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Binocular summation in strabismus

A thesis submitted in partial satisfaction of the requirements for the degree Master of Science in

Clinical Research

By

Stacy Lynn Pineles

2013

ABSTRACT OF THE THESIS

Binocular summation in strabismus

By

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Masters of Science in Clinical Research

University of California, Los Angeles, 2013

Professor Robert Elashoff, Chair

Strabismus, or ocular misalignment is a common ocular disorder, affecting 3-5% of the population. Untreated strabismus can lead to permanent loss of vision from amblyopia or loss of binocular function and depth perception. This work aimed to further define objective and functional measures to characterize strabismus surgery outcomes and to further define the binocular experience of patients with strabismus using binocular summation as the outcome. The study findings suggest that strabismus causes a decrease in binocular summation compared to normal control subjects.

The thesis of Stacy Lynn Pineles is approved.

Elliot Landaw

Joseph Demer

Katrina Dipple

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University of California, Los Angeles

2013

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Chapter 1 – Expanded Introduction:

Strabismus, or binocular misalignment, is a common ocular disorder affecting 3-5% of the population.[1] Strabismus surgery is the most commonly performed ocular surgery in children.[2] Strabismus can take many forms, including horizontal, vertical, or torsional deviations. Although strabismus is common, there is a dearth of randomized clinical trials assessing surgical interventions for strabismus.[3-5] Aside from the lack of large clinical trials, there is also a lack of reliable functional measures that can be utilized in assessing outcomes after ocular realignment. Most studies of strabismus surgery outcomes only use ocular alignment measurements and do not evaluate functional visual outcomes.[6-9] In addition to being subject to examiner bias, ocular alignment measurements do not necessarily reflect functional outcomes, and in many cases, do not necessarily reflect binocular visual function. Because strabismus surgery is so commonly performed, it is crucial to develop reliable patient-oriented functional outcomes, such as how a subject's binocular function will change post-operatively. In many cases of strabismus, ocular realignment does not reflect the degree to which binocular function has changed. Stereopsis is occasionally used as a surrogate for binocular visual function; however, in cases of infantile-onset strabismus, stereopsis often cannot be achieved.[10] In addition, tests of stereoacuity are subject to binocular cues, and do not provide any information regarding coarser binocular function. Therefore, in long-standing cases of strabismus, such as adult onset consecutive deviations, other functional measures of binocularity may provide insight into the benefit of ocular realignment, and would be useful in assessing post-operative function. In many cases of adult strabismus without diplopia, ocular realignment is thought only to improve psychosocial aspects of the subject's life; however, it is likely that there are uncharacterized changes in binocularity demonstrated by binocular summation (BiS) measures.

BiS is defined as the superiority of binocular over monocular viewing on visual threshold tasks,[11] and can be attributed either to (1) "probability summation" – which assumes complete independence of the two eyes and predicts an enhancement of binocular over monocular vision

due to the statistical consideration that a binocular observer has two opportunities to detect weak signals, or (2) "neural summation" – the result of binocularly-enhanced performance that exceeds what would be expected from probability summation alone. Neural BiS has been shown to stem from interactions most likely in layer V1 of the visual cortex,[12,13] and occurs for several electrophysiological and psychophysical tasks, and is most easily demonstrated at low contrast spatial frequencies.[14] In the past four decades, BiS for low contrast stimuli has been well studied in normal subjects, and several important details have been elucidated. First, the magnitude of BiS in normal subjects, which is most commonly defined for a particular psychophysical task as: **BiS = Binocular Score / Better Eye Score** often approximates $\sqrt{2}$[15,16] or greater. [17-20] A theoretical explanation for the $\sqrt{2}$ approximation is that the visual system integrates both signal and uncorrelated noise from each eye, resulting in a two-fold increase in signal transduced. Since the noise amplitude is the $\sqrt{}$ of the sum of the monocular variances, the signal to noise ratio is $2/\sqrt{2}$, or $\sqrt{2}$. This theory involves purely excitatory pathways in binocular combination; more recent theories have introduced a two-stage model, which predict a higher BiS ratio[17] and assume both excitatory and inhibitory pathways[21] are involved in signal processing.

Advanced age[22] and interocular differences (IOD) in visual acuity (VA) both have detrimental effects on BiS. Subjects with large IODs in VA, either artificially induced by neutral density filters,[23] glare,[24] or due to pathologic states such as unilateral cataract,[25] anisometropia[26] or amblyopia[27] have decreased BIS. Studies of the role of retinal correspondence have shown that stimulation of non-corresponding points outside of the fusional range results in decreased neural summation.[11,28-31] In cases that exceed the tolerated range of IODs, a destructive neural interaction occurs, which is known as **Binocular Inhibition: Binocular Score / Better Eye Score < 1** The mechanism of binocular inhibition is not well defined, but is likely related to inter-ocular suppressive mechanisms in layer V1,[13,32] and most commonly occurs in subjects with large IODs in VA.

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There are very few studies that evaluate BiS and inhibition in subjects with strabismus; however, it is logical that strabismus should impact a subject's capacity for BiS. Based on previous studies showing that IODs play a key role in determining a subject's capacity for BiS, it is likely that if a manifest strabismus exists, the degraded image that falls outside of the fovea of the deviated eye may lead to an induced IOD in VA and therefore a decrease in BiS, or even *binocular inhibition*. Studies described above have defined the detrimental effect on BiS of stimulating two non-corresponding retinal points.[28-31] Aside from the correspondence of retinal points, the location of stimuli appears to play a role in a subject's capacity for BiS; amblyopic subjects with poor foveal BiS have been shown to demonstrate normal levels of summation in the retinal periphery.[33] This further argues for variations in levels of BiS in strabismus. Finally, in subjects with early-onset strabismus, there may be cortical abnormalities, including fewer binocularly driven cells, which contribute to abnormal BiS. A subgroup of patients that may respond differently is patients with large IODs in VA as the *etiology* of their strabismus ("sensory" strabismus). It is conceivable that realignment in this subgroup could *worsen* BiS by realigning a poorly seeing eye and inducing a more noticeable IOD in bifoveal VA.

BiS for low contrast acuity (LCA) can be measured in several ways. In adults, it has been measured using laboratory-based forced-choice procedures to determine contrast threshold,[17,22,27] low contrast letter charts,[34,35] and pattern stimulus visual evoked potential.[36-40] In children, BiS has been demonstrated as early as the fourth month of life,[41] and is most commonly measured using pattern-stimulus visual evoked response (VER) with moderate contrast levels.[42,43] BiS in normal infants may be higher than adults, with normalization to adult levels by 6 months.[39,42]

BiS has been studied in amblyopic subjects in several reports with conflicting results. Early studies argued that amblyopic subjects showed decreased BiS, or even binocular inhibition, when compared with normal controls.[44,45] The degree of BiS loss (and binocular inhibition) appears to be directly related to IOD in VA.[27] However, more recent studies have

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demonstrated that although BiS is decreased in amblyopic subjects, it can be improved by normalizing the IOD with neutral density filters,[32] revealing that amblyopes likely retain the neural mechanisms for BiS, but are at a disadvantage secondary to IODs and strabismus.

BiS has been less well studied in **strabismic populations** than in purely amblyopic populations; the few existing reports evaluated mainly subjects with infantile-onset strabismus. Most published studies utilize < 20 subjects with any single strabismus sub-type; many report BiS using visual evoked response (VER) in subjects less than 5 years of age. The results of these previous studies are conflicting, probably secondary to the small sample sizes, differing experimental conditions, and the variability in strabismus subtypes being compared. However, the majority have found that BiS may be decreased in some forms of strabismus, including large angle esotropia (ET),[37,38,42,46] decompensated exotropia (XT),[38] and simulated vertical strabismus in normal subjects.[36,40] Small angle ET has also been studied, with some investigators demonstrating a decrement in BiS in this sub-group,[36,38-40] and others reporting normal levels of BiS.[38] This discrepancy may be in part due to failures to characterize amblyopia or suppression and to account for IODs in VA.

Although these previous studies have laid groundwork for future studies of BiS in strabismus, they have not adequately addressed many strabismus sub-types, including acquired ET, intermittent and constant XT, cyclovertical deviations, and consecutive deviations in older patients. The studies lack standardization and adequate sample size. Furthermore, they all utilized only VER as their primary outcome, and have not evaluated accessible outcomes such as letter chart LCA.

Chapter 2: Manuscript

Introduction

Strabismus is a common ocular disease, occurring in 2-5% of the population.[47] Most clinicians who treat strabismic patients are aware of multiple inexplicable visual complaints in this population, including preference to close one eye to perform complex visual tasks, or in visually confusing settings, even when diplopia is absent. Although effective treatments for strabismus exist, our understanding of the functional binocular visual deficits in strabismus lags behind our knowledge of treatment. Currently, binocular function is assessed in clinical settings by evaluating fusion and stereoacuity.[48] However, some tests of stereoacuity and fusion have questionable validity because of monocular cues or dissociative testing methods. All tests of stereoacuity and fusion require a minimum level of visual acuity in each eye to assess binocular status. In addition, patients with early onset and/or longstanding strabismus typically perform poorly on such tests and show little improvement with treatment, so stereoacuity and fusion are not useful as clinical trial outcomes or in patient management in these cohorts.

Binocular summation (BiS), defined as the superiority of binocular over monocular performance on visual threshold tasks[11] , is a measure of binocular function that is not well characterized in strabismic patients. Unlike stereoacuity, BiS is not affected by monocular cues and can be reasonably assessed in patients with poor vision in one eye or who have had childhood strabismus interfering with the development of fusion potential. For fifty years, BiS has been well studied in normal subjects, and several important details have been elucidated. First, BiS improves performance on psychophysical tests at low contrast in normal subjects by approximately 40%[15,16] or greater.[17,19,20,49] In addition, it is known that advanced age[22] and interocular differences in visual acuity (VA) both impair BiS.[11,22,35,50] When interocular differences in VA are very large, a destructive neural interaction can occur, known as *Binocular Inhibition*, diminishing the subjects binocular score compared to that of the better eye. In these

cases, subjects see better monocularly than binocularly. Binocular inhibition, or a lack of BiS, may explain some of the previously inexplicable symptoms described by patients with strabismus.

It is tempting to think that strabismus would impair BiS. Based on previous studies showing that interocular differences in VA play a key role in determining a subject's capacity for BiS, we hypothesized that when a manifest strabismus causes an image to fall extrafoveally in the deviated eye, this may lead to an induced interocular difference in resolution of a target for a particular visual task, and therefore decrease BiS, or even produce *binocular inhibition*. The purpose of this study was to evaluate the effect of strabismus on BiS using a battery of psychophysical tasks that are clinically relevant and easy to use, and to determine whether strabismus is associated with binocular inhibition.

Methods

This study was approved by the University of California, Los Angeles Institutional Review Board and conformed to the requirements of the United States Health Insurance Portability and Accountability Act. Strabismic patients were recruited during the years 2010-2012 from the pre-operative clinic of four of the co-authors (SLP, JLD, FGV, SJI) during pre-operative visits. Exclusion criteria included any history of amblyopia, age less than 3 years or greater than 80 years, dissociated vertical or horizontal deviation as their sole form of strabismus, pathologic nystagmus, neurologic disease, or any structural lesion causing an interocular difference in visual acuity (after refraction) exceeding 0.3 logMAR. Non-strabismic control subjects were recruited amongst staff at the Jules Stein Eye Institute, as well as family members of patients who were seen between the years of 2010-2011. Control subjects were included only if they had no history of eye disease other than refractive error.

All subjects underwent a screening examination in which their visual acuity was tested using the Early Treatment of Diabetic Retinopathy (ETDRS) protocol with their habitual refractive correction.[51] If visual acuity was worse than 0.20 logMAR in either eye, a manifest

refraction was performed and the study tests were performed with this refraction. Next, binocular alignment was measured at distance (5 m) and near (30 cm) using cover/uncover and alternate prism cover testing. Right eye, left eye, and binocular testing was performed in order randomly assigned prior to testing that was consistently maintained for each subject, for the various psychophysical and electrophysiological tests. All testing was performed by trained technicians experienced in the examination of patients for research studies with adherence to detailed standard protocols, including written scripts and instructions for testing. The following tests were performed (in order of presentation to the subjects):

High Contrast Visual Acuity

Visual acuity (VA) was tested using the ETDRS protocol.[51] at 3 meters. The score VA was the number of letters identified correctly, with a maximum score of 70 (Snellen equivalent 20/12.5).

Low Contrast Visual Acuity (LCA)

Sloan acuity was tested (Precision Vision, La Salle, IL) at low contrast levels of 2.5%, followed by 1.25%, using the ETDRS protocol at 3 meters in a dimly-lit room. Sloan charts have a similar format to the ETDRS charts (5 letters per line) with each Sloan chart corresponding to a different contrast level. The low contrast acuity score is the number of letters identified correctly, with a maximum score of 70 (14 lines). Pelli-Robson charts (Metropia Ltd, UK) were also used to test contrast sensitivity at 1 m for each eye individually and binocularly.

Sweep Visual Evoked Potential (VEP)

Sweep VEP was tested using the PowerDiva (digital infant vision assessment) sweep VEP system in a dark room.[52] The stimuli were phase-reversal sine-wave gratings presented on a 17.5 29x38 cm high-resolution video monitor 1 m away at 50.3 cd/m² mean luminance. The active electrode was positioned on the midline of the scalp 1 cm above the inion, referenced to an ear-clip on the right ear and a ground on the left ear. Stimuli consisted of a horizontal square-wave grating (fixed spatial frequency of 1 cycle/degree) with a contrast range swept from 2 to 90% at 7.2 Hz fixed temporal

frequency. Contrast thresholds were measured by sweeping ten contrast levels over a 10-second trial with log steps. Log steps were used because contrast response functions are monotonically increasing functions associated linearly with increasing *log contrast* over a range of near-threshold contrasts. At least five sweeps were obtained, and sweeps with a signal to noise ratio>3:1 were averaged to calculate contrast threshold.[53]

Statistical Analysis

The demographic features of control and strabismic subjects were compared using Student's t-test for continuous variables, and chi square test for categorical variables. For letter charts (ETDRS, Sloan 2.5%, and 1.25%), BIS was calculated by dividing the better eye score into the binocular score (binocular/better eye score). For subjects who were unable to see any letters (letter score of zero), a score of 1 was substituted for the individual eye scores such that the BiS fraction could still be created (without having to divide by zero). A second analysis excluding these patients was also performed to evaluate for bias induced by this method of score replacement. For contrast threshold tasks (Pelli-Robson and sweep visual evoked potential), the contrast threshold was converted to contrast sensitivity (1/contrast threshold), and then BIS was calculated by dividing the better eye contrast sensitivity score into the binocular score. As a conservative correction for test variability, a BiS score exceeding 1.1 was required to demonstrate BiS. A value of 1.1 would indicate a 5-letter binocular improvement over that of the better eye. Similarly, binocular inhibition was considered to exist when the BiS score was 0.9 or less, to indicate a 5-letter or more decrement in vision with binocular vision compared to the better eye alone. The mean BIS scores for strabismic subjects were compared with those of normal controls using a a Hotelling T-test since there were five different tests per patient, as well as a t-test analysis for each individual test. The percentage of patients in each group demonstrating BiS and binocular inhibition was compared using Fisher's exact test. Linear regression analysis was then performed to evaluate the effect of age, a known covariate for BIS,

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and the presence or absence of strabismus. Finally, additional covariates such as age of

strabismus onset (based on clinical history), age at surgery (if there was a history of previous

strabismus surgery), and angle of deviation were evaluated using linear regression.

Results

Demographic Features

Sixty strabismic and eighty control subjects were enrolled. The mean age of the control

subjects was 34±15 years (range: 2.5-66 years, median 32 years), and 39±26 years (range: 2.2-

80 years, median 34 years) for the strabismic subjects (p=0.14). Demographic and visual acuity

information are summarized in Table 1. Thirty-nine percent of control subjects and fifty-five

percent of strabismic subjects were male (p=0.08). Sub-types of strabismus were: esotropia

acquired after 8 years of age (n=11), intermittent exotropia (n=11), early onset esotropia with

onset before 1.5 years (n=8), consecutive exotropia after surgery for infantile esotropia (n=7),

acquired hypertropia after age 1.5 years (n=7), presumed congenital superior oblique palsy

(n=6), childhood esotropia with onset between 1.5 and 8 years (n=5), mixed acquired horizontal

and vertical strabismus with horizontal and vertical component each larger than 10 D in central

distance gaze (n=3)., and acquired exotropia with onset after 1.5 years (n=2),

TABLE 1. Demographic and visual acuity information for subjects

	Age (years) mean±SD	VA OU (letters) mean±SD	IOD VA (letters) mean±SD	Angle of Distance strabismus (PD) mean±SD	Percent with diplopia
Control (n=80)	34 ±15 range: 2.5-66 median 32	60 ± 6 range: 44-70 median 61	3.8±4 range: 0-26 median 3	0±0 range: 0-0 median 0	0/80=0%
Strabismic (n=60)	39 ±26 range: 2.2-80 median: 34	56 ± 7 range: 27-68 median 55	4.8 ± 10 range 0-53 median 5	22±15 range: 0-65 median 19	19/60=32%
P-Value[1]	0.14	0.01	0.05		

[1] Two sample t-test
Abbreviations:
SD: standard deviation, VA: Visual acuity, IOD: interocular difference in visual acuity

Binocular Summation

Mean BiS is summarized in Table 2 for all groups. There was a significant overall decrement in BiS between strabismic and control subjects (Hotelling T^2=3.80, p-value = 0.0035). Subsequent univariate t-tests revealed a significant difference between control and strabismic subjects for the 2.5% (F=8.08, p=0.0053) and 1.25% low contrast Sloan charts (F=7.8, p=0.0062). Univariate t-tests did not find significant effects of treatment on BIS Pelli (F=3.7024, p-value = .571), BIS Sweep (F = .078, p-value = .78), or BIS VA (F=1.13, p-value = .29).

For the lowest contrast level (1.25%), strabismic patients overall demonstrated *binocular inhibition* with a mean BiS of 0.9. Therefore, overall, this group showed a detrimental effect of binocularity compared to monocular viewing with the better eye. In contrast, the normal control subjects on average had a 50% improvement (ratio=1.5) during binocular viewing compared with better eye monocular viewing. This analysis was repeated with censoring of subjects in whom zero letters were seen and had a substitution of a letter score of "1" for their individual eye scores on the 2.5% or 1.25% LCA charts (n=5). These results were similar (Table 3) to those with substituted values.

Table 2: Mean Binocular Summation Scores[1]

	ETDRS VA mean±SD	2.5% Sloan LCA mean±SD	1.25% Sloan LCA mean±SD	Pelli-Robson Contrast Sensitivity mean±SD	Sweep VEP Contrast Sensitivity mean±SD
Strabismus (n=60)	1.01 ± 0.07	1.0 ± 0.3	0.9 ± 0.4	0.99 ± 0.1	0.99 ± 0.45
Controls (n=80)	1.02 ± 0.05	1.3 ± 0.4	1.5 ± 1.0	0.97 ± 0.06	1.03 ± 0.49
P-value[2]	0.29	**0.0053**	**0.0062**	0.57	0.78

[1] Binocular summation score calculated as a ratio between the binocular letter score and the better eye letter score (binocular score/better eye score)
[2]Univariate t-test (2-tailed)
SD: standard deviation, ETDRS: early treatment diabetic retinopathy study, VA: visual acuity, LCA: low contrast acuity; VEP: Visual Evoked Potential

Table 3: Mean (±SD) Binocular Summation Scores[1] Excluding Subjects Seeing Zero Letters Binocularly

	ETDRS VA Letters Mean ± SD	2.5% Sloan Letters mean ± SD	1.25% Sloan Letters mean ± SD	Pelli-Robson Contrast Sensitivity mean ± SD	Sweep Visual Evoked Potential Contrast Sensitivity mean ± SD
Strabismus (n=55)	1.0 ± 0.07	1.0 ± 0.3	0.8 ± 0.4	0.99 ± 0.1	0.99 ± 0.44
Controls (n=80)	1.0 ± 0.05	1.3 ± 0.4	1.5 ± 1	0.97 ± 0.06	1.03 ± 0.49
P-value[2]	0.9	**0.005**	**<0.001**	0.4	0.7

SD: standard deviation, ETDRS: early treatment diabetic retinopathy study, VA: visual acuity, LCA: low contrast acuity

[1] Binocular summation score calculated as a ratio between the binocular letter score and the better eye letter score for the ETDRS, 2.5% Sloan, and 1.25% Sloan letter charts. For the Pelli-Robson and Sweep Visual Evoked Potential contrast threshold tests, the binocular summation score was calculated as a ratio between the better eye contrast threshold score and the binocular contrast threshold score.

[2]Univariate t-test (2-tailed)

For comparison, the percentage of subjects with BiS (BiS score >1.1) and binocular inhibition (BIS score <0.9) were compared (Table 4). The percentage of patients demonstrating BiS for the 2.5% LCA and 1.25% LCA was significantly higher in control than in strabismic subjects (p<0.001, p<0.001, respectively), while the percentage of patients demonstrating binocular inhibition for the 2.5% and 1.25% LCA contrast thresholds was significantly higher in strabismic subjects (p<0.0001 for both). For the 2.5% and 1.25% LCA tests, the percentage of subjects not demonstrating any summation or inhibition (BiS ratio between 0.9 and 1.1) was 25% and 25% for the control subjects and 59% and 65% for the strabismic subjects for the 2.5% and 1.25% LCA charts, respectively. Of these subjects, the majority of the control subjects (58% and 53%) had BiS ratios greater than one while the majority of the strabismic subjects (52% and 80%) had BiS ratios less than one for the 2.5% and 1.25% LCA charts, respectively.

Table 4: Percentage of Subjects with Binocular Summation and Binocular Inhibition[1,2]

	ETDRS Letters			2.5% Sloan Letters			1.25% Sloan Letters			Pelli-Robson Contrast Threshold			Sweep Visual Evoked Potential Contrast Threshold		
	S	C	P	S	C	P	S	C	P	S	C	P	S	C	P
% Patients with Binocular Summation (BiS>1.1)	7%	10%	0.8	25%	75%	**<0.0001**	21%	64%	**<0.0001**	9%	0	0.1	32%	36%	0.7
% Subjects with Binocular Inhibition (BiS < 0.9)	5%	0	0.1	16%	0	**<0.0001**	44%	11%	**<0.0001**	3%	12%	0.1	49%	46%	0.9

[1] Binocular summation score calculated as a ratio between the binocular letter score and the better eye letter score for the ETDRS, 2.5% Sloan, and 1.25% Sloan letter charts. For the Pelli-Robson and Sweep Visual Evoked Potential contrast threshold tests, the binocular summation score was calculated as a ratio between the better eye contrast threshold score and the binocular contrast threshold score.

[2] P-Values Calculated by Two-tailed Fisher Exact Test

Abbreviations: S: strabismus, C: control, BiS: Binocular summation score, ETDRS: early treatment diabetic retinopathy study

Multiple Linear Regression Model

Given the known decrement in BiS with increasing age, a multiple linear regression model of

BiS scores was developed incorporating as co-variates age and strabismus vs. control status

(Table 5). Scatterplots of BiS ratio vs. age are presented in Figure 1 for both strabismic and

control groups. P-values for the regression coefficient for the strabismus vs. control variable

were statistically significant for the 2.5% LCA (p=0.007), 1.25% LCA (p<0.0001), and Pelli-

Robson (p=0.02) but not for ETDRS VA or Sweep VEP -- this suggests that strabismus is

associated with decreased BiS even after correcting for age for Sloan low contrast letter charts,

but not for high contrast ETDRS charts and sweep VEP contrast thresholds. In addition, other

co-variates were examined by linear regression to evaluate potential associations with

diminished BiS, including age of onset, age at surgery, presence of diplopia, and angle of

deviation. No additional significant associations were found; however the study was not
sufficiently powered to rule out these possible associations.

Table 5: Linear regression model evaluating the association of strabismus, and increasing age with decreased binocular summation

Co-Variate		ETDRS VA	2.5% Sloan LCA	1.25% Sloan LCA	Pelli-Robson Contrast	Sweep VEP Contrast
Strabismus vs. Control Status	Regression Coefficient	0.007	0.08	0.25	-0.03	0.008
	P-value	0.3	**0.007**	**<0.0001**	**0.02**	0.85
Age (years)	Regression Coefficient	-0.0002	-0.002	0.001	4×10^{-5}	-0.0002
	P-value	0.5	0.08	0.9	0.4	0.4
R^2 Value		0.02	0.11	0.1	0.07	0.008

ETDRS: early treatment diabetic retinopathy study, VA: visual acuity, LCA: low contrast acuity, VEP: visual evoked potential
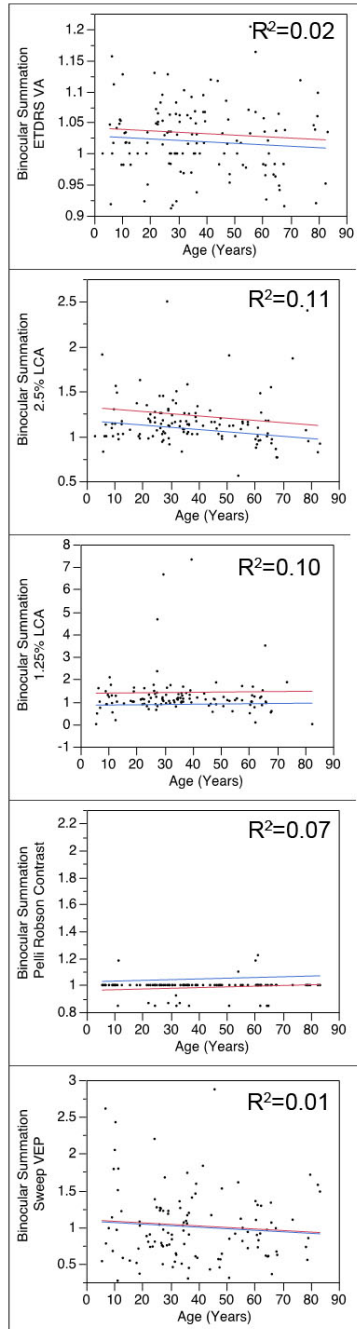
Figure 1: Scatterplot representations for multiple linear regression models of binocular summation accounting for age and strabismic vs. control status. Regression lines for strabismic patients are depicted in blue and for control subjects in red. R^2-values are depicted for each visual outcome. Strabismic vs. control status was the only statistically significant variable for 2.5% Sloan low contrast acuity (2.5% LCA, p=0.007), 1.25% Sloan low contrast acuity (1.25% LCA, p<0.0001), and Pelli-Robson Contrast threshold (p=0.02). Neither age nor strabismus vs. control status were significantly associated with increased binocular summation for high contrast Early Treatment Diabetic Retinopathy Study visual acuity chart (ETDRS VA) or Sweep visual evoked potential (VEP) contrast thresholds.

Discussion

Strabismic patients often have visual complaints that are difficult to characterize, but frequently these patients prefer to close one eye to achieve their best vision. Although the presence of diplopia can explain diminished binocular vision in many cases, it is not always perceived and is seldom the sole explanation for visual deficits. Our data suggests that strabismic patients often have decreased BiS and even binocular *inhibition* for very low contrast tasks.

Currently, clinicians use tests of stereoacuity and fusion to diagnose and monitor binocular visual deficits in strabismus. The present results demonstrate that there other functional binocular deficits existing in this patient group. Furthermore, some standard tests of stereopsis and fusion are less useful in this population as they are subject to monocular cues or use dissociative measures which might affect their validity. In addition, tests of stereoacuity and fusion require a minimum level of vision in both eyes, and often requires a baseline level of ocular alignment during the formative period of childhood development during which stereopsis is acquired.[10]. Therefore, in long-standing cases of strabismus, such as adult onset consecutive deviations, other functional measures of binocularity may be necessary to provide insight into the functionality of binocular vision and for use in following functional binocular vision over time, as well as for assessing the impact of ocular realignment surgery on binocular function. Many cases of adult strabismus without diplopia are thought only to impact the psychosocial aspects of the subject's life; however, in this study, we found that there are uncharacterized changes in binocularity that can be demonstrated by BiS measurements in subjects with strabismus.

BiS can be attributed either to (1) "probability summation" – which assumes complete independence of the two eyes and predicts enhancement of binocular over monocular vision due to the statistical consideration that a binocular observer has two opportunities to detect weak signals, or (2) "neural summation" – the result of binocularly-enhanced performance that exceeds what would be expected from probability summation alone. Neural BiS for various

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electrophysiological and psychophysical tasks has been shown to arise from interactions most likely in cortical layer VI, and is most easily demonstrated at low contrast.[54] Previous studies have shown that in normal patients, BiS often approximates √2 or greater, corresponding to a 40% improvement.[54] Our data confirms these studies in that the BiS ratio for control subjects was 1.3±0.4 and 1.5±1.0 for the 2.5% and 1.25% LCA charts, respectively. Interestingly, control subjects did not exhibit BiS for the contrast threshold tasks (Pelli-Robson chart and the sweep visual evoked potential), with BiS values of 0.96±0.07 and 1.03±0.49. These tests may be less sensitive clinical measures of BiS than the 2.5% and 1.25% LCA charts. It is not surprising that control subjects did not exhibit mean BiS >1.0 for the ETDRS, charts since it is well known that BiS is more enhanced for lower contrast tests. Interestingly, there were a few control subjects (n=9) who demonstrated binocular inhibition for the 1.25% LCA test. We believe this may be in part due to test-retest variability or patient fatigue. In addition, age or undiagnosed interocular difference for LCA may have contributed to the finding of binocular inhibition in these subjects. Despite this, we still found a significant difference between the control and strabismic subjects. Similarly, we might have expected more than 64% of the control subjects to exhibit binocular summation for the 1.25% LCA test. One potential explanation for this finding is our stringent definition of summation to be a BiS ratio greater than 1.1 instead of 1.0. If we use the definition of 1.0, then we would have found that 71 patients (89%) of the subjects would have had summation. Therefore, this finding can largely be explained by a small subgroup of patients who displayed summation but did not meet our criteria. There is also the potential that some of our control subjects were not visually "normal". Our screening criteria consisted of visual acuity, refraction, and ocular motility examinations. Therefore, the possibility of subjects with subtle abnormalities in contrast sensitivity may have been inadvertently included.

There is strong published evidence that advanced age[22] and large interocular VA differences both have detrimental effects on BiS. In addition, studies of the role of retinal

correspondence have shown that stimulation of non-corresponding points outside of the fusional range decreases neural summation.[29,31,55,56] In cases that exceed the tolerated range of interocular VA differences, binocular inhibition occurs (BiS<1.0). The mechanism of binocular inhibition is not well defined, but is likely related to inter-ocular suppressive mechanisms in layer VI,[57,58] and most commonly occurs in subjects with large interocular differences in VA. Based on the foregoing studies, we hypothesized that if a manifest strabismus exists, the degraded image that falls outside of the fovea of the deviated eye may lead to an induced difference in resolution of a particular target, and therefore cause a decrease in BiS, or even *binocular inhibition* on clinical testing. Our data supports this notion in that the mean BiS for the 1.25% LCA chart was 0.9 for strabismic subjects; and only 21% of the strabismic subjects demonstrated BiS for this measure, compared to 64% of control subjects (p<0.0001).

BiS has been studied in amblyopic subjects in several conflicting reports. Early studies argued that amblyopic subjects showed decreased BiS, or even binocular inhibition, when compared with normal controls.[44,45] The degree of BiS loss (and binocular inhibition) appears to be directly related to interocular difference in VA.[27] However, more recent studies have demonstrated that although BiS for contrast sensitivity is decreased in amblyopic subjects, it can be improved by normalizing the interocular difference with neutral density filters,[59] revealing that amblyopes likely retain the neural mechanisms for BiS, but are at a disadvantage secondary to interocular differences in VA. We chose to exclude amblyopic subjects from our study for this reason.

BiS has been less well studied in non-amblyopic strabismic populations than in purely amblyopic populations; the few existing reports evaluated mainly subjects with infantile-onset strabismus. Most published studies utilized less than 20 subjects,[36-40,42,43,46,60] and reported BiS using flash or pattern visual evoked response, often in subjects less than age 5 yrs. Results of these previous studies are conflicting, probably secondary to small sample sizes, differing experimental conditions, and the variability in strabismus subtypes being compared. However,

the majority found that BiS may be decreased in some forms of strabismus, including large

angle esotropia,[37,38,42,46] decompensated exotropia,[38] and simulated vertical strabismus in

normal subjects.[36,40] Most of these studies utilized only visual evoked responses as their

primary outcome, and did not evaluate clinically accessible outcomes, such as letter chart LCA.

In the current study, the decrement in BiS due to strabismus was most significant on the

Sloan 2.5% and 1.25% letter charts, which are readily available for clinical use. The finding of

decreased BiS (and a mean binocular inhibition for 1.25% letter charts) continued to be

significant even after accounting for the known covariate of age, as well as other predicted

covariates such as the angle or type of strabismus.

In addition to describing a novel method by which to assess and potentially track

binocular function in strabismic patients, we have also shown that BiS is most readily

demonstrated using Sloan low contrast letter charts. Both 2.5% and 1.25% contrast levels were

highly useful in differentiating strabismic from control subjects. This finding has been similarly

described in a large cohort of patients with multiple sclerosis.[35] In addition, when BiS was

calculated as a ratio between the binocular score and the better eye score, the normal control

subject mean was close to the estimated 1.414 (or $\sqrt{2}$) that has been commonly reported for BiS

in other laboratory psychophysical measures.

The results of our study should be understood within the context of its limitations. First,

sweep VEP measurements were performed at only one spatial frequency and at one temporal

frequency. Since BiS for VEP contrast sensitivity is dependent on spatial and temporal

frequency,[61] it is possible that different results might have been possible at different spatial or

temporal frequencies. This study included a wide range of ages and strabismus sub-types.

Multiple types of patients were included in order to evaluate the over-arching hypothesis that

BiS is diminished by strabismus. However, we were unable to look at specific strabismus sub-

groups. We are currently recruiting larger subgroups of specific strabismus types so that we

may address this question. In addition, we are following these patients longitudinally to evaluate

the impact that strabismus surgery has on BiS. Although the study was designed to include similar patient groups based on visual acuity and age, there was a clinically small (< 0.1 logMAR) but statistically significant difference in high contrast visual acuity and interocular difference between the strabismic and control groups. Finally, there were a few patients (n=5) who were unable to provide a measurable response for the lowest contrast 1.25% LCA task – these patients were assigned to a default value of 1 so that the BiS ratio score could be computed. However, our secondary analysis excluding these patients revealed strikingly similar results thereby diminishing concern related to induced bias from these five subjects.

Despite its limitations, this study represents the largest cohort of strabismic patients and normal subjects tested with clinically available tests to evaluate BiS. BiS is an easily measured parameter representing a difference in binocular visual function between strabismus patients and normal subjects that may represent a parameter that can be followed over time to monitor for changes in binocular function and post-operative changes after strabismus surgery. Our data from strabismic subjects showing sub-normal BiS and possible binocular inhibition suggests that strabismus impairs binocular vision more than previously appreciated.

Chapter 3: Appendix

Statistical Analysis

For this analysis, the Hotelling T^2 test was used to show that there is a difference between the two groups taking the fact that there were five different tests performed. In addition, univariate tests were used and the results showed that the two Sloan tests (2.5% and 1.25%) significantly demonstrated BiS. Given the very low p-values, no additional adjustments were performed to account for multiple comparisons. In addition, we felt that the significant result of the Hotelling test, which was performed first, created an umbrella for the multivariate results whereby it was reasonable to avoid correction for multiple comparisons when the subsequent individual t-tests were performed. For the two-group binary analysis, the 2-sided Fisher exact test was used, and for the quantitative analyses, a standard 2-group t-test was used. For the Sloan letter charts (ETDRS, 2.5% LCA, and 1.25% LCA), the histogram of results was fairly Gaussian in distribution. For the Pelli-Robson and sVEP results, the distributions were more uniform. However, given that the sample size was somewhat large, the t-test was still used under the umbrella of the central limit theorem.

Sample size calculation for study described above.

For sample size calculations, we made several conservative assumptions. First, of the multiple measures proposed to measure BiS, we assumed that the LCA letter/picture charts would be the least sensitive, since they represent the least precise instrument. This proved to be incorrect, but this regardless was our original assumption. We therefore based our estimates for sample size on recent data from the PI regarding BiS of low contrast letter chart scores in subjects with optic neuritis and healthy controls. We believed that subjects with strabismus are likely to have a larger detrimental effect on BiS than the optic neuritis subjects overall, because strabismic subjects have poor VA as the deviated eye views visual targets via a non-foveal region. In contrast, the poorer seeing eye of optic neuritis subjects in our study had a minimal difference in LCA from normal control subjects (9±10 vs. 11±11 letters, respectively). We

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therefore believed that using normal control subject and optic neuritis subject data provided a

conservative estimate of the necessary sample size for this study.

Table: Sample size calculations based upon study of optic neuritis vs. healthy control subjects

	α=0.05, β=0.2	α=0.05, β=0.1	α=0.01, β=0.2	α=0.01, β=0.1
N1 (Binocular – Better) for controls	7 letters	7 letters	7 letters	7 letters
N2 (Binocular – Better) for optic neuritis	5 letters	5 letters	5 letters	5 letters
Std. Dev1,Std Dev2	5, 6 letters	5, 6 letters	5, 6 letters	5, 6 letters
Power	80%	90%	80%	90%
Sample Size per group	94 Subjects	131 Subjects	153 Subjects	199 Subjects

Although we did not meet this sample size completely, we still found significant differences,

which shows that our sample size estimation was indeed conservative. For the purpose of this

thesis, we analyzed the data prior to reaching full recruitment completion.

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