Anomalous Retinal Correspondence: Neuroanatomic Mechanism in Strabismic Monkeys and Clinical Findings in Strabismic Children

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Background: Anomalous retinal correspondence (ARC) is a neural adaptation to eye misalignment in which non-corresponding retinal points are linked in the visual cortex to provide binocular fusion. ARC within the striate cortex would require that horizontal neurons link right-eye and left-eye ocular dominance columns (ODCs) separated by a distance in the cortex proportional to the angle of strabismus. Two hypothetical mechanisms are possible: (1) The ODCs can be linked by axons of horizontal neurons that project monosynaptically from a right-eye to a left-eye ODC. The further apart the ODCs, the longer the axons; hence, axon length should be greater in subjects with strabismus than in healthy subjects (elongated axon, monosynaptic hypothesis). In this case, the clinical probability of developing ARC should be independent of the angle of strabismus, until an upper-limit angle of strabismus is reached equally to the maximal length of axons available to link nonadjacent ODCs, at which point an abrupt decline of ARC probability should be evident. (2) Alternatively, ODCs can be linked by a chain of horizontal neurons, the number of which increases as the distance among ODCs increases; axon length in subjects with strabismus would be expected to be the same as in healthy subjects (normal axon, polysynaptic hypothesis). In this case, the greater the angle of strabismus, the more horizontal neurons and synapses required for linkage, and the greater the probability of signal degradation. Thus, the clinical probability of developing ARC through a polysynaptic mechanism should be inversely proportional to the angle of strabismus. The purpose of this study was to test these 2 hypotheses neuroanatomically in primates and clinically in children.

Methods: For the neuroanatomic portion of the study, biotinylated dextran amine was injected into ODCs of area V1 to label individual neurons. The length of the horizontal axons from these neurons was then compared in strabismic and normal monkeys. In the clinical portion of the study, the medical records of 192 children with strabismus were reviewed retrospectively. The angle of strabismus (prism cover test) and the presence of ARC (Bagolini striated lenses, Worth/Polaroid 4-dot) were recorded. Plots of the presence of ARC as a function of the angle of strabismus were obtained.

Results: There was no significant difference in axon length between healthy (7.02 ± 0.83 mm) and strabismic monkeys (6.60 ± 1.07 mm) (P = .16). In children with strabismus, ARC decreased as the angle of strabismus increased (P < .05). ARC was more prevalent in children who had primary or postsurgical deviations of ≤4° to 5° (8-10 PD), corresponding to ≤2 horizontal axon lengths in the foveal striate visual cortex.

Conclusions: The visual cortex adapts to strabismus by combining information from paired ODCs of opposite ocularity that, because of the eye misalignment, are nonadjacent and separated by abnormally long distances across the striate cortex. The cortex appears to achieve the linkage, not by elongating neuronal axons, but by using chains of neurons that have normal-length axons. The visual cortex is most successful stochastically at achieving this linkage (ie, developing ARC) when the gap that must be bridged is no greater than 4° to 5° (8-10 PD), or the retinotopic distance in the foveal visual field is spanned by 2 normal V1 neurons. (J AAPOS 2000;4:168-74)
A nomalous retinal correspondence (ARC) is an adaption to ocular misalignment that allows subnormal binocular fusion.\textsuperscript{1-3} ARC occurs when noncorresponding points on the hemiretina are linked in the visual cortex to create a common visual direction.

A search for a mechanism of ARC should logically begin in the primary visual cortex (V1) because V1 is the first locus in the visual pathway that contains binocular neurons.\textsuperscript{4} Recent neuroanatomic studies have revealed that in healthy primates, horizontal neurons in V1 connect equally to adjacent same-eye and opposite-eye ocular dominance columns (ODCs), providing the neuroanatomic basis for binocular vision (Figure 1, A).\textsuperscript{5} In contrast, there are fewer (about 50\% less) horizontal connections among adjacent ODCs in strabismic primates, especially in layers 2/3 and layer 4b.\textsuperscript{5} These remaining horizontal neurons would have to link right-eye ODCs to nonadjacent left-eye ODCs, which would be separated by a distance in the cortex proportional to the angle of strabismus, to establish ARC within the striate cortex.

The linkage of nonadjacent ODCs could be achieved by 1 of 2 possible mechanisms. The axons of an individual horizontal neuron could elongate to project directly from a right-eye ODC to a left-eye ODC (Figure 1, B, elongated axon, monosynaptic hypothesis). The greater the angle of strabismus, the further apart the ODCs and the longer the axons are; axon length should be greater in strabismic subjects than in healthy subjects. In addition, the clinical probability of developing ARC should be independent of the angle of strabismus, until an upper-limit angle of strabismus is reached equally to the maximal length of axons available to link nonadjacent ODCs, at which point an abrupt decline of ARC probability should be evident (Figure 1, C). Alternatively, nonadjacent ODCs could be linked by a chain of horizontal neurons (Figure 1, B, normal length axon, polysynaptic hypothesis). The greater the angle of strabismus, the more distant the corresponding ODCs in V1 are, the more horizontal neurons are required for linkage, and the greater are the number of synapses across which signals for ARC must flow. Signal strength in the central nervous system is known to decrease systematically as the number of synapses in a circuit increases; the clinical probability of developing ARC should decrease as the angle of strabismus increases (Figure 1, D).\textsuperscript{6}

The purpose of this study was to determine which of these 2 mechanisms (elongated axon, monosynaptic versus normal axon, polysynaptic mechanism) provides the best explanation for the development of ARC, both experimentally and clinically. In the first part of this study, an anatomic labeling experiment was carried out to measure axon length of horizontal neurons in strabismic and healthy primates. In the second part, the medical records of children with strabismus were reviewed to determine the relationship between the angle of misalignment and the presence of ARC.

\section*{METHODS}

\subsection*{Eye Alignment and Acuity in Strabismic and Healthy Monkeys}

Five macaque monkeys (3 strabismic and 2 healthy) were used in the experiments. Two of the 3 strabismic monkeys (monkeys AR and JE) had a natural esotropic strabismus in the first 4 weeks of life. The third strabismic monkey (monkey RD) had a small-angle esotropia induced by alternate occlusion of the eyes from birth to age 9 months. The animals had normal visual acuity in each eye (≤0.5 octave difference in acuity between the eyes), documented by R. G. Boothe with a bar-press grating stimulus acuity task at the Yerkes Regional Primate Center in Atlanta, Georgia. Cycloplegic refractions were performed in infancy and adult life to rule out significant hyperopia.

At adult age, the animals were shipped to Washington University where they were trained to fixate on small tracking targets using positive feedback rewards. Eye movement recordings showed constant, nonparalytic (comitant) esotropia, and in the 2 animals with the smaller esotropias (RD and JE), there was evidence of a residual “motor fusion” capacity. The angle of strabismus measured under conditions of binocular viewing (ie, the heterotropia) was 25\% to 50\% smaller than the angle of strabismus under conditions of monocular viewing (ie, the heterophoria). Monkey RD had a constant esotropia of less than 10 PD (1 PD = 0.57°), and monkeys JE and AR had constant esotropias of 20 PD and 30 PD, respectively. The 2 healthy monkeys were orthotropic and served as control subjects. The experimental protocol was approved by the Washington University Animal Studies Committee.

\subsection*{Neuroanatomic Labeling and Analysis of Monkey Cortex}

Neuroanatomic labeling experiments were carried out on each animal to compare binocular connections in V1 of strabismic versus healthy monkeys.\textsuperscript{5,7} The animal was sedated by an intramuscular injection of atropine and ketamine. The pupils were dilated with mydriatic drops, and several hundred spot burns were applied to the optic nerve head of the left eye using an indirect ophthalmoscope laser. Seven days later the animals were resedated, and under deep general anesthesia, 10 to 15 3-mm burr holes were drilled over the operculum of the striate cortex (ie, extending across the entire noncalcaneous or foveal cortex in the monkey). Small durotomies were made at the base of each burr hole, and biotinylated dextran amine (BDA) was injected using pulse-air driven micropipettes, which were lowered into the cortex to a depth of approximately 1 mm. BDA is a tracer taken up by individual neuronal soma near the site of injection and transported anterogradely to label axonal projections and terminal synaptic boutons of neurons.\textsuperscript{5,8}

After a survival time of 72 hours, the animal was humanely killed by an overdose of barbiturate, the brain
was perfused, the occipital lobes were removed and briefly immersed in fixative, and the cortex was unfolded and flattened for sectioning tangential to the pial surface. Alternate 50-µm sections were processed to reveal BDA or were stained for cytochrome oxidase (CO) using the protocol of Tootell et al. CO is an intracellular respiratory enzyme that serves as a marker of premortem neuronal activity. The laser abolished activity in neurons driven by the left eye, causing downregulation of CO in those ODCs. By superimposing alternate sections stained for BDA and CO, we could determine whether an individual BDA injection had been made into a row of right-eye (CO-rich) or left-eye (CO-poor) ODC, which appeared as alternating dark and light stripes in a CO-stained tangential section. BDA labeling was quantified by aligning adjacent BDA- and CO-stained sections, using blood vessels running radially through the cortex as reference marks. The axons and dendrites of individual neurons, the ODCs within which they resided, and the neighboring ODCs to which they connected were identified. The maximal axon length of BDA-labeled horizontal neurons in layers 2/3 and 4b of V1 of healthy and strabismic monkeys was measured.
sured using NIH Image software. Axon lengths were compared using the *t* test with significance defined as *P* < .05.

**Clinical Study of Children With Strabismus**

In the second part of the study, clinical data were collated from a retrospective review of medical records of 192 consecutive children. They were examined in our unit at the St Louis Children’s Hospital and were documented to have constant, concomitant heterotropia, with or without prior strabismus surgery or prior occlusion therapy. Exclusion criteria were coexisting deviation other than uncomplicated horizontal heterotropia, such as oblique muscle overaction and poorly controlled dissociated vertical deviation; sensory deprivation strabismus and/or amblyopia of greater than 2 Snellen lines difference between the 2 eyes at the time of testing; other ocular diseases; other systemic or neurologic diseases; and a history of head trauma.

The inclusion criteria were met by 105 patients with esotropia and 87 patients with exotropia, and they were reviewed. The mean age at sensorial testing was 4 years (range, 4 weeks to 11 years) in the esotropic group and 6.5 years (range, 6 weeks to 16 years) in the exotropic group. The magnitude of strabismus was recorded as the mean heterotropia at near fixation (one-third m), as measured by the single prism cover test, wearing best correction spectacles when indicated. The presence of ARC was tested using one or more of the following: Bagolini striated lenses, the Worth/Polaroid 4-dot test, and the Titmus/Randot stereotest, all tested at one-third m viewing distance. ARC was scored as present if patients reported one or more of the following: 2 lines at right angles intersecting at their midpoints (with or without a gap) on Bagolini testing or 2 reds and 2 greens or a total of 4 dots on Worth/Polaroid testing. These tests of two-dimensional fusion were supplemented by testing for stereopsis. If the child achieved a threshold of 3000 arc sec or better on Titmus/Randot stereotesting, stereopsis was tabulated as present. Plots of the angle of deviation against the presence of ARC were tabulated for the 192 patients. Differences in the prevalence of ARC between patients with esotropia and patients with exotropia were tested for significance using the *χ*² test. The relationship between the prevalence of ARC and the angle of strabismus was tested for significance using the *F* test, with significance defined as *P* < .05.

**RESULTS**

**Neuroanatomic Findings in Strabismic Monkeys**

Two of the 3 strabismic animals we studied had evidence of residual motor fusion: when an eye was covered, their angles of strabismus were larger than the angles recorded under conditions of binocular viewing. A residual motor fusion capacity of this kind is typical of humans who have ARC and smaller angles of strabismus (monofixation syndrome). The presence of motor fusion in these animals served as indirect evidence that the strabismic monkeys were an appropriate animal model for the study of ARC. The monkey (RD) with an angle of strabismus (<10 PD) closest to that of humans who have monofixation syndrome displayed the most consistent motor fusion response. Detailed analysis of the ocular motor behavior of the monkeys is the subject of a separate report.

The axonal length analysis revealed no substantial differences among the 3 strabismic animals, and their results are therefore reported as grouped data. Figure 2 shows plots of maximal axon length of horizontal neurons in layers 2/3 of cortical area V1 (ie, upper binocular layer). A, Axons of normal and B, axons of strabismic monkeys as a function of eccentricity of injection site from the representation of the foveola (foveola = eccentricity of zero). All horizontal axons shown here projected orthogonal to ODCs, connecting neurons in right- or left-eye ODCs to neurons in ODCs of opposite ocularity.
pared with $6.60 \pm 1.07$ mm (range, 5.5-9.0 mm) in the 3 strabismic monkeys. The difference in axon length between the strabismic and control groups was not statistically significant ($t$ test, $P = .164$). According to standard retinotopic maps of the striate cortex of the macaque monkey, the axon length of a single, typical neuron (approximately 7 mm) could join visual receptive fields up to 2.5° away from the foveola in the opercular (ie, macular) cortex.12

**Clinical Observations in Children With Strabismus**

ARC was present in 77% of the patients with esotropia and 36% of the patients with exotropia ($\chi^2$, $P < .05$). A plot of the angle of deviation and the presence of ARC are shown in Figure 3. ARC decreased systematically as the angle of esotropia increased ($F$ test, $P = .003$). A similar trend was found by plotting the angle of deviation and the presence of ARC in patients with exotropia (Figure 3); however, the trend in patients with exotropia was not statistically significant ($F$ test, $P = .24$). ARC was most prevalent in children who had primary or postsurgical deviations of ≤4° to 5° (approximately 8-10 PD), both in the esotropic and exotropic groups. Stereopsis was documented in 73% of the children who had evidence of ARC using two-dimensional fusional tests (eg, Bagolini lenses or the Worth/Polaroid 4-dot test). No child had stereopsis who lacked ARC using Bagolini lens or Worth 4-dot testing criteria or had a constant heterotropia >12 PD.

**DISCUSSION**

This study was designed to answer 2 major questions: (1) What is the clinical relationship between the angle of strabismus and the likelihood of ARC? and (2) What is the simplest neuroanatomic mechanism for ARC? Do individual horizontal neurons in the primary visual cortex (V1) adapt to any angle of strabismus by lengthening their axons so that nonadjacent ODCs of the right and left eye can be linked to create fusion (the elongated axon, monosynaptic neuron hypothesis)? If not, is there a neuroanatomic building block in V1 that could explain the high prevalence of fusion/ARC in small-angle strabismus and the low prevalence in large-angle strabismus? The results of our clinical study indicate that ARC decreases systematically as the angle of strabismus increases, and ARC is most prevalent in children with deviations of ≤4° to 5° (or 8-10 PD). Our neuroanatomic results show that there is no difference in axon length between healthy and strabismic primates, indicating that ARC must be created by using horizontal neurons with normal axon lengths (supporting the normal axon, polysynaptic hypothesis).

According to Van Essen et al's12 retinotopic maps of the striate cortex of the macaque monkey, the maximal axon length of an area V1 neuron as measured in our animals could have joined receptive fields of the deviated eye that were up to 2.5° (ie, 4-5 PD) away from the foveola of the fixing eye. That ARC is most prevalent in children with deviations of ≤8 to 10 PD (≤4°-5°) strongly suggests that the visual cortex is most successful at achieving ARC when it can combine information from nonadjacent ODCs that are no more than 1-to-2 horizontal neuron units apart.

**Prevalence of Anomalous Retinal Correspondence**

Bagolini (1967)1 and Parks (1969)11 emphasized that ARC is common in children who have small-angle strabismus and rare in children who have large-angle strabismus. However, a review of the literature reveals that the actual relationship between the presence of ARC and the angle of strabismus has been the subject of surprisingly few systematic studies. Jampolsky (1951)13 reported that ARC was
prevalent in smaller angle strabismus and present in more than 90% of patients who had a constant esotropia of ≤15 PD. Jampolsky published his study as a response to an earlier report by Adler and Jackson14 that claimed, paradoxically, a greater probability of ARC in large-angle (≥30 PD) strabismus. Jampolsky delineated the definitive and methodological shortcomings of the Adler and Jackson study, which when taken into account, effectively nullified the discrepancy between his and their results. Bagolini1 tabulated the results of his testing of 165 adults and children with esotropia, published as part of his definitive work on ARC in 1967. He demonstrated a systematic relationship between the prevalence of ARC and the angle of strabismus: the prevalence was more than 90% with esotropia <10 PD, and less than 16% with esotropia >40 PD. Burian and Luke (1970)15 published a study 3 years later in general agreement with the conclusions of Jampolsky and Bagolini, but the authors subdivided their cases into only 2 broad groups: those with strabismic deviations greater than and those with deviations less than 30 PD. ARC occurred more frequently in the Burian and Luke patients with deviations ≤30 PD.

To the best of our knowledge, there have been no reports before this study that have systematically examined the prevalence of ARC in children with small-, moderate-, and large-angle esotropic and exotropic strabismus. In agreement with Jampolsky, Bagolini, and Burian and Luke, our results show that ARC is most prevalent in children who have strabismic angles <15 to 30 PD. ARC decreases systematically as the angle of strabismus increases, and ARC is the rule (>90%) in children who have a primary or postsurgical esotropia of ≤4° to 5° (i.e., ≤8-10 PD), which confirms the clinical dictum of Parks and reinforces the clinical study of Bagolini. An effective argument can also be made that ARC is qualitatively more robust in this group with ≤10 PD on the basis of the high prevalence of gross stereopsis in these children. Stereopsis serves as additional evidence for ARC in patients who have small angle strabismus, as indicated by these 3 authors:

1. “Squinting patients with anomalous binocular vision showed some significant stereosensitivity in comparison to the group without binocular vision.”11
2. “...in the so-called ARC patients with 8A or less of deviation who can fuse the Worth 4 dots, who demonstrate a fusional vergence amplitude, and who simultaneously perceive the streaks on each retina created by Bagolini striated lenses, stereopsis is invariably demonstrated...”16
3. “There can be no argument that gross stereopsis (usually less than 120 minutes of arc) is a common finding in patients with anomalous correspondence and smaller-angle esotropia or microtropia and may occasionally even be demonstrable with random dot stereograms.”17

Our use of striated lenses and Worth/Polaroid tests as measures of ARC is a valid and widely clinically used methodology, supported by the work of Bagolini.1-3 A patient with a constant heterotropia cannot have fusion without some form of ARC. Bagolini demonstrated that the prevalence of ARC is stimulus dependent and that the use of striated lenses and the Worth 4 dot is a more sensitive method for detecting harmonious ARC than is use of the synoptophore (as shown in Figure 1, p. 348 Bagolini [1967]). Bagolini also emphasized the value of testing fusional vergence as an indirect assay for ARC, as we did in the strabismic monkeys.2 We emphasize that we did not correlate clinical features other than the angle of strabismus with the presence of ARC (e.g., a history of extensive occlusion therapy or the age of onset of a constant deviation). Our goal was to focus on the issue of the relationship between the prevalence of ARC and the angle of horizontal heterotropia in children with good visual acuity in both eyes, irrespective of other clinical features.

**Mechanisms in Visual Cortex**

In the nonhuman primate portion of the study, we found that horizontal neurons in strabismic monkeys have the same axon length as those in healthy monkeys, and they do not adapt to strabismus by lengthening V1 axons. If the neuroanatomic mechanism for ARC resides in V1 (see below), nonadjacent ODCs of opposite ocularity must be linked by a chain of normal-length horizontal neurons. A chain of neurons translates to a chain of synaptic connections with degradation of signal quality as the number of connections increases. An appropriate analogy for this signal degradation is to recall the dinner party exercise in which a verbal message is transmitted from one person to the next around the table, eventually returning to the originator. The degradation of the original message conveyed in such an exercise is famous. The distortion increases predictably as the number of diners (connections) increases. In the case of ODCs, this degradation-at-each-connection rule would predict that signals for binocular fusion (correlated activity signals) would weaken as the distance among ODCs representing corresponding retinal loci increases. We confirmed this stochastic prediction in the clinical part of our study by demonstrating that ARC decreases systematically in children with strabismus as the angle of strabismus increases.

The maximal axon length of horizontal neurons in V1 of both strabismic and healthy monkeys was about 7 mm. According to the standard retinotopic map of the striate cortex of the macaque monkey, a single neuron in a foveal, right-eye ODC could connect to a neuron in a left-eye ODC that was no farther than 2.5° away from the left eye’s fovea.12 We found that ARC is most prevalent in children with deviations ≤5° (8-10 PD). Extrapolating the monkey findings to the human patients, one would conclude that V1 is most successful at achieving ARC when it can link nonadjacent right-eye and left-eye ODCs that are no more than 2 horizontal neuron lengths apart.

Several investigators have suggested that the neuroanatomic mechanism for ARC may reside in areas out-
side of V1. The large receptive fields of cells found in the LS gyrus allow integration of input from a large area of retina, so that axon terminals would not have to travel a long distance to create ARC. Following this logic, Daw has postulated that the neurons play a major role in driving vergence eye movement to the secondary visual cortex.

It is possible that ARC occurs in humans and monkeys as the result of binocular interactions downstream from area V1 in extrastriate cortex. However, our findings suggest that one need not invoke an extrastriate mechanism for ARC in primates, for the following reasons. First, although binocular connections in V1 of naturally strabismic monkeys are reduced, about 50% of binocular connections remain even in large-angle strabismus. Second, a robust clinical-neuroanatomic correlation exists in V1, in that the humans with the highest likelihood of ARC have a strabismus of 2° to 5°, corresponding to 1 to 2 foveal V1 horizontal neuron lengths. Third, if extrastriate cortex were the principal locus for ARC in primates, one would predict from known neuroanatomy that ARC would occur commonly even in very large angles of strabismus. The extrastriate area MT in monkeys is the homologue of LS gyrus in cats, and the neurons of MT have receptive fields much larger than those of V1. Area MT is also known to play a major role in binocular fusion and stereopsis in monkeys. So far as is known, horizontal axon lengths in the visual cortex do not differ from area to area. The axon lengths we report here (approximately 7 mm) could, in MT, link the foveola of the right eye to an eccentric point in the left eye >40° away from the foveola. Robust ARC would thus be expected in primates, even with angles of strabismus >70 PD. This was not true in the strabismic monkey who had large-angle strabismus, and it was not true in the children with strabismus whom we studied. Finally, if the extrastriate cortex were the dominant locus for ARC in strabismic primates, one would expect to find many more binocularly responsive neurons in area MT than in area V1. However, physiologic recordings from MT and V1 in strabismic monkeys have shown equivalent low percentages of neurons that retain any binocular responsiveness.

**Phenomenon of Microtropia**

The importance of the neuroanatomic result reported here extends beyond the issue of ARC. It has explanatory value when applied to the ocular motor phenomenon of microtropia or monofixation syndrome. Binocular V1 neurons play a major role in driving vergence eye movements in monkeys, and the ≤2-neuron-unit rule we describe corresponds exactly to the stable angle of vergence misalignment observed in humans who have microtropia.

**References**