Research Highlight

Visualizing Neuronal Adaptation Over Time After Treatment of Strabismus

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Despite the frequency of developmental strabismus, we do not understand the primary cause of eye misalignment in otherwise normal children. Since the 1800s, strabismus has been treated using similar methods and rationale. The first current approach includes spectacle correction or eye patching, which fails to result in normal alignment in 40% of the children treated.[1] If patching fails, a surgical alteration of eye alignment is performed, where the muscles are made "stronger" or "weaker" by changing their effective length and/or the site of their insertions onto the sclera. For many of these children, these approaches produce successful outcomes, including orthotropic eye alignment and normal binocular vision. However, there are many children for whom surgical treatment fails.[2] Longitudinal studies have shown that over 10 and 20 year periods, the failure rates are as high as 50% to 80%.[3–6] There are almost 9000 published studies on the effects of strabismus surgery, yet the fundamental cause(s) of its failure to produce and maintain long-term, normal eye alignment is still not understood. The publication by Pullela et al.[7] provides us great insight into the process of neuronal changes that occurs longitudinally, both acutely and chronically, after resection/recession surgery using a well-established model for infantile strabismus.[8]

Recent studies have examined changes to the extraocular muscle structure after various types of strabismus surgery and demonstrated that there was significant adaptation of the operated extraocular muscles.[9,10] In resected, recessed, or tenotomized muscles, myofiber cross-sectional areas decreased within 7 days of surgery. There was also an increase of labeled muscle precursor cells into the myofibers of the operated muscles at a rate 10 times that seen in control muscles.[9,10] This rapid muscle remodeling corresponds to the 1-week time point shown in an earlier report from the Das laboratory,[11] where there was already close to a 10 degree worsening of the surgically-induced improvement in eye alignment. What was perhaps more compelling were the coordinated alterations in the unoperated muscle discovered on the contralateral side.[10,12] The manifestation of bilateral changes in muscle size and myosin expression corresponds to the bilateral change in the postsurgical eye alignment within even this 1-week time period.[7,8]

In a series of studies, it has been clearly shown that the angle of misalignment is driven by the motor neurons,[13,14] which in turn are driven by supranuclear areas that project onto these motor neurons.[15–20] The power of the study by Das and colleagues is based on their ability to record changes to motor neuron activity before and after a corrective surgery and correlate this activity with changes in eye alignment in adult non-human primates.[7] The results show that the neuronal drive to the "strengthened" medial rectus muscle is actually reduced, which would drive the eye alignment back into a more exotropic state, thus "undoing" the effects of muscle surgery. By 6 months, neuronal drive had returned to presurgical values, maintaining the original exotropia in these monkeys. Interestingly the second monkey showed a different pattern of neuronal drive changes. In this case, the oculomotor system increased the neuronal drive to the "weakened" muscle, again negating the effect of the attempted correction by recession on this muscle and pushing the alignment back to a more exotropic state. These studies provide important perspectives on how eye alignment is controlled. First, the ocular motor system detects changes in muscle force generation after surgery and actively works to return the eyes to their original angle of misalignment. Second, there appears to be significant plasticity in how the oculomotor system responds to perturbations, with two very different patterns of changes in neuronal drive. Both of these changes yielded the same net result, which worked against the initial corrective surgical intervention. These observations are extremely important because they suggest that the most efficacious way to ensure a permanent correction of childhood onset strabismus deserves further study. For example, determining how to "readapt" the visuo- and oculomotor systems to the surgically or pharmacologically altered "new" eye alignment could significantly improve efficacious outcomes.

The other important discovery in this publication by Das and colleagues is the demonstration that the neuronal drive to the unoperated muscles on the contralateral side also changes.[7] These changes are coordinated and opposite to those seen in the neuronal drive to the treated muscles. Similar types of coordinated changes to untreated extraocular muscles on the contralateral side also have been demonstrated following growth factor treatment of extraocular muscles in adult strabismic monkeys.[21] These data also indicate why surgery of only one muscle can be effective for treating strabismus.[22,23]

How these changes in post-surgical eye alignment are controlled at the motor neuron and muscle level are not understood. One prediction is that strabismus surgery results in altered levels of neurotrophic factors within the muscles and/or motor neurons. Mechanism of action could include anterograde and/or retrograde transport of these molecules, which have the potential to alter properties of both neuronal and muscle cell structure and function. So far, little work has been reported to assess how various neurotrophic factors changed as a result of extraocular muscle resection or recession. However, it is known that when limb skeletal muscles were either unweighted or overloaded, altered levels of a number of neurotrophic factors occurred.[24,25] A number of studies have demonstrated

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Investigative Ophthalmology & Visual Science

that the extraocular motor system, including both neurons and muscles, express higher levels of neurotrophins compared to brainstem and spinal cord motor systems.[26] More support for neurotrophins playing a role in the onset and/or maintenance of strabismus comes from microarray studies showing dysregulation of ciliary neurotrophic factor and glial derived neurotrophic factor, among others, in muscles from strabismic humans.[27,28] Complementary studies show the ability of increases in various neurotrophic factors to induce strabismus in infant monkeys (McLoon LK, et al. *IOVS* 2016;56:ARVO E-Abstract 1395).[29] Finally, oculomotor neuronal drive based on visual error from upstream visual structures may also be at play in working against successful correction after surgical alignment, and understanding these mechanisms could offer an extraordinary asset for clinicians.

The strength of the study by Das and colleagues lies in the ability to correlate pre- and postsurgical eye alignment with neuronal recordings performed pre- and postsurgically over a period of 6 months in the treated monkeys.[7] Although the ophthalmology field has hypothesized that the failure of strabismus surgery may lie in the inability of the oculomotor system to adapt to a significant alteration in eye alignment produced by the surgical manipulation, this is the first demonstration that the motor neurons specifically alter their firing rates and actively compensate for what was perceived by the visuo- and oculomotor systems as an "incorrect" eye position. This study answers a basic and long-standing question but also raises interesting new hypotheses that can be tested. How does vision affect these changes? It has been shown that even transient strabismus induced by surgery results in a breakdown of cortical binocularity.[30] Would the neuronal drive change if the monkeys were placed in the dark? Would visual therapy be possible to readapt the system to the altered visual field being seen after surgery? If the surgery had resulted in a fully corrected eye alignment, would the end result have been more stable? Does the age of the animal and cause and duration of the strabismus affect these results? As these strabismic monkeys were prism-reared as infants to induce their exotropia, it seems reasonable to extrapolate findings to naturally occurring strabismus. However, the reversal to the corrective effect reported here might not exactly match the challenge clinicians face after surgical manipulation of the extraocular muscles. For that matter, the etiology of strabismus is often unknown and could include different critical variables.

As with any paradigm-shifting research, this study indicates that to improve the outcomes of strabismus surgery, we must learn how to modulate the brain's solution to dealing with the lack of normal eye alignment. To do this, we need to fully understand the way oculomotor neurons control the eye muscles and the resultant eye position and eye movements in both health and disease. For example, a series of recent studies have focused on using retrogradely transported neurotrophic factors to modulate the central control of eye muscles and eye position and cause or treat strabismus.[21,31–33] This paper from the Das laboratory provides significant support for the quest to develop methods to modulate motor neuron functional properties to find a successful and long-lasting treatment for childhood onset strabismus.

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