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SPECIAL COLLECTION

Amblyopia: Challenges and Opportunities
The Lasker/IRRF Initiative for Innovation in Vision Science

PERSPECTIVE

Cortical correlates of amblyopia

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Abstract

There are many levels of disorder in amblyopic vision, from basic acuity and contrast sensitivity loss to abnormal binocular vision and global perception of motion and form. Amblyopia treatment via patching to restore acuity often leaves other aspects of vision deficient. The source for these additional deficits is unclear. Neural correlates of poor binocular function and acuity loss are found in V1 and V2. However, they are generally not sufficient to account for behaviorally measured vision loss. This review summarizes the known cortical correlates of visual deficits found in association with amblyopia, particularly those relevant to binocular vision and higher-order visual processing, in striate and extrastriate cortex. Recommendations for future research address open questions on the role of suppression and oculomotor abnormalities in amblyopic vision, and underexplored mechanisms such as top-down influences on information transmission in the amblyopic brain.

Keywords: Striate cortex, Extrastriate cortex, Interocular suppression, Sensitive periods, Visual-motor integration

Introduction

In clinical cases of amblyopia, the common standard for diagnosis and treatment is the presence and severity of monocular acuity loss. Treatment of amblyopia is typically benchmarked by improvements in acuity, where a reduction in the interocular difference in acuity is the treatment goal. However, it is known that amblyopic individuals, even those who have been treated for acuity losses, often suffer a diversity of deficits related specifically to binocular and/or high order visual functions (Daw, 2014). These additional deficits are also present in animal models, particularly non-human primates (Kozma and Kiorpes, 2003). Investigation of cortical correlates of amblyopic vision in animal models has been focused mainly on primary rather than higher order visual cortex, although there have been a few studies of neural deficits beyond V1 (Bi, Zhang, Tao *et al.*, 2011; El-Shamayleh, Kiorpes, Kohn *et al.*, 2010; Shooner, Hallum, Kumbhani *et al.*, 2015; Tao, Zhang, Shen *et al.*, 2014). Here, we discuss what is known from both human studies and animal models of amblyopia regarding the cortical correlates of visual deficits found in association with amblyopia, particularly those relevant to binocular vision and high-order vision in striate and extrastriate cortex, and relevant associated visual behaviors. Here we focus mainly on anisometropic and strabismic amblyopia, rather than the more severe deprivation amblyopia, which is comparatively rare in humans.

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Binocular vision

While cortical responses to stimulation of an amblyopic eye are degraded, meaning that the range of spatial stimuli to which amblyopic eye neurons respond is often reduced, the severity of these monocular changes does not fully explain changes in the visual behavior (Shooner et al., 2015). Furthermore, binocular cortical responses are strongly reduced both in anisometropic and strabismic individuals with amblyopia (Smith et al., 1997; Kiorpes et al., 1998; Bi et al., 2011). Understanding the cortical correlates of the binocular combination of visual information is, therefore, essential in understanding the deficits associated with amblyopia.

Binocular vision—suppression

Even during normal binocular viewing, competition between inputs from the two eyes occurs at the cortical level. When the binocular inputs are discordant, there is a need to eliminate or adjust the signals so as to prevent diplopia or confusion. Depending on the degree of discordance, input from one eye can be suppressed (dichoptic masking) or the two retinal images will alternate (binocular rivalry) (Schor, 1977). It is unclear if these two processes are mechanistically distinct, particularly beyond the level of V1, but both are likely relevant for the range of retinal disparity seen in anisometropic and strabismic patients with amblyopia. In fact, the depth of suppression can vary depending on the type of amblyopia: weaker suppression is seen in anisometropic amblyopia (similar to dichoptic masking) compared to strabismic amblyopia (similar to

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rivalry suppression) (Harrad et al., 1996). Moreover, patients with strabismus lacking suppressive mechanisms frequently experience diplopia—this is particularly true when strabismus occurs later in adult life due to paralytic causes. Neural correlates of binocular suppression induced either by incongruities present in the retinal images in patients with amblyopia or created artificially in normal individuals have been found in LGN, V1, and V2 (Sengpiel et al., 1995; Sengpiel & Blakemore, 1996).

The anatomical substrate for silencing the retinal input from one eye in favor of another could be independent of amblyopia; however, in the case of amblyopia, suppression or rivalry may be invoked on a more sustained basis, potentially leading to a less reversible rewiring of normal circuitry. Since suppression is common across normal and amblyopic individuals when confronted with different images in the two eyes, we propose that suppression itself is not a circuit abnormality; rather, the stimulus leading to aberrant suppression should be corrected. This is consistent with treatments to correct either the anisometropia or eye misalignment in patients with amblyopia. An alternative hypothesis is that some pathological adaptation to the mismatched visual input must be overcome to fully correct abnormal cortical binocular interactions; in which case, the time course and extensiveness of correction could depend on age and plasticity of the brain. Therefore, the development of appropriate treatments will diverge depending on the cortical correlate of amblyopic suppression when compared to normal vision or across types of amblyopia.

Questions regarding the degree of suppression found across the visual field are particularly relevant to amblyopia. Suppression itself can vary dramatically depending on the stimulus used (Joosse et al., 1997, 2000), and suppressive mechanisms could vary depending on the degree or type of amblyopia. Because the size of receptive fields and the degree of acuity loss in amblyopia differ across the visual space, the mechanisms of suppression and the sensitivity to retinal disparities, and thus the suppressive response, could be very different depending on whether stimuli are foveal or peripheral (Sireteanu & Fronius, 1981, 1989). For example, many corrected patients with strabismus retain a small angle strabismus that could recruit high levels of local suppression, perhaps most dramatically in the fovea. Physiological recordings from animal models are typically biased away from the fovea due to the difficulty of recording foveal responses and the lack of a fovea in some animal models. Therefore, physiological data relevant to the implications of small foveal disparities are limited. Correlates of foveal suppression should be investigated further.

Many studies on binocular suppression have focused on neural correlates in V1; however, the extent to which downstream visual areas contribute to suppression either in normal or amblyopic vision is unclear. Strabismic amblyopic macaques are found to have increased binocular suppressive interactions in both V1 and V2; the V2 result may be established as a feedforward consequence or may be qualitatively different, but the degree of change is similar in the two areas (Bi et al., 2011). In general, it is unknown whether amblyopia represents a feedforward dominance of the fellow eye or the feedback selection of the dominant eye's input *via* a top-down attentional mechanism that originates in the extrastriate cortex. However, the representation of the amblyopic eye feeding forward is clearly compromised (Bi et al., 2011; Shooner et al., 2015) and likely contributes to abnormal binocular interactions. While the contribution of extrastriate areas to amblyopia is likely complex (discussed below), knowing the higher-order cortical correlates of rivalry or suppression and their time courses of development could be illuminating in understanding whether suppression of the amblyopic eye input is driven by low or high-level processing.

Binocular vision—stereopsis

One of the major benefits of correlated binocular input is stereoscopic depth perception, which is based on disparities between the locations of objects on the two retinae. Both absolute and relative disparities are important for depth perception, but the ability to code for relative disparity is essential for stereoacuity, which may be severely impaired in amblyopic individuals. While neural correlates of absolute disparity have been recorded in V1, relative disparity seems to be encoded elsewhere (Cumming & Parker, 1999; Parker & Cumming, 2001). V2, MT/V5, and V4 have all been shown to exhibit neural correlates of relative disparity and thereby stereoscopic depth perception (Thomas et al., 2002; Umeda et al., 2007; Krug & Parker, 2011). However, it has been suggested in humans that absolute disparity is encoded by the dorsal stream, while the ventral stream is the source of neural coding for relative disparity (Neri et al., 2004). While studies have been done on relative disparity tuning in V1 and V2 of strabismic monkeys (Mori et al., 2002; Nakatsuka et al., 2007), to date no recordings have been done in amblyopic primates performing relative depth tasks. This type of data could be central to understanding where in visual cortex stereoacuity deficits are most pronounced. Alternatively, because the loss and recovery of stereoacuity in human patients with amblyopia is not fully understood and may be different depending on the disparity range in question (Giaschi et al., 2013), locating a brain region of interest, especially in an animal model, could be clouded by insufficiencies in characterization of the deficits themselves. In addition, human anisometropic patients with amblyopia recover stereoacuity more readily than their strabismic counterparts (Astle et al., 2011; Ding & Levi, 2011; Wallace et al., 2011; Levi et al., 2015), so it is important to consider both populations in future studies. It could perhaps be more beneficial to study the recovery of stereoacuity in human patients with amblyopia using techniques such as high-density electroencephalography (EEG) (Cottereau et al., 2012) or functional MRI (fMRI) to obtain a more complete picture of the origin of the deficits and changes that take place during recovery.

An underexplored area of research in regard to the disruption of stereoacuity in patients with amblyopia involves the circuitry associated with vergence, which likely has both sensory and motor contributions. Because vergence is the scaffold for stereopsis, a loss in cortical binocular combination could result in a disconnect between sensory and motor circuits that serve fusion. Data from nonhuman primate models suggest that indeed there is a relative independence of sensory and motor fusion, but that stereo and vergence anomalies exist at both coarse and fine levels of disparity (Harwerth et al., 1997; Fredenburg & Harwerth, 2001). However, accommodative vergence is essentially normal in strabismus and amblyopia, despite disrupted disparity vergence, suggesting that some motor aspects of vergence remain functional (Kelly et al., 2016; Kenyon et al., 1980, 1981). It is an open question whether the loss of disparity vergence has differential importance for the recovery of fine or coarse stereoacuity, and whether it contributes differentially to coding disparities across retinotopic space in amblyopic individuals. Considerable work has been done in the past on the circuitry underlying vergence in animal models other than primates (Hughes, 1972; Stryker & Blakemore, 1972; Zuidam & Collewijn, 1979). However, it is unclear how relevant studies in mammals lacking a true fovea will be in understanding the circuitry behind and the deficits in vergence in amblyopic primates; more work is needed to draw a comparison across species. The interplay between motor and visual circuitry in amblyopia emphasizes the importance of

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studies beyond V1 and perhaps an emphasis on whole-brain mapping, which can be best achieved using high-resolution EEG and fMRI methods.

Extrastriate cortex

The majority of studies of neural loss in amblyopia have been directed at striate cortex, V1. Here, in addition to the reduced binocularity discussed above, neurons driven by the amblyopic eye show reduced acuity (Kiorpes et al., 1998) and contrast sensitivity (Movshon et al., 1987), but otherwise relatively normal receptive field properties. Studies of extrastriate areas are motivated by the findings that the losses in V1 sensitivity are not sufficient to explain the behaviorally measured deficits (Kiorpes et al., 1998; Shooner et al., 2015) and that patients and animal models show high-order functional vision deficits, including deficits in motion perception, which persist in some cases after "successful" treatment with patching (Lerner et al., 2003; Levi et al., 2007; Rislove et al., 2010; Grant & Moseley, 2011; Giaschi et al., 2015); see Hamm et al. (2014) for a recent review of higher-order deficits. The search for the correlates of these losses should avoid the simplistic notion of pairing a visual behavior with an anatomical brain region and instead focus on pinpointing the location of a breakdown in information transmission along a processing stream that is essential to a visual behavior.

Extrastriate cortex—additional deficits beyond V1

Neural recording beyond V1 in animal models, especially nonhuman primates, have found an amplification of losses seen in V1, as well as qualitatively different abnormalities. Amblyopic V2 shows abnormalities of the receptive field structure and orientation tuning that are not seen in V1 (Bi et al., 2011; Tao et al., 2014). Deficiencies at the level of V2 correlate strongly with those seen behaviorally in the same animals. Ocular dominance imbalance is amplified in V2 and MT/V5 compared with V1 (El-Shamayleh et al., 2010; Bi et al., 2011). Functional losses in motion sensitivity are reflected in population models of MT processing, although not consistently at the single unit level (El-Shamayleh et al., 2010). These and other recent studies (Shooner et al., 2015) highlight the need to understand the neural output at each stage, including interneuronal interactions and correlations, to fully appreciate the quality of the information feeding forward from the amblyopic eye. Functional imaging studies have also made important contributions toward understanding at what levels of the visual hierarchy correlates of functional losses might be found. For example, population receptive fields measured by fMRI can be analyzed for both their size and position to address questions regarding amblyopic losses in resolution or topological precision between visual areas (Clavagnier et al., 2015). These methods will contribute substantially to the understanding of neural deficits beyond V1 and how these deficits are fed forward or backward along processing streams.

Extrastriate cortex—hierarchical critical periods

Across sensory systems, both sensory behaviors and associated neural structures exhibit distinct periods of maturation, suggesting a differential level of plasticity across the brain during certain periods of life (Hensch, 2005). Symptoms of amblyopia are not fully explained by V1 deficits, suggesting that circuit abnormalities could be found outside of V1. One hypothesis is that a cascade of development, where downstream (extrastriate) areas do not mature until upstream input has matured (V1), would leave higher-level visual behaviors differentially vulnerable to amblyopia and to inadvertent treatment effects.

High-order deficits may persist in treated patients with amblyopia perhaps because treatment is focused on low-level functions, specifically monocular acuity. If extrastriate areas are actually more plastic than V1, due to longer or later critical periods, treatment focusing on V1 functionality could overly impact high-order visual behaviors. For example, patching an eye for long enough to effect a change in V1 could produce novel deprivation amblyopia in a higher-order cortical area. On the other hand, since the identified deficits in neuronal acuity at the level of V1 do not account fully for the behavioral losses or predict higher-order losses, treating acuity alone is unlikely to affect the degree of higher-order deficits. Again, it is important to understand the differential contribution of feedforward and feedback causality in amblyopia, as well as the nature of the developmental hierarchy, to determine which points in the cortical stream of information should be the focus of treatment for full recovery.

What is the best way to measure sequential cortical maturation? Functional MRI data have been helpful in understanding neural correlates of amblyopia, but these data represent a very coarse scale of analysis and are difficult to obtain in young children. Multiunit physiological recording across brain areas, ages, and behavioral tasks is technically quite challenging and has not been attempted. A useful technique for understanding brain maturation as well as changes related to amblyopia is high-density EEG (Cottereau et al., 2012), which can be implemented in a noninvasive and spatially broad way to track the development of many brain areas across age. EEG recording can also be made in other species, and in correlation with psychophysics, the results can be compared with direct neural measurements.

Open questions and recommendations

- The role of oculomotor abnormalities in the assessment of behaviorally measured visual losses remains an open question. Retinal image motion from unsteady fixation does not contribute significantly to poor contrast sensitivity of patients with amblyopia (Higgins et al., 1982), but it does appear that acuity losses can be explained to at least some degree by fixation instability (Chung et al., 2015). Furthermore, oculomotor deficits contribute to abnormalities and inaccuracies in visually guided reaching and other visuomotor behaviors (Grant & Moseley, 2011; Niechwiej-Szwedo et al., 2011, 2014), and these deficits are not accounted for by the reduced visual acuity of amblyopic eyes (Niechwiej-Szwedo et al., 2012; Niechwiej-Szwedo et al., 2016). It will be important for future studies to determine the role of oculomotor abnormalities in stereoscopic deficits and disparity vergence errors as well as losses in visual sensitivity.
- The disruption of neural mechanisms related to suppression and balanced ocular selection are not well understood. Many psychophysical studies have described these deficits, but little is known of the physiological bases. It will be important for future studies to combine awake physiological recordings with behavioral assays of these important binocular functions. In addition, temporal aspects of binocular interaction are

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understudied. Reports of longer latency for amblyopic eye signals to reach the cortex (Niechwiej-Szwedo et al., 2014; McKee et al., 2016) suggest that eye selection could favor the earliest arriving signals, triggering suppression of the amblyopic eye. Alternatively, eye selection could be influenced by top-down signals feeding back from downstream extrastriate areas or disrupted attentional mechanisms (Montero, 1999; Hou et al., 2016). However, some recent work shows intact attentional resources in patients with amblyopia (Kiorpes et al., 2013; Roberts et al., 2016), although attention problems have been found in children with amblyogenic refractive errors (Atkinson et al., 2002). Studies directed at discriminating these alternatives are urgently needed.

- The majority of psychophysical and clinical studies of amblyopia are conducted under free-viewing conditions, with the assumption that the retinal area of the highest sensitivity—typically the fovea—is directed at the target. In the case of anomalous retinal correspondence, this could be a locus other than the fovea. Little is known about visual sensitivity at nonfoveal loci or whether suppressive mechanisms respond differently to conflicting signals at the foveal *vs.* peripheral loci. Moreover, most neurophysiology to date reflects parafoveal rather than foveal neuronal properties; Shooner et al. (2015) is an exception. Future studies should include evaluation of function at multiple areas of the visual field, and neurophysiological investigations should include evaluation of foveal neuronal properties.
- On a related point, much current, as well as past, research on neural mechanisms of amblyopia are conducted in species lacking a fovea, often with deprivation as the model. It is at present unclear what the relationship is to the effects of amblyopia, more typically strabismic or anisometropic amblyopia, in primates. Comparative studies are needed to understand the relevance of circuit anomalies found in afoveate species following deprivation and neural correlates of amblyopia in primates. Nonhuman primates should remain the animal model of choice given the shared evolutionary history with humans, and similarity in cortical organization and nature of amblyopic deficits.
- Amblyopic individuals are now known to have many visual deficits beyond visual acuity, which is the metric assessed clinically and monitored during standard treatment. The additional deficits include binocular as well as monocular losses, high-order perceptual losses as well as threshold elevation, fellow eye deficits, and abnormalities of visuomotor control. Many of these deficits persist despite the successful treatment of acuity with patching or other methods. This raises the question of whether the treatment of amblyopia should move beyond patching or include more "global" therapies with the aim of improving high-level as well as low-level visual function.
- The field would benefit from increased application of assessment tools such as whole-brain fMRI and high-density EEG methods to address open questions regarding the mechanisms of amblyopia development and recovery during treatment. To understand the progression of development, as a hierarchical or holistic process, and the relationship between the organization of feed forward and feedback projections and critical periods for amblyopia, as well as critical brain areas involved in recovery during treatment, these coarser-scale tools have the potential to provide valuable information to move the field forward.

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