia (Sengpiel & Blakemore, 1996; Sengpiel et al., 1994), with the notion of rivalry between columns in striate cortex driven by the two eyes. It still requires a domination of fixation by one of the eyes, as do most theories of amblyopia. Such domination could depend on synchronization of responses that vary between strabismic and fellow eyes (Engel et al., 1990; Konig et al., 1993).

Recent technical advances in brain stimulation (Thompson et al., 2008) and in perceptual learning (Levi, 2012, Li et al., 2013) techniques have suggested that strabismic amblyopia may soon be addressed with novel treatments. However, despite the wide range of approaches with identification of primary visual cortex as the initial site of strabismic amblyopia (Crewther & Crewther, 1990; Hess, 1991) and with further embellishment of suppression in downstream processing (Kiorpes & McKee, 1999), there has been little advance in understanding why primary visual cortical neurons become amblyopic. Here we question whether the focus on spatial properties of neurons in trying to understand a spatial acuity deficit may have obscured investigation of a possible abnormality in the timing of geniculo-cortical signalling in amblyopia. Such temporal aspects of receptive field definition and the relative contribution of latency of firing to spatial properties of neurons have been developed to a sophisticated level (Cai, DeAngelis, & Freeman, 1997; DeAngelis, Ohzawa, & Freeman, 1993), but have not been applied to amblyopia models.

1.2. Lagged LGN cells

In the late 1980s, Mastronarde (1987b) described a bimodal distribution of latencies to half peak amplitudes of firing for cells of the lateral geniculate nucleus (LGN) in paralysed respired cat, suggesting a classification of cat lateral geniculate neuron receptive fields into 'lagged' and 'non-lagged' responses (Humphrey & Weller, 1988; Mastronarde, 1987a, 1987b). Humphrey and Weller (1988) further suggested that most LGN cells are approximately space–time separable and that the lagged and non-lagged cells represent the modes of a continuous and very broad distribution of temporal responses in the LGN. The function of this temporal dispersion of geniculo-cortical afferents contained in the lagged/non-lagged classification has not been established unequivocally. Saul and Humphrey (1992) suggested that temporal dispersion might be the basis of establishing the emergent property of direction selectivity in cortical cells, based on the finding that strobe-rearing of kittens virtually eliminated cortical receptive fields containing mixed lagged and non-lagged timing. While recent recordings in awake behaving monkey have generalised the phenomenon of the lagged/non-lagged division to primate (Saul, 2008b) studies of direction selective simple cells have challenged the direction selective rationale for lagged/non-lagged inputs (Peterson, Li, & Freeman, 2004). However, to date, the existence of a lagged/non-lagged classification of geniculate cells in human is moot.

The temporal response properties of lagged neurons are remarkable for the modifiability of visual latencies by non-visual inputs. Stimulation of the cholinergic input from the reticular formation (Cucchiaro, Uhlrich, & Sherman, 1988; Francesconi, Muller, & Singer, 1988; Hartveit & Heggelund, 1993) results in shortening of visual latencies, particularly in the lagged class of LGN neurons. These midbrain projections are thought to subserve arousal, and can dramatically modulate the time course of neural response between periods of low firing rate interjected with low-threshold burst firing and more conventional firing patterns (Lu et al., 1995). Indeed Uhlrich et al., called into question the existence of lagged neurons as a separate class, with differences in latency postulated to be due to differences in degree of mid-brain activation (Uhlrich, Tamamaki, & Sherman, 1990). However, direct stimulation studies in paralyzed cats demonstrate that the two classes remain separable, (Hartveit & Heggelund, 1992, 1993; Saul &