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Article

Nonhuman Primate Studies to Advance Vision Science and Prevent Blindness

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Abstract

Most primate behavior is dependent on high acuity vision. Optimal visual performance in primates depends heavily upon frontally placed eyes, retinal specializations, and binocular vision. To see an object clearly its image must be placed on or near the fovea of each eye. The oculomotor system is responsible for maintaining precise eye alignment during fixation and generating eye movements to track moving targets. The visual system of nonhuman primates has a similar anatomical organization and functional capability to that of humans. This allows results obtained in nonhuman primates to be applied to humans. The visual and oculomotor systems of primates are immature at birth and sensitive to the quality of binocular visual and eye movement experience during the first months of life. Disruption of postnatal experience can lead to problems in eye alignment (strabismus), amblyopia, unsteady gaze (nystagmus), and defective eye movements. Recent studies in nonhuman primates have begun to discover the neural mechanisms associated with these conditions. In addition, genetic defects that target the retina can lead to blindness. A variety of approaches including gene therapy, stem cell treatment, neuroprosthetics, and optogenetics are currently being used to restore function associated with retinal diseases. Nonhuman primates often provide the best animal model for advancing fundamental knowledge and developing new treatments and cures for blinding diseases.

Key words: amblyopia; eye movement; gene therapy; optogenetics; primate; prosthetics; strabismus; visual system

General Introduction to Primate Vision and Eye Movements

Much of human and nonhuman primate behavior is dependent on vision and directing gaze at objects of interest. Loss of sight is disabling and significantly decreases the quality of life. Optimal visual performance of human and nonhuman primates depends heavily upon retinal specializations, frontally placed eyes, and binocular vision. The oculomotor system is responsible for maintaining precise eye alignment during fixation and generating eye movements to support clear vision. The visual systems of human and nonhuman primates share similar anatomical and functional organization, which facilitates applicable research. Furthermore, the application of techniques used to study visual and eye movement functions in behaving nonhuman primates has revolutionized our understanding of complex visual-motor mechanisms in other areas of neuroscience including memory, decision making, visually guided limb movements, navigation, reward, and attention (Leigh and Zee 2015; Roelfsema and Treue 2014). These fundamental discoveries made in nonhuman primate studies are leading to new therapeutic interventions. This is not to diminish the importance of research in lower mammals or other preparations. However, when the goal is to understand sophisticated visual-motor behavior in health and disease, a nonhuman primate preparation offers many essential advantages. In this review, we consider aspects of the functional organization of visual and oculomotor systems of nonhuman primates and its application to advancing treatment of developmental and acquired diseases that compromise vision in humans.

Primate visual system specializations

Primates have developed complex mechanisms to see the world clearly during object or self-movement. Binocular coordination of eye movements ensures that the image of an object of interest is placed on or near the center of the fovea of each eye. Other equidistant scene elements fall on the Vieth-Müller circle or horopter (Howard and Rogers 2002; Leigh and Zee 2015; Turski 2016) and impinge on corresponding points of each retina. This precise active eye alignment function, called motor fusion, allows later stages of the visual system to combine information from each eye to produce a percept of single vision, known as sensory fusion. Sensory fusion also supports a percept of stereoscopic depth for targets located slightly in front of or distant to the horopter (Panum's Area). A target displaced outside Panum's area is perceived as two distinct objects (Harrold and Grove 2015). Failure of the oculomotor system to develop correct eye alignment and coordinated binocular eye movements can lead to strabismus, visual suppression, and impaired visual acuity (amblyopia). Acquired disorders in oculomotor control can lead to eye misalignment, double vision (diplopia), fixation instability (nystagmus), and oculomotility disorders. The visual and oculomotor specializations responsible for frontal vision and related volitional oculomotor control in human and nonhuman primates are not well developed or are even absent in lower mammals.

Retina

The retina forms as an outpouching of the embryonic forebrain (optic vesicle) and is part of the central nervous system. The retina contains a number of neural elements including photoreceptors (PRs; rods and cones), bipolar neurons that connect PRs to retinal ganglion cells (RGCs). Horizontal cells, and amacrine horizontal cells and amacrine neurons provide lateral connections within the retina to further process the information that is projected to the brain. Major visual properties created in the retina include "On" or "Off" channels, color-coding, and noncolor-coding channels, sustained and transient neuronal response dynamics at light onset and offset.

The primate retina is not uniform from center to periphery. Rather, it contains a central foveal region where the density of retinal neurons is highest. The fovea is located at the optical axis of the eye subtending approximately 3° of visual angle (Curcio et al. 1987; Dacey 2000). The primate visual system uses this feature to emphasize central vision where acuity is highest. Loss of central vision leaves one legally blind and unable to perform many critical tasks. The peripheral aspects of the retina support visual orienting and motion perception but not the high acuity vision and complex visual-motor behavior that humans depend on for most daily tasks. Damage to the retina associated with genetic or acquired diseases leads to various visual impairments and blindness. Examples include macular degeneration, glaucoma and color blindness.

Retinal Projections

RGC axons leave the eye at the optic disk (blind spot) where they form the myelinated optic nerve. The optic nerve carries visual information that contributes to the formation of multiple distinct visual pathways supporting different aspects of visual perception, oculomotor control, and homeostatic functions. Table 1 summarizes these pathways and their primary roles in vision and eye movements. In this review, we focus on those pathways that play a role in supporting clear vision and binocular coordination of eye movements. These pathways deliver visual information related to the contralateral visual hemi-field to primary visual cortex (V1) and the superior colliculus (SC). This is achieved by a partial decussation of the optic nerves at the optic chiasm, such that RGCs from the nasal retina project to the contralateral side, and those of the temporal retina project ipsilaterally. These patterns of projection can be compromised in albinism and other genetic defects (Guillery et al. 1984). Lesions of the optic nerve and tract produce visual scotomas in characteristic retinotopic locations. Human and nonhuman primates share essentially the same pattern of projections and cortical organization, which is a major advantage for studying normal and pathological sensory-motor behavior.

Retino-Geniculo-Striate Pathway

The retino-geniculo-striate pathway plays a dominant role in visual perception. RGCs from each eye deliver visual information to alternating layers of the lateral geniculate nucleus (LGN) for eventual combination in V1. Neurons in the LGN are sensitive to visual information associated with either the left or right eye. Furthermore, different classes of RGCs project to different layers of the LGN (Dacey 2000; Nassi and Callaway 2009). The noncolor-coding, large cell body-sized class of RGC projects to the ventral magnocellular layers of the LGN. The color-coding, medium-sized RGCs project to the dorsal layers of the LGN, and the small-sized RGCs project to intercalated layers of the LGN. These parallel pathways support different aspects of visual-oculomotor function. Signals from left and right eyes are brought together in V1, mostly outside layer-4, to create binocularly sensitive neurons essential for sensory fusion and stereopsis. The retinal-geniculo-striate pathway is essential for high acuity visual function in primates. Further, a large proportion of V1 is dedicated to central vision (e.g., central 5–10°). The peripheral retina plays an important role in visual orienting responses, motion perception, and retinal image stabilization through reflex optokinetic and ocular following responses (Mustari and Ono 2007). Lesions confined to V1 lead to cortical blindness in the contralateral hemifield.

Extrastriate Visual Areas

Visual information processed in V1 is delivered to extrastriate cortical areas where further extraction of visual information occurs (Gattass et al. 1990; Goodale and Milner 1992). Two major visual streams are well recognized. First, the "dorsal stream" is formed by V1 neurons that project to the middle temporal visual area (MT). This pathway strongly features information related to visual motion including depth (DeAngelis 2000; DeAngelis and Uka 2003; Kaskan et al. 2010). MT along with the neighboring middle superior temporal area contribute to motion perception and deliver signals to distal areas that control eye movements. Dorsal stream lesions can lead to motion scotomas and eye movement defects (Leigh and Zee 2015). Second, the ventral stream pathways involve V1 projections to V2 and other cortical areas approaching the temporal lobe (V4). Ventral stream extrastriate cortical areas play a role in determining "what" an object is and its color. Ventral stream cortical lesions lead to characteristic deficits including prosopagnosia (face blindness), color agnosia, and defective object recognition. There are extensive connections between cortical areas in these streams (Felleman and Van Essen 1991; Lynch and Tian 2006) that likely play a role in visual processing, eye movements, and overall behavioral integration according to context.

Table 1 Visual pathways and functions

Retino-recipient brain regions	Role in vision	Affiliated eye movements
Lateral geniculate nucleus (retinotopic mapping)	Principal pathway for visual perception Retinotopic mapping for visual location and perception. Color (parvocelluar) and noncolor (magnocellular) channels	Volitional saccades, smooth pursuit, vergence, ocular following
Superior colliculus (retinotopic mapping)	Retinotopic map for visual orienting, visual attention	Saccades, microsaccades and smooth pursuit
Accessory Optic System terminal nuclei (LTN, DTN, MTN) and pretectal nucleus of the optic tract (NOT)	Reflex visual following (optokinesis) Visual-vestibular interaction	Optokinesis and modifying vestibular ocular reflex
Pretectal olivary nucleus (PON)	PON—visual afferent control of pupil size	
Pregeniculate nucleus	Gating visual stimuli	saccades
Pulvinar	Visual attention	Fixation and saccades
Hypothalamus, suprachiasmatic nucleus	Light entrainment of circadian rhythms	none

Eye movements are driven by cortical projections to specific brainstem regions that are related to reflex and volitional classes of eye movements (Buttner-Ennever 2006; Leigh and Zee 2015; Ono and Mustari 2009). Lesions of extrastriate cortical areas or their specific brainstem regions are associated with different eye movement deficits, which can compromise visual function in both human and nonhuman primates. These problems cannot be studied in lower mammals that lack comparable visual-motor capability.

Nature-Nurture in Visual Development

The primate visual and oculomotor systems are immature at birth and sensitive to injury. At least 3–5% of children born in the United States suffer from either a genetic or acquired problem in visual and eye movement functions. Some of these disorders are treatable, if addressed early enough. The development of mature visual function requires coordinated binocular visual and eye movement experience during an early sensitive period. If any component of the visual or oculomotor system is defective, impaired postnatal experience could lead to miscalibration of neural circuits from V1 to motor neurons (Horton 2006; Horton and Hocking 1996, 1997; Kiorpes 2016; Mustari and Ono 2011; Tychsen and Lisberger 1986; Walton and Mustari 2015).

Visual Development Progression

Human and nonhuman primates follow a similar developmental sequence for visual acuity (Boothe and Fulton 2000; Kiorpes 2006). A 1-week-old macaque has comparable visual acuity to that of a 1-month-old human infant. Acuity values are significantly advanced but not fully mature until at least 12 weeks and 1 year of age for nonhuman primates and human infants, respectively. The first 6 weeks (macaque) and 6 months (human) of life comprise highly sensitive periods for visual acuity development. The majority of developmental comparative studies between human and nonhuman primates have focused on the time course of spatial vision development and its relationship to amblyopia. The defining characteristic of amblyopia is loss of vision even when the optical properties of the eye are intact. Amblyopia is common and difficult to treat (Boothe and Fulton 2000; Levi et al. 2015; Kiorpes 2016). Neurophysiological studies in nonhuman primates have been essential in discovering neural correlates of normal and pathological visual development (Kiorpes 2016).

Neurophysiological studies in infant nonhuman primates have demonstrated that neurons in V1 have specialized visual receptive field properties needed to code aspects of the visual scene. These include sensitivity to the direction of visual motion, orientation of visual contours, and eye preference. These properties exist in rudimentary form even without postnatal visual experience (Kiorpes 2016). However, normal postnatal visual experience is required to develop and refine the full dynamic range of properties in V1 and V2 neurons (Chino et al. 1997; Maruko et al. 2008). More advanced visual capabilities like separating visual objects from background, object recognition, face recognition, and contour integration may depend on the development and elaboration of neurons in extrastriate cortical areas beyond V1. There is some evidence that development of visual cortical function may follow a hierarchical pattern, flowing from V1 to dorsal and ventral stream cortical areas (Kiorpes and Movshon 2004; Kourtzi et al. 2006; Kiorpes 2016). Similarly, aspects of the development of oculomotor function may also have extended sensitive periods related to development of motion processing or other properties (Kiorpes 2016; Tusa et al. 2001). The nonhuman primate provides an ideal model for studying these progressions because they appear to follow those seen in humans although with a faster time scale.

Development of Binocular Vision and Strabismus

The development of binocular visual sensitivity of neurons in V1 requires postnatal experience (Hubel and Wiesel 1968; Kumagami et al. 2000; Nakatsuka et al. 2007; Smith et al. 1992, 1997). Early onset restriction in coordinated binocular visual experience can lead to strabismus (Figure 1) and amblyopia in human and nonhuman primates. This can occur naturally in cases of congenital cataract or significant differences in the optical properties of each eye.

Disruption of V1 neuronal binocular sensitivity is thought to play a primary role in strabismus (misaligned eyes) and amblyopia disorders. Evidence for this was obtained in neurophysiological and anatomical studies of V1 (Boothe and Fulton 2000; Hubel and Wiesel 1968). These studies discovered an alternating pattern of left or right eye dominated neurons across V1. These so-called ocular dominance domains (columns) alternated at 500-μm intervals across V1 (Hubel and Wiesel 1968). Subsequent anatomical studies using appropriate staining or imaging methods found the same pattern of alternating left and right eye

Figure 1 Developmental strabismus in human and nonhuman primates.

domains in sections cut tangential to layer-4 of V1 (Horton and Hocking 1996; Hubel and Wiesel 1969; LeVay et al. 1985). In normal primates there is a preponderance of monocular neurons in layer-4 and binocularly sensitive neurons in infra- and supragranular layers. Both innate and experiential factors play crucial roles in establishing ocular dominance columns in striate cortex (Crair et al. 1998; Horton 2006). If one eye is compromised during the early sensitive period, it will lose territory in V1, which is thought to be a significant contributor to amblyopia. How this process of loss occurs is not fully understood but gene expression differences have been found between deprived and nondeprived layers of the LGN in association with amblyopia (Cheng et al. 2008). This points to molecular processes that control outcomes related to the early sensitive period that may eventually be relevant to treating developmental eye diseases.

Extrastriate visual areas may also play a role in aspects of amblyopia (Kiorpes 2016). This is because the properties of neurons in V1 show less severe deficits than suggested by amblyopic vision *per se*. The onset time, duration, and type of visual deprivation are important variables in determining the severity of visual impairments (Horton and Hocking 1997; Hubel et al. 1977; LeVay et al. 1980; Tusa et al. 2002; Tychsen 2007; Mustari et al. 2008). Single unit recording studies have shown that visual experience is necessary to refine the spatial, binocular, and disparity sensitivities of V1 and V2 cortical neurons (Chino et al. 1997; Harwerth et al. 1990; Kiorpes et al. 1998; Kourtzi et al. 2006; Nakatsuka et al. 2007; Zhang et al. 2005). Infant cortical neurons have less mature speed, direction, and disparity sensitivity compared to mature V1 neurons (Chino et al. 1997; Zhang et al. 2005; Zheng et al. 2007). It is likely that refinements of disparity sensitivity and precise control of eye alignment are co-dependent. Disruption of this interaction could be a primary cause of sensory-induced strabismus (Chino et al. 1997; Kumagami et al. 2000; Tusa et al. 2002).

Cascade of Events During Early Development

Full visual function depends on the oculomotor system. Both innate and experiential factors contribute to the development of both vision and eye movements. Defects at any location in the visual and oculomotor systems could disrupt the normal interactions between these systems and the cascade of events leading to mature vision. For example, genetic defects that limit motor fusion would prevent sensory fusion, leading to strabismus and amblyopia. Similarly, loss of sensory fusion and defective development of binocular, disparity sensitive neurons may deprive critical cortical and brainstem centers of the error signals needed to guide the development of normal eye alignment, gaze holding, and eye movements (Das 2011; Fleuriet et al. 2016; Kiorpes et al. 1996; Mustari and Ono 2011; Walton et al. 2013, 2014; Walton and Mustari 2015; Wong et al. 2003).

Animal Models for Visual and Eye Movement Development

The etiology of strabismus is usually not known, so appropriate animal models with frontally placed eyes are needed to advance knowledge to improve treatments and develop cures (Tusa et al. 2002; Tychsen 2007; Willoughby et al. 2012, 2015a, 2015b). Treatment of strabismus often begins with optical correction using prism spectacles, patching protocols to encourage the use of the weak eye or surgical adjustments of extraocular muscles to improve alignment, thus allowing normal development of binocular vision to proceed. However, these treatments are not always successful (Von Noorden and Campos 2002). This might be because the problem associated with eye misalignment might not be eye muscles per se but abnormalities in the brain regions that drive eye movements. For example, during purely horizontal target motion strabismic subjects generate horizontal eye movement of the attending eye and abnormal oblique movements of the fellow eye. The abnormal vertical component of motion of the fellow eye is referred to as a cross axis eye movement. This disorder has often been attributed to overaction of an oblique extraocular muscle or misplaced eye muscle pulley (Demer et al. 1995; Von Noorden and Campos 2002). Although this could be the case in some instances, in strabismic, nonhuman primates it was discovered that oculomotor neurons are driving vertical rectus eye muscles to drive the cross axis eye movements (Das and Mustari 2007). Selecting the best corrective strategy for a cross-axis eye movement could be guided by MRI studies that reveal the state of the extraocular muscles (Peragallo et al. 2015). Therefore, fundamental research into neural mechanisms of well-characterized strabismic eye movements of nonhuman primates provides important perspectives and guides for best treatment options.

In normal macaques neurons in V1, V2, MT, and middle superior temporal area are often sensitive to stimuli presented to either eye. However, the same areas of strabismic macaques have diminished binocular sensitivity (Chino et al. 1997; Kiorpes et al. 1996; Mustari et al. 2008). These defects in cortical binocular visual sensitivity could be passed on to brainstem neurons in the nucleus of the optic tract (Table 1) and other circuits responsible for calibrating eye alignment, eye movement, and gaze stability (Mustari et al. 2001). Development of cortical and brainstem binocular sensitivity is required for mature volitional smooth pursuit and reflex optokinetic eye movements of macaques and presumably in children. Similarly, recent studies in strabismic macaques have discovered that neurons in the

paramedian pontine reticular formation no longer are associated with purely horizontal saccades but also respond during vertical saccades (Walton and Mustari 2015; Walton et al. 2013). The SC also plays a major role in driving conjugate, visually guided saccades. The SC does this by coding the retinotopic location of novel targets for saccades. In normal subjects both eyes are aligned on a target, but in strabismus the angle of eye misalignment results in different retinotopic error signals for each eye. Recent studies from several laboratories report that the influence of the SC in generating new saccades for the attending and fellow eye might be altered in strabismus (Economides et al. 2016; Fleuriet et al. 2016; Upadhyaya et al. 2016). Other brainstem areas like the supraoculomotor area appear to code the angle of misalignment rather than vergence angle as would be the case in normal subjects (Das 2012). These effects could be due to alterations in neural circuits in different cortical and brain regions responsible for converting visual signals into commands for gaze holding, eye alignment, eye movement, and binocular coordination (Walton and Mustari 2017). Neurophysiogical studies in nonhuman primates are rapidly advancing our understanding of developmental strabismus, and this will provide important perspective on treatment and cures of this common disease.

Because of the similarities in the organization and development of their visual and oculomotor systems, nonhuman primates provide an ideal animal model to advance treatments and cures for human diseases. A number of approaches have been employed to create nonhuman primates with developmental strabismus (Tusa et al. 2002). Current approaches all alter the early binocular visual experience in a manner that leads to strabismus with all of the syndrome components including eye misalignment, latent nystagmus, asymmetric smooth pursuit, and saccade disconjugacy seen in humans. Access to the strabismic nonhuman primate allows behavioral, neurophysiological, and novel treatment studies to be evaluated before being applied to humans (McLoon et al. 2016b; Pullela et al. 2016). The most effective means for producing the animal models for strabismus actually use variants of current treatment modalities.

Figure 1 shows a child with naturally occurring strabismus and a macaque model for this condition. Such misalignments must be corrected early to prevent damage to the development of binocular neurons in V1 and beyond. The strabismic eye misalignments in both the child and macaque are characterized by an outward deviation of the nonattending eye (Figure 1). This can be readily appreciated by noting that the corneal light reflex is centered over the pupil of the attending eye and displaced to the edge of the pupil of the fellow eye. In the animal model shown in Figure 1 (right panel) the macaque was treated with daily alternating monocular patching (using an opaque contact lens) for the first months of life. Different approaches for generating appropriate nonhuman primate models for developmental strabismus have been developed and are described below (Tusa et al. 2002).

Optical Methods

Optical methods aimed at altering visual afferent signals include atropine application to defocus one eye; daily alternating monocular occlusion with an opaque contact lens for the first 3 months of life; and wearing prism goggles that deviate the optical axis of one eye horizontally and the other eye vertically for the first 3 months of life, which produces an esotropia or exotropia according to applied optical deviations (Tusa et al. 2002).

Surgical Methods

These methods are aimed at strengthening or weakening individual extraocular muscles. Resection/recession of specific extraocular muscle/s produces exotropia or esotropia according to the muscles involved. Botulinum-A toxin provides a method to temporally weaken a specific overacting muscle (Scott 1980) or to create strabismus (Kiorpes et al. 1996).

Growth Factors

Treatment of individual extraocular muscle with growth factors like IGF-1 can strengthen individual eye muscles and affect strabismus (McLoon et al. 2016b). This method depends on slow release of a growth factor on a specific muscle to improve function (McLoon et al. 2016a, 2016b). The nonhuman primate provides an ideal animal model to test the efficacy of novel treatments before moving to clinical application (Tusa et al. 2002; Willoughby et al. 2015a).

NHPs Models and Human Clinical Trials

The application of discoveries in vision science to improve treatment and cures for blinding diseases falls into different categories and approaches. Both developmental and acquired diseases can compromise vision. In some cases, there is a known genetic defect; in others deficient early viewing experience can compromise vision.

Treatment for Congenital Cataract

Early treatment for congenital cataract is essential to preventing loss of vision. Removing the defective lens alone would leave the eye profoundly defocused leading to amblyopia. Studies conducted in nonhuman primates (Boothe et al. 2000) helped develop an intraocular lens implant technique to provide a cure for loss of clear vision in children with congenital cataract and aphakia (Kumar and Lambert 2016). Some of this work built on the earlier findings related to the sensitive period for development of binocularity, reviewed above. It was discovered that alternating patching of the eyes during the early sensitive period could preserve acuity in both eyes and prevent amblyopia (Boothe et al. 2000). There are rare forms of strabismus associated with genetic defects, especially in consanguineous families (for example, Engle 2002, 2007; Graeber et al. 2013; Ye et al. 2014). In some cases the genetic defects are associated with signaling molecules that guide pathway formation, motor neuron development, and muscle growth (Agarwal et al. 2016; Altick et al. 2012). Some forms of strabismus could be amenable to gene therapy and editing in the future.

Gene Therapy

Gene therapy using viral vectors offers promise for developing effective treatments and cures for retinal diseases (Garoon and Stout 2016; Vandenberghe 2017). There are at least 150 genes identified that are associated with different eye diseases. The most common genetic defects target the retina (PRs) or pigment epithelium. Discovering genotype/phenotype correlations associated with different eye diseases can offer a path to early treatment and prevention of blindness. A major concern is to test the efficacy and safety of any therapeutic approach. Using the nonhuman primate eye to evaluate treatment approaches for humans offers many advantages because of the similarity in anatomical organization of their eyes. Currently, adeno-associated virus

(AAV) or lentivirus approaches have been used with success in some clinical trials. Treatment of Leber's congenital amaurosis-type 2 provides an example where subretinal injections of AAV vectors that induce production of the missing retinal pigment epithelium protein delay disease progression. Similarly, AAV vectors have shown promise in curing color blindness in nonhuman primates (*Saimiri sciureus*) by inducing production of a missing cone opsin in the retina (Mancuso et al. 2010; Neitz and Neitz 2014). A major advantage in treating these diseases using intraocular (subretinal or intravitreal) AAV injections is that the progress of the treatment can be followed using noninvasive methods employing a retinal fundus camera to visualize neurons expressing green fluorescent protein that has been included in the viral vector. A major advantage of working with nonhuman primates is that the ocular anatomical barriers are similar to those of humans. Therefore, safe delivery or access of AAV vectors to retinal neurons can be rigorously evaluated before going to clinical trials (Boye et al. 2012; Ramachandran et al. 2016).

Glaucoma

Glaucoma is a blinding disease due to damage and loss of RGC axons as they leave the eye (Carreon et al. 2016). The most common cause of glaucoma is thought to be elevated intraocular pressure. This can occur due to deficient outflow of fluid from the anterior chamber of the eye through a complex network of tissue called the trabecular network. The etiology of glaucoma is complex and appropriate animal models are needed to advance knowledge and develop improved treatments. The structure of the trabecular network in the anterior chamber of the eye is similar in human and nonhuman primates (Xin et al. 2016). Further, this network appears to function in a similar manner in controlling aqueous humor flow from the anterior chamber of the eye in nonhuman and human primates (Carreon et al. 2016; Ilic et al. 2015; Zarbin 2015).

Stem Cell Treatments

In cases where retinal neurons have degenerated due to genetic diseases, replacing those neurons with stem cells is showing promise for treatment. Inherited diseases like retinitis pigmentosa and Stargardt macular dystrophy provide examples where clinical trials involving human derived embryonic stem cells (hESC) are being used as possible treatments (Sachdeva and Eliott 2016). For example, in Stargardt's disease hESC-derived retinal pigment epithelial cells have been delivered, subretinally, to replace defective retinal pigment epithelium (RPE) (Sachdeva and Eliott 2016). Intravitreal injections of retinal progenitor cells are being tested for treatment of retinitis pigmentosa. Similarly, hESC-derived RPEs are being evaluated for treatment of different forms of age-related macular degeneration (Hanus et al. 2016). A potential advantage of retinal stem cell treatment to replace neurons in the retina is that the distances between neural elements are short. The problem of regenerating long pathways in the central nervous system, for example, between the eye and brain has not been solved in any mammalian system.

Neuroprosthetics

Attempts to restore vision using intraocular (retinal) or V1 cortical implants has provided some benefit (Fernandez and Normann 2016; Lewis et al. 2016; Maghami et al. 2014). These systems deliver microelectrical stimulation to neural elements in the retina or cortex to activate visual pathways. The main idea is that if points in the retinotopic map are activated, then functional vision could be restored in blind individuals. At least some of the limited potential for significant visual restoration using prosthetics is due to the sparse nature of the electrode arrays employed. Even though the number of stimulus elements has increased from 10 to more than 200, this still falls far short of the million RGC axons leaving the eye or orders of magnitude more neurons in V1. Nevertheless, some restoration of visual function occurs with these devices demonstrating a proof of concept (Olmos de Koo and Gegori 2016; Maghami et al. 2014 for review). The extensive capability of the vision research community to assess visual and oculomotor function using nonhuman primates comprises an important resource for developing improved prosthetic devices. With further miniaturization and combination with optogenetics (below), it might be possible to improve devices active over a large enough surface area of the retina or V1 to restore useful visual function.

Studies in nonhuman primates have allowed development of prosthetics for treatment of other pathologies. The cochlear implant for restoration of hearing and the vestibular prosthesis for restoration of balance provide good examples, both of which were pioneered successfully in nonhuman primate studies (Lewis 2016; Phillips et al. 2015a, 2015b). We now have a new combined cochlear implant and vestibular prosthetic in clinical trials for use in cases with profound loss of sensory hair cells in the cochlea and vestibular apparatus (Phillips et al. 2015b). Deep brain stimulation for treatment of Parkinson's disease provides another valuable example where prosthetics developed in nonhuman primate studies moved to successful clinical treatment of movement disorders (DeLong and Wichmann 2015). There are a number of brain-machine interfaces that are now in clinical trials involving treatment of spinal cord injury (Milovanovic et al. 2015; Mojarradi et al. 2003). In some cases, quadriplegic patients have been able to control artificial limbs using advanced brain-machine interfaces that acquire and process signals from the parietal cortex related to intended movements (Andersen et al. 2014). Development of effective brain-machine interfaces requires detailed knowledge of neural circuits obtained in neurophysiological studies in nonhuman primates.

Optogenetics

The new field of optogenetics offers promise in developing new knowledge about the role of specific classes of neurons and pathways in the visual and oculomotor systems (El-Shamayleh et al. 2016; Jazayeri et al. 2012). Recent studies indicate that visual-oculomotor behavior of macaques can be affected by light activation of optogenetic channels in V1 (Jazayeri et al. 2012). The extension of this method with new AAV promoters to target specific neurons with either excitatory or inhibitory channels could advance neuroprosthetics. Such advances would allow activation or inactivation of specific neurons in a given circuit rather than nonspecific electrical stimulation provided in current prosthetics. Developing advanced prosthetics that take advantage of optogenetic channels must be developed in nonhuman primates because of the similar functional organization of visual and visual-motor pathways.

Gene Editing

The emerging field of gene editing using the CRISPR/Cas9 system could help produce testable animal models for genetic

diseases (Go and Stottmann 2016; Luo et al. 2016). Using this approach, defective genes could be replaced with functional ones. This approach could also be effective in generating new animal models for complex eye diseases to facilitate basic and applied research to develop cures. Nonhuman primates could provide ideal animal models for testing safety and efficacy of these new approaches.

General Summary

Research using nonhuman primates has advanced our understanding of the visual and oculomotor systems over the last several decades. Because of strong similarities in functional and anatomical organization of these systems in human and nonhuman primates, fundamental discoveries are leading to more treatment options. Further, research in the visual and oculomotor systems of nonhuman primates, using emerging methods including stem cells, gene therapy, neuroprosthetics, and optogenetics will advance fundamental knowledge needed to develop new treatments and cures for developmental and acquired diseases involving the eyes and nervous system.

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