Strabismus and the Oculomotor System: Insights from Macaque Models

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Abstract

Disrupting binocular vision in infancy leads to strabismus and oftentimes to a variety of associated visual sensory deficits and oculomotor abnormalities. Investigation of this disorder has been aided by the development of various animal models, each of which has advantages and disadvantages. In comparison to studies of binocular visual responses in cortical structures, investigations of neural oculomotor structures that mediate the misalignment and abnormalities of eye movements have been more recent, and these studies have shown that different brain areas are intimately involved in driving several aspects of the strabismic condition, including horizontal misalignment, dissociated deviations, A and V patterns of strabismus, disconjugate eye movements, nystagmus, and fixation switch. The responses of cells in visual and oculomotor areas that potentially drive the sensory deficits and also eye alignment and eye movement abnormalities follow a general theme of disrupted calibration, lower sensitivity, and poorer specificity compared with the normally developed visual oculomotor system.

1. INTRODUCTION

Binocular alignment and the binocular coordination of eye movements are important in foveate species to maintain binocular fusion and stereopsis (Leigh & Zee 2015, von Noorden & Campos 2002). The developmental loss of sensory or motor fusion leads to strabismus in about 2–4% of all children, making this disorder a significant public health issue (Govindan et al. 2005, Greenberg et al. 2007). The common thread among the causes of strabismus is a disruption of binocular vision during the early critical period for development that likely leads to a cascade of developmental disruption in the neural visual and oculomotor areas of the brain and, eventually, to misaligned eyes. Many seminal behavioral, anatomical, and physiological studies have revealed various aspects of visual sensory deficits, including their neural substrate, that are associated with the strabismic condition, and these are reviewed elsewhere (Crawford 2000, Crawford et al. 1996, Kiorpes 2015). However, there has been less investigation into disruptions in oculomotor (eye movement) circuits, although these structures must also be involved in maintaining steady-state strabismus and driving the behavioral eye movement abnormalities that are often associated with strabismus. The purpose of this review is to summarize our understanding of the behavioral and neural properties of strabismus as it relates to the oculomotor system. The reader is directed to other review articles for discussions of amblyopia and its relation to strabismus (Birch 2013; Kiorpes 2006; Levi 2006, 2013; Levi et al. 2015). Also, this review is narrowly focused on studies conducted in animal models of strabismus, mostly the macaque monkey, and the insights gained from these studies. Ocular misalignment can also be due to genetic factors involving extraocular muscles (e.g., congenital fibrosis of the extraocular muscles, Marfan's syndrome), neuroanatomical mis-wiring (e.g., congenital cranial dysinnervation disorders, such as Duane's syndrome), or other primary muscle pathologies (e.g., dysthyroid ophthalmopathy), but these conditions are rare and not duplicated in macaque animal models. For the purpose of this review, a more restrictive definition of strabismus is used wherein eye misalignment is manifest in childhood in an otherwise normal neurological system.

2. ANIMAL MODELS OF STRABISMUS

Kiorpes and colleagues (1985) examined the incidence of strabismus in a colony of *Macaca nemestrina* monkeys (pig-tailed macaques) and found an incidence of approximately 4%. The incidence of strabismus in other macaque species in unknown and could be lower. Given the difficulties in finding naturally strabismic monkeys, an artificially induced strabismus in animals has been the most practical and popular method for using an animal model for investigation. Broadly, surgical or sensory approaches have been used to develop animal models for strabismus. Each technique has its advantages and disadvantages, making each specifically suitable for certain types of investigation.

2.1. Surgical Methods to Induce Strabismus

Surgical methods to induce strabismus in animal models do so by disrupting motor fusion, for example by rectus muscle resection, recession or, more commonly, by tenotomy (muscle disinsertion). When applied in infant animals, the fundamental approach is to introduce an abrupt and large change in the length–tension relationship of one or more of the extraocular muscles (EOM) early in the developmental critical period. A consequence of the surgery is that the developing visual oculomotor system is unable to recalibrate patterns of innervation to the EOM to cope with the sudden appearance of noncorresponding visual information from the two eyes.

Therefore, along with the change in EOM contractility that occurs due to surgical manipulation of the muscle, there is an accompanying disruption in binocular vision. Disruption of binocular vision during this initial period leads to strabismus because it is the critical period for development of eye alignment, stereopsis, and binocular sensitivity (Boothe et al. 1985, Harwerth et al. 1986, Kiorpes 2015). Surgical methods have a long history of being used to induce strabismus in kittens (Hubel & Wiesel 1965) and also in adult and infant monkeys (Crawford & von Noorden 1979b; Economides et al. 2007; Horton et al. 1999; Kiorpes et al. 1996, 1998). Surgery to only one eye, as has most commonly been implemented in kittens and monkeys, tends to also induce amblyopia, especially if the surgical intent is to induce esotropia (Chino et al. 1983, Harwerth et al. 1983, Hubel & Wiesel 1965, Kiorpes et al. 1998, Scholl et al. 2013). Another related method for disrupting the normal function of the EOM and also disrupting the developing binocular visual system is to inject pharmacological agents, such as botulinum toxin, to weaken eye muscles (Kiorpes 1992).

Perhaps the primary advantage of using the surgical method is the simplicity and immediacy of the technique. EOM tenotomy is a relatively simple surgery and the animal is noticeably strabismic immediately after the procedure. Recovery from surgery occurs with minimal complications and little postsurgical management. After postsurgical healing, animals can be housed with other animals in social settings, therefore minimizing stress to the animal. However, a disadvantage of the surgical method, especially in infant monkeys, is that often the tenotomized muscle will reattach to the globe (Economides et al. 2007). It is not clear when muscle reattachment occurs and what factors influence it. However, the experimental outcome can be a small misalignment that is difficult to study as an animal model. A problem specific to using surgery to create esotropia (lateral rectus tenotomy) is that the monkeys can still fuse images when looking at near objects, which could preserve binocular vision and contribute to a failure to induce misalignment. The potential for resolving the strabismus, and also the potential for developing amblyopia, can be minimized by operating on both eyes [e.g., performing a bilateral medial rectus tenotomy to induce exotropia (Economides et al. 2007)]. A second point to consider when employing the surgical technique is that changes in EOM contractile properties due to surgery lead to, in the short term, disruption of dynamic eye movements in addition to the desired change in static alignment. A disruption in eye movements is likely to stimulate oculomotor adaptive responses, both at the local EOM and the central innervational levels. For example, experimental EOM palsy in adult monkeys can lead to increased central innervation to compensate for the reduced saccadic gain (Optican et al. 1985). Economides and colleagues (2007) reported that despite reattachment of the tenotomized medial rectus muscle, there was a sustained deficit of adduction, which is not typical of human strabismus. Also unknown is the influence of EOM proprioception, which is likely to be affected by surgery (Steinbach & Smith 1981; Steinbach et al. 1987, 1988). The steady-state strabismus and dynamic properties of eye movements in surgically treated animals are bound to be the sum of the aforementioned primary and adaptive factors. Therefore, the surgical approach may not be preferred when investigating central strabismus mechanisms that assume an intact periphery, for example, when investigating the neural basis for misalignment. However, using this model would be feasible for other types of studies, such as those that aim to investigate the visual consequences of misalignment (e.g., visual suppression and alternating fixation), including its neural basis (Adams et al. 2015, Horton et al. 1999).

2.2. Sensory Methods to Induce Strabismus

Sensory methods to induce strabismus disrupt sensory fusion (and, therefore, binocular vision) in infancy by employing special rearing conditions. Early studies in kittens used a monocular lid suture method to disrupt binocular vision and induce strabismus (Crawford et al. 1975, Wiesel

& Hubel 1965). Quick and colleagues (1989) attempted four different monocular deprivation methods in nonhuman primates and found that abnormal visual experience (disrupting binocular vision) in the first months of life in an infant monkey is sufficient to produce strabismus (Boothe & Brown 1996). In addition to strabismus, monocular occlusion induces a unilateral form-deprivation amblyopia and, therefore, is not a desirable method for studies examining oculomotor control in strabismus. Bilateral lid suture techniques in infant monkeys have also been successful in inducing strabismus and fusion maldevelopment nystagmus. However, the induced nystagmus is usually large, making this method more suitable for investigating nystagmus mechanisms rather than strabismus mechanisms (Mustari et al. 2001, Tusa et al. 2001). To minimize the presence of amblyopia, a variation of the monocular occlusion method is to alternately occlude each eye (Das et al. 2005, Tusa et al. 2002). In the daily alternating monocular occlusion (daily AMO) method, an occluding patch (opaque goggles or a contact lens) is placed in front of one eye. The following day, the patch is switched to the other eye and, thereafter, the patch is alternated daily for a period of 4 to 6 months (a major portion of the critical period in a monkey). Because visual experience during development is never binocular, the animal develops significant strabismus. Also, because the animal receives approximately equal visual experience from each eye (just not at the same time), amblyopia is minimal.

Another sensory paradigm that is popular and well validated for inducing strabismus is the optical prism-viewing paradigm (optical strabismus) (Crawford & von Noorden 1980, Smith et al. 1979). In the optical prism-viewing procedure, infant animals look through a base-down or base-up prism placed in front of one eye and a base-in or base-out prism placed in front of the other eye. In our laboratory, 20 diopter horizontal and vertical Fresnel prisms are fitted in a lightweight helmet-like device that the infant monkey wears for the first 4 months of life, starting from 1–2 days after birth (**Figure 1**). In the case of prism rearing, visual information is simultaneously available via each eye, but the visual axes are deviated, leading to binocular noncorrespondence. The presence of both horizontal and vertical prisms prevents the animal from overcoming the prisms and fusing the images from each eye. It is suspected that the noncorresponding vision in the two eyes stimulates

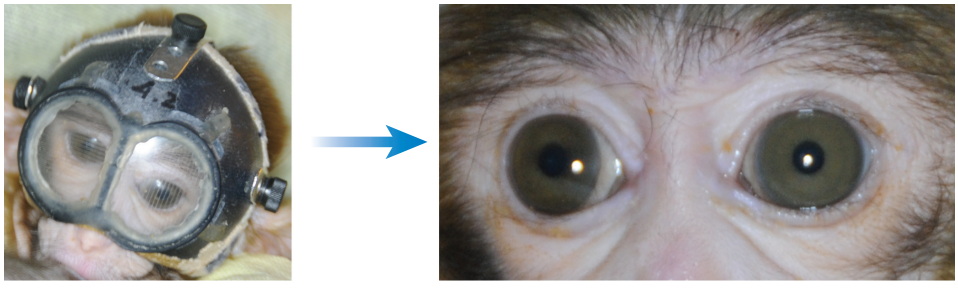

Figure 1

Optical prism rearing of infant monkeys for the first 4 months of life starting from day 1 after birth results in permanent strabismus. (*Left*) Infant monkey viewing through 20-diopter horizontal and vertical Fresnel prisms. (*Right*) The same monkey photographed after developing exotropia. Exotropia is evident from the relative position of the corneal light reflex in each eye obtained by using a ring-shaped light source surrounding the camera lens and pointed at the monkey. In the left eye, the corneal light reflex is centered on the pupil, but in the right eye, the light reflex is nasal to the pupil. Quick & Boothe (1989, 1992) established that a deviation of 1 mm from the pupil center is equivalent to approximately 14° of eye deviation in monkeys. In this particular animal, the exotropic eye deviation is estimated at approximately 30°, and was verified when the animal was fitted with scleral search coils for precise measurement of eye position at approximately 4 years of age.

suppressive mechanisms in the cortex leading to a disruption in the development of binocular vision and, thereafter, to strabismus (Boothe et al. 1985, Crawford et al. 1996).

An advantage of sensory paradigms, such as AMO or optical strabismus, is that the primary insult is directed at the visual information available to the brain, leaving the periphery intact. In that sense, these models might best mimic human sensory strabismus and are most suitable for studying the basic oculomotor mechanisms that are driving the eyes to be misaligned. Aside from the practical difficulties of handling and rearing infant monkeys under special viewing conditions for the first several months of life (which require significant infrastructure support), a potential disadvantage of sensory paradigms is that it is generally not possible to predict whether the animal will end up with an exotropia or an esotropia. Because the brain is sensitive to the quality and amount of vision during the rearing period, small changes in compliance with the rearing procedures may bias the system toward esotropia or exotropia or even normal alignment (Wensveen et al. 2011). The AMO rearing paradigm seems to yield more exotropes than esotropes, but the prism-rearing paradigm (optical strabismus) seems to yield more esotropes than exotropes, although both rearing paradigms can yield either condition. Although both the AMO and the optical rearing paradigms disrupt the monkey's binocular vision during the critical period of visual and oculomotor development (binocular noncorrespondence in the prism-reared monkey and binocular deprivation in AMO), a potential difference is that only the optical strabismus paradigm is likely to result in binocular competition leading to increased suppression and disruption of binocular vision. It is believed that this type of binocular competition and suppression leading to strabismus is most representative of the human condition.

2.3. Critical Period of Development of Binocularity and the Induction of Strabismus

It is well known that there are different critical periods for the development of different aspects of visual function (Harwerth et al. 1986, Kiorpes 2015). In a study on a cohort of infant monkeys, O'Dell & Boothe (1997) found that fine stereoacuity (less than 88 s of arc) emerged at around 4 weeks of age. This onset of stereoacuity seems to match quite nicely with the onset of disparity sensitivity in area V2 (Maruko et al. 2008). However, to obtain strabismus using sensory methods, the disruption of binocular vision must begin very soon after birth (probably during the first week) (Tusa et al. 2002). Disrupting binocular vision using prisms after about 2–4 weeks of age, that is, around or just before the age of onset of measurable fine stereoacuity, results in permanent disruption in sensory markers for binocular vision—such as a reduction of disparity sensitivity, lack of binocular summation, increase of suppression, and disruption of binocular properties of cortical neurons—but it does not result in appreciable eye misalignment (Crawford et al. 1996, Kumagami et al. 2000). Coarse stereopsis (88–1,760 s of arc) emerges at around 2 weeks of age (O'Dell & Boothe 1997); and studies have shown that disparity sensitivity is adult-like within the first week of birth in V1 cells, although the overall responsiveness of the cells is lower than in the adult (Chino et al. 1997). Perhaps this coarse signal is sufficient to calibrate the oculomotor system and drive the eyes toward alignment even if binocular vision is disrupted shortly thereafter due to sensory disruption. Surgical methods to induce strabismus do not seem to be as sensitive to timing.

2.4. Animal Model of Acquired Strabismus: Trochlear Nerve Section

Although the majority of studies using animal models focus on studying developmental strabismus, they have also proved useful for examining acquired strabismus. A series of studies by

Dr. David Zee and colleagues at Johns Hopkins University School of Medicine (Shan et al. 2007a,b; Tian et al. 2007) investigated the common condition of superior oblique palsy (SOP) using a nonhuman primate model. In these studies, an acute denervation of the SO muscle was effected in juvenile rhesus monkeys by sectioning the trochlear nerve transcranially at the level of the cavernous sinus. Later histological analysis of the orbit showed that transection of the trochlear nerve preferentially affected the global layer fibers of the SO and relatively spared the orbital layer fibers (Demer et al. 2010). Immediately after the procedure, the animals showed vertical and torsional eye misalignment and eye movement disruption characteristic of human SOP (Shan et al. 2008). These investigators examined the longitudinal change in alignment following SOP induction and found that patching one eye (either the normal or paretic eye) after SOP induction led to a short-term reduction in misalignment followed by a gradual increase in misalignment in the longer term. The speculation is that proprioceptive mechanisms are responsible for the short-term improvement in eye alignment (Quaia et al. 2008, Shan et al. 2011). The involvement of proprioception in developmental strabismus is unknown and deserves further study.

3. OCULOMOTOR PROPERTIES OF STRABISMUS REPLICATED IN ANIMAL MODELS

Animal models replicate a host of eye alignment and eye movement properties seen in humans with strabismus. **Figure 2** shows the results of exotropic eye misalignment in one juvenile monkey reared with daily AMO for the first 4 months of life (**Figure 2*a*,*b***) and results in another juvenile monkey reared with optical prisms for a similar duration (**Figure 2*c*,*d***). Also shown is esotropic strabismus in a third juvenile monkey reared with daily AMO for the first 4 months of life (**Figure 2*e*,*f***). Surgical induction of strabismus in monkeys produces similar results (Economides et al. 2007). Data in **Figure 2** are represented in a Hess screen chart format and show that the covered (nonfixating) eye is deviated horizontally in each case. In addition to primary horizontal misalignment, sometimes a smaller vertical misalignment is observed in the animal models. **Figure 2*c*,*d*** illustrates a small vertical strabismus, as the right eye is deviated upward when viewing with the left eye, and conversely, the left eye is deviated downward when the animal views with the right eye.

Many humans with strabismus present with dissociated deviations in addition to primary horizontal misalignment (Brodsky 2007, Guyton 2000). In Dissociated Vertical Deviation (DVD), the nonfixating eye is deviated upward relative to the fixating eye, and the clinical observation is that the nonfixating eye drifts upward upon occlusion. Unlike a vertical tropia, DVD does not fit the Hering framework of a weak muscle because the position of the nonfixating eye is always upward relative to the fixating eye (Guyton et al. 1998). The equivalent in the horizontal plane is known as Dissociated Horizontal Deviation (DHD) wherein patients show different horizontal strabismus angles depending on whether they view with the right or left eye. The hypothesis is that a secondary convergence drive is applied on top of the primary misalignment and this convergence signal varies depending on the fixating eye (Brodsky 2007). Animal models of sensory strabismus (AMO or prism reared) can show DVD, DHD, or both (Das et al. 2005, Tychsen et al. 2000). **Figure 2*a*,*b*** and ***e*,*f*** show animals with varying levels of DVD, and all animals in **Figure 2** show varying levels of DHD.

Fusion maldevelopment nystagmus (previously known as latent nystagmus), and nasotemporal asymmetry in monocular optokinetic nystagmus and monocular smooth pursuit are associated with infantile strabismus and have also been replicated in animal models (Mustari et al. 2001; Richards et al. 2008; Tusa et al. 2001, 2002; Tychsen et al. 2008). Both of these conditions result from disruption of binocularity in visual cortical and subcortical areas that leads to a disorder

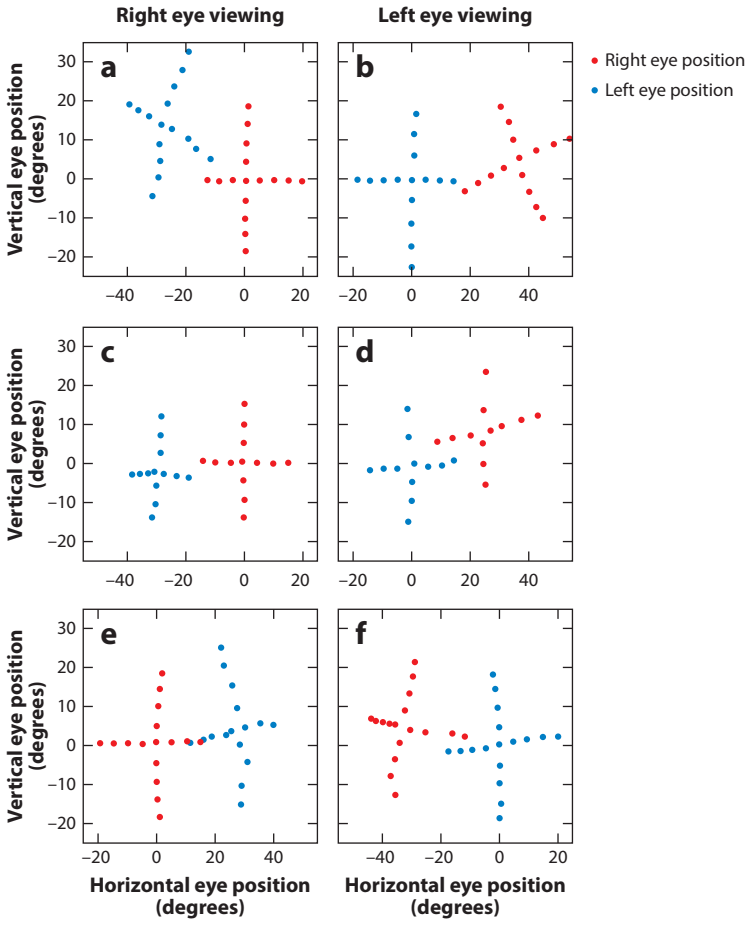

Figure 2

Horizontal misalignment, pattern strabismus, and dissociated vertical and horizontal deviations in animal models of strabismus. Data in all panels were acquired from juvenile, trained strabismic monkeys during monocular fixation on targets along the horizontal or vertical meridian. Data in the left column were acquired during right eye viewing, and data in the right column were acquired during left eye viewing. Positive values indicate rightward or upward eye positions in all figures; negative values show leftward or downward positions in all figures. The right eye position is shown in red and the left eye position in blue. (*a*,*b*) Data from a monkey reared using the alternating monocular occlusion (AMO) method with exotropia (the covered eye is abducted), A patterns, dissociated vertical deviation (DVD), and dissociated horizontal deviation (DHD). (*c*,*d*) Data from a prism-reared monkey with exotropia, vertical tropia, and a small amount of DHD. (*e*,*f*) Data from an AMO monkey with esotropia (the covered eye is adducted), small A pattern, and small amounts of DVD and DHD.

of motion processing (Mustari et al. 2001, 2008; Tychsen et al. 2010). Fixation instability in strabismus and amblyopia is not only due to fusion maldevelopment nystagmus. Increased drifts and other forms of nystagmus also contribute to fixation instability (Pirdankar & Das 2016, Tusa et al. 2001). A recent study in humans has suggested that increased fixation instability in strabismus could result in increased errors in determining the strabismus angle when using clinical testing methods, such as prisms and alternate cover testing (Economides et al. 2016). In addition

to nasotemporal asymmetry, an up–down asymmetry—that is, better optokinetic responses to upward motion than to downward—has also been observed in monkeys (Ghasia & Tychsen 2014).

The loss of binocular vision and eye misalignment affect the yoking of eye movements, which is a feature of the normal oculomotor system. Disconjugate eye movements have been observed in both human strabismus (Ghasia et al. 2015, Kapoula et al. 1997) and in animal models (Fu et al. 2007, Walton et al. 2014). In their examination of horizontal saccade disconjugacy in monkeys with strabismus, Fu et al. (2007) showed that both the pulse and step components of the movement were disconjugate and depended on gaze position. Walton and colleagues (2014) examined vertical and oblique saccade disconjugacy and concluded that part of the disconjugacy was the result of the nonfixating eye moving in a direction different from the fixating eye—that is, the control of saccade direction is affected in the deviated eye of the strabismic animal. Although eye movements themselves are disconjugate, saccadic or smooth-pursuit adaptation paradigms in strabismic monkeys yield conjugate changes in gain in the two eyes (Das et al. 2004, Ono et al. 2012).

Monkey models have also replicated another property of human strabismus: alternating fixation or fixation-switch behavior (Agaoglu et al. 2014b, Das 2009, Economides et al. 2007). Thus, strabismic patients with relatively little amblyopia can switch the eye of fixation depending on the location of the object they want to fixate, and this fixation-switch feature of strabismus is likely the result of visual suppression of portions of each eye's retina. Analyses of the spatial patterns of fixation switch in strabismic humans and monkeys have provided insight into how visual information from the two eyes is processed and converted into action in strabismus (Agaoglu et al. 2014b; Das 2009; Economides et al. 2012, 2014; van Leeuwen et al. 2001). Fundamentally, the results support the idea that fixation-switch behavior follows from suppression of a portion of the temporal retina in exotropes and a portion of the nasal retina in esotropes. However, in exotropes the fovea and portions of the temporal retina immediately adjacent to the fovea (or in esotropes the portions of the nasal retina adjacent to the fovea) are not suppressed because both humans and animals switch fixation when the target appears in these retinal locations, a finding that is also in agreement with visual suppression maps obtained psychophysically (Economides et al. 2012). In another study, motion information from an optokinetic stimulus available only to the fovea of the deviated eye was found to drive optokinetic nystagmus, although this was weaker than when the stimulus was viewed directly, suggesting that interocular suppression of the fovea of the deviated eye was still present but incomplete (Agaoglu et al. 2015b).

4. WHAT FACTORS GOVERN EYE MISALIGNMENT AND DISRUPTION OF EYE MOVEMENTS IN STRABISMUS?

The literature often describes strabismus in terms of the underaction or overaction of the EOM. However, this nomenclature is simply a matter of convenience based on a description of state and not of mechanism (Das 2008, Demer 2001). The previous discussion about the sensory disruption of binocular vision leading to eye misalignment emphasizes that developmental strabismus begins as a brain problem. But which factors govern the steady state of misalignment in strabismus? Evidence points to roles for both neural and mechanical (muscle-related) factors that eventually determine the state of eye misalignment and the constellation of eye movement deficits observed in strabismus. Further, it is likely that central and peripheral adaptation affects the steady state of misalignment throughout the duration of the condition (**Figure 3**).

4.1. Role of Mechanical Factors in Driving Strabismus

Although it is clear that the brain is involved in the development of eye misalignment in sensory forms of strabismus, it does not necessarily follow that the brain is involved in maintaining eye

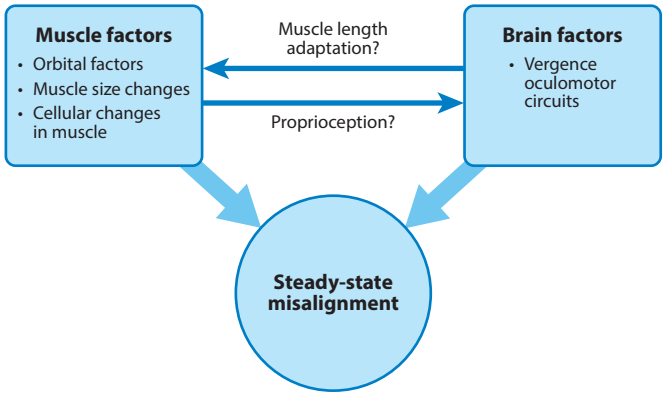

Figure 3

Both muscle and brain factors are responsible for maintaining steady-state misalignment. It is likely that one influences the other, and this influence might change over time.

misalignment once the critical period has passed. It is possible that the EOM adapts to the deviated position of the eyes, which would allow the brain to return to its normal state. This concept is referred to as muscle-length adaptation (Guyton 2006). Support for muscle-length adaptation comes from experiments in rabbits, in which the EOM was recessed or resected, and in monkeys, in which a muscle was detached and sutured to the orbit (Christiansen et al. 1996, Scott 1994). When the monkeys were examined a few weeks later, it was found that the muscle that had been surgically repositioned had added sarcomeres, implying that the resting length of the muscle had changed to account for the muscle stretch and restricted motility imposed upon it by surgery (Scott 1994). Other studies have documented (*a*) hypertrophic or hypotrophic muscles and mislocalization of muscle pulleys in some forms of human strabismus, (*b*) increases in satellite cell activity in rabbit EOM following resection, (*c*) alterations in neuromuscular junction density following treatment of EOM with botulinum toxin, and (*d*) changes in muscle fiber characteristics and neuromuscular junction density in patients with nystagmus, all of which suggest that muscle remodeling can influence the final state of strabismus and eye movement disruption (Berg et al. 2012, Christiansen & McLoon 2006, Harrison et al. 2007, Oh et al. 2002, Schoeff et al. 2013). However, an examination of the EOM in monkeys with prism-reared strabismus and no prior surgical treatment found no gross changes in muscle or muscle pulleys (Narasimhan et al. 2007), although cellular characteristics of the muscle and contractility were not measured.

4.2. Role of Brain Areas in Driving Strabismus

So what role, then, does the brain have in the development and maintenance of abnormal eye alignment and abnormal eye movements associated with the strabismus condition (Ghasia & Shaikh 2013)? Invasive studies in non-human primates, which recorded neural activity from a variety of brain areas associated with oculomotor control, have provided some insight. In this section, we summarize the results of these studies starting from the periphery (motor nuclei) and moving to central brain structures (cortex).

4.2.1. Motor nucleus. The first direct evidence that brain activity is a major contributor in determining the state of strabismus came from neural recording studies in the oculomotor and abducens nuclei of monkeys with either surgically or sensory-induced strabismus. These studies

showed that neuronal activity in the oculomotor and abducens nuclei could account for part, if not most, of the horizontal eye deviation and could also account for eye alignment changes due to A and V patterns (Agaoglu et al. 2014a, Joshi & Das 2011, Walton et al. 2015). Also, vertical deviation due to the DVD and the change in DVD with abduction and adduction was accounted for by activity from vertical motoneurons in the oculomotor nucleus (Das & Mustari 2007). Therefore, animal studies and some recent human studies have lent strong support to the idea that the brain is intimately involved in determining the strabismus state on a moment to moment basis (Ghasia & Shaikh 2013, Ghasia et al. 2015). However, the finding of neural involvement does not conflict with the notion of muscle influence. It is likely that both factors are contributors and that the relative contribution of brain and muscle varies from subject to subject and also over time (**Figure 3**).

4.2.2. Supraoculomotor area. The supraoculomotor area (SOA) is the region in the brain immediately dorsal and dorsolateral to the oculomotor nucleus. Also called the midbrain near-response region, this area of the brain contains cells whose responses are correlated with vergence eye movements (Judge & Cumming 1986, Mays 1984). Both convergence cells (cells that increase their firing rate during convergence, i.e., near-response cells) and divergence cells (cells that increase their firing rate during divergence, i.e., far-response cells) have been located in this area, although convergence cells appear to outnumber divergence cells (Mays 1984). These cells show no modulation of firing rate during conjugate eye movements, such as saccades or smooth pursuit, making them exclusively related to vergence. Further, these cells are monosynaptically connected with medial rectus motoneurons in the nearby oculomotor nucleus (Zhang et al. 1992), thereby providing a pathway by which a vergence tone can be maintained in the medial rectus muscle.

Das (2012) has shown that these neurons carry a signal related to horizontal eye misalignment, thereby identifying a neural correlate for strabismus angle. **Figure 4*a–d*** shows data from an example SOA cell in an exotropic monkey during a task in which the animal fixated on a stationary target (at a fixed distance of 57 cm) with either his right eye or left eye (monocular alternate cover testing). Changing fixation from the right eye to the left eye induced an increase in exotropia (**Figure 4*a***), and this increase in divergent strabismus angle was accompanied by a reduction in the firing rate of the cell (**Figure 4*c***). The reverse pattern was observed when changing fixation from the left eye to the right eye (**Figure 4*b*,*d***). Thus, the firing rates of this and other near-response cells in the SOA showed increased activity for smaller angles of exotropia. The firing rates of far-response cells in the SOA showed increased activity for larger angles of exotropia. Comparisons of the population responses of near-response cells from this brain area in strabismic and normal monkeys yielded potential insight into the neural mechanisms of eye misalignment (**Figure 4*e***).

In the normal monkey, the threshold at which near-response cells began to fire was close to 0° of convergence (i.e., near-response cells are largely turned off when looking at an object at optical infinity). However, the threshold in the exotropic monkey was shifted well into exotropia (i.e., divergent state). This finding suggests that the cells are active in maintaining the state of exotropia (or, in other words, the exotropic state was the set point or zero point for the system). The second observation is that the neuronal sensitivity (the change in firing rate per degree change in convergence in the normal monkey, or equivalently the firing rate per degree change in eye misalignment in the strabismic monkey) was significantly higher in the normal than in the strabismic monkey. An implication of the lower neuronal sensitivity in exotropic strabismus could be that the reduced signal from the SOA to the oculomotor nucleus results in the modification of the vergence tone of medial rectus (MR) muscles and, therefore, provides a neural basis for misalignment. Interestingly, SOA neurons did not encode changes in strabismus angle due to A

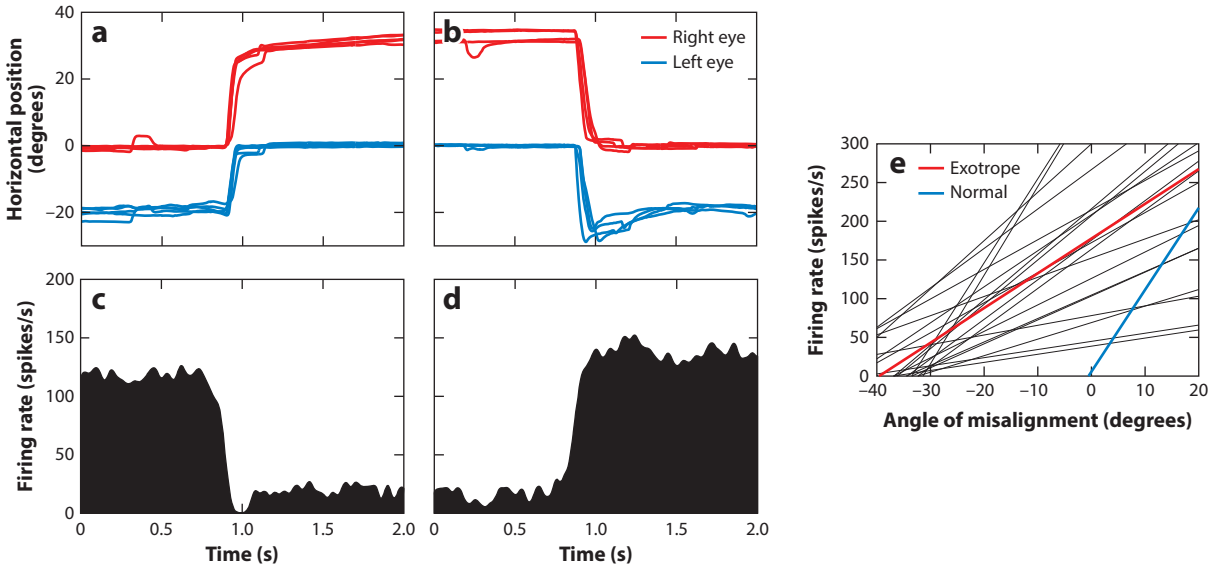

Figure 4

Activity of strabismus-related near-response cells in the supraoculomotor area (SOA) of a strabismic monkey with exotropia. (*a*,*b*) Multiple trials of a cover test in which the monkey switched fixation from (*a*) the right eye to the left eye or (*b*) vice versa while viewing a stationary target at 0°. (*c*,*d*) Average firing rate during cover testing. When the animal is viewing with his right eye, the strabismus angle is approximately 20° exotropia and when he views with his left eye, the strabismus angle is approximately 37° exotropia. The average firing rate is significantly higher when viewing with the right eye (smaller strabismus angle) compared with viewing with the left eye (larger strabismus angle). Right eye is shown in red and the left eye in blue. (*e*) Relationship (*black lines*) between the strabismus angle and firing rate for a population of cells in the SOA of a monkey with exotropia. The red line is the population average in the strabismic monkey, and the blue line is the population average from a set of near-response cells in a normal monkey, derived from Mays (1984). Note that both the threshold and the slope of the strabismic monkey SOA population (*red line*) are different from those in the normal monkey (*blue line*). Figure reproduced from Das (2012) with permission.

and V patterns of strabismus, suggesting that the neural circuitry that drives A and V pattern strabismus may be different (Das 2012). One caveat of the findings from the SOA is that neural responses from this area might be related to the underlying misalignment, the DHD, or both.

4.2.3. Brainstem pontine areas. The paramedian pontine reticular formation (PPRF) is a brainstem structure that is critical in the production of horizontal saccades (Fuchs et al. 1985). In normal monkeys, the excitatory burst neurons (EBNs) in the PPRF encode the horizontal component of saccadic eye movements, and the EBNs in the rostral interstitial nucleus of the medial longitudinal fasciculus encode the vertical component of saccadic eye movements (Fuchs et al. 1985, King et al. 1981, Luschei & Fuchs 1972). Two studies by Walton and colleagues (Walton & Mustari 2015, Walton et al. 2013) have examined the PPRF in strabismic monkeys and found deviation from normal characteristics. Electrical stimulation of the PPRF in normal monkeys results in a characteristic horizontal conjugate movement of the two eyes toward the side of the stimulation. However, in strabismic monkeys, electrical stimulation of this area results in a variety of movement directions, depending on the stimulation site, including movements with significant vertical components (Walton et al. 2013). Further, the horizontal and vertical components of the movement of the two eyes are frequently unequal (i.e., disconjugate eye movements were elicited by electrical stimulation). Neural recordings from EBNs in the PPRF have also shown that

many neurons have a preferred direction that is significantly deviated from horizontal (Walton & Mustari 2015). Together, both of these studies suggest that the PPRF is not calibrated in strabismic monkeys to resemble the normal monkey. Rather, it may be organized to be even more monocular than observed in normal monkeys (Zhou & King 1998). Further, it has been hypothesized that the observed deviations in the PPRF and cross-coupling between horizontal and vertical saccade generators could be the sources of disconjugate saccadic eye movements and A and V patterns of strabismus (Walton & Mustari 2015). The examination of saccadic cross-coupling in humans with strabismus has provided support for this hypothesis (Ghasia et al. 2015).

4.2.4. Cerebellum. The cerebellum is involved in almost all aspects of oculomotor control, both for online control and also as the substrate for adaptation and plasticity (Kheradmand & Zee 2011, Patel & Zee 2015). This section focuses on the cerebellar role in binocular aspects of eye movements, as they are most likely to be related to strabismus.

The cerebellar vermis projects to the caudal fastigial nucleus (cFN), and there is a direct projection from the cFN and the adjacent posterior interposed nucleus (PIN) to the contralateral SOA and the nearby Edinger–Westphal nucleus. Together with an ipsilateral feedback connection from the SOA to the cFN and PIN, this might form a vergence motor pathway that balances the vergence tone applied to the two eyes (May et al. 1992, Noda et al. 1990). Vergence-related neurons in the cFN are related to the near response, with increased firing occurring during convergence eye movements and near accommodation (Zhang & Gamlin 1996). Microstimulation in some areas of the cFN induces convergence eye movements in monkeys (Murakami et al. 1991). Neuronal activity in the ventrolateral part of the PIN suggests that this structure may have a complementary role to that of the cFN in eye movement control (Robinson & Fuchs 2001). Unlike vergence neurons in the cFN, vergence neurons in the PIN are related to the far response; that is, they increase their activity during divergence eye movement and during the relaxation of accommodation (Zhang & Gamlin 1998). Therefore, the physiological activity of cells in the cFN and PIN also supports a possible role in binocular control wherein far-response neurons in the PIN, along with the near-response neurons in the FN, form a push–pull system that, via projections to the SOA, sets the vergence tone in eye muscles.

Humans with various types of diffuse cerebellar degeneration experience binocular deficits, such as horizontal and vertical phoria and tropia, that depend on orbital position, saccade disconjugacy, and also disconjugate postsaccadic drift (Ghasia et al. 2016, Kheradmand & Zee 2011, Versino et al. 1996). Patients with damage to their cerebellar cortex or to the superior cerebellar peduncle (which carries the output of FN and PIN) sometimes present with eye misalignment and disruption in vergence eye movements (Hoyt & Good 1995, Ohtsuka et al. 1993, Williams & Hoyt 1989). In nonhuman primate studies, experimental midline cerebellectomy (removal of the vermis) produces, in addition to saccade and smooth-pursuit deficits, incomitant esodeviation, disconjugate eye movements, and disruption of phoria adaptation (Takagi et al. 1998, 2000, 2003). Also, using muscimol to inactivate the FN in monkeys reduces the size and speed of convergence (Gamlin & Zhang 1996).

Motivated by the evidence suggesting a possible role of the cerebellum in binocular control, Joshi & Das (2013) investigated the possible contribution of the cFN and the PIN to maintaining the state of eye misalignment in strabismic monkey models. In that study, the investigators used muscimol (a γ-aminobutyric acid A agonist) to pharmacologically inactivate either the cFN or the PIN in exotropic and esotropic strabismic monkeys. The major finding was that inactivation of the cFN produced a divergent change in eye misalignment (a reduction of esotropia and an increase in exotropia). **Figure 5** shows the saccadic hypermetria and also the reduction in esotropia following inactivation of the right cFN in a strabismic monkey. Inactivation of PIN was performed in the

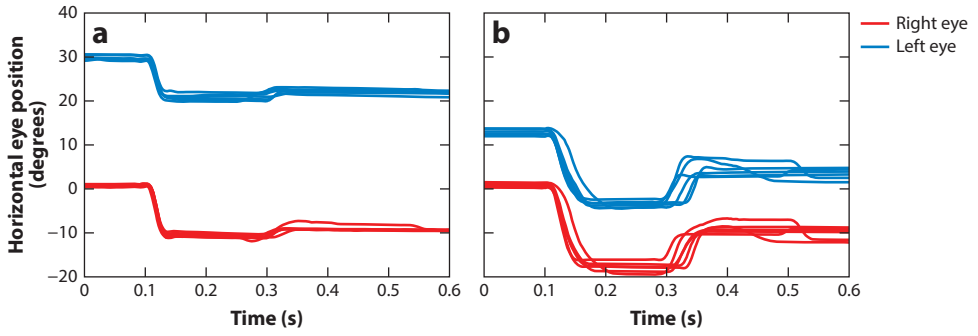

Figure 5

Effect of muscimol inactivation of the left caudal fastigial nucleus (cFN) in a monkey with esotropia reared using the alternating monocular occlusion method. Plots show multiple trials of leftward 10° saccades (*left*, preinactivation data; *right*, postinactivation data) while the animal viewed with his right eye. Postinjection, an overshoot of leftward saccades (ipsilesional hypermetria, characteristic of cFN lesions) and also a reduction in esotropia were observed. The right eye position is shown in red and the left eye position in blue. Data for this plot are from Joshi & Das (2013).

exotropic monkey, and this experiment resulted in a convergent change in eye misalignment. Thus, the cFN and PIN exert significant and complementary influences on the steady-state strabismus angle. Interestingly, inactivation of the cFN or PIN did not produce any changes in the A-patterns, much like the findings of the recording studies in the SOA.

4.2.5. Cortex. Investigations of cortical areas in animal models of strabismus began in area V1 with the examination of ocular dominance columns and ocular dominance distributions. Since the time of Hubel & Wiesel (1970), it has been known that form-deprivation amblyopia leads to a shift of the ocular dominance distribution toward the good eye (Crawford & von Noorden 1979b). In strabismus, the principal observation is the large-scale reduction of binocular cells in V1 and V2 (Crawford & von Noorden 1979a, Crawford et al. 1984). Further, there is an overall reduction in disparity processing and an increase in suppressive binocular interactions in V1 (Mori et al. 2002, Smith et al. 1997, Zhang et al. 2005). It is likely that these observed disruptions to binocularity and increased suppression in the visual cortex result in cascading disruptions throughout the visual oculomotor system and, ultimately, lead to eye misalignment and eye movement abnormalities in addition to visual sensory deficits.

Several studies have examined V1 ocular dominance columns using cytochrome oxidase (CO) staining in adult and infant monkeys and found evidence for suppression of parts of the retina (Adams et al. 2013, 2015; Fenstemaker et al. 2001; Horton et al. 1999; Tychsen & Burkhalter 1997). Recently, Adams and colleagues (2013, 2015) for the first time directly compared the patterns of cortical activity in exotropic monkeys (as derived from CO staining of the striate cortex) with patterns of visual suppression that might be expected in alternating exotropia, and they found that, indeed, the peripheral temporal retina was suppressed in exotropia and that the fovea of the deviated eye was not suppressed. **Figure 6** schematically shows the patterns of suppression and the associated CO staining of ocular dominance columns in exotropia. Thus, the anatomical studies matched the behavioral data of visual suppression and alternating fixation (fixation-switch) from humans and monkeys, thereby providing a neural substrate where visual suppression might be occurring (Agaoglu et al. 2014b; Das 2009; Economides et al. 2007, 2012).

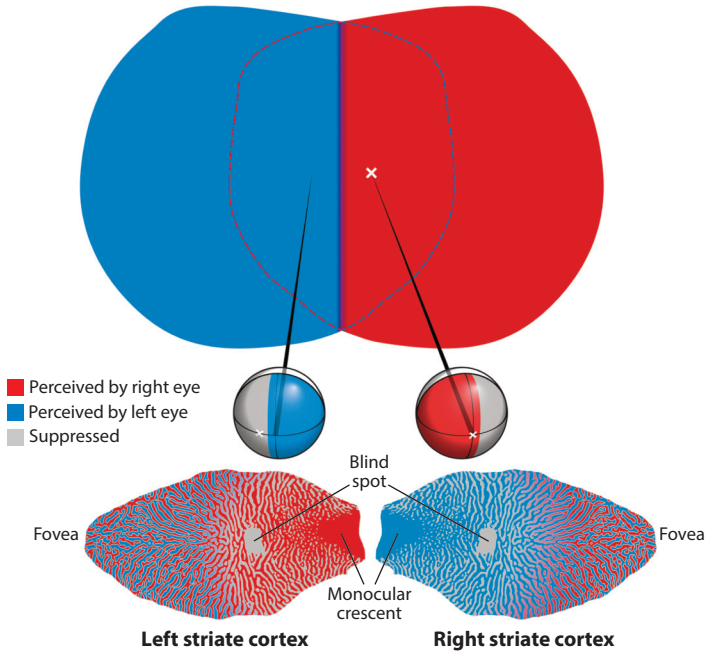

Figure 6

Schematic representation showing the match between visual suppression patterns and V1 ocular dominance column structure in exotropia. The top part of the figure shows a schematic of visual suppression patterns in exotropia as determined psychophysically and also as predicted from spatial patterns of fixation-switch behavior in humans and monkeys with exotropia. The subject fixates on the fixation spot (*white x*) with his right eye, and the left eye is deviated to the left. In exotropia, the peripheral temporal retina is suppressed in each eye. However, portions of the retina immediately temporal to the fovea (equivalent to approximately half of the strabismus angle) and the nasal retina are not suppressed. The bottom part of the figure shows the pattern of ocular dominance columns as derived from cytochrome oxidase staining. The staining also shows suppression of the peripheral temporal retina in each eye (*only red* or *only blue columns*). The fovea and portions of the central field are not suppressed (*alternating red* and *blue columns*). Figure reproduced with permission from Adams et al. (2013).

CO staining of the visual cortex in strabismic monkeys has also suggested there is a loss of binocularity and a nasalward bias, which could be related to the nasotemporal asymmetry of visual motion processing and fusion maldevelopment nystagmus observed in strabismic monkeys and humans (Tychsen & Boothe 1996, Tychsen & Burkhalter 1997, Tychsen & Lisberger 1986). Examination of MT cortex in strabismic monkeys has shown there is a significant loss of binocular cells, but visual motion sensitivity is preserved overall (Kiorpes et al. 1996). Similarly, MST cortical cells in strabismic monkeys showed a reduction in binocular responses to visual motion. The eye motion sensitivity of MST cells in these monkeys was also disrupted: Many cells responded only to nasalward movement. Therefore, MT and MST are proposed to be important components of the neural substrate for the nasotemporal asymmetry observed during smooth-pursuit eye movements in strabismus (Mustari & Ono 2011, Mustari et al. 2008). Both MT and MST project to the brainstem area known as the nucleus of the optic tract (NOT), and it has been shown that fusion maldevelopment nystagmus is associated with a loss of binocularity and a strong bias toward motion information from the contralateral eye in neurons in NOT (Mustari et al. 2001). Muscimol inactivation of NOT resulted in elimination of the fusion maldevelopment nystagmus, underscoring

the importance of the MT–MST → NOT pathway for this eye movement abnormality (Mustari et al. 2001, Tychsen et al. 2010). A similar disruption of the binocularity of NOT cells has also been observed in cats with strabismus (Cynader & Hoffmann 1981, Distler & Hoffmann 1996).

4.3. Disruptions in a Slow Vergence Circuit as the Neural Basis for Eye Misalignment

The neural circuitry for vergence eye movements is under some debate, with competing hypotheses falling under the category of a Hering framework or a Helmholtz framework (Leigh & Zee 2015). Under a Hering framework for neural control of eye movements, vergence is a separate binocular eye movement subsystem that is independent of conjugate eye movement systems, such as saccades and smooth pursuit. In the opposing Helmholtz framework, the brain encodes the movements of each eye independently; that is, there is monocular control of the two eyes (King & Zhou 2000, Zhou & King 1998). In an attempt to bridge the differences, a recently proposed amalgamated framework has suggested that static alignment and slow vergence are under the control of the traditional Hering circuitry, but fast vergence eye movements are more Helmholtz-like, that is, controlled monocularly (Cullen & Van Horn 2011). Therefore, in this amalgamated framework, a reorientation of the eyes in depth (three-dimensional gaze movement) would be first partially achieved by Helmholtz-like independent monocular control of the two eyes that brings each eye close to the target. Thereafter, to secure fine alignment and the best binocular vision, binocular control via a slow vergence circuit is imposed.

Although the Hering and Helmholtz frameworks are still under active investigation, the question to be addressed in this review is their potential utility in understanding the neural mechanisms of strabismus. As discussed earlier in this section, studies investigating the motor nuclei, SOA, PPRF, and the cerebellum have shown that central structures are responsible for many aspects of the strabismic state, including eye alignment and eye movement disconjugacy. Based on the above series of studies, a proposed framework is that normal alignment is achieved by activity that is balanced across convergence and divergence cells in a slow vergence pathway. Developmental disruption within this pathway, in the form of a static bias, is responsible for setting the state of static misalignment (Joshi & Das 2013). One arm of this circuit involves the cFN–PIN → SOA → medial rectus motoneurons → MR muscle pathway. A complementary, yet unidentified, pathway likely provides a strabismus signal to the lateral rectus muscle. Recent studies in normal monkeys have suggested that the rostral superior colliculus plays a part in vergence eye movements, and a pathway from the rostral superior colliculus to the abducens nucleus has been hypothesized as providing a slow vergence signal to the LR muscle (Van Horn et al. 2013). This pathway could potentially provide the strabismus signal to the LR muscle. Eye movement deficits associated with strabismus, such as saccade disconjugacy and alternating fixation, may be due to the disruption of fast vergence circuits.

5. ANIMAL MODELS AND TREATMENT OF STRABISMUS

In addition to using animal models to further our understanding of basic strabismus mechanisms, strabismus animal models have provided the opportunity to investigate certain aspects of treatment strategies that are not easily approachable via human studies. Two of these avenues for research are discussed below: (*a*) correlating the timing of strabismus repair with metrics of visual and oculomotor deficits and (*b*) using growth factors to alter extraocular muscle strength and potentially treat strabismus.

5.1. Timing of Strabismus Repair

One of the controversies surrounding the treatment of strabismus in children has been over identifying when to treat the misalignment using surgical or other methods. The controversy stems from the fact that the strabismus angle may be unstable in infancy and may even spontaneously resolve in a small percentage of children, supporting a view that strabismus surgery must be delayed until early childhood when the strabismus angle has stabilized (Simonsz & Kolling 2011). However, early surgery might permit the developing visual oculomotor system to recover, or at least preserve, any remaining binocular function following eye realignment. Dr. Lawrence Tychsen and his colleagues at Washington University in St. Louis (Richards et al. 2008; Tychsen et al. 2004, 2008; Wong et al. 2003) have tested this hypothesis and examined the timing of strabismus repair in nonhuman primate models. In their studies, infant nonhuman primates were prism-reared starting from the first day after birth. A strabismus repair was simulated in these animals by simply removing the prism goggles, and animals were grouped based on whether they underwent repair at 3 weeks of age (early repair) or at 6 weeks of age (late repair). Some animals were kept in prism goggles until they were 24 weeks old. The goal was to consider whether the timing of the repair had any correlation with the magnitude of sustained visual and oculomotor deficits that were present in these animals. Their finding was that the late-repair group (6 or 24 weeks of age) suffered from larger deficits by all visual (sensory) and oculomotor (motor) measures that they examined. For example, the late-repair animals showed larger strabismus angles and DVD, larger nasotemporal asymmetry in smooth pursuit and optokinetic nystagmus, and increased fusion maldevelopment nystagmus compared with the other groups. Taken together, these data suggest that earlier treatment is likely to be most effective in preserving as much normal visual oculomotor function as is possible. However, a caveat is that if the visual system is inherently abnormal there may be no possibility of restoring or preserving binocular function, regardless of the age at which surgical correction is attempted. If so, earlier treatment may have no better outcome than late treatment.

5.2. Use of Animal Models to Develop and Test New Treatments for Strabismus

Surgical methods, such as resection or recession, act to alter muscle strength (e.g., weakening an overacting lateral rectus muscle by recession surgery to treat exotropia) and, therefore, realign the eyes. Following the same rationale, any method that can alter muscle strength can potentially treat strabismus. Pharmacological agents such as botulinum toxin (Scott et al. 1990) and, more recently, bupivacaine (Miller et al. 2013) have been used in humans to alter muscle strength. The use of botulinum toxin as a possible treatment for strabismus was first devised and validated in monkeys before its adoption in human clinical trials and, thereafter, in clinical practice (Scott et al. 1973). Because botulinum toxin functions effectively to weaken a strong muscle and bupivacaine can strengthen a weak muscle, together they provide an option for treating agonist–antagonist muscle pairs (Scott et al. 2009). Another agent, ricin-mAbs35 has also been shown to be effective in weakening the EOM in rabbits (Christiansen et al. 2002). A disadvantage of pharmacological agents is that they are mostly effective in treating small-angle strabismus and often repeat treatments are required. Also, the immediate postoperative effect of a muscle-weakening agent such as botulinum toxin can be to render the muscle paralytic and this may necessitate patching the treated eye for a few days in cases in which double vision develops (Scott 1981).

Recent work in animal models has suggested that applying growth factors directly to the EOM has the potential to alter EOM strength and, therefore, to eventually be adopted as an alternative treatment for strabismus. Unlike botulinum toxin or ricin, growth factors act to increase muscle strength. Applying insulin-like growth factor (IGF) 1 or 2 to rabbit EOM significantly increased muscle force generation (both IGF1 and 2) in the short term and also

increased muscle cross-section area (IGF1 only) in the short term (Anderson et al. 2006, McLoon et al. 2006, McLoon & Christiansen 2003). Because the effects of a single application of growth factors were short lived, an alternative approach using implanted, slow-release pellets containing IGF1 has been attempted and found to provide a longer-term increase in muscle contractile forces (McLoon et al. 2006). Applying sustained-release growth factors to infant monkey EOM has been shown to be effective in inducing strabismus, although the results were a little unexpected (Willoughby et al. 2012, 2015)—that is, applying IGF1 to both medial recti did not induce any misalignment, but applying IGF1 to only one medial rectus induced exotropia instead of esotropia, as might have been expected with increased MR strength.

It should be noted that any treatment that focuses on changing muscle contractility is faced with the challenge of how the brain will react to the treatment, and the success or failure of the treatment ultimately depends on whether neural and muscle plasticity acts to reinforce the initial improvement after treatment (Agaoglu et al. 2015a).

FUTURE ISSUES

1. Human strabismus is often categorized into specific forms such as accommodative esotropia, convergence insufficiency, or intermittent exotropia. Can we create specific animal models that model each of these conditions?
2. What is the role of EOM proprioception in the development of eye alignment and in the maintenance of strabismus?
3. What other oculomotor neural structures drive eye misalignment? What is the neural substrate for strabismus properties, such as DVD, DHD, and A and V patterns?
4. What are the neural mechanisms that underlie visual suppression in strabismus and how do they influence oculomotor behavior, such as a fixation switch?
5. What is the nature of the neural and muscular plasticity that occurs after strabismus correction surgery or alternative therapies such as growth factor application, and how can they be manipulated to influence the outcome of strabismus surgery?
6. Is eye movement instability in strabismus a consequence of increased noise in the visual system or is it a consequence of a noisy, uncalibrated oculomotor system?

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