

Acute onset incomitant image disparity modifies saccadic and vergence eye movements

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New-onset impairment of ocular motility will cause incomitant strabismus, i.e., a gaze-dependent ocular misalignment. This ocular misalignment will cause retinal disparity, that is, a deviation of the spatial position of an image on the retina of both eyes, which is a trigger for a vergence eye movement that results in ocular realignment. If the vergence movement fails, the eyes remain misaligned, resulting in double vision. Adaptive processes to such incomitant vergence stimuli are poorly understood. In this study, we have investigated the physiological oculomotor response of saccadic and vergence eye movements in healthy individuals after shifting gaze from a viewing position without image disparity into a field of view with increased image disparity, thus in conditions mimicking incomitance. Repetitive saccadic eye movements into a visual field with increased stimulus disparity lead to a rapid modification of the oculomotor response: (a) Saccades showed immediate disconjugacy ($p < 0.001$) resulting in decreased retinal image disparity at the end of a saccade. (b) Vergence kinetics improved over time ($p < 0.001$). This modified oculomotor response enables a more prompt restoration of ocular alignment in new-onset incomitance.

disparity results. This is a trigger for vergence eye movements, which realign the visual axis.

Vergence is a slow, disconjugate eye movement, which moves the eyes in opposite directions so that images of a single object are placed simultaneously on the fovea of each eye (Leigh & Zee, 2006). Vergence eye movements are the most prominent but not the only type of disconjugate eye movements. Saccades as well may show disconjugacy (i.e., the saccadic amplitude of the two eyes may differ; Averbuch-Heller, Lewis, & Zee, 1999; Straumann, 2007). A failure of the ocular alignment is clinically known as strabismus. A latent strabismus is present only when fixation of one eye is interrupted, whereas a manifest strabismus is present without interruption of the visual axis. The terms *phoria* and *tropia* are used to describe latent and manifest strabismus, respectively (von Noorden & Campos, 2002). Orthophoria is the condition of binocular fixation in which the lines of sight meet at a distant or near point of reference in the absence of a fusion stimulus. Strabismus may be classified into a concomitant and an incomitant type (von Noorden & Campos, 2002). *Incomitance* refers to the fact that the magnitude of ocular misalignment changes with the viewing direction. *Concomitant* strabismus is characterized by little variability of the strabismus angle in the different viewing positions, whereas the angle of deviation depends on the viewing direction in incomitant strabismus. Incomitant strabismus may be the result of a cranial nerve palsy and is commonly acquired in adulthood (J. P. Lee, 1996). Compensatory mechanisms to new-onset incomitance

Introduction

Binocular vision critically depends on the alignment of the visual axis, such that objects are represented on corresponding retinal areas. If the axis deviates, image

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are poorly investigated. From clinical experience, it is known that a new-onset incomitant strabismus becomes concomitant over time. The physiological state of orthophoria in all viewing directions in healthy individuals is possibly the result of continuous adaptive processes that drive the oculomotor system toward concomitance (Liesch & Simonsz, 1993).

Three processes are conceivable that may improve efficient ocular alignment after a saccade is made into a field of gaze with increased stimulus disparity. First, the saccadic amplitude of the two eyes may change independently so that the saccadic landing point moves in the same direction as the disparity of stimuli, resulting in a compensation of stimulus disparity at the end of a saccade. Such a saccadic disconjugacy has been described after training with incomitant stimulus disparity in healthy individuals (Averbuch-Heller et al., 1999; Eggert & Kapoula, 1995; Tyler, Elsaid, Likova, Gill, & Nicholas, 2012), in amblyopic persons (G. F. Maxwell, Lemij, & Collewijn, 1995), in strabismic humans (Kapoula, Bucci, Eggert, & Garraud, 1997), and in monkeys with induced strabismus (Fu, Tusa, Mustari, & Das, 2007). If saccadic disconjugacy does not entirely compensate for the disparity, a subsequent vergence response is required for single binocular vision. Thus, a second possible compensatory mechanism may be that the speed of a vergence response improves, resulting in faster restoration of binocular vision. Although it is known that the speed of a vergence movement depends on the stimuli and on the context (Takagi, Oyamada et al., 2001), the vergence response kinetics in the situation of incomitant disparity have not been investigated. A third possible compensatory mechanism might be incomitant phoria adaptation. Phoria adaptation, also known as prism adaptation, is a modification in the alignment of the eyes, which can be induced by sustained fixation of a visual stimulus in different spatial depths or by prolonged viewing through a prism in front of one eye (Kim, Vicci, Granger-Donetti, & Alvarez, 2011; Kim, Vicci, Han, & Alvarez, 2011). Incomitant phoria adaptation has been described for vertical incomitance (J. S. Maxwell & Schor, 1994; Schor, 1983; Sethi & North, 1987) but not for the more common horizontal incomitance. In this study, we have not investigated phoria adaptation; instead, we focused on investigating saccadic disconjugacy and the subsequent vergence response kinetics in a situation with horizontal incomitant image disparity. For this purpose, we searched for immediate changes and for adaptation, here defined as gradual change of a response over time, of the oculomotor response of healthy participants.

Material and methods

Ethical approval

The study was conducted with approval of the local ethic committee (Bern, Switzerland). All participants gave informed written consent in accordance with the Declaration of Helsinki.

Participants

Healthy participants with normal or corrected-to-normal vision took part in the experiments. None of the participants had a manifest strabismus or complained about double vision. All participants were tested without optical corrections. In Experiment 1, 16 participants (12 female; median age = 28 years, range = 21–61 years) participated. Nine participants were emmetropic, four participants had mild or moderate myopia (less than six diopters [dpt]), and three participants were presbyopic. In Experiment 2, 16 participants (four female; median age = 23.5 years, range = 22–57 years) participated. Eight participants were emmetropic, seven participants had mild or moderate myopia, and one participant was presbyopic.

Experiment 1

Apparatus

Participants were seated in front of a haploscopic setup, which allowed the stimulation of both eyes independently (Figure 1A). The haploscope consisted of two thin film transistor liquid crystal displays (TFT-LCD, 22 in., 75 Hz, 1024 × 768 pixels; LG, Seoul, South Korea) located on either side of the participant. Visual stimuli were projected via angled dichroic mirrors onto the eyes. The optic distance from the front to the screen was 54 cm (screen-mirror distance of 50 cm plus eye-mirror distance of 4 cm). All experiments were performed in a dark room. Head position was stabilized with a chin rest and a front rest to minimize any influence from the vestibular system on eye movements. Eye movements of both eyes were recorded at 1000 Hz using an infrared video-based desktop eye tracker (EyeLink 1000 V 4.56, SR Research Ltd., Mississauga, Ontario, Canada). The experiment was programmed with the software Experiment Builder (SR Research Ltd.). Each experiment started with the alignment of the optical system. Therefore, central stimuli on the left- and right-sided screen were moved until stimuli were perceived as a single image. Then we used the alternate cover test to fine adjust the screens until no phoria was detectable when switching the fixation from left stimulus viewed with the left eye to the right stimulus viewed with the

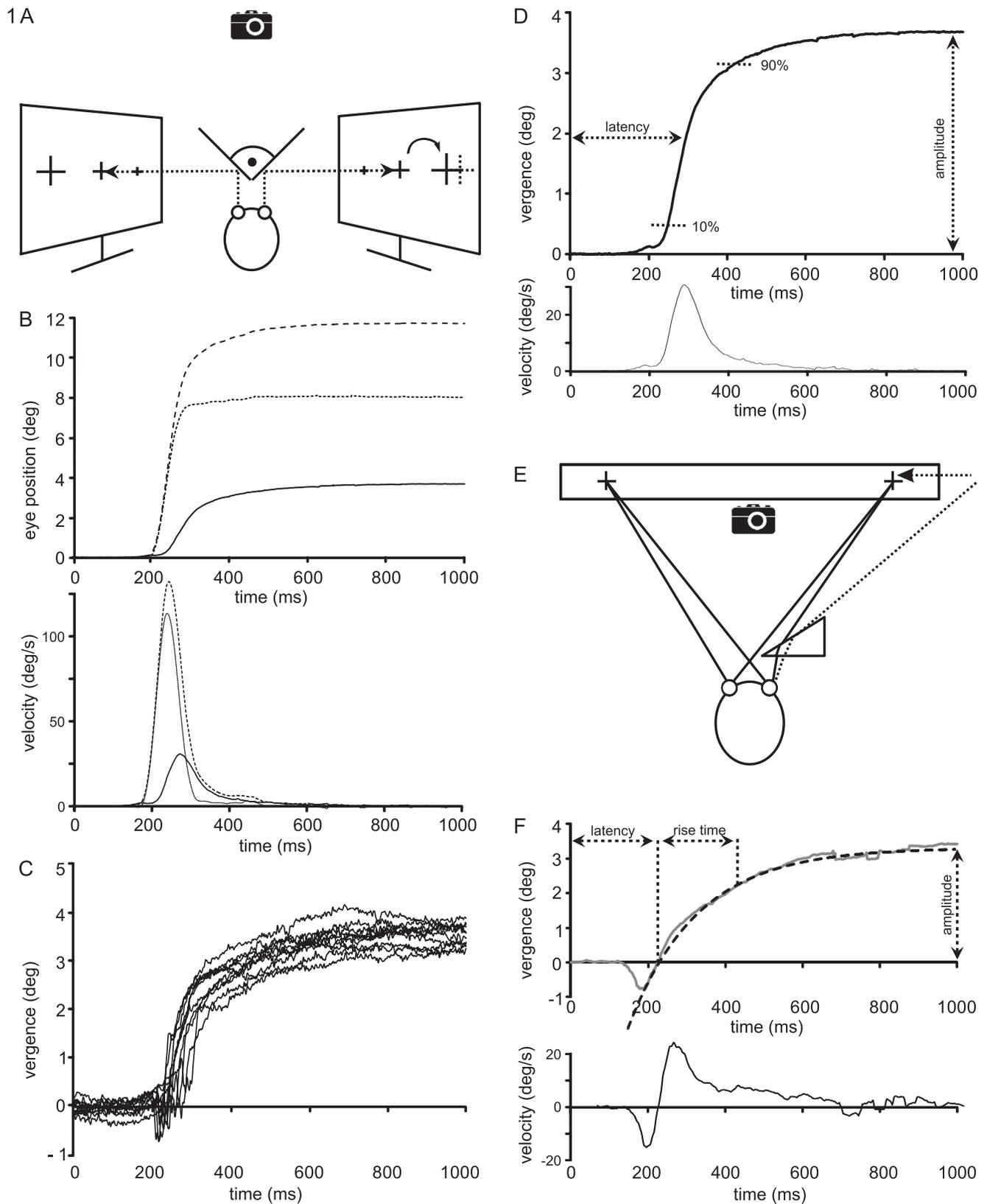


Figure 1. Experimental setup and data processing for Experiments 1 and 2. (A) Experimental design of Experiment 1 using the haploscopic setup. Target stimuli from two screens located on either side of the participant are projected over two mirrors so that participants perceive one single screen in front of them. Vergence movements are elicited by shifting one of the two stimuli along the

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horizontal axis. Participants make saccades from a binocular stimulus in the middle (without disparity) to a lateral binocular stimulus (8° to the right or to the left) presented with disparity in order to elicit a vergence response. (B) Vergence eye movements (solid line) were obtained by subtracting the x-positional value of the right eye (dotted line) from the x-positional value of the left eye (dashed line). As a result, positive vergence values indicate convergence and negative values diverging eye movements. The corresponding vergence velocity is shown below. (C) Superimposed raw vergence traces of the first 10 consecutive vergence eye movements of 1 participant. (D) Parameters used for analysis of Experiment 1: The vergence latency was defined as time span from the vergence stimulus onset (0 ms) until the curve reached peak velocity (horizontal arrow). The mean vergence velocity was determined for the time span that is required for the vergence response to increase from 10% to 90% (dotted lines) of its final value (right end of the horizontal arrow). The amplitude (vertical arrow) was determined at 1000 ms after vergence stimulus onset. (E) Experimental design for Experiment 2. A target stimulus is shifted from left to right. The right target is viewed through a six-diopter prism (3.42°), which is placed either base in or base out, resulting in divergence and convergence eye movements, respectively. (F) Parameters used for analysis of Experiment 2: The vergence response (solid gray) is fitted with an exponential fit (dashed black). The intersection of the exponential fit with the zero level was defined as onset of the vergence response from which vergence latency was derived. Rise time (i.e., τ) was defined as the time span required to reach $1 - 1/e = 63.2\%$ of its final value. Amplitude was defined as vergence amplitude 1000 ms after stimulus onset.

right eye. The eye tracker was then calibrated binocularly on three horizontal points. Therefore, stimuli were presented to one eye only while recording both eyes. This procedure results in calibration position values without incomitance or phoria in side gaze. Calibration was accepted if the accuracy of the validation was better than 1° . Before each of the two blocks, the accuracy of gaze was tested with a drift check, in which the actual position of gaze in the center of the screen is compared with the calibrated point. If the drift of gaze was too large, calibration was repeated.

Stimuli

The experiment consisted of two blocks of 160 trials (*baseline* block and *disparity* block). Each trial started with a stimulus in the center of each screen. Stimuli were black crosses (diameter of 0.5° with 0.1° of line thickness) on a white background on each of the two monitors. After a random interval of 1500–3000 ms, the central stimulus was replaced by a stimulus that was located either 8° to the left or 8° to the right, remaining again visible for a random period of 1500–3000 ms. Participants were instructed to visually track the stimuli. The location of stimulus appearance was randomly distributed with a ratio of 1:4 for left- and right-sided stimuli, respectively. Thus, one out of five goals was located on the left side, and four out of five goals were located on the right side. In the baseline block, targets on the right side were presented without stimulus disparity, and targets on the left side were shown with a lateral disparity of 4° . To create stimulus disparity, the stimulus on the right monitor was shifted by 4° horizontally, requiring a convergent eye movement for fusion. In the disparity block, stimuli on both sides were presented with an incomitant disparity of 4° .

No stimulus disparity was present for the central stimulus.

Data analysis

For the analysis of saccadic amplitude, we exported the first saccades with an amplitude greater than 4.5° after stimulus onset for each trial. Saccades with directional error greater than 13.5° were excluded. To assess saccadic disconjugacy, we subtracted the saccadic amplitude of the right eye from the saccadic amplitude of the left eye. Thus, positive values indicate a convergent eye movement during a saccade. Saccadic disconjugacy was calculated for the baseline as well as for the disparity block for each participant and each trial.

To obtain the vergence response, the horizontal gaze position of the first 1000 ms after stimulus onset of the right eye was subtracted from the horizontal gaze position of the left eye for each trial (Figure 1B). As before, positive values represent convergent eye movements and negative values divergent eye movements. To address the kinetics of the vergence response, we determined the mean velocity to rise from 10% to 90% of its asymptotic value for each trial and each participant (Figure 1D). As an estimate of vergence latency, we used the time span from vergence stimulus onset (0 ms) to the peak velocity of the vergence response. The amplitude was defined as the mean difference from a baseline level (50 ms before the vergence stimulus) to a level at which the curve reached a steady state again (950–1000 ms after vergence stimulus). For creating graphs, five subsequent trials were averaged in each participant for each of the measured parameters (mean velocity, latency, amplitude). Then, data from all participants were averaged. For data analysis, Data Viewer (V 1.11.1, SR Research), Excel (Microsoft), and

Clampfit V 10.3.1.4 (2011, Molecular Devices, LLC) were used.

For statistical analysis, we used a linear mixed-effects model with vergence mean velocity, latency, or amplitude as the dependent variables and trial number as the independent variable. The latter was used as measure of time. The change of a dependent variable over subsequent trials is here defined as “adaptation.” Participants were used as random effect. Values are reported as mean with the 95% confidence intervals (CIs). Statistical significance was defined as p values below 0.05. To select between different fitting models (random intercept, random slope, or combined), we used Akaike’s Information Criterion (AIC) and chose the best model by the principle “smaller is better.” Analyses were performed using the MIXED procedure in SPSS (IBM SPSS Statistics 21).

Experiment 2

Apparatus

For Experiment 2, participants were seated 63 cm from a 20-in. CRT monitor (ViewSonic G220fb) with a resolution of 1024×768 pixels and a refresh rate of 60 Hz. Eye movements were recorded as described in Experiment 1. Each participant was calibrated with a nine-point horizontal-vertical calibration grid at the beginning of the experiment. Calibration was accepted if the positional error did not exceed 1° . Drift check (see Experiment 1) was used to control the accuracy of gaze before each of the three blocks.

Stimuli

The experiment started with a no-disparity block followed by a disparity block, which was followed by another no-disparity block. The no-disparity blocks consisted of 25 trials each, and the disparity block consisted of 100 trials. For half of the participants, this sequence was done once with a lateral stimulus disparity shift (see below for explanation) in the first sequence, followed by a medial stimulus disparity shift in the second sequence. For the other half of the participants, this order was reversed. Each trial started with a stimulus on the left, which remained visible during a random period of 1900 ms (i.e., when vergence response reached steady state) to 2700 ms to prevent temporal predictability of stimulus onset. The left stimulus was then replaced by a stimulus 20° to the right. A larger saccade distance as compared with the first experiment was used to clearly separate the view without prisms from the view with prisms. The right stimulus also remained visible for a random period between 1900 and 2700 ms. The next trial started again with the stimulus on the left side.

Stimuli were black circles with a diameter of 1° of visual angle. In the no-disparity blocks, the stimulus on the left and the right side were viewed without prisms, thus with no disparity. In the disparity blocks, a prism was placed in front of the right eye such that the left stimulus could be seen directly (not through the prism) but the stimulus on the right was seen through the prism (Figure 1E). Prisms were always placed in front of the right eye. The infrared video camera tracked the eyes from below the prism (i.e., the eyes were never recorded through any prisms or glasses). We used a six-prism diopter prism (pdpt, 6 pdpt = 3.42°), which was placed either base in or base out. Base-in prisms resulted in a lateral shift of the perceived stimulus of the right eye; thus, a lateral shift of image disparity resulted in a divergent fusional eye movement. When the prism was placed base out, participants experienced a medial shift of the perceived right image. This resulted in a convergent fusional eye movement.

Data analysis

As for Experiment 1, the vergence responses were obtained by subtracting the horizontal gaze position of the left and the right eye from each other. Again, we excluded all trials with missing or incomplete values in the first 1000 ms after vergence stimulus onset. To adjust the baseline to 0, we subtracted the average vergence response of the first 50 ms from each trial. To reduce noise, the average of two consecutive trials was used for further analysis. As in Experiment 2, the saccade artifact of the vergence response was considerable; the analysis as used in Experiment 1 was not applicable. We thus decided to analyze the vergence response by fitting an exponential curve ($y[x] = M \times \exp[-x/Tau] + A$) between 250 and 1000 ms after stimulus onset (Figure 1F). We then used Tau , M , and A for statistical analysis. The time constant Tau (time span for the response to reach $1 - 1/e = 63.2\%$ of its final, asymptotic value) is used as a measure for the rise time of the response. M is the maximal amplitude, whereas A is the steady-state amplitude level to which the exponential curve rises or decays to. Here, A is used as a measure of the final amplitude of the vergence response. The latency was defined as the time from stimulus onset until the point of time when the fitted exponential curve crosses the zero level of the x -axis (latency [$x = 0$] = $Tau \times -\ln[-A/M]$; \ln = natural logarithm). Next, we excluded all rise time values that were not between 60 and 1000 ms and all latency values not between 60 and 600 ms as obvious outliers. For data analysis, we used SR Research EyeLink Data Viewer V 1.11.1, Excel, and WinWCP V 4.4.7 (Dr. John Dempster, University of Strathclyde, Scotland).

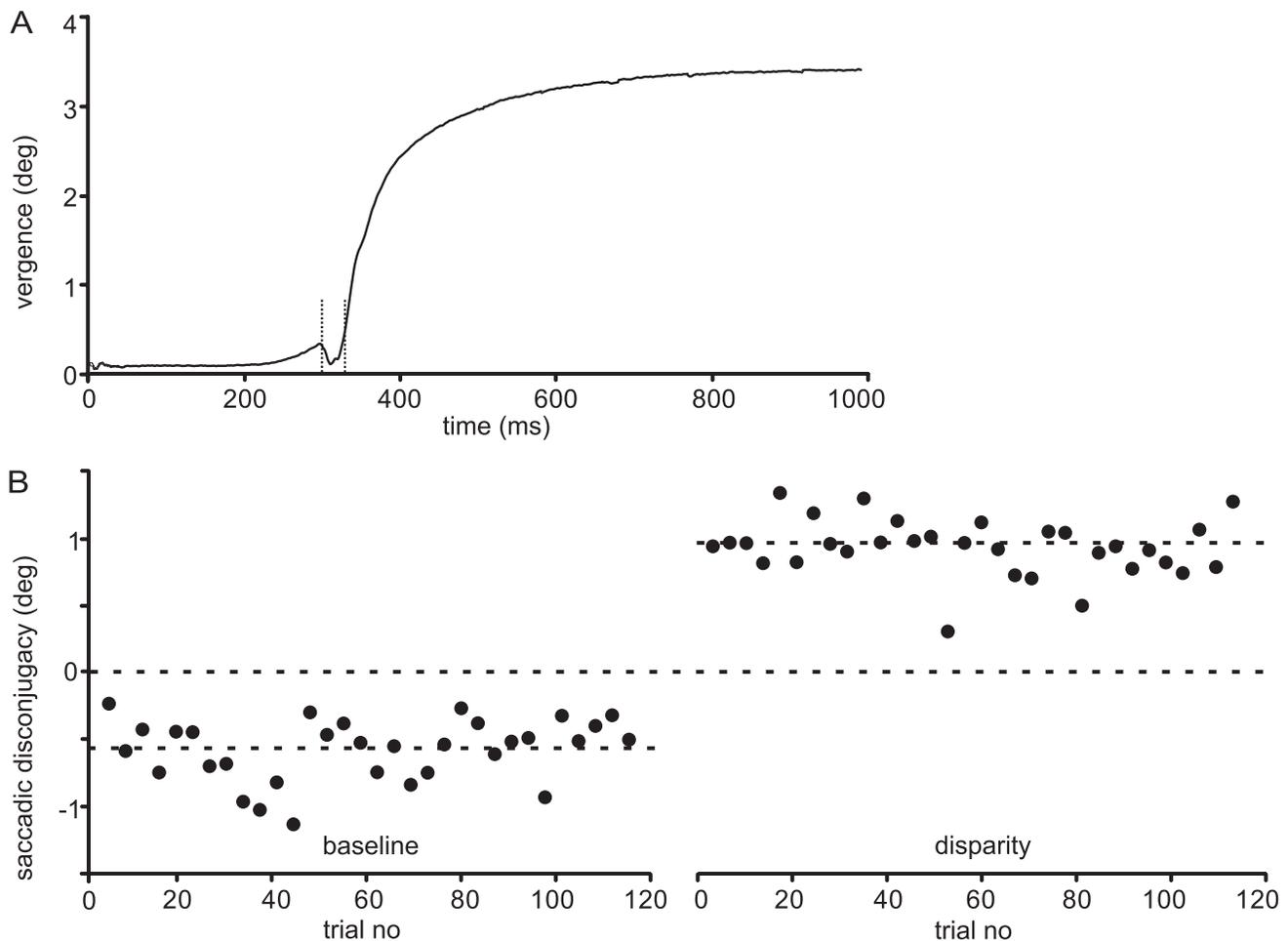


Figure 2. Analysis of saccadic disconjugacy. (A) Temporal relation of a combined saccade-vergence eye movement. Convergence trials from one participant were aligned to the saccadic onset at 300 ms (first vertical dashed line). Saccades lasted an average of 27.64 ms (median = 25 ms, range = 18–42 ms; second vertical dashed line) and ended before the main convergence eye movement. (B) Saccadic disconjugacy, the difference of the saccadic amplitude of the right eye and the left eye during baseline and during disparity block. Saccadic disconjugacy was significantly increased when disparity was present.

Also for this experiment, we used a linear mixed model with rise time, latency, or vergence amplitude as dependent variables. Independent variables were prism orientation (base in and base out) and trial number. To compare the adaptation between the two prism orientation conditions, we used the interaction term of prism orientation and trial number. Participants were used as random effects. To select between different possible mixed-effects models, we again used the AIC. p -values and 95% CIs are reported.

Results

Experiment 1

In the first experiment, incommittant stimulus disparity was achieved using a haploscopic setup. The

response that was made from a gaze position without stimulus disparity into a viewing direction with increased stimulus disparity consisted of a saccade followed by a vergence response (Figure 2A). To address the temporal relation of the saccade and the vergence response, we aligned the vergence response to the saccade onset in one participant. We found that the vergence eye movement started before saccade onset (data not shown). The peak of the vergence response, however, was reached after saccadic landing. Next, we analyzed saccadic disconjugacy (i.e., the difference of saccadic amplitude of the left and the right eye; Figure 2B). Saccades to binocular stimuli without disparity during the baseline block showed a slightly negative disconjugacy ($-0.53 \pm 0.03^\circ$ standard error of the mean [SEM]). Disconjugacy significantly increased when saccades were made into a field of view with stimulus disparity ($0.69^\circ \pm 0.04^\circ$ SEM, $p < 0.001$). To investigate

	Mean change per 10 trials	95% confidence interval		Degrees of freedom	Significance p
		Lower bound	Upper bound		
Mean velocity ($^{\circ}/s$)	0.45	0.62	0.28	1503.637	<0.001
Latency (ms)	-0.44	-1.32	0.45	1326.574	0.336
Amplitude ($^{\circ}$)	3.75×10^{-3}	10.92×10^{-3}	-3.43×10^{-3}	1667.139	0.306

Table 1. Adaptation of the convergence response in Experiment 1.

whether the disconjugacy is an adaptive process (i.e., shows a gradual change over time) or rather an immediate modification of the response by the stimulus conditions, we performed a regression analysis. We found that saccadic disconjugacy in conditions of incommittant stimulus disparity did not change over time ($p = 0.782$).

Next, we investigated the vergence response that took place after the saccadic eye movement in the disparity block. We found a significant increase of the mean

convergence velocity over subsequent trials ($p < 0.001$). The mean velocity increased by more than 50% over the course of 128 trials with a mean change of $0.45^{\circ}/s$ per 10 trials. We found no significant effects of trial number neither on vergence latency nor on vergence amplitude ($p = 0.336$ and $p = 0.306$, respectively; Table 1; Figure 3 [whiskers indicate *SEM*]).

To investigate whether the increase of the mean vergence velocity was limited to a single viewing direction or whether it may transfer to a vergence

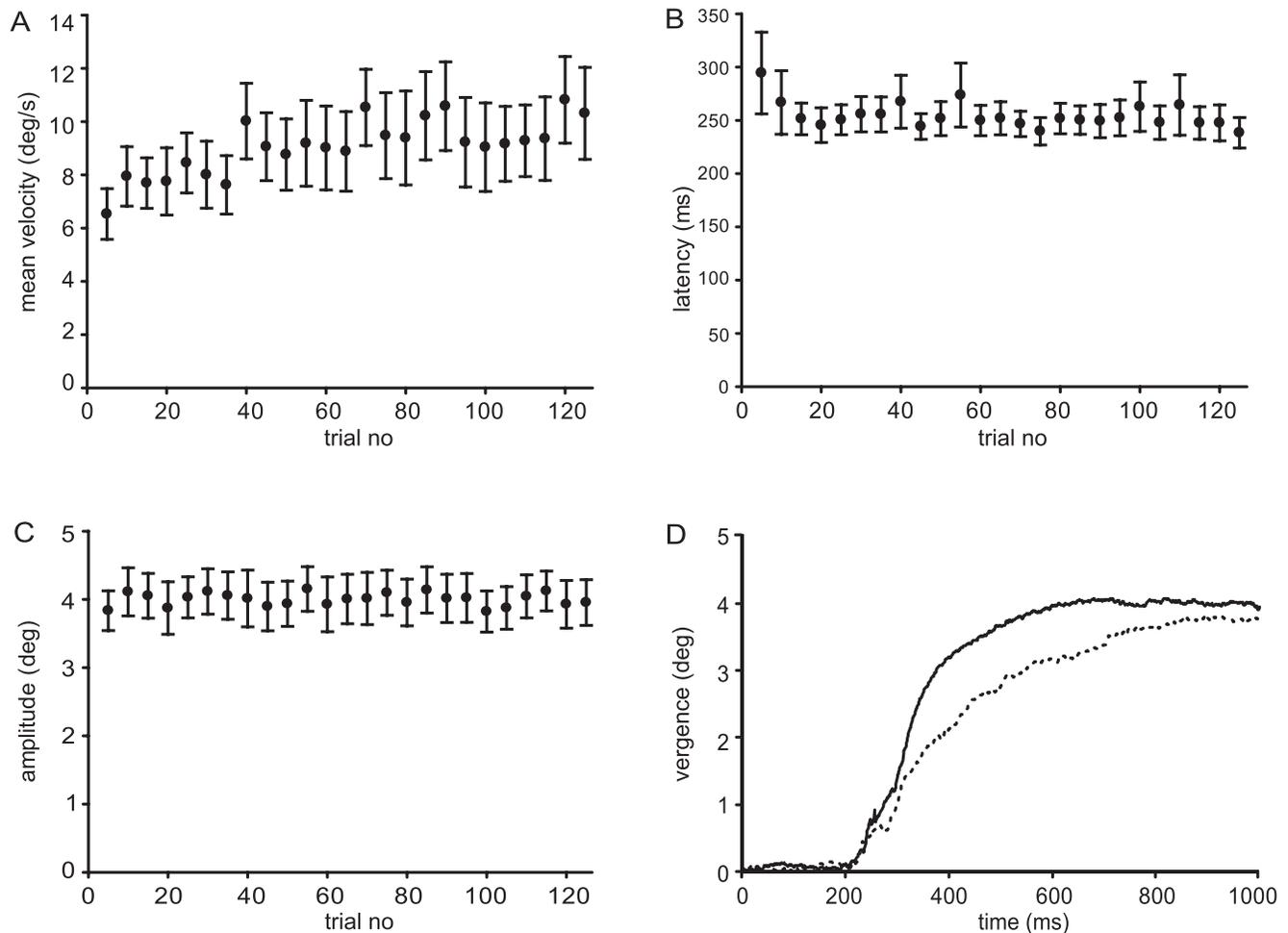


Figure 3. Vergence adaptation induced by incommittant stimulus disparity with a haploscopic setup. Scatter plots show averaged mean velocity, latency, and amplitude for 128 trials. Whiskers indicate standard error of the mean (*SEM*). We found a significant increase of mean velocity in the course of 128 trials (A). Neither latency (B) nor amplitude (C) showed significant changes in the course of the experiment. (D) Superimposed traces of averaged first five trials (dashed lines) and last five trials (solid lines) show the increase of vergence velocity in the course of subsequent trials with no significant change of amplitude or latency.

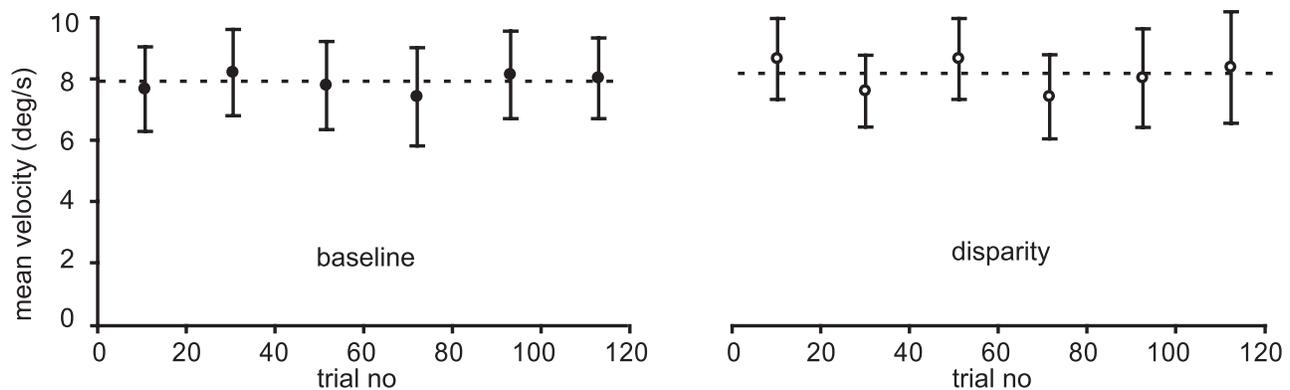


Figure 4. Mean velocity of convergence eye movement trials from Experiment 1 after left-going saccades. In the baseline block, every fifth trial was a left-going saccade with an image disparity of 4° requiring a vergence eye movement, whereas right-going saccades required no vergence eye movement. In the disparity block, right targets were presented with an image disparity of 4° as well. Therefore, a vergence eye movement after saccades in both directions was required. Mean velocity of the vergence eye movements in left gaze during baseline and adaptation did not show any differences.

movement in a different gaze direction, we measured vergence velocity in the left-going trials during the baseline block and during the disparity block. Of note, during the baseline condition, only one out of five trials was left going whereas all right-going trials had no stimulus disparity. We found no adaptation of the vergence velocity in left-going trials in either condition ($p = 0.429$ for the baseline and $p = 0.648$ for the disparity block). Moreover, the mean vergence velocity in left-going trials was not different between baseline and disparity blocks ($p = 0.394$; Figure 4).

Experiment 2

In Experiment 2, we asked whether the vergence velocity increase elicited by incommittant stimulus disparity depends on the experimental paradigm and whether it is limited to convergent eye movements only. For this purpose, we created disparity with prisms rather than a haploscope, and we tested both convergent and divergent eye movements. Saccadic eye movements from a left- to a right-sided stimulus, which was viewed through a prism with one eye (instead of the haploscopic setup), successfully in-

duced a vergence response too. Because only trials with stimulus disparity on one side elicit a vergence response, we excluded trials from the no-disparity blocks. First, we compared the responses of convergent and divergent eye movements. For this purpose, we used prism orientation as single independent variable; rise time, latency, and vergence amplitude as dependent variables; and participants as random effect in the mixed model. We found that rise time and latency were significantly smaller in divergent responses as compared with convergent responses (rise time divergence = 229.7 ± 6.0 ms [$M \pm SEM$], convergence = 258.3 ± 7.6 ms; latency divergence = 190.4 ± 3.6 ms; convergence = 240.5 ± 3.5 ms; $p < 0.001$ for both; Table 2). To compare the amplitude of convergent and divergent responses, we used absolute values. We found that the absolute value of the mean vergence response was not different between convergent and divergent eye movements (rise time divergence = $-3.85^\circ \pm 0.03^\circ$, convergence = $3.86^\circ \pm 0.03^\circ$; $p = 0.236$). Next, we investigated whether the vergence response kinetics changed in the course of 100 trials. For this, we used trial number as independent variable and participants as random effects. The linear mixed-effects models showed a significant decrease of the rise time over subsequent trials for both convergence (elicited by a medial image disparity shift) and

	Convergence			Divergence			Significance p
	Mean	95% confidence interval		Mean	95% confidence interval		
		Lower bound	Upper bound		Lower bound	Upper bound	
Rise time (ms)	258.3	243.2	273.3	229.7	217.9	241.6	<0.001
Latency (ms)	240.5	233.7	247.3	190.4	183.4	197.4	<0.001
Amplitude ($^\circ$)	3.86	3.79	3.93	-3.85	-3.91	-3.78	0.236

Table 2. Parameters of convergence and divergence eye movements.

	Mean change per 10 trials	95% confidence interval		Degrees of freedom	Significance <i>p</i>
		Lower bound	Upper bound		
Convergence (medial disparity shift)					
Rise time (ms)	-28.17	-36.26	-20.09	408.512	<0.001
Latency (ms)	-10.28	-14.07	-6.49	408.278	<0.001
Amplitude (°)	-0.07	-0.11	-0.03	409.972	0.002
Divergence (lateral disparity shift)					
Rise time (ms)	-13.87	-19.95	-7.79	411.628	<0.001
Latency (ms)	-2.53	-5.85	0.79	412.051	0.135
Amplitude (°)	0.03	-0.14	0.20	9.499	0.683

Table 3. Adaptation of the vergence response over 100 trials in Experiment 2.

divergence eye movements (elicited by a lateral shift of image disparity; $p < 0.001$ for both conditions). We also found a decrease of latency and amplitude over subsequent trials for convergent responses ($p < 0.001$

for latency and $p = 0.002$ for amplitude) but not for divergent responses ($p = 0.135$ for latency and $p = 0.683$ for amplitude; Table 3; Figure 5). Finally, we investigated whether the adaptation of convergence

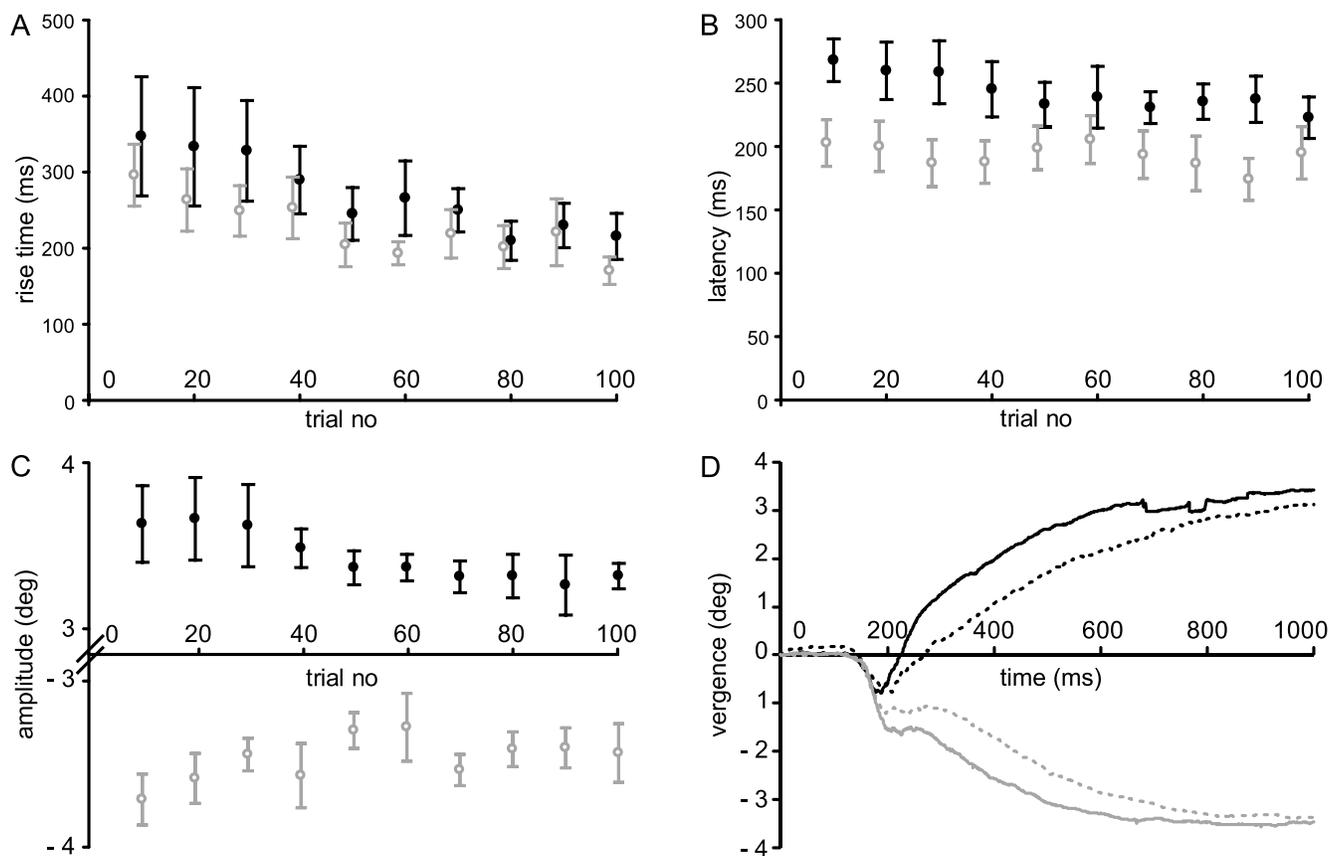


Figure 5. Results of Experiment 2 showing adaptation of the vergence response induced with prisms. Scatter plots show averaged results for rise time, latency, and amplitude during 100 trials of the disparity block. Black dots represent convergent eye movements, gray dots divergent eye movements. Whiskers indicate the standard error of the mean. Each data point represents data from 160 valid trials (two were averaged to smooth vergence values before curve fitting, five were averaged to smooth data after curve fitting, and then data from all 16 participants were averaged). Rise time (A), latency (B), and amplitude (C) decrease significantly in the course of subsequent convergent movements (prism orientated base out), thus indicating adaptation. For divergent eye movements, we observed significant adaptation only of rise time but not for latency or amplitude. (D) Superimposed traces of averaged first five trials (dashed lines; black for convergence, gray for divergence) and last five trials (solid lines; black for convergence, gray for divergence) illustrate the adaptive change of rise time and to a lesser extent latency and amplitude for convergence and divergence eye movements.

	Mean change per 10 trials	95% confidence interval		Degrees of freedom	Significance p
		Lower bound	Upper bound		
Rise time (ms)	−10.43	−21.06	0.21	826.576	0.055
Latency (ms)	−6.23	−12.41	−0.05	828.546	0.048
Amplitude (°)	−0.01	−0.07	0.05	829.521	0.683

Table 4. Statistical comparison of the adaptation between convergence and divergence.

and divergence eye movements differed from each other. For this purpose, we investigated the interaction of the independent variables of prism orientation (base in and base out) and trial number and participants as random effects. We found a trend to a faster adaptation of rise time and a longer latency for convergence than for divergence eye movements ($p = 0.055$ and $p = 0.048$ for rise time and latency, respectively; Table 4).

Discussion

We found that acute-onset incommittant image disparity in healthy participants leads to a rapid change of both, the initial saccade that is made into a field of gaze with increased image disparity and the subsequent vergence response. Saccades show an immediate disconjugacy, which is present from the beginning. Vergence movements in turn rather show a gradual increase of their slope over a few minutes. All oculomotor changes induced by the incommittant image disparity act toward a more rapid restoration of binocular single vision after an eye movement into a field of disparity. The effect of the increased efficacy of the vergence response is dependent on the adapted viewing direction and thus was not found in other gaze directions. The increased vergence response was found for convergence and divergence eye movements and was independent of the experimental design (haploscope or prism).

Saccadic disconjugacy

Our finding of vergence response beginning before and continuing after the saccadic response raises the possibility that the vergence movement continues during the saccadic movement and thereby creates disconjugacy. Thus, saccadic disconjugacy may be the result of an overlapping vergence response rather than an independent regulation of saccadic planning. A coincident saccadic and vergence movement was also found by other groups (Averbuch-Heller et al., 1999; Tyler et al., 2012). Schultz and Busetini (2013) studied saccadic adaptation in the macaque monkey with a

predictive double-step paradigm: A second stimulus (disparity stimulus) is provided after initiation of the first saccadic eye movement. They found that in late predictive adaptive trials, there is already presaccadic vergence activity, and the entire disparity error is compensated perisaccadically. Our results are in agreement with previous reports showing saccadic disconjugacy in incommittant stimulus disparity (Averbuch-Heller et al., 1999; Eggert & Kapoula, 1995). In accordance with Eggert and Kapoula (1995), we found disconjugacy immediately after disparity onset, not requiring adaptation. Averbuch-Heller et al. (1999) also found disconjugacy of saccades in prism-induced incommittance. In contrast to our results, they found a gradual increase of disconjugacy over the first few trials, however. In addition, they observed a progressive incorporation of the vergence eye movement into the saccade. Whereas in their first trials the saccade was followed by the vergence eye movement, in the subsequent trials the vergence was more and more integrated in the saccadic eye movement. They observed a nearly complete integration of the divergence after 8–10 gaze shifts; however, the convergence was incorporated only up to 85%. A possible explanation for this discrepancy might be that they used larger saccades as well as larger disparities. With this setup, participants might first have had to perform the saccade before perceiving the disparity. After a few trials, participants were alert of the disparity in the corresponding direction and therefore were able to incorporate the vergence eye movement already into the saccade. As becomes obvious in Figures 2A and 3D, saccadic disconjugacy accounts for little of the total vergence response in our conditions. A possible explanation for this is the finding of Kumar, Han, Dell’Osso, Durand, and Leigh (2005) who tested vertical combined saccade-vergence eye movements and found that vergence eye movements increased with the required vergence angle and with increased saccadic size.

Vergence kinetics

A novel finding of our study is the gradual change of vergence velocity over subsequent trials when gaze was shifted from a view without disparity into a field of

view with increased disparity. The situation of incommittant image disparity is comparable to the common clinical situation of a sixth cranial nerve palsy, in which the abduction is deficient, or an internuclear ophthalmoplegia (INO) with impaired adduction. Both lead to an image disparity in one viewing direction but not in the others (Fernandez-Ruiz, Diaz, Aguilar, & Hall-Haro, 2004). Although many patients suffer from transient double vision after shifting gaze toward the affected side, some seem not to be disturbed. The adaptive improvement of the vergence response described above is one mechanism that helps to compensate incommittant image disparity.

Convergence and divergence

A comparison of convergence and divergence eye movements in Experiment 2 revealed a significantly longer rise time for convergence as compared with divergence eye movements. The observation of different kinetics between convergence and divergence has been made before and is consistent with the hypothesis that these two eye movements are regulated by independent systems (Hornig, Semmlow, Hung, & Ciuffreda, 1998; Hung, Zhu, & Ciuffreda, 1997; Jaschinski, Svede, & Jainta, 2008; Y. Y. Lee, Chen, & Alvarez, 2008; Tyler et al., 2012). Mays, Porter, Gamlin, and Tello (1986) investigated vergence velocity neurons in monkeys and indeed found separate burst cells for convergence and divergence firing specifically when the corresponding eye movement was induced but not with other movements. For both cell types, firing rate was associated with the vergence velocity. We found that both convergence and divergence eye movements exhibit adaptive changes over time, indicating that both neuronal networks are susceptible for an adaptive process. Jainta, Bucci, Wiener-Vacher, and Kapoula (2011) as well as Alvarez et al. (2010) measured vergence velocity in patients suffering convergence insufficiency before and after repetitive convergence exercises. Interestingly, Alvarez et al. (2010) showed increased peak velocity in convergence but not in divergence in these patients, which confirms the assumption of different regulation mechanisms. Our findings are in line with the finding of increased kinetics after training, but importantly, we found similar improvements in healthy individuals. Moreover, we show the temporal dynamics of the adaptive response. A protocol not unlike ours was also used by Yuan and Semmlow (2000): They measured the peak velocity of convergence responses in four normal subjects before and after a large number of either repetitive vergence or repetitive saccadic eye movements. However, they found a reduction of the

peak velocity over the course of 100 repetitive vergence responses. They attributed this decrease to an effect of fatigue. We cannot exclude that fatigue influenced the responses in our experiments as well. But because in our study the velocity is increasing, the accuracy of the movement is improving, and the latency is decreasing, it is unlikely that fatigue had a big contribution. The reason why the effect of fatigue is less pronounced in our experiments is unclear. Possibly our paradigm required less effort for a vergence response and was thus less fatiguing. In addition, the increase in vergence velocity might also be due to phoria adaptation, which we did not assess in the current study. Kim, Vicci, Han, et al. (2011) discussed this issue: They investigated the influence of phoria adaptation on convergence peak velocity and found that convergence responses measured after near phoria adaptation were significantly faster than responses after far adaptation. Satgunam, Gowri-sankaran, and Fogt (2009) also showed increased vergence peak velocity and vergence amplitude for convergence after sustained convergence and additionally showed a decrease for the velocity and amplitude for divergence. Assuming that our repetitively performed convergence eye movements also led to a change in phoria toward a more convergent eye position, this would explain our measurement of an increase of vergence velocity.

Site of adaptation in the central nervous system

It would be of interest to know where vergence adaptation is located within the human brain and whether there is a single site in the central nervous system for adaptation of convergence and divergence eye movements or whether adaptation takes place in independent sites. Significantly different speed of adaptation between convergence and divergence eye movements would argue for distinct adaptive sites. Our finding of a trend toward significance, however, does not allow drawing such a conclusion. Given the qualitative similarities of adaptation seen for convergence and divergence, we assume that rather a single site is responsible for both types of adaptation.

Different studies investigated the neural substrates of vergence eye movements and vergence adaptation. Using functional magnetic resonance imaging, the posterior parietal cortex (PPC), frontal eye fields (FEFs), cerebellar vermis, and the midbrain were shown to be part of the network required for vergence responses (Jaswal, Gohel, Biswal, & Alvarez, 2014). In a recent study, Alvarez, Jaswal, Gohel, and Biswal (2014) investigated patients with convergence insufficiency before and after therapy with home reinforcement. They found that vergence

training led to an increase of the blood oxygenation level–dependent response in FEF, PPC, and cerebellar vermis. Possibly, our paradigm led to activation of similar regions. In accordance with this, Takagi, Tamargo, and Zee (2003) found that lesions of the cerebellar vermis in primates resulted in an esodeviation in absence of disparity cues, a loss of concomitance, an abnormal saccadic yoking producing saccadic disconjugacy, defects in prism-induced phoria adaptation, and disturbances in the dynamic properties of disparity-induced vergence. This indicates an important role of the cerebellar vermis in vergence and vergence adaptation. On the cellular level, Prsa and Thier (2011) showed Purkinje cell involvement in vergence adaptation in monkeys.

A different study characterized saccades in humans arising during symmetrical vergence and investigated the underlying neuronal substrate (Coubard & Kapoula, 2008). Although the authors could not exclude an interaction of saccade and vergence mediated by omnipause neurons, they strongly assume that the interaction of saccades and vergence occurs at a higher level: Both the FEF and the superior colliculus control saccades and vergence eye movements, and the authors argue for the superior colliculus to be the critical structure for saccades during vergence. In particular, the rostral superior colliculus encodes position errors for multiple types of eye movements, including microsaccades, small saccades, smooth pursuit, and fixation. Van Horn, Waitzman, and Cullen (2013) addressed whether the rostral superior colliculus contributes to the development of neural signals that are suitable for controlling vergence eye movements. They found that vergence eye movements can be evoked in monkeys using microstimulation in the rostral superior colliculus. Moreover, they identified a novel population of neurons that either increased (i.e., convergence neurons) or decreased (i.e., divergence neurons) their activity during vergence eye movements. Those neurons dynamically encoded changes in vergence angle during vergence tracking, fixation in three-dimensional space, and the slow binocular realignment that occurs after disconjugate saccades. They were completely unresponsive during conjugate saccades or the rapid component of disconjugate saccades (i.e., fast vergence) and conjugate smooth pursuit.

In summary, the FEF, PPC, and cerebellar vermis seem to play a crucial role in adaptation, and at least in the rostral superior colliculus, neurons for convergence and divergence can be discriminated by their activity.

Types of vergence adaptation

In the past, two experimental paradigms have been used to induce adaptive changes in the vergence system:

phoria adaptation (also known as prism adaptation) and dynamic disparity vergence adaptation (Alvarez, Bhavsar, Semmlow, Bergen, & Pedrono, 2005; Graf, Maxwell, & Schor, 2003; Kim, Vicci, Granger-Donetti, et al., 2011; Y. Y. Lee, Granger-Donetti, Chang, & Alvarez, 2009; Semmlow & Yuan, 2002). For this, vergence stimuli were presented with the double-step paradigm (Kim, Vicci, Granger-Donetti, et al., 2011; Takagi, Oyamada, et al., 2001; Takagi, Trillenber, & Zee, 2001) or the step-ramp paradigm (Munoz, Semmlow, Yuan, & Alvarez, 1999). In the double-step paradigm, a first vergence stimulus is followed by a second vergence stimulus with a short delay between the steps. The second step may be a stimulus with a larger (increasing paradigm) or with a smaller vergence demand (decreasing paradigm). Results showed that the vergence response after training with an increasing double-step paradigm shows increased peak velocity whereas training with a decreasing paradigm resulted in decreased peak velocity (Munoz et al., 1999; Takagi, Oyamada, et al., 2001; Takagi, Trillenber, et al., 2001). This vergence double-step paradigm shares many similarities with double-step saccadic adaptation, widely used to study saccade adaptation: Essentially, it provides an error signal at the end of an open-loop response. The error signal leads to adaptive changes in the course of subsequent trials to match the response to the final stimulus rather than to the first stimulus (Alahyane & Pélisson, 2005; Hatada, Rossetti, & Miall, 2006; Hopp & Fuchs, 2004).

In our experiments, we have not assessed the phoria level, which represents the late tonic phase of a vergence response. The change of vergence velocity that we observed after increased image disparity in side gaze shares several similarities with the adaptation induced with double-step or step-ramp stimuli: Both can be observed after only few trials, both primarily affect the vergence velocity, and it can be found for convergence and divergence. It is conceivable that both involve the same neuronal mechanism, which has been speculated to be located in the cerebellar vermis (Kim, Vicci, Granger-Donetti, et al., 2011; Takagi, Oyamada et al., 2001). However, there are fundamental differences between the experimental paradigms that make them barely comparable. The most obvious difference is that in our experiments, no error signal is provided: The vergence stimuli at the beginning and at the end of each trial are the same.

Beside the change of the vergence kinetics (i.e., mean velocity and rise time), we also found a significant adaptation of the amplitude of convergence but not of divergence movements in the second experiment. This seems intriguing at first sight. However, we measured the amplitude 1 s after stimulus onset. Although this fits well in the steady state of adapted responses, this is less the case for the unadapted responses, where steady

state is barely reached (see Figure 3D). We thus cannot exclude that the adaptation of vergence amplitude might be the consequence of the prominent change in the response kinetics rather than a true adaptation of steady-state amplitude. We thus wish to remain cautious on the adaptation of amplitude.

Furthermore, we found a significant reduction of vergence latency for prism-induced convergence responses. This reaction time effect was neither significant with the haploscopic setup nor for the divergence response. The effect on vergence latency is not only less robust but also more difficult to interpret. Because the onset of a vergence response had to be determined from the time of vergence stimulus onset (0 ms) to the time of peak velocity of the vergence response (Experiment 1) or by extrapolation of a mathematical curve fit (Experiment 2), we cannot exclude that the kinetics of the responses artificially lead to apparent changes in latency. On this background, we are cautious with the interpretation of our finding of reduced vergence latency as well and rather underline the adaptive changes of velocity and rise time, which are more marked and robustly present in all conditions.

Conclusion

New-onset incommittant disparity leads to two distinct modifications of the oculomotor response: (a) Saccades become disconjugate, thus reducing the disparity, and (b) vergence velocity increases over time. Both changes together help improve efficacy of the oculomotor response in new-onset disparity.

Keywords: vergence, eye movement, saccade, plasticity, adaptation, binocular vision

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Competing interests

None of the authors has competing interests to declare.

Author contributions

Muriel Dysli: collection, analysis and interpretation of data, manuscript writing; Fabian Keller: collection

and analysis of data, proofreading of manuscript; Mathias Abegg: conception and design of the experiments, analysis of data, manuscript writing.

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