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INVESTIGATING MECHANISMS OF STRABISMUS IN NON-HUMAN PRIMATES

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Strabismus affects 2–4% of the infant population, with infantile esotropia being the most common form in Western populations[1, 2]. Investigations of strabismus found in the literature are primarily oriented towards describing different forms of strabismus and evaluating outcomes of surgical intervention. However there are a small number of research groups that have tried to improve our basic understanding of strabismus mechanisms by performing studies in non-human primates. In this issue of the journal, one of the leading groups led by Dr. Larry Tychsen of Washington University in St. Louis describe their studies examining properties of naturally occurring esotropia in macaque monkeys[3]. They have used a comprehensive approach to their investigation by examining eye alignment and eye movement behavior, using anatomical methods to analyze binocularity in primary visual cortex (area V1) and using anatomical and MRI methods to analyze extraocular muscles. They make several important points.

First, their data shows quite convincingly that non-human primates with naturally occurring esotropia show the constellation of ocular motor disorders (horizontal eye misalignment, A and V patterns, dissociated vertical deviation (DVD), small pursuit/optokinetic nystagmus asymmetry, and low velocity latent nystagmus) that are often observed in strabismic humans. Monkey models for strabismus that have induced eye misalignment via different sensory or surgical methods also show a similar range of oculomotor deficits [4–7]. Therefore an important finding of the present study is that it implies that currently available monkey models of strabismus are indeed mechanistically representative of the human condition.

A second important result is that orbital anatomy is normal in the naturally occurring sensory-strabismic animals. While this result may not be surprising to some, it is very important because often strabismus is described in terms of relative “weakness” or “strength” of specific extraocular muscles. It is essential to understand that the apparent “overaction” or “underaction” of extraocular muscles is a description of state and not a description of mechanism. Data provided in the current paper underscores this distinction. These data agree with and validate data from animal models of sensory strabismus that show normal orbital anatomy including normal sizes for extraocular muscle [8, 9]. Results from our laboratory demonstrate that motoneuron activity in the third nerve nucleus of exotropic animals reflects

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the state of horizontal eye misalignment, A-patterns, and DVD. These same results also indicate that disruption in neural circuits (and not disruption in the extraocular muscles is responsible for sensory infantile strabismus [10]. Other mechanical factors, such as muscle length adaptation or levels of expression of extraocular muscle-specific myosin isoforms, may help to determine extraocular muscle contractility in a strabismic patient. The role of these factors, however, is not yet understood.[11–14] Additional investigation is needed in these areas.

The authors have used anatomical evaluation of visual cortex to suggest that the severity of eye alignment and eye movement deficits is related to the severity of disruption of binocularity in area V1. Although the result is intriguing, we must be cautious in assuming a direct correlation, partly because anatomical studies do not reveal how much *functional* disruption of binocular connections has occurred. For example, some excellent neurophysiological studies of binocularity in V1 suggest that there are residual binocular suppressive connections in the strabismic animal [15, 16]. It is not clear how these suppressive connections affect the final strabismic state and the related eye movement deficits. Adding to the complexity is that there are many stages of visual and oculomotor processing beyond V1 that potentially play a role. For example, the cerebellum is thought to play a role in binocular control [17]. Extraocular muscle proprioception may also help in maintaining eye alignment [18]. Consequently disrupting binocularity in V1 may have unknown non-linear effects on the development of response properties of these downstream areas. Therefore further study of oculomotor areas downstream of V1 is needed to fully understand the source of behavioral deficits in strabismus.

This crucial study validates strabismus mechanisms discovered via studies in monkey models and also suggests ideas for further investigation. This is an exciting time in our field. Researchers are now able to study strabismus using a variety of techniques, including psychophysics, oculomotor behavior, MRI, physiology and anatomy. They also have the appropriate animal models in which to ask fundamental questions about strabismus mechanisms and their neural substrates. Primate studies have already helped to clarify our thinking about some important issues such as the relationship between binocular vision and development of strabismus. The expectation is that similar other studies will not only continue to help us understand mechanisms but will also help guide the development of strabismus therapies[19].

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