Published in final edited form as:

Optom Vis Sci. 2015 January ; 92(1): 107–114. doi:10.1097/OPX.0000000000000441.

Effect of Artificial Scotomas on Open-loop Disparity Vergence Eye Movements

Dongsheng Yang, MD, PhD, Richard W. Hertle, MD, Mingxia Zhu, PhD, Zheng Tai, Eric Hald, PhD, and Matthew Kauffman, MD

Department of Ophthalmology, Shanghai Children's Hospital, Jiaotong University, Shanghai, China (DY, ZT), Vision Center, Department of Ophthalmology, The Children's Hospital of Akron, Northeast Ohio Medical University, Akron, Ohio (DY, RWH, MK), Optometry Centre, School of Chemical and Life Sciences, Singapore Polytechnic, Singapore (MZ), and Department of Biomedical Engineering, University of Minnesota, Twin Cities, Minneapolis, Minnesota (EH)

Abstract

Purpose—To investigate the effect of an artificial scotoma on open-loop disparity vergence responses and vergence control mechanisms, we examined open-loop disparity vergence responses to disparity stimuli using monocular artificial scotomas in normal subjects.

Methods—Using a mirror haploscope with two computer monitors, we delivered disparity stimuli on a pair of random dot patterns subtending 40×30 degrees at 47 cm from each eye. The scotomas were black circles located in the center of a random dot pattern for the left eye. Eye movements of both eyes were recorded with a magnetic search coil system.

Results—We first found that the amplitudes of disparity vergence responses were gradually decreased and the latency of disparity vergence responses were moderately increased as the size of the scotomas was increased. Secondly, monocular responses from each eye were symmetrical although the stimuli to each eye were asymmetrical.

Conclusions—The results suggest that the monocular eye movements in disparity vergence are controlled by a binocular central mechanism, not driven separately by monocular inputs in the open-loop window.

Keywords

vergence; eye movements; disparity; ocular motor control; version

Vergence eye movements serve to align both eyes on the same target for single binocular vision. When a target moves in the midsagittal plane, symmetrical vergence eye movements occur; with targets located to one side of the midsagittal plane, asymmetrical vergence movements are induced.^{1–5} Maxwell and Schor's⁶ research has shown evidence supporting a single binocular control mechanism for vergence while others endorse the role of a strong monocular component.^{3–5} Enright suggested that the asymmetrical vergence occurred

because each eye independently responds to its own stimulus.³ To better understand control mechanisms underlying vergence eye movements, we have investigated open-loop disparity vergence responses and monocular responses in the vergence responses to asymmetrical disparity stimuli with monocular artificial scotomas.

Open-loop disparity vergence responses (DVR) are automatic and can be elicited in monkeys and human subjects at ultra-short latency, 55 ms for monkeys and 85 ms for human.^{7–11} It has been shown that DVR emanate from binocularly processed visual signals mediated by the medial superior temporal area of the cortex (MST)¹² We are particularly interested in the open-loop DVR because they provide a direct measure about the relationship between motor responses and sensory input of disparity. The disparity can be sensed directly by disparity-selective neurons in an early stage of the visual system.^{13–15} Another advantage is open-loop responses leave little chance for other factors, such as attention, to influence them during this period of time. When a longer time was allowed to obtain a full fusion of disparate stimuli, vergence is heavily influenced by visual feedback. In the present study, we report how a monocular artificial scotoma (MAS) influences the amplitude, latency, and symmetry of the DVR.

The artificial scotoma is similar to a clinical condition of suppressive scotoma in patients with childhood strabismus¹⁶. Suppressive scotoma are common in strabismic subjects. The effect of artificial scotoma impact on vergence provides the potential for clinical application in suppressive scotoma measurements.

METHODS

Subjects

Four subjects (24 to 46 years old) participated in this study. Two of them were experienced investigators and two were paid naïve subjects. All four had normal best-corrected visual acuity and were taking no neurologically acting medications. The protocol was approved by the Institutional Review Board of The University of Pittsburgh. All procedures observed the Declaration of Helsinki and informed consent was obtained from all subjects

Stimuli

Dichoptic stimuli were established using a mirror haploscope consisting of two computer monitors with a resolution of 1280×1024 pixels and a vertical refresh rate of 70 Hz. A stimulus pattern with white random dots on a black background was displayed on each monitor. The size of the pattern subtended $40^\circ \times 30^\circ$ (Width $\times$ Height) at a viewing distance of 47 cm. The size of a white dot was one degree at this viewing distance. The luminance of the patterns was 0.5 cd/m^2 for black dots and 85 cd/m^2 for white dots. The right pattern and left pattern had equal average luminance.

Experimental Procedures

Normal DVR experiments, subjects were seated with their heads stabilized with a chin and forehead rest. A pair of random-dot patterns was presented on each monitor. Subjects were instructed to look at a 0.3° white-black circle in the centers of the two patterns. When the

subjects' eyes were stabilized (no saccades exceeded $9^\circ/\text{sec}$) within a $2^\circ \times 2^\circ$ window for 500 ms, the first pair of patterns with zero disparity was replaced by second pair of patterns which had a horizontal disparity step. Eighteen horizontal crossed/uncrossed disparities (0.2° , 0.4° , 0.8° , 1.2° , 1.6° , 2.4° , 3.6° , 6.4° , and 12.8°) were generated by equally displacing the random dots to nasal or temporal side of the first pair of the patterns. A single disparity step was applied to 5 pairs of different patterns to prevent a potential effect from local features of a specific pattern.

Artificial scotoma experiment. To generate an artificial scotoma, black areas of 2.5° , 7.5° , 15° , 22.5° and 30° were applied to the center of the pattern for the left eye. For the purpose of comparison, a condition of a non-scotoma stimulus was also included. A 0.3° white-black circle was positioned in the center of the black area as a fixation target. The disparities of 1.2° that induced maximum DVR for most of subjects were used for the scotoma experiment.

Data Acquisition

Horizontal and vertical eye movements of each eye were recorded with an electromagnetic technique (Remmel Labs) using scleral search coils embedded in a silastin ring (SKALAR). Following application of 1–2 drops of anesthetic (Proparacaine HCl), coils were placed on each eye. The AC voltages induced in the scleral search coils were led off to a phase-locked amplifier that provided separate DC voltage outputs proportional to the horizontal and vertical positions of the eye with corner frequencies (-3 dB) at 1 K Hz. Peak-to-peak voltage noise levels were equivalent to an eye movement of 1–2 min of arc. Eye movement data, along with timing marks and stimulus codes, were recorded using REX-VEX real-time experimental system (Laboratory of Sensorimotor Research, NEI of NIH). Usually 3–5 blocks of data were collected in each experimental session depending on how long subjects want to wear the coils. Each block consisted of 95 trials [(18 disparity conditions + 1 control condition with zero disparity) $\times$ 5 (times/patterns)]. More than 100 trials for each condition were obtained from each subject in multiple sessions. Coil wearing time for each session was usually 30 minutes although sometimes 60 minutes. All stimulus conditions were randomized.

Data Analysis

Horizontal and vertical eye positions obtained from the calibration were each fitted with a third-order polynomial to linearize the horizontal eye position data recorded during the experiment. Horizontal eye position signals were then smoothed with a Matlab internal function called six mean absolute deviation method (6 MAD method). Rightward movements (nasal ward for the left eye) were defined as positive. Onset of DVR was determined with a relative velocity criterion of $0.75^\circ/\text{sec}$ and the criterion for onset of monocular responses was $0.4^\circ/\text{sec}$. The latency of open-loop DVR was from the onset of the stimuli to the initial point of the responses. The amplitude of the vergence and the monocular responses were estimated by measuring the change in vergence and monocular responses from the initial point to the maximum point of the responses. Because the starting time and the length of open-loop windows varied dependent on the length of the latencies, so the starting position of the measurement windows had to be adjusted accordingly. A fixed

length of 80 ms was used to measure amplitudes of the vergence and monocular responses in order to obtain comparable data of amplitudes. Velocities of the DVR were obtained by two-point backward differentiation of the position data.

For the purpose of direct comparison among subjects and conditions, the effect of scotomas was normalized using the following formula:

$$P = (Max - Low) / Max \times 100\% \quad (1)$$

where the *Max* is the amplitude of the maximum response among all conditions of different scotoma sizes. It was usually from a non-scotoma or a small scotoma condition. The *Low* was amplitudes of any other responses from larger scotoma conditions. *P* is converted to percentage units by timing 100%.

RESULTS

Normal DVR responses

Open-loop disparity vergence responses (DVR) were elicited by horizontal disparity in each of the four subjects. An example of the initial DVR to a 1.2° crossed disparity stimulus is shown in Figure 1. The velocity profile and latency are essentially the same as previously described.^{9,10}

The vergence responses were calculated from the difference between left and right eye movements. Convergence was defined positive and divergence was negative. The amplitude of the DVR (the change in horizontal vergence position) was plotted as a function of stimulus disparity (disparity tuning curves) in Figure 2 for each of the four subjects. The pattern of the disparity tuning curve is similar to previously reported results.¹⁰ The mean for all subjects' responses is also presented in Figure 2. In this figure, responses to small disparity steps were increased as the size of disparity steps was increased. This is the servo range over which small increases in the input elicited roughly proportional increases in the output in the compensatory direction. All curves peak with steps around 1.2° or so and then decline. Therefore, disparity of 1.2° was selected for scotoma experiment. For the largest disparity, such as 12.8°, the DVR is down to baseline level.

Effect of Scotoma on the Amplitude of the DVR

The amplitude of the DVR was reduced by adding a monocular scotoma. This is illustrated in Figure 3, which shows mean convergence velocity profiles from a typical subject. The reduction of DVR in amplitude was quantified and normalized to maximum responses using the formula (1) and demonstrated in Figure 4. The data were not normalized to non-scotoma responses. This is because some non-scotoma responses were not the largest responses. If the data were normalized to the non-scotoma responses, some values would be over 100%, which could be confusing. The amplitude of the DVR was gradually decreased as the size of scotoma was increased. In most cases, the reduction in DVR amplitude occurred when the scotoma was as small as 7.5°, and the amplitude continued to decrease as the size of scotoma increased. Minimum responses usually occurred with the largest scotoma. The maximum reduction in DVR amplitude varied from 30% to 75% among subjects.

Effect of Scotoma on the Latency of the DVR

The latency of the DVR became longer with larger scotomas. Latency data for all subjects are listed in Table 1.

Effect of Scotoma on each Eye's Responses

Responses from each eye were symmetrical when asymmetrical stimuli with scotomas was presented to the left eye. The mean velocity profiles of the symmetrical monocular responses from a typical subject are displayed in Figure 5. The monocular responses for each condition were also statistically analyzed with a student T test. Summarized monocular responses of convergence and divergence for each subject are shown in Figure 6 and Figure 7, respectively. For most subjects and conditions, right eye and left eye responses are symmetrical. Asymmetrical responses were labeled with stars. However, subject D has stronger responses in his left eye for convergent conditions although the scotoma stimulated the left eye.

DISCUSSION

Effect of Scotoma on the DVR

It was reported that vergence responses decreased as stimulus decreased in size and increased in retinal eccentricity when binocularly symmetrical stimuli were used.^{17–21} In the present study, we have demonstrated that the amplitude of DVR gradually decreased as the size of a monocular artificial scotoma increased. This may be similar to a clinical condition of suppressive scotoma in patients with childhood strabismus. Suppressive scotoma is a common condition present in strabismic subjects. Several studies have shown that the vergence eye movements of strabismic subjects were much lower or absent in humans,^{16,22–24} and in strabismic monkeys.^{25–26} Additionally, we also observed that the latency of DVR was elongated when scotomas were large. It has been demonstrated that the latency was usually longer when stimuli were small,^{17, 27–31} when peripheral disparities were used,¹⁷ and in strabismic patients with anomalous correspondence.²² Comparing our results with those from strabismic patients, our results may be used as a reference for objective evaluation of scotoma suppression in strabismic patients.

Effect of Scotomas on the Symmetry of Monocular Responses

When monocular responses were inspected, we found that the left eye responses (rightward movements for convergence and leftward movements for divergence) and right eye responses (leftward movements for convergence and rightward movements for divergence) were both gradually decreased as the scotomas were increased in size and were mainly symmetrical even when the scotoma was large (Figure 5), although in a few conditions asymmetrical responses occurred. These results support the theory that vergence is controlled by a single binocular control mechanism. In our case, if the open-loop vergence responses were controlled by an independent monocular mechanism, right eye responses and left eye responses should not have been decreased symmetrically. Therefore, the symmetrical monocular responses provide a basis for Herring's Law of equal innervations. This finding is consistent with Maxwell and Schor's observation.⁶

In contrast to our observation, Enright examined asymmetrical slow-velocity vergence induced by asymmetrical targets and found that subjects were often able to make smooth, slow, “saccade-free” asymmetrical convergence movements that were appropriate in magnitude and velocity to the target location. He suggested that the occurrence of “saccade-free” asymmetrical convergence suggests that during binocular viewing, each eye can respond independently to that eye’s view of the target.³ Using a similar stimulus paradigm, Zhou and King showed that pre-motor neurons in the paramedian pontine reticular formation that were thought to encode conjugate velocity commands for saccades actually encode monocular commands for either right or left eye saccades. They considered this a violation of the Hering’s law of equal innervation.^{2, 5} Enright has also recorded asymmetrical vergent saccades^{4, 32} and suggested that the pulse components generated for each eye depend on weighted averaging of visual stimuli that impinge on both eyes, but step components for each eye depend only on that eye’s visual input. It is well known that eye movements require a phasic increase or burst of neural activity in the ocular motor nuclei – the pulse of innervations. Once at its new position, the eye must be held there against elastic restoring forces that tend to return the globe to its central position. To hold the eye in an eccentric position requires a steady contraction of the extraocular muscles, arising from a new tonic level of neural activity – the step of innervation. Neurophysiological evidence indicates that the position command is generated from the velocity command by mathematical process of integration with respect to time. A neural network or neural integrator integrates velocity-coded signals into position-coded signals.³³ Slower eye movements, such as vergence eye movements, are also synthesized from velocity and position commands.³⁴ Therefore, the open-loop vergence which is a pulse component of the vergence eye movements should be symmetrical because it is induced by weighted averaging of visual stimuli that impinge on both eyes. Our results agree with the suggestion made by Enright.³²

We like to point out that our results do not contradict Zhou and King’s results.^{2, 5} In Zhou and King’s report the responses to fast gaze shifts was monocular at the pre-motor neurons level, but binocular at the motor neuron level. In contrast, we recorded slow vergence responses to disparity encoded at a binocular processing level.

Symmetry of vergence eye movements can be influenced by other factors. For example, vergence eye movements became asymmetrical when a subject’s fixation position was not centered.^{35,36} It has also observed that monocular preferences influence the symmetry of vergence eye movements under natural viewing conditions.^{28,30} Asymmetrical vergence sometimes occurred when symmetrical stimuli were presented.²⁹ However, it is difficult to make a direct comparison with our results because different stimulus targets or very small targets were used in those studies.

In conclusion, artificial scotomas decreased the vergence. However, the monocular responses were symmetrical, which supports Herring’s Law of equal innervations.

Acknowledgments

This project is partly supported by a grant from the NEI (EY015797).

References

1. Mitchell DE. Properties of stimuli eliciting vergence eye movements and stereopsis. *Vision Res.* 1970; 10:145–62. [PubMed: 5440779]
2. King WM, Zhou W. Neural basis of disjunctive eye movements. *Ann N Y Acad Sci.* 2002; 956:273–83. [PubMed: 11960811]
3. Enright JT. Slow-velocity asymmetrical convergence: a decisive failure of “Hering’s law”. *Vision Res.* 1996; 36:3667–84. [PubMed: 8976997]
4. Enright JT. Monocularly programmed human saccades during vergence changes. *J Physiol.* 1998; 512 (Pt 1):235–50. [PubMed: 9729633]
5. Zhou W, King WM. Premotor commands encode monocular eye movements. *Nature.* 1998; 393:692–5.
6. Maxwell JS, Schor CM. Symmetrical horizontal vergence contributes to the asymmetrical pursuit of targets in depth. *Vision Res.* 2004; 44:3015–24. [PubMed: 15474574]
7. Busetini C, Miles FA, Krauzlis RJ. Short-latency disparity vergence responses and their dependence on a prior saccadic eye movement. *J Neurophysiol.* 1996; 5:1392–410. [PubMed: 8727386]
8. Masson GS, Busetini C, Miles FA. Vergence eye movements in response to binocular disparity without depth perception. *Nature.* 1997; 389:283–6.
9. Busetini C, Fitzgibbon EJ, Miles FA. Short-latency disparity vergence in humans. *J Neurophysiol.* 2001; 85:1129–52. [PubMed: 11247983]
10. Yang D, FitzGibbon EJ, Miles FA. Short-latency disparity-vergence eye movements in humans: sensitivity to simulated orthogonal tropias. *Vision Res.* 2003; 43:431–43. [PubMed: 12536000]
11. Sheliga BM, FitzGibbon EJ, Miles FA. Human vergence eye movements initiated by competing disparities: evidence for a winner-take-all mechanism. *Vision Res.* 2007; 47:479–500. [PubMed: 17118422]
12. Takemura A, Inoue Y, Kawano K, Quaia C, Miles FA. Single-unit activity in cortical area MST associated with disparity-vergence eye movements: evidence for population coding. *J Neurophysiol.* 2001; 85:2245–66. [PubMed: 11353039]
13. Cumming BG, Parker AJ. Responses of primary visual cortical neurons to binocular disparity without depth perception. *Nature.* 1997; 389:280–3. [PubMed: 9305841]
14. Cumming BG, Parker AJ. Binocular neurons in V1 of a wake monkeys are selective for absolute, not relative, disparity. *J Neurosci.* 1999; 19:5602–18. [PubMed: 10377367]
15. Cumming BG, Parker AJ. Local disparity not perceived depth is signaled by binocular neurons in cortical area V1 of the Macaque. *J Neurosci.* 2000; 20:4758–67. [PubMed: 10844045]
16. Cipolli C, Bolzani R, Corazza R, Gualdi G, Orciuolo M, Campos E. Vergence movements in comitant strabismus. *Percept Mot Skills.* 1990; 71:1259–64. [PubMed: 2087379]
17. Hampton DR, Kertesz AE. Fusional vergence response to local peripheral stimulation. *J Opt Soc Am.* 1983; 73:7–10. [PubMed: 6827391]
18. Boman DK, Kertesz AE. Horizontal fusional responses to stimuli containing artificial scotomas. *Invest Ophthalmol Vis Sci.* 1985; 26:1051–6. [PubMed: 4019095]
19. Hung GK, Semmlow JL, Sun L, Ciuffreda KJ. Vergence control of central and peripheral disparities. *Exp Neurol.* 1991; 113:202–11. [PubMed: 1868903]
20. Stevenson SB, Reed PE, Yang J. The effect of target size and eccentricity on reflex disparity vergence. *Vision Res.* 1999; 39:823–32. [PubMed: 10341968]
21. Schor C, Wesson M, Robertson KM. Combined effects of spatial frequency and retinal eccentricity upon fixation disparity. *Am J Optom Physiol Opt.* 1986; 63:619–26. [PubMed: 3766690]
22. Schoessler JP. Disparity-induced vergence responses in normal and strabismic subjects. *Am J Optom Physiol Opt.* 1980; 57:666–75. [PubMed: 7425090]
23. Kenyon RV, Ciuffreda KJ, Stark L. Dynamic vergence eye movements in strabismus and amblyopia: asymmetric vergence. *Br J Ophthalmol.* 1981; 65:167–76. [PubMed: 7225309]
24. Boman DK, Kertesz AE. Fusional responses of strabismics to foveal and extrafoveal stimulation. *Invest Ophthalmol Vis Sci.* 1985; 26:1731–9. [PubMed: 4066209]

25. Yildirim C, Tychsen L. Disjunctive optokinetic nystagmus in a naturally esotropic macaque monkey: interaction between nasotemporal asymmetries of versional eye movement and convergence. *Ophthalmic Res.* 2000; 32:172–80. [PubMed: 10828738]
26. Tychsen L, Wong AM, Burkhalter A. Paucity of horizontal connections for binocular vision in V1 of naturally strabismic macaques: Cytochrome oxidase compartment specificity. *J Comp Neurol.* 2004; 474:261–75. [PubMed: 15164426]
27. Semmlow JL, Hung GK, Horng JL, Ciuffreda K. Initial control component in disparity vergence eye movements. *Ophthalmic Physiol Opt.* 1993; 13:48–55. [PubMed: 8510948]
28. van Leeuwen AF, Collewijn H, Erkelens CJ. Dynamics of horizontal vergence movements: interaction with horizontal and vertical saccades and relation with monocular preferences. *Vision Res.* 1998; 38:3943–54. [PubMed: 10211386]
29. Horng JL, Semmlow JL, Hung GK, Ciuffreda KJ. Dynamic asymmetries in disparity convergence eye movements. *Vision Res.* 1998; 38:2761–8. [PubMed: 9775324]
30. Kawata H, Ohtsuka K. Dynamic asymmetries in convergence eye movements under natural viewing conditions. *Jpn J Ophthalmol.* 2001; 45:437–44. [PubMed: 11583663]
31. Wick B, Bedell HE. Magnitude and velocity of proximal vergence. *Invest Ophthalmol Vis Sci.* 1989; 30:755–60. [PubMed: 2703318]
32. Enright JT. The remarkable saccades of asymmetrical vergence. *Vision Res.* 1992; 32:2261–76. [PubMed: 1288003]
33. Arnold DB, Robinson DA. The oculomotor integrator: testing of a neural network model. *Exp Brain Res.* 1997; 113:57–74. [PubMed: 9028775]
34. Gamlin PD, Clarke RJ. Single-unit activity in the primate nucleus reticularis tegmenti pontis related to vergence and ocular accommodation. *J Neurophysiol.* 1995; 73:2115–9. [PubMed: 7623103]
35. Yang D, Zhu M, Kim CH, Hertle RW. Vergence nystagmus induced by motion in the ground plane: normal response characteristics. *Vision Res.* 2007; 47:1145–52. [PubMed: 17367837]
36. Zhu M, Hertle RW, Yang D. Relationships between versional and vergent quick phases of the involuntary version-vergence nystagmus. *J Vis.* 2008; 8:11. [PubMed: 18831647]

Figure 1. Velocity profiles of open-loop disparity vergence induced by a crossed disparity of 1.2° with 0° scotoma. The latency of the DVR is about 85–90 ms.

Figure 2.

Disparity tuning curves for four subjects. The thick solid line is the mean of responses from four subjects. Positive changes in vergence position correspond to convergence, whereas negative changes in vergence position relate to divergence. Horizontal disparity steps ranged from 0° to 12.8° . Positive steps correspond to crossed disparity, and negative steps correspond to uncrossed disparity. The peak of the responses is around disparity step of 1.2° .

Figure 3. DVR Velocity profiles for six different monocular scotoma sizes. The numbers at the end of each velocity profile indicate the size of scotoma. The data shown is from one of our subject.

Figure 4.

Normalized reduction of DVR amplitudes vs. monocular scotoma sizes for four subjects. The normalization was performed using formula (1). The reduction was proportioned to the maximum responses from a zero or a small scotoma condition. The maximum reduction varied from about 30% to 75% among subjects.

Figure 5.

Mean velocity files from various scotoma sizes (SS) from one of the subjects. The solid thicker lines represent vergence eye movements, the dashed lines are for the movements of the right eye, and the dotted lines for the movements of the left eye. The left panel is for convergent eye movements and the leftward movement of the right eye is reversed for an easy comparison with rightward movements of the left eye. The right panel is for divergent eye movements and the rightward movement of the left eye is reversed for a comparison with leftward movements of the right eye. The two eye's movements are superimposed in most conditions.

Figure 6. Comparison of right and left eye responses in convergence eye movements at different scotoma sizes. Solid bars are for the right eye and empty bars are for the left eye responses. The star (*) indicate a significant difference ($p < 0.05$) between the two eyes. A, B, C, and, D represent 4 different subjects.

Figure 7.

Comparison of right and left eye responses in divergence eye movements at different scotoma sizes. Solid bars are for the right eye and empty bars are for the left eye responses. The star (*) indicate the significant difference ($p < 0.05$) between the two eyes. A, B, C, and, D represent 4 different subjects.

Table 1

Latencies of vergence responses (ms)

Scotoma size	Convergence	Divergence
0 ⁰	97.1 ± 9.5 ms	86 ± 11.5 ms
2.5 ⁰	97.3 ± 8.5 ms	100.4 ± 9.4 ms
7.5 ⁰	100.6 ± 8.7 ms	99.6 ± 7.2 ms
15 ⁰	104.6 ± 8.4 ms	96.4 ± 4.0 ms
22.5 ⁰	110.5 ± 4.6 ms	99.1 ± 4.6 ms
30 ⁰	117 ± 6.6 ms	113.1 ± 12.5 ms