Two Patterns of Interocular Delay Revealed by Spontaneous Motion-in-Depth Pulfrich Phenomenon in Amblyopes with Stereopsis

Yidong Wu,¹ Alexandre Reynaud,² Chunwen Tao,¹ Yu Mao,¹ Zhifen He,¹ Jiawei Zhou,¹ and Robert F. Hess²

¹The Eye Hospital, School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, Zhejiang, China ²McGill Vision Research, Department of Ophthalmology and Visual Sciences, McGill University, Montreal, Quebec, Canada

Correspondence: Jiawei Zhou, Wenzhou Medical University, 270 Xueyuan West Road, Wenzhou 325027, China; zhoujw@mail.eye.ac.cn.

Received: November 8, 2019 Accepted: January 3, 2020 Published: March 17, 2020

Citation: Wu Y, Reynaud A, Tao C, et al. Two patterns of interocular delay revealed by spontaneous motion-in-depth Pulfrich phenomenon in amblyopes with stereopsis. *Invest Ophthalmol Vis Sci.* 2020;61(3):22. https://doi.org/10.1167/iovs.61.3.22 **P**URPOSE. To assess interocular delays in amblyopes with stereopsis and to evaluate the relationship between interocular delays and the clinical characteristics.

METHODS. Twenty amblyopes with stereopsis (median, 400 arcseconds) and 20 controls with normal or corrected to normal visual acuity ($\leq 0 \log$ MAR) and normal stereopsis (≤ 60 arcseconds) participated. Using a rotating cylinder defined by horizontally moving Gabor patches, we produced a spontaneous Pulfrich phenomenon in order to determine the interocular delays, that is, the interocular phase difference at which ambiguous motion in plane was perceived. Two spatial frequencies—a low (0.95 cycles/degree [c/d]) and a medium (2.85 c/d) spatial frequency—were tested.

RESULTS. The absolute interocular delays of the amblyopic group was significantly longer than that of the controls at both low or medium spatial frequencies (P < 0.01). However, the interocular delays was not always in favor of the fellow eye: 35% of the amblyopes (7/20) showed a faster processing of the amblyopic eye than that of the fellow eye at 0.95 c/d and 29.5% (5/17) at 2.85 c/d. No significant correlation was found between interocular delays and the clinical characteristics (e.g., age, treatment history, stereoacuity, and magnitude of anisometropia) in this amblyopic cohort.

CONCLUSIONS. The interocular delays in amblyopes with stereopsis might result from either a faster or slower processing of the amblyopic eye relative to the fellow eye. This work provides important additional information for binocular processing of dynamic visual stimuli in amblyopia. However, the special role between this form of interocular delays and patients' clinical characteristics remains unknown.

Keywords: amblyopia, Pulfrich phenomenon, interocular delay

A pendulum swinging laterally back and forth across the observer's visual field (in a coronal plane) is perceived to follow a curved trajectory in depth (in a transverse plane) when seen binocularly with a neutral density filter in front of one eye. This phenomenon, first described by Carl Pulfrich,¹ is explained as the result of a processing delay between the two eyes induced by the luminance decrement. Possible mechanisms might involve either changes in the pure disparities over time for disparity sensors^{2–5} or changes to sensors that encode motion/disparity conjointly.^{6–9}

Amblyopes who developed rudimentary stereopsis (e.g., 550 arcseconds) may experience a spontaneous Pulfrich phenomenon.¹⁰ Similarly, this phenomenon has been assumed to be due to a processing delay of the information coming from the amblyopic eye.^{10–12} Reynaud and Hess's work¹³ aimed to assess this form of interocular delay and determine whether this form of interocular delay can be modulated by stimuli's spatiotemporal properties. Surprisingly, they found that the spontaneous motion-in-depth Pulfrich phenomenon seemed to be in favor of the ambly-

opic eye in five of eight amblyopes, which indicated that the processing concerned with amblyopic eye stimulation may be faster than that associated with fellow eye stimulation under conditions of binocular viewing. A definitive conclusion, however, could not be made because only eight amblyopes were tested in their study and for most of the patients, their magnitude of the interocular delay was not that different from that of controls (six of eight amblyopes within the range of mean \pm 3 SD of controls).

Here, using a similar structure-from-motion defined cylinder as that used by Reynaud and Hess,¹⁵ we reexamine this issue as to there being different patterns of interocular delays in a larger amblyopic cohort and control group. Considering that the amblyopic eye is generally impaired more seriously (i.e., the two eyes are more imbalanced) at higher spatial frequency,^{14,15} we selected a relatively low spatial frequency (LSF; 0.95 cycles/degree [c/d]) and a medium spatial frequency (MSF; 2.85 c/d) as test stimuli. We also evaluated the relationship between the form of the interocular delay and the clinical characteristics of the amblyopes.

Copyright 2020 The Authors iovs.arvojournals.org | ISSN: 1552-5783



1

Methods

Participants

Twenty amblyopes (mean age: 22.75 ± 6.1 years old; mean \pm SD; 14 males) with stereopsis (median, 400 arcseconds; range, 100-800 arcseconds; Yan's randot test¹⁶) and 20 normal controls (mean age, 23.90 \pm 1.7 years old; eight males) with normal or corrected to normal visual acuity $(\leq 0 \text{ logMAR})$ and normal stereopsis $(\leq 60 \text{ arcseconds}, \text{Yan's})$ randot test) participated in this experiment. The eye dominances of the normal controls were defined by the holein-the-card test.¹⁷ The clinical details of the amblyopes are reported in the Table. One control was excluded from data analysis because his psychometric function was abnormal (i.e., inverted-see Data analysis). Written informed consent was obtained from all participants or from the parents or legal guardian of participants aged less than 18 years old. This research has been approved by the ethical committee of Eye Hospital affiliated to Wenzhou Medical University and conformed to the Declaration of Helsinki.

Apparatus

The experiments were programmed and controlled on a Macmini computer A1347 (Apple, Cupertino, CA) with Matlab R2014a (MathWorks, Natick, MA) using the Psychophysics toolbox.^{18–20} A 27-inch 3D-Ready LED monitor LG D2792PB (LG Life Science, Seoul, South Korea) was used to achieve dichoptic presentation, placed at a viewing distance of 90 cm. The monitor was gamma corrected with a maximal luminance of 250 cd/m². It had a resolution of 1920 × 1080 and a refresh rate of 60 Hz. The participant viewed the stimuli in a dim lit room, wearing passive polarized 3D glasses, which had the effect of decreasing the luminance to approximately 43% and a crosstalk of 1%.

Stimuli

The paradigm was the same as in Reynaud and Hess' studies.^{13,21} The stimulus was a structure-from-motion defined cylinder of 18° width and 12° height, consisting of Gabor patches oscillating horizontally with a sinusoidal speed of 18°/s (Fig. 1A). The stimulus was presented dichoptically for 800 ms. The interocular phase of the oscillation was consistent between all trajectories of Gabor patches and was varied from trial to trial to generate strong to ambiguous percepts of the cylinder rotating in depth.^{22,23} We tested two sizes of Gabor patches, namely, 0.15° and 0.45°, corresponding to spatial frequencies of MSF (2.85 c/d) and LSF (0.95 c/d), respectively. Gabor patches were presented at a fixed contrast of 80% and had the same aspect ratio in both conditions, with a bandwidth of 1.36 octaves. The number of Gabor patches was set to 200 in the MSF condition and 66 in the LSF condition.

Procedures

Participants were asked to report to whether they saw the cylinder rotating clockwise or counterclockwise in a block design paradigm (Figs. 1A and 1B). A constant stimuli method was used to measure the proportion of perceived direction as a function of the interocular spatial phase difference. Interocular phase difference was picked within (-1.5° , -0.75° , -0.375° , -0.1875° , -0.0938° , -0.0469° , -0.0234° , 0° , 0.0234° , 0.0469° , 0.0938° , 0.1875° , 0.375° , 0.75° , and 1.5°), in which a negative value would generate perception of a counterclockwise rotating cylinder and a positive value would generate perception of a clockwise rotating cylinder (Fig. 1B). These 15 interocular phase difference values were repeated 10 times in a block; different interocular phase configurations were randomized in different trials. Each observer performed three blocks for each spatial frequency condition in a randomized order.

Data Analysis

As illustrated in Figure 1C, participant's psychometric function was fitted with a logistic function forced between 0 and 1. The estimated midpoint of the logistic function defines the point of subjective equality (PSE), that is, the point at which participants perceived the cylinder with a report of 0.5 clockwise and 0.5 counterclockwise. The PSE value was taken to indicate the processing delay of the left eve relative to the right eve. To simplify the comparisons between groups and between spatial frequencies, we computed two derivative measures of the fitted PSE: (i) the rectified PSE (rPSE), which is indicative of the processing delay of the amblyopic/nondominant eye relative to the fellow/dominant eye. For individuals whose left eye was the amblyopic/nondominant eye, the rPSE equals the PSE; for individuals whose right eye was the amblyopic/nondominant eye, the rPSE equals the -PSE. Hence, a negative rPSE indicates that the amblyopic eye/nondominant eye is delayed and a positive rPSE indicates that the amblyopic eye/nondominant is in advance; (ii) the absolute value of PSE (i.e., |PSE|) is indicative of the absolute interocular processing delay for individuals.

RESULTS

Spontaneous Motion-in-Depth Pulfrich Phenomenon Tested at LSF

Observers' rPSE and absolute value of PSE (|PSE|) at LSF are plotted in Figures 2A and 2B, respectively. One control participant was excluded from data analysis for LSF condition because the fitting of his psychometric function did not converge. The average rPSE of the controls was –0.001 \pm 0.052° (95% confidence interval [CI], -0.027 to 0.025°) and was –0.077 \pm 0.475° (95% CI, –0.299 to 0.146°) for amblyopes. For most controls, the rPSEs were slightly offset from 0°, whereas the rPSEs were much more variable in amblyopes. Accordingly, 13 of 20 (65%) amblyopes had a negative rPSE. This means that 65% of the patients (13/20) had a slower processing of the amblyopic eye than that of the fellow eye, whereas 35% of the patients (7/20) had a faster processing of the amblyopic eye than that of the fellow eye. The average value of the |PSE| was $0.038 \pm 0.035^{\circ}$ (95%) CI, 0.021–0.055°) in controls and 0.303 \pm 0.368° (95% CI, 0.130-0.475°) in amblyopes. The |PSE| of the amblyopes was significantly larger than that of controls (P < 0.01; twosided Mann-Whitney U test), indicating a much longer interocular delay in patients with amblyopia. The larger SD of the amblyopic group also indicates much more variability in this group. Figure 2C shows the slope of the fitted psychometric function. The slope of the amblyopes is significantly shallower than that of controls (P < 0.01; two-sided Mann-Whitney U test). This means that the performance of the controls is more consistent than that of amblyopes in the motion-in-depth Pulfrich task.

Two Patterns of Interocular Delay in Amblyopia

TABLE. Clinical Details of the Amblyopic Participants

				Visual Acuity					
	Sex/Age	Туре	Refraction OD/OS	(logMAR) OD/OS	Strabismus (pd)	RDS (Arc Seconds)	History	rPSE at LSF	rPSE at MSF
A1	M/26	anis	$+4.00/-1.00 \times 100$ +1.50/-0.75 × 135	$0.40 \\ -0.08$	Ø	200	Detected at 6 years old, patched for 1 year	-0.011	0.069
A2	M/21	anis	Plano	-0.18	Ø	100	Detected at 10 years old	0 170	0.138
	, = 1	unio	$+4.00/-1.50 \times 175$	0.10	2	100	patched occasionally until 13	0.170	0.190
A3	M/12	depr	+3.00/-1.00 × 180 +0.50	0.70 0	Ø	400	Detected capsular cataract at 11 years old, then underwent surgery and patched until now and has received vision therapy for 3 months	-0.082	-0.058
A4	F/19	anis	-0.50 +5.00/-1.00 imes 180	-0.08 0.82	Ø	600	Detected at 13 years old, no treatment	0.162	-0.058
A5	M/23	mix	-3.50/-1.50 imes 105 -6.00	$0.52 \\ -0.08$	HP L/R 4	400	Detected at 7 years old, patched until 9 years old	-1.374	2.604
A6	M/28	anis	$-1.00/-0.50 \times 30$ +3.50/-0.75 × 180	-0.08 0.22	Ø	200	Detected at 15 years old, no treatment	0.891	-1.727
A7	M/27	anis	+0.50 +2.50	0 0.22	Ø	100	Detected at 9 years old, patched for 1 month	-0.010	-0.032
A8	F/22	anis	-6.00/-3.00 × 75 -6.00	$0.22 \\ -0.08$	XP 10	100	Detected at 13 years old, patched occasionally for 1 year	-0.604	-0.180
A9	F/19	mix	-1.50/-4.50 × 180 +1.00/-6.50 × 175	0.10 0.22	X(T) 15	100	Detected at 12 years old, ther received strabismus surger for X(T) and patched occasionally for 6 months	n -0.074 y	-0.163
A10	M/21	anis	$+4.50/-1.00 \times 21$ -1.75	1 0	Ø	800	Detected at 18, no treatment	-0.252	-
A11	M/37	anis	$+2.5/-0.50 \times 90$ $+3.50/-3.25 \times 81$	0 0.22	Ø	200	Detected at 17 years old, no treatment	0.210	0.551
A12	M/10	anis	Plano +3.75/-0.75 × 180	$\begin{array}{c} -0.18\\ 0.10\end{array}$	Ø	400	Detected at 9 years old, patched occasionally till now	-0.844	-2.673
A13	F/21	anis	-0.50/-0.50 imes 180 + 3.25/-1.00 imes 180	0 0.70	Ø	400	Detected at 16 years old, no treatment	0.293	-1.085
A14	M/23	anis	$-3.25/-0.50 \times 11$ +2.50/-1.50 × 10	-0.08 0.22	Ø	400	Detected at 6 years old, patched for 1 year	0.502	2.232
A15	M/25	anis	-0.50 +5.00/-3.00 imes 178	0 0.70	Ø	400	Detected at 18 years old, no treatment	-0.162	-
A16	F/32	anis	$+6.50/-1.00 \times 80$ $-2.50/-0.50 \times 90$	0.82 0	Ø	600	Detected at 15 years old, patched occasionally for 6 months	-0.334	-
A17	M/24	anis	$-14.25/-1.00 \times 180$ $-7.75/-0.75 \times 10$	0.70	Ø	400	Detected at 18 years old, no treatment	0.028	-0.074
A18	M/20	anis	$+0.25/-1.25 \times 70$ $-0.75/-0.75 \times 180$	0.10 -0.08	Ø	200	Detected at 20 years old, no treatment	-0.014	-0.017
A19	F/20	anis	$+0.50/-0.50 \times 180$ $-2.75/-0.5 \times 180$	0.10	Ø	400	Detected at 20 years old, no treatment	-0.027	-0.251
A20	M/27	anis	$-5.00/-1.50 \times 20$ +0.50	-0.08 0.40	Ø	400	Detected at 18 years old, patched for 3 months	-0.008	-0.297

anis, anisometropic; depr, deprivation; HP, hypophoria; mix: strabismic + anisometropic; OD, right eye; OS, left eye; pd: prism diopters; RDS, randot stereoacuity; XP, exophroia; X(T), intermittent exotropia.

Spontaneous Motion-in-Depth Pulfrich Phenomenon Tested at MSF

Three amblyopes failed to perform the test at MSF, probably because of visibility issues. Their results, therefore, were excluded from analysis for the MSF condition. In Figures 3A and 3B, we plotted observers' rPSE and absolute value of PSE (|PSE|) at MSF. The average rPSE was $-0.017 \pm 0.071^{\circ}$ (95% CI, -0.051 to 0.017°) for controls and $-0.060 \pm 1.213^{\circ}$ (95% CI, -0.684 to 0.564°) for amblyopes. The average |PSE| was $0.054 \pm 0.047^{\circ}$ (95% CI, $0.031-0.077^{\circ}$) for controls and $0.718 \pm 0.963^{\circ}$ (95% CI, $0.223-1.213^{\circ}$) for



FIGURE 1. Illustration of the stimuli. (**A**) The stimuli composed of Gabor patches was presented dichoptically. (**B**) The phase difference in the oscillation of the Gabor patches between the two eyes generates a percept of a motion-defined cylinder rotating in depth. When the interocular phase difference of less than 0° , the cylinder is seen rotating counterclockwise; when the interocular phase difference equals 0° , the percept is ambiguous with Gabor patches moving to the left and to the right in the same plane; when the interocular phase difference was fitted with a logistic function. The midpoint of the logistic function at 0.5 performance defines the PSE. A negative value of PSE means the left eye was delayed.

amblyopes. Similarly, the absolute value of PSE (|PSE|) was larger for amblyopes than for controls (Fig. 3B; two-sided Mann–Whitney *U* test, *P* < 0.01), indicating a much longer interocular delay in patients with amblyopia. Five of the 17 amblyopes (29.5%) exhibited a positive rPSE (Fig. 3B), indicating that the amblyopic eye was faster than the fellow eye in processing the motion-in-depth Pulfrich task at MSF. In addition, |PSE| of amblyopes was significantly larger at MSF than that at LSF (two-tailed Wilcoxon signed rank test, P = 0.02). This means that the amblyopes' interocular delays were much longer at MSF. Also, there were larger SD and wider CI of rPSE in amblyopic group at MSF compared with LSF, suggesting much more variability at higher spatial frequency. For the control group, no statistical difference of



FIGURE 2. Interocular delay at LSF: controls vs. amblyopes. (**A**) The rPSE at LSF. Data points falling in the shaded area indicate that the amblyopic eye/nondominant eye was slower than the fellow eye. (**B**) The absolute value of the PSE at LSF. A larger value indicates a longer interocular delay. (**C**) The slope of the fitted psychometric function at LSF. Each point represents one individual observer: *circle*, control; *triangle*, amblyope. ***P < 0.01, two-sided Mann–Whitney U test. Error bars represent SEs.



FIGURE 3. Interocular delay at MSF: controls vs. amblyopes. (A) The rPSE at MSF. Data points falling in the shaded area represent that the amblyopic eye/nondominate eye was slower than the fellow eye. (B) The absolute value of the PSE at MSF. A larger value indicates longer interocular delay. (C) The slope of the fitted psychometric function at MSF. Each point represents one observer: *circle*, control; *triangle*, amblyope. Error bars represent SEs. ***P < 0.01, two-sided Mann–Whitney *U* test.

|PSE| was found between the two tested spatial frequencies (P = 0.38; two-tailed Wilcoxon signed rank test). Among 17 amblyopes who completed the task at MSF, the polarity of the rPSE of 2 participants changed from negative to positive and of 4 participants changed from positive to negative compared with the LSF condition.

In Figure 3C, we plotted the slope of the fitted psychometric function at MSF. Consistent with the previously described data at LSF, the controls performed more consistently than the amblyopes (two-sided Mann–Whitney *U* test, P < 0.01). Moreover, the slope at MSF was strongly correlated with the slope at LSF for both controls (Spearman correlation, r = 0.759; P < 0.01) and amblyopes (Spearman correlation, r = 0.929, P < 0.01). Compared with the slope at LSF, the slope at MSF was significantly steeper in normal controls (two-tailed Wilcoxon signed rank test, P < 0.01) and was marginally shallower in amblyopes (two-tailed Wilcoxon signed rank test, P = 0.076). These results indicated that the controls performed more consistently, whereas the amblyopes tended to perform more inconsistently at MSF than at LSF in the motion-in-depth Pulfrich task.

Spontaneous Motion-in-Depth Pulfrich Phenomenon: MSF vs. LSF

Figures 4A and 4B show the relationship of rPSE at the two tested spatial frequencies for controls (Fig. 4A) and

amblyopes (Fig. 4B). For both controls and amblyopes, no significant correlation was found between their rPSE at LSF and MSF (Pearson correlation, r = 0.220, P = 0.38; Spearman correlation, r = 0.056, P = 0.83). However, the rPSEs of the controls (Fig. 4A) generally fall around the identity line, whereas the rPSEs of the amblyopes (Fig. 4B) are dispersed widely on either side of the identity line. These results (Figs. 4A and 4B) may explain why there is difference on the |PSE| between the two spatial frequencies for the amblyopic group, whereas no significant difference was found on rPSE.

Two Patterns of Spontaneous Motion-in-Depth Pulfrich Phenomenon in Amblyopes: Relationship With Patients' Clinical Characteristics

So far, we have shown that the interocular delays in amblyopes are significantly longer than those in controls. However, in amblyopes we found two patterns of spontaneous motionin-depth Pulfrich phenomenon in different patients, that is, either a faster or a slower processing associated with amblyopic eye stimulation compared with fellow eye stimulation. It is interesting to know whether these two patterns of interocular delay correlate with any clinical characteristics of amblyopia. The Table shows the clinical details and the value of rPSE of amblyopes. Similar to the findings from Reynaud and Hess,^{13,21} several patients' interocular delays were



FIGURE 4. Interocular delays: LSF vs. MSF. (**A**) Scatterplot between control individuals' rPSEs at MSF and LSF. (**B**) Scatterplot between amblyopic individuals' rPSEs at MSF and LSF. An enlarged version of the central area of the plot is shown on the right. In **A** and **B**, data falling on the diagonal line indicate that the processing delay of the nondominate/amblyopic eye relative to the dominate/fellow eye was consistent at the two tested spatial frequencies; data points falling into the shaded area represent participants for whom the nondominate/amblyopic eye was faster at MSF. Each point represents one observer: *circle*, control; *triangle*, amblyope. Error bars represent SEs.

equivalent to that of controls. We therefore only included patients whose rPSEs were different from that of (mean \pm 3S D) the normal controls in the following analysis, that is, 12 of 20 amblyopes (60%) were included in the LSF condition and 8 of 17 amblyopes (47%) were included in the MSF condition.

In Figure 5, we plotted individual's rPSEs (Fig. 5A at LSF and Fig. 5B at MSF) or |PSE|s (Fig. 5C at LSF and Fig. 5D at MSF) as a function of the interocular visual acuity difference. We found no significant correlation (P > 0.60) for any of these conditions. In fact, whether at LSF or at MSF, an amblyope with a greater interocular visual acuity difference could exhibit either shorter or longer processing delay of the amblyopic eye relative to the fellow eye (i.e., rPSE); also, the absolute processing delay could be shorter or longer relative to the fellow eye (i.e., |PSE|). We also analyzed the correlation between rPSE or |PSE| and the patients' age, treatment history (i.e., had ever received treatment or not), stereoacuity (measured by Yan's randot test¹⁶), as well as the magnitude of any associated anisometropia. No statistically significant correlation was found in any of these cases (P > 0.11).

DISCUSSION

Using a paradigm that exploits the Pulfrich phenomenon,²¹ we show that the interocular delay experienced by amblyopes with stereopsis can be interpreted as either a slowing or a speeding up of visual processing associated with amblyopic eye stimulation relative to that of the fellow eye. These "two patterns" of posited interocular delay revealed by the spontaneous motion-in-depth Pulfrich phenomenon occur for both LSF (0.95 c/d) and MSF (2.85 c/d) stimulation.

Similar to Reynaud and Hess' study,¹³ we found that the interocular delays (i.e., rPSE) revealed by the spontaneous Pulfrich phenomenon were close to 0 degrees in normal controls (Figs. 2A and 3A). This indicates that the two eyes of normal adults are temporally balanced. However, the rPSEs of amblyopes showed a considerable variability compared with that of controls. To clarify the different patterns of interocular delays in amblyopes, we classified those cases with a rPSE outside the range of mean \pm 3 SD of controls as abnormal interocular delays. Reynaud and Hess¹³ report that

two of eight of their amblyopic participants were outside the normal range for the MSF condition: one patient had a faster processing associated with amblyopic eye stimulation relative to that of the fellow eye and the other showed the reverse pattern. Based on similar criteria, here we show that 8 of 17 amblyopes in the MSF condition and 12 of 20 amblyopes in the LSF conditions had abnormal interocular delays. Our current study supports the proposal that there are two patterns of interocular delay in amblyopes with stereopsis.

We also show that the |PSE| at both the two tested spatial frequencies were greater in amblyopes than in controls. This finding indicates that the eyes of the amblyopes are generally more temporally imbalanced than that of the controls. Additionally, the |PSE| at MSF was significantly larger than that at LSF. This finding suggests that the eyes of amblyopes may be more temporally imbalanced at higher spatial frequencies. In binocular spatial processes, there is evidence that the two eyes of the amblyopes are generally more imbalanced at higher spatial frequency for contrast thresholds,²⁴⁻²⁶ and suprathreshold contrasts.^{27,28} In this study, we show that the spatial frequency-dependent imbalance of amblyopes is also applicable to the temporal aspect of interocular processing. Our results thus provide additional support for the current notion that amblyopes are more binocularly imbalanced than controls, especially at higher spatial frequencies.14,15

For the cases whose interocular delay (in terms of rPSE) were out of the range of mean \pm 3 SD of controls, we further showed that the amounts of interocular delay, in either rPSE or |PSE|, were not significantly correlated with patients' clinical characteristics, including interocular visual acuity difference, age, treatment history, stereoacuity and degree of anisometropia. This finding was true for both of the spatial frequencies that we tested in this study.

In the spatial domain, it has been suggested^{29,30} that the interocular suppression is tightly linked to the severity of amblyopia (e.g., the interocular visual acuity difference). However, we showed that interocular delay is not correlated with interocular visual acuity difference (Fig. 5). This finding would indicate that an abnormal interocular delay in ambly-opes might not result from the same mechanism as the visual deficits in binocular spatial processes. Reynaud and Hess²¹



FIGURE 5. Relationship between the interocular delay and the interocular visual acuity difference in amblyopes whose rPSE are outside the range of mean \pm 3 SD of the controls. (**A**) The relationship between rPSE and interocular visual acuity difference at LSF. (**B**) The relationship between rPSE and interocular visual acuity difference at MSF. (**C**) The relationship between the absolute value of the PSE and interocular visual acuity difference at MSF. (**D**) The relationship between the absolute value of the PSE and interocular visual acuity difference at MSF.

found that, similar to binocular spatial processes,^{31,32} the spontaneous motion-in-depth Pulfrich phenomenon is also contrast-gain controlled. Thus, it is likely that these different binocular spatial and temporal processes might involve similar interocular contrast-gain control stage and separate additional visual processes later.^{33–35}

Reynaud and Hess²¹ found that an interocular contrast difference could generate a Pulfrich phenomenon in normal people. In our study, because the stimuli were presented at a fixed physical contrast, the relative visibility of the stimuli may have been different³⁶ between the two eyes for the observers with amblyopia. Hence, one might expect the processing of the amblyopic eye to be slower because it is likely to perceive a lower contrast. However, no meaningful correlation between interocular contrast sensitivity ratio and the interocular delay (rPSE) was found in amblyopia.¹³ By reducing the contrast of the Gabor patches seen by the fellow eve by 60%, Reynaud and Hess¹³ found that the fellow eve became relatively slower by a shift in PSE of approximately 0.2°. This value is much smaller than the average |PSE| of 0.7° reported here for amblyopes in the same condition (MSF). These observations suggest that the unmatched visibility between the eyes at suprathreshold contrast level may not be responsible for the two patterns of spontaneous Pulfrich phenomenon, but might have contributed to the binocular temporal processing in amblyopia.

Only two strabismic amblyopes were included in this prospective study because most of the strabismic amblyopes were not able to perform the Pulfrich task, probably owing to binocular misalignments.³⁷ For the two amblyopes with strabismus, that is, A5 and A9 (Table), only participant A5's rPSE was out of the range of mean \pm 3S D of controls. We, thus, cannot make a clear conclusion on the difference between different sub-types of amblyopia.

Amblyopia, as a neurodevelopmental disorder, is typically characterized by spatial processing deficits.^{14,15,38-41} However, accumulating evidence shows that there are temporal deficits within the visual pathway driven by the amblyopic eye. Hamasaki and Flynn⁴² suggested that the amblyopic eye shows longer reaction time to detect a 0.25° spot of light. Manny and Levi⁴³ suggested that the amblyopic eye performs poorly in detecting movement or flicker at a temporal frequency of 0.5 to 8.0 Hz. Wesson and Loop⁴⁴ demonstrated decreased contrast sensitivity at different temporal frequencies in the amblyopic eye. Spang and Fahle⁴⁵ found that temporal resolution of the amblyopic eye decreased in a task of segregating time-defined figure–ground stimulus. Huang et al.⁴⁶ found that the amblyopic eye exhibited a poorer ability to discriminate temporal asynchrony of a flickering target, suggesting a foveal lowlevel temporal processing deficit. Additionally, the temporal deficits of amblyopes received support from both electrophysiologic^{43,47} and functional magnetic resonance imaging work.⁴⁸ Despite different visual tasks and experimental methods, all of these studies revealed that the amblyopic eve was slower than the fellow eve in visual processing. However, other electrophysiologic studies suggested the opposite view. Greenstein et al.⁴⁹ reported that response latencies of the amblyopic eye measured with multifocal visual evoked potential were shorter than normal in strabismic amblyopes. Using single-unit recording in anisometropic amblyopic monkeys, Wang et al.⁵⁰ found that the response onset of the amblyopic eye was faster than normal, particularly in a high-contrast condition. These two studies indicated that the processing time of the amblyopic eye might be faster than that of the fellow eye in monocular stimulation condition-which is different from our binocular paradigm-and might explain why we also observed a faster processing of the amblyopic eye in a subset of amblyopes. Notably, most aforementioned temporal deficits were studied monocularly, whereas the interocular processing delay in this study is based on dynamic stimuli in binocular viewing condition.

Recently, Tao et al.⁵¹ showed that there are temporal synchrony deficits within the eye and between eyes in amblyopia. They found that the temporal synchrony thresholds of amblyopes under dichoptic viewing was significantly higher than that under monocular configuration. These results suggest that amblyopes' temporal deficits in dichoptic viewing condition cannot be explained by the monocular (amblyopic eye) deficits alone. Put differently, the temporal processing delay within the amblyopic eye may not necessarily result in an interocular temporal processing delay coming from the amblyopic eye, but rather in more general disruptions of temporal processing.46,52 We, thus, do not believe our findings could be fully explained by a temporal processing deficit limited to the amblyopic eye. We suspect that the two patterns of interocular delay observed in this study are the consequence of abnormal interocular interaction.

In conclusion, we show that there are two patterns of interocular delay in amblyopes who have rudimentary stereopsis when binocularly viewing dynamic visual stimuli, namely, pattern 1—the processing associated with amblyopic eye stimulation is slower than that of the fellow eye; and pattern 2—the processing associated with amblyopic eye stimulation is faster than that of the fellow eye. Further studies are needed to explore the underlying mechanisms and to evaluate how this form of interocular processing delay affects the binocular perception and real-world performance of amblyopes in daily life.^{53–56} It would be also interesting to see whether we can manipulate this delay precisely in combination with binocular treatments.^{57–59}

Acknowledgments

The authors thank Seung Hyun (Sam) Min for his very kind help in correcting our English.

Supported by the National Natural Science Foundation of China Grants NSFC 31970975 and 81500754, the Qianjiang Talent Project QJD1702021, the Project of State Key Laboratory of Ophthalmology, Optometry and Visual Science, Wenzhou Medical University K171206 and the Wenzhou Medical University grant QTJ16005 (JZ), the Canadian Institutes of Health Research Grants CCI-125686, NSERC grant 228103, and an ERA-NET Neuron grant JTC2015 (RFH). The authors alone are responsible for the content and writing of the paper.

Disclosure: Y. Wu, None; A. Reynaud, None; C. Tao, None; Y. Mao, None; Z. He, None; J. Zhou, None; R.F. Hess, None

References

- 1. Pulfrich C. Die Stereoskopie im Dienste der isochromen und heterochromen Photometrie. *Naturwissenschaften*. 1922;10:553–564.
- 2. Julesz B, White B. Short term visual memory and the Pulfrich phenomenon. *Nature*. 1969;222:639.
- 3. Morgan M. Stereoillusion based on visual persistence. *Nature*. 1975;256:639–640.
- Morgan MJ, Castet E. Stereoscopic depth perception at high velocities. *Nature*. 1995;378:380–383.
- Read JC, Cumming BG. All Pulfrich-like illusions can be explained without joint encoding of motion and disparity. *J Vis.* 2005;5:901–927.
- 6. Regan D. Binocular correlates of the direction of motion in depth. *Vision Res.* 1993;33:2359–2360.
- Cumming BG, Parker AJ. Binocular mechanisms for detecting motion-in-depth. *Vision Res.* 1994;34:483–495.
- Anzai A, Ohzawa I, Freeman RD. Joint-encoding of motion and depth by visual cortical neurons: neural basis of the Pulfrich effect. *Nat Neurosci*. 2001;4:513–518.
- 9. Harris JM, Nefs HT, Grafton CE. Binocular vision and motion-in-depth. *Spat Vis.* 2008;21:531–547.
- 10. Tredici TD, von Noorden GK. The Pulfrich effect in anisometropic amblyopia and strabismus. *Am J Ophthalmol.* 1984;98:499–503.
- 11. Hamasaki DI, Flynn JT. Amblyopic eyes have longer reaction times. *Invest Ophthalmol Vis Sci.* 1981;21:846.
- 12. Giuseppe N, Lucia R, Stefania R. Visual reaction times in strabismic amblyopia: a case-control study. *Acta Biomedica*. 2007;78:182.
- Reynaud A, Hess RF. An unexpected spontaneous motionin-depth Pulfrich phenomenon in amblyopia. *Vision*. 2019;3:54.
- 14. Ding J, Klein SA, Levi DM. Binocular combination in abnormal binocular vision. *J Vis.* 2013;13:14.
- 15. Kwon M, Wiecek E, Dakin SC, Bex PJ. Spatial-frequency dependent binocular imbalance in amblyopia. *Sci Rep.* 2015;5:17181.
- Li S, Zou H, Wei C. Stereoscopic visual acuity in types of ametropic amblyopia in children. *J Pediatr Ophthalmol Strabismus*. 2014;51:105–110.
- Dane A, Dane S. Correlations among handedness, eyedness, monocular shifts from binocular focal point, and nonverbal intelligence in university mathematics students. *Percept Mot Skills*. 2004;99:519–524. doi:10.2466/pms.99.2.519-524.
- 18. Brainard DH. The psychophysics toolbox. *Spat Vis.* 1997;10:433–436.
- 19. Pelli DG. The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat Vis.* 1997;10:437–442.
- 20. Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C. What's new in psychoolbox-3. *Perception*. 2007;36:1.
- 21. Reynaud A, Hess RF. Interocular contrast difference drives illusory 3D percept. *Sci Rep.* 2017;7:5587.
- 22. Treue S, Husain M, Andersen RA. Human perception of structure from motion. *Vision Res.* 1991;31:59–75.
- 23. Dodd JV, Krug K, Cumming BG, Parker AJ. Perceptually bistable three-dimensional figures evoke high choice probabilities in cortical area MT. *J Neurosci*. 2001;21:4809–4821.

- 24. Hess RF, Howell ER. The threshold contrast sensitivity function in strabismic amblyopia: evidence for a two type classification. *Vision Res.* 1977;17:1049–1055.
- 25. Levi DM, Harwerth RS. Spatio-temporal interactions in anisometropic and strabismic amblyopia. *Invest Ophthalmol Vis Sci.* 1977;16:90–95.
- Bradley A, Freeman RD. Contrast sensitivity in anisometropic amblyopia. *Invest Ophthalmol Vis Sci.* 1981;21:467–476.
- Reynaud A, Hess RF. Is suppression just normal dichoptic masking? Suprathreshold considerations. *Invest Ophthalmol Vis Sci.* 2016;57:5107–5115.
- 28. Zhou J, Reynaud A, Yao Z, et al. Amblyopic suppression: passive attenuation, enhanced dichoptic masking by the fellow eye or reduced dichoptic masking by the amblyopic eye? *Invest Ophthalmol Vis Sci.* 2018;59:4190–4197.
- Li J, Thompson B, Lam CSY, et al. The role of suppression in amblyopia. *Invest Ophthalmol Vis Sci.* 2011;52:4169–4176.
- Zhou J, Huang P-C, Hess RF. Interocular suppression in amblyopia for global orientation processing. *J Vis.* 2013;13:19.
- 31. Ding J, Sperling G. A gain-control theory of binocular combination. *Proc Natl Acad Sci USA*. 2006;103:1141–1146.
- 32. Meese TS, Georgeson MA, Baker DH. Binocular contrast vision at and above threshold. *J Vis.* 2006;6:1224–1243.
- Huang C-B, Zhou J, Zhou Y, Lu Z-L. Contrast and phase combination in binocular vision. *PLoS One*. 2010;5:e15075– e15075.
- 34. Huang C-B, Zhou J, Lu ZL, Zhou YF. Deficient binocular combination reveals mechanisms of anisometropic amblyopia: signal attenuation and interocular inhibition. *J Vis.* 2011;11:10.
- 35. Hou F, Huang C-B, Liang J, Zhou Y, Lu Z-L. Contrast gaincontrol in stereo depth and cyclopean contrast perception. *J Vis.* 2013;13:3.
- Hess RF, Bradley A. Contrast perception above threshold is only minimally impaired in human amblyopia. *Nature*. 1980;287:463–464.
- 37. Read JCA. Stereo vision and strabismus. *Eye.* 2015;29:214–224.
- 38. Mckee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *J Vis*. 2003;3:380–405.
- Baker DH, Meese TS, Mansouri B, Hess RF. Binocular summation of contrast remains intact in strabismic amblyopia. *Invest Ophthalmol Vis Sci.* 2007;48:5332–5338.
- Zhou J, Liu R, Feng LX, Zhou YF, Hess RF. Deficient binocular combination of second-order stimuli in amblyopia. *Invest Ophthalmol Vis Sci.* 2016;57:1635–1642.
- 41. Birch EE. Amblyopia and binocular vision. *Prog Retin Eye Res.* 2013;33:67–84.
- 42. Hamasaki DI, Flynn JT. Amblyopic eyes have longer reaction times. *Invest Ophthalmol Vis Sci.* 1981;21:846–853.

- 43. Manny RE, Levi DM. The visually evoked potential in humans with amblyopia: pseudorandom modulation of uniform field and sine-wave gratings. *Exp Brain Res.* 1982;47:15–27.
- 44. Wesson MD, Loop MS. Temporal contrast sensitivity in amblyopia. *Invest Ophthalmol Vis Sci.* 1982;22:98–102.
- 45. Spang K, Fahle M. Impaired temporal, not just spatial, resolution in amblyopia. *Invest Ophthalmol Vis Sci.* 2009;50:5207–5212.
- Huang PC, Li JR, Deng DM, Yu MB, Hess RF. Temporal Synchrony Deficits in Amblyopia. *Invest Ophthalmol Vis Sci.* 2012;53:8325–8332.
- Chadnova E, Reynaud A, Clavagnier S, Hess RF. Latent binocular function in amblyopia. *Vision Res.* 2017;140:73– 80.
- 48. Farivar R, Thompson B, Mansouri B, Hess RF. Interocular suppression in strabismic amblyopia results in an attenuated and delayed hemodynamic response function in early visual cortex. *J Vis.* 2011;11:16.
- 49. Greenstein VC, Eggers HM, Hood DC. Multifocal visual evoked potential and automated perimetry abnormalities in strabismic amblyopes. *J AAPOS*. 2008;12:11–17.
- Wang Y, Zhang B, Tao X, Wensveen JM, Smith ELR, Chino YM. Noisy spiking in visual area V2 of amblyopic monkeys. *J Neurosci.* 2017;37:922–935.
- 51. Tao C, Wu Y, Gong L, et al. Abnormal monocular and dichoptic temporal synchrony in adults with amblyopia. *Invest Ophthalmol Vis Sci.* 2019;60:4858–4864.
- 52. Meier K, Giaschi D. Unilateral amblyopia affects two eyes: fellow eye deficits in amblyopia. *Invest Ophthalmol Vis Sci.* 2017;58:1779–1800.
- Webber AL, Wood JM, Gole GA, Brown B. The effect of amblyopia on fine motor skills in children. *Invest Ophthalmol Vis Sci.* 2008;49:594–603.
- 54. Burgmeier R, Desai RU, Farner KC, et al. The effect of amblyopia on visual-auditory speech perception: why mothers may say "Look at me when I'm talking to you". *JAMA Ophthalmol.* 2015;133:11–16.
- 55. Kosovicheva A, Ferreira A, Vera-Diaz FA, Bex PJ. Effects of temporal frequency on binocular deficits in amblyopia. *Vision Res.* 2019;163:52–62.
- 56. Birch EE, Castaneda YS, Cheng-Patel CS, et al. Selfperception in children aged 3 to 7 years with amblyopia and its association with deficits in vision and fine motor skills. *JAMA Ophthalmol.* 2019;137:499–506.
- 57. Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. *Vision Res.* 2015;114:4–16.
- 58. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. *J AAPOS*. 2015;19:401–405.
- 59. Sauvan L, Stolowy N, Denis D, et al. Contribution of shorttime occlusion of the amblyopic eye to a passive dichoptic video treatment for amblyopia beyond the critical period. *Neural Plast.* 2019;2019:6208414.