Binocular Summation for Reflexive Eye Movements: A Potential Diagnostic Tool for Stereodeficiencies

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PURPOSE. Stereoscopic vision, by detecting interocular correlations, enhances depth perception. Stereodeficiencies often emerge during the first months of life, and left untreated can lead to severe loss of visual acuity in one eye and/or strabismus. Early treatment results in much better outcomes, yet diagnostic tests for infants are cumbersome and not widely available. We asked whether reflexive eye movements, which in principle can be recorded even in infants, can be used to identify stereodeficiencies.

METHODS. Reflexive ocular following eye movements induced by fast drifting noise stimuli were recorded in 10 adult human participants (5 with normal stereoacuity, 5 stereodeficient). To manipulate interocular correlation, the stimuli shown to the two eyes were either identical, different, or had opposite contrast. Monocular presentations were also interleaved. The participants were asked to passively fixate the screen.

RESULTS. In the participants with normal stereoacuity, the responses to binocular identical stimuli were significantly larger than those induced by binocular opposite stimuli. In the stereodeficient participants the responses were indistinguishable. Despite the small size of ocular following responses, 40 trials, corresponding to less than 2 minutes of testing, were sufficient to reliably differentiate normal from stereodeficient participants.

CONCLUSIONS. Ocular-following eye movements, because of their reliance on cortical neurons sensitive to interocular correlations, are affected by stereodeficiencies. Because these eye movements can be recorded noninvasively and with minimal participant cooperation, they can potentially be measured even in infants and might thus provide an useful screening tool for this currently underserved population.

Keywords: ocular following, stereopsis, binocular vision

Species with two frontally facing eyes compare information originating from the two retinas (i.e., extract interocular correlations) to enhance depth perception (stereopsis) and guide vergence eye movements. These benefits introduce a vulnerability: disruption of the normal development of binocular vision, which in humans mostly occurs during the first 6 months of life (the critical period), can lead to loss of (or severely limited) vision in one eye (ambylophia), and/or strabismus. Early treatment results in much better outcomes, making early detection of stereodeficiencies highly desirable. Unfortunately, current diagnostic tests are either cumbersome or require patient cooperation, making them poorly suited for large-scale screening of infants and children under the age of 2, especially in a primary-care setting.

We recently demonstrated that, unlike perceptual measures such as visual acuity and contrast matching, ocular following responses (OFRs) are much stronger for binocular than monocular stimuli (i.e., they exhibit strong binocular summation). We also found that this binocular summation is exquisitely sensitive to the interocular correlation between the images presented to the two eyes under binocular stimulation. This indicates that, in participants with normal stereovision, OFRs are mediated by disparity-sensitive cortical neurons. If this is indeed the case, one would expect OFRs in stereodeficient participants (whose cortical neurons are thought to be insensitive to interocular correlations) to not show such sensitivity, potentially making them a useful diagnostic tool.

Here we tested this hypothesis by measuring OFRs induced by fast-drifting one-dimensional (1D) noise patterns characterized by different interocular correlations. Monocular stimulation conditions were also interleaved. The results confirm our hypothesis and warrant further investigation and development of this method as a potential screening tool for stereodeficiencies.

METHODS

Participants

A total of 10 human participants, 5 with normal vision (aged 22–55; 1 woman) and 5 affected by a stereodeficiency (aged 43–72; 1 woman), participated in the study. All of the participants, normal and stereodeficient, had normal or corrected-to-normal visual acuity (i.e., 20/20 in each eye), and thus none had amblyopia (defined as a visual acuity deficit of neural origin that cannot be optically corrected). They also all had normal color vision (scoring 16/16 on the Ishihara test) and normal contrast sensitivity (scoring 1.50 or higher in each eye with the Pelli Robson test). The participants with normal vision...
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TABLE. Visual Capabilities of Stereodeficient Participants

| Subject | Sex | Age, y | Randot, arcsec | Worth 4 Dot | Pelli Robson OD/OS | Dominant Eye | Rx OD | Rx OS | Surgeries | Patching |
|---------|-----|--------|----------------|-------------|-------------------|-------------|-------|-------|-----------|----------|
| S1      | M   | 55     | >800           | 2 red       | 1.95/1.95         | 9° eso      | OD    | -6.25 +1.25 × 60 | -4.25 +1.50 × 110 | OS       | Yes      |
| S2      | M   | 43     | >1600          | 3 green     | 1.65/1.65         | 3° eso      | OS    | None (Lasik)    | None (Lasik)    | No       | No       |
| S3      | F   | 78     | >3500          | 3 green     | 1.65/1.65         | 6° eso      | OD    | -1.75 +1.25 × 135 | Plano +1.50 × 110 | No       | Yes      |
| S4      | M   | 47     | >400           | 2 red       | 1.65/1.50         | None        | OD    | -2.00 +0.50 × 60 | +3.00 +0.50 × 155 | No       | No       |
| S5      | M   | 55     | >3500          | Alternates  | 1.95/1.95         | 12° LHT     | OD    | +0.25 +1.50 × 40 | +0.75 +1.00 × 40 | 3        | Yes      |

M, male; F, female; OD, right eye; OS, left eye; eso, esotropia; LHT, left hypertropia.

had normal stereocuity (i.e., better than 40 arcsec, evaluated using the Titmus/Randot test). The participants with stereodeficient vision were selected to represent a broad range of stereodeficiencies, although they do not include all the pathophysiologies that can lead to impaired stereopsis; the results of the tests aimed at characterizing their visual function and treatment history are listed in the Table.

Experimental protocols were approved by the institutional review board (National Eye Institute, Bethesda, MD, USA) concerned with the use of human participants, and informed consent was obtained from each participant. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki); all personal identifiable information was handled in accordance with the privacy directives of the Intramural Research Program of the National Institutes of Health.

Apparatus

The participants sat in a dark room with their head stabilized using chin and forehead padded supports and a headband, facing a single monitor (VIEWPixx/3D; VPixx Technologies, Saint-Bruno, Quebec, Canada), located 50 cm in front of the corneal vertex. The monitor covered 53 cm × 37 cm, with a resolution of 1920 × 1080 pixels (60Hz). The screen had a mean luminance of 6.0 cd/m², and they were presented within a square aperture (28 cm × 28 cm) centered on the screen. The aperture was placed at eye level, following a physiological feeling of a top anesthetic (proparacaine hydrochloride). The output (sampled at 1000 Hz) was calibrated at the beginning of each recording session by having the participant look at targets of known eccentricity. Peak-to-peak noise levels resulted in an uncertainty in eye position recording of less than 0.05°.

The experiment was controlled by two computers: one running the Real-time EXperimentation software package to manage the workflow and acquire and store the data and the other directly connected to the monitor to generate the required visual stimuli in response to REX commands. This was accomplished using the Psychophysics Toolbox 3.0.8, a set of Matlab (Mathworks, MA, USA) scripts and functions.

Behavioral Paradigm

The trials were presented in blocks, and each block contained one trial for each stimulus condition. All conditions within a block were randomly interleaved. The participants with stereodeficient vision were not accustomed to wearing eye coils and thus were unlikely to tolerate them once the effect of the topical anesthetic wore off; furthermore, having them come back for multiple sessions was impractical. Accordingly, we limited data collection to 500 trials (50 repetitions per condition) collected in a single session. This is much less than what is customary in ocular following studies, resulting in lower signal-to-noise ratios. The control participants were also limited to a single session of the same duration for comparison purposes.

Each trial began with the screen filled with a binocular blank, mid-luminance (6.0 cd/m²), background. A central fixation cross was then presented to the dominant eye only. Monocular presentation of the fixation cross was then presented to the dominant eye only. Monocular presentation of the fixation cross was chosen to prevent stereodeficient participants, who usually suppress one of the monocular images, from alternating, in an uncontrolled manner, the eye used to fixate across trials. Our choice of using the dominant eye was arbitrary and considered not influential. Each participant was instructed to fixate the center of the cross and avoid blinking or making saccadic eye movements. After the participant maintained fixation for 800 to 1100 milliseconds within a square (1° on the side) invisible window placed around the fixation point, the fixation cross disappeared, and the visual stimulus sequence was presented for approximately 200 milliseconds. Subsequently, the screen was blanked (again at mid-luminance), signaling the end of the trial. After a short intertrial interval, a new trial was started. If the participant blinked or if saccades were detected during the stimulus presentation epoch, the trial was discarded and repeated within the block. Blinks during the fixation and intertrial interval were allowed and encouraged.

Visual Stimuli

Stimuli had a mean luminance of 6.0 cd/m², and they were presented within a square aperture (28 cm × 28 cm) centered on the screen. Outside the aperture the screen was blank at mid-luminance. Stimuli consisted of low-pass filtered horizontal 1D random line stimuli. Each stimulus was obtained by randomly assigning either a high or a low luminance value (symmetric around mean luminance) to each consecutive pair of pixel rows (0.06°); the resulting stimulus was then low-pass filtered in the Fourier domain (the gain of the filter was zero above 0.75 cpd and one below 0.375 cpd; the transition followed a raised-cosine function). Finally, the root mean square contrast of the stimulus was set to 24% (which kept the Michelson contrast below 100%, thus preventing saturations). We
imposed a fixed value of root mean square contrast (as opposed to Michelson contrast) because with noise stimuli root mean square contrast has been shown to be a better indicator of stimulus strength.11,12 Motion of the stimulus was simulated by shifting either up or down (by an integer number of rows at each frame), a pattern larger than the screen behind the fixed aperture (i.e., the stimulus did not “wrap around”). The drift speed was approximately 50°/s. The stimuli could be presented either to a single eye or to both eyes. During monocular presentations, a mid-luminance blank screen was presented to the other eye (Fig. 1). During binocular presentations, the two monocular images drifted at the same speed and in the same direction. Three different types of binocular stimuli were used, each characterized by a different interocular correlation. In the first stimulus the two monocular images were identical. This is a binocularly correlated (interocular correlation = 1.0) stimulus, with zero disparity, and we refer to it as binocular-same. In the second stimulus, the two monocular images were generated independently. This is a binocularly uncorrelated (interocular correlation = 0.0 on average) stimulus, and we refer to it as binocular-different. In the third stimulus one monocular image is obtained by contrast-reversing the other. This is a binocularly anticorrelated (interocular correlation = -1.0) stimulus, with zero disparity, and we refer to it as binocular-opposite. Comparing responses to binocular-same and binocular-opposite stimuli is particularly interesting, as they are identical, both globally and locally, in terms of spatial frequency content, temporal frequency content, and contrast, and differ only in interocular correlation. With binocular-different stimuli this is true only on average.

We selected horizontal stimuli to avoid having to carefully position the stimulus as a function of each subject tropia, a common concern in studies of binocular function in strabismic participants. In four of five of our participants with stereodeficient vision, the eye misalignment was either very small or largely horizontal. With horizontal gratings drifting vertically, horizontal misalignments do not introduce any disparity (except at the stimulus aperture), ensuring that the interocular correlation of the stimuli was only marginally affected by tropias in our participants. The last stereodeficient participant had a large vertical deviation, making his results open to multiple interpretations.

Data Analysis

Calibrated eye position traces were differentiated using a 21-point finite-impulse-response acausal filter (47 Hz cutoff frequency). Trials with saccadic intrusions and unstable fixation that went undetected at run time were removed using an automatic procedure aimed at detecting outliers.13 Average temporal profiles of the velocity of the instrumented eye, time-locked to stimulus onset, were then computed over the remaining trials, separately for each stimulus condition. To remove the effect of components of the eye response related to the disengagement of fixation,14,15 the difference between the OFRs to upward and downward motion directions was then computed. Finally, the magnitude of the ocular following response was estimated by computing the average difference eye speed within a time window (80–160 milliseconds from stimulus onset), which was selected based on the typical latency of OFRs to the stimuli used here.5 Unless otherwise noted, statistical analyses, including computations of standard errors and significance values, were carried out using nonparametric, bootstrap-based methods.16 A detailed description of the bootstrap procedures used can be found elsewhere.15

RESULTS

In our previous study,5 carried out in participants with normal vision, we discovered that (1) presentation of a drifting stimulus to both eyes induces a much stronger OFR than presenting it to one eye only, (2) binocular-different and binocular-opposite (i.e., contrast reversed) stimuli induce weaker OFRs than binocular-same stimuli, and (3) OFRs are conjugate for all monocular and binocular conditions.

Here we report the results of similar experiments in which we tested both normal and stereodeficient participants, which we expected to behave quite differently. Our previous experiments included a large number of conditions, which required many testing sessions with each participant. This was not practical in a clinical setting, and we thus reduced the number of conditions by restricting the stimulus to a single contrast level and five stimulus conditions (Fig. 1): monocular left, monocular right, binocular-same, binocular-different, and binocular-opposite (see Methods). Because the stimuli (low-pass filtered horizontal 1D noise patterns) drifted (at a speed of approximately 50°/s) either up or down, the total number of conditions was 10. We collected 50 trials per condition in a
single session, lasting approximately 15 minutes. To quantify the strength of the OFR we computed, separately for each condition, the mean vertical eye velocity of the instrumented eye in a fixed time window (80–160 milliseconds from stimulus onset). Drifts unrelated to stimulus motion were discounted, separately for each stimulus type, by subtracting the mean velocity induced by upward drifting stimuli that induced by downward drifting stimuli. We call this last measure the OFR magnitude.

In Figure 2A, we plot the OFR magnitude for all conditions, for participants with normal (black symbols) and stereodeficient (red) vision. Because absolute values of the OFR vary widely across participants, the data have been normalized by the OFR to the binocular-same stimuli; the OFRs for the two monocular conditions have been averaged. Confirming what we showed previously (using slightly different stimuli), in participants with normal vision (black), binocular-same stimuli induce the strongest responses, followed by binocular-different stimuli; binocular-opposite stimuli induce even weaker responses, very similar to those induced by monocularly presented stimuli. The participants with stereodeficient vision (red) differ from participants with normal vision in two ways. First, monocular responses appear to be relatively stronger, although there is overlap between the groups. Importantly, they exhibit minimal differences across binocular conditions: interocular phase relationships do not matter in participants with stereodeficient vision. The response to binocular-opposite stimuli was significantly smaller than that of binocular-same stimuli in each participant with normal vision \( (P < 0.001) \), but it was not in any participant with stereodeficient vision \( (P > 0.05) \). The average opposite/same ratio was 0.517 (0.123 SD) for the participants with normal vision, and 1.043 (0.06 SD) for the participants with stereodeficient vision, and their difference was highly significant \( (P < 0.0001, \text{two-tailed} \ t\text{-test}) \), even with our relatively small population size. The participants with normal vision and the participants with stereodeficient vision thus produced clearly distinct OFRs in response to our dichoptic stimuli. To highlight this aspect more clearly, in Figure 2B we plot the OFR magnitude to binocular-opposite versus that of monocular stimuli, in both cases divided by the OFR to binocular-same stimuli. The differential sensitivity between normal (black) and stereodeficient (red) participants emerges within 10 blocks, indicating that collecting 40 trials might be sufficient to diagnose a stereodeficiency.
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A retrospective power analysis based on our study can be used to inform the choice of the sample size required for future studies. This can be done by simply parametrically sampling from the (assumed Gaussian) distributions (one for the participants with normal vision and one for the participants with stereodeficient vision) from which our samples might have originated and performing a sample-size power calculation on each sample. We found that the commonly used power \(\alpha = 0.8\) is achieved in >95% of the samples with \(\leq 5\) participants (in each group), and 8 participants are needed if power = 0.95 is desired. These should be considered lower bounds for future studies (see the Discussion section).

**DISCUSSION**

We demonstrated that participants with normal vision, but not participants with stereodeficient vision, exhibit OFRs that are strongly sensitive to interocular correlation, making these eye movements potentially useful to diagnose stereodeficiencies and to study the development of stereopsis.

It is interesting to note that our stimuli, consisting of horizontal lines, are not associated with horizontal disparities, which underlie stereopsis (and are thus normally used to diagnose stereodeficiencies). That they reveal abnormal binocular interactions is, however, not particularly surprising because neurophysiological studies in primates \(20,21\) have demonstrated that responses of disparity selective cells are modulated by both vertical and horizontal disparity. It is then reasonable to presume that all of these cells would be affected by abnormal binocular development. The fact that we find such a clear anomaly in OFR sensitivity to interocular correlations along the vertical axis in a population identified by their abnormal perception of horizontal disparity supports these arguments.

Most stereodeficiencies emerge in the first 3 to 6 postnatal months, when fusion and sensitivity to absolute disparities (coarse stereopsis) develop \(2,22-27\) and must be treated promptly and aggressively to prevent amblyopia and stereodeficiencies.\(^1\)\(^3\)\(^8\) It is thus not surprising that the development of diagnostic tests appropriate for infants has been keenly pursued. Perceptual binocular gain at threshold is sizeable in normal, but absent in strabismic, participants\(^29-33\); however, it can only be measured in cooperating participants and is thus of limited use with those younger than 2 years of age. Video pupillometry was once thought promising, \(34\) but it was subsequently found to be unreliable.\(^35\) Visual-evoked potentials provide more consistent results,\(^2,22,27,28\) but they are not easily recorded in the clinic. The opto-kinetic nystagmus reflex is present from birth,\(^36\) and it sheds its nasal/temporal asymmetry as stereopsis emerges,\(^37\) making it yet another potential diagnostic tool.\(^38,39\) The stimuli required to evoke it are, however, hard to produce in a standard clinical setting. Both of these last two tests must be administered by trained personnel and require relatively expensive equipment and long testing times, making them unsuitable for a primary-care setting, where large-scale screenings are usually carried out.

We have shown here that ocular following recordings, with their minimal requirements for participant cooperation, might prove valuable. Although it is not currently known at what age OFRs emerge, available evidence points to an early onset. In monkeys, magnocellular neurons in the lateral geniculate nucleus appear early during embryonic development\(^40\) and are already functional 1 week after birth\(^41\); large-scale stimuli moving rapidly are detected as early as 10 days postbirth.\(^42-45\) In humans, bilateral horizontal movements are detected in the clinic. The opto-kinetic nystagmus reflex is present from birth,\(^36\) and it sheds its nasal/temporal asymmetry as stereopsis emerges,\(^37\) making it yet another potential diagnostic tool.\(^38,39\) The stimuli required to evoke it are, however, hard to produce in a standard clinical setting. Both of these last two tests must be administered by trained personnel and require relatively expensive equipment and long testing times, making them unsuitable for a primary-care setting, where large-scale screenings are usually carried out.

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substrate of global motion perception and OFRs, develop very early. Less clear is when the connections that carry these visual signals to the oculomotor periphery develop. Encouragingly, smooth pursuit, which is mediated by the same cortical and cortico-ponto-cerebellar connections as the OFRs, is already present at 2 months of age. If OFRs are present before the development of stereopsis, we expect them to be initially insensitive to interocular correlation and to acquire sensitivity to it as disparity-sensitive neurons develop. Continued insensitivity would be indicative of abnormal stereo-development and suggest the need for further evaluation and possibly intervention. The limiting factor in the usefulness of this test will be the frequency of false-positives (i.e., participants with normal vision with OFRs insensitive to interocular correlations). Although we have not encountered any in our small sample, it is important to note that the presence of neurons sensitive to binocular disparity is a necessary but not a sufficient condition for such sensitivity to emerge. For example, if the ocular following system were to pool across all motion sensitive neurons regardless of their preferred disparity, no overall sensitivity would be observed, and yet stereopsis could be perfectly normal. Based on our previous study, we concluded that OFRs are preferentially driven by neurons tuned to zero disparity, but how widely this holds across the stereo-normal population remains to be verified.

For OFRs to be a useful screening tool for binocular deficiencies, some alterations of our recording protocol will be necessary. In all experiments presented here, we collected at least 500 trials from each participant; however, as few as 40 trials, which can be collected in less than 2 minutes, might be sufficient to reveal a binocular abnormality (Fig. 2C). We noted previously that a power calculation based on our results suggests a minimum sample size of 5 to 8 participants per group. A larger sample is advisable in infants for three reasons. First, before binocular interactions are fully matured, infants with normal vision may show weaker binocular summation than adults with normal vision (i.e., a smaller effect). Second, responses in infants may be more variable than in adults, and reducing the number of trials might further increase variability. Finally, in our study, eye movements were recorded using search coils, which are rarely available in clinical settings and should be possible to deliver the stimuli and record the eye movements using a single inexpensive portable device (such as a smartphone or a tablet computer), facilitating large-scale screening even in underserved/developing communities.

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