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RESEARCH NOTE

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Effects of diazepam on the latency of saccades for luminance and binocular disparity defined stimuli

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Abstract Saccadic latency is composed of separate sensory and motor processing delays. Therefore, any alteration in the sensory processing should effect the saccadic latency. Because the highest density of benzodiazepine (Bz) binding sites is located in cerebral cortex, sensory processing of stimuli in this cortical area is expected to be substantially effected by administration of Bzs. It is well known that sensory processing of binocular disparity occurs in the cerebral cortical areas and therefore the latency of saccades to stimuli defined by binocular disparity should be substantially affected by Bz intake. In this study, we tested this prediction by comparing the latency of saccadic eye movements for binocular disparity defined stimuli (stereo stimuli) with those for luminance contrast defined stimuli (luminance stimuli), after diazepam or placebo. Eye movements were mainly recorded by use of the magnetic search coil technique, and the study was performed in a randomized, double-blind way. Although diazepam prolonged the latency of saccades for stereo and luminance stimuli, the percentage increases in saccadic latency for the stereo stimuli were significantly larger than those for the luminance stimuli. Saccadic peak velocity, and saccadic amplitude, also significantly decreased after diazepam under conditions of stereo and luminance stimuli. However, there was no significant difference for either saccadic peak velocity or amplitude between the two types of target. The results suggest that the latency of saccades to binocular disparity defined random-dot stimuli could more sensitively reflect the pharmacodynamic effects of Bzs on the cerebral cortex.

Keywords Eye movements · Saccadic latency · Dynamic random-dot stereograms · Benzodiazepines

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Introduction

Benzodiazepines (Bzs) are a class of drugs widely prescribed in the treatment of various physical and emotional disorders (Blackwell 1973; Fraser 1998; Woods et al. 1992). Since specific Bz binding sites were found in areas of the central nervous system (CNS), such as cerebral cortex and pons, known to participate in vision and oculomotor control (Möhler and Okada 1978; Rothenberg and Selkoe 1981; Speth et al. 1978), eye movement tests have been frequently utilized to assess the pharmacodynamic effects of such CNS-active drugs in recent years (de Visser et al. 2003; Hopfenbeck et al. 1995; Roy-Byrne et al. 1993; Tian et al. 2003). In previous reports, saccadic peak velocity was reduced after Bz administration and reflected a specific drug effect in brainstem areas (Ball et al. 1991; Potokar et al. 2000; Rothenberg and Selkoe 1981; Roy-Byrne et al. 1993; Tedeschi et al. 1986). However, the highest density of Bz binding sites are located in the cerebral cortex (Braestrup et al. 1977; Möhler and Okada 1978; Speth et al. 1978) thus suggesting that a larger effect of Bz administration is possible in sensory processing of stimuli in cortical areas.

It is known that saccadic latency is determined by both sensory and motor processing delays (Leigh and Zee 1999) and thus compared to saccadic velocity, it should be more sensitive to Bz application. Therefore, to seek a more sensitive measure of Bz effects, including effects in cortical areas, we investigated the effects of diazepam on saccadic latency. Specifically, we compared latency of saccadic eye movements to binocular disparity defined random-dot stimuli (stereo

stimuli) with those to luminance contrast defined stimuli (luminance stimuli) after diazepam or placebo, because binocular disparity is mainly processed in the cerebral cortex (e.g. Hubel and Wiesel 1970; Poggio et al. 1985; for reviews, see DeAngelis 2000; Gonzalez and Perez 1998).

Materials and methods

Subjects

Ten volunteers aged 19–30 served as subjects. All had normal or corrected-to-normal visual acuity and normal stereopsis. None had prior experience with Bzs or any other sedative hypnotics, and none had taken any medication in the past month. Tea, coffee, and alcohol were forbidden for more than 24 h preceding the experiment.

Written informed consent was obtained from each subject before the study, after all procedures and risks had been explained. The experiment was approved by the Institutional Human Subjects Review Board and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Stimuli and apparatus

Stimuli were displayed on a 21 in., short-persistence monitor, located 57 cm in front of the observer with a visual angle of 40°×30° for each eye. The video display mode was set on 800×600 pixels with a frame refresh rate of 120 Hz. Stimuli were viewed with a pair of crystal shutter glasses which alternated synchronization with the monitor by use of the vertical blank signals (Lipton 1991). The odd frames were presented to the left eye and the even frames to the right eye.

Luminance stimuli

A white square (1°×1°, luminance 30 cd m^{-2}, background 15 cd m^{-2}) was presented at the center of the screen as a fixation target. After a random time interval of 2–4 s, the square shifted randomly to the left or right. The amplitude of target displacement was randomly selected to be 4° or 8°. After the step displacement, the target remained visible on the screen for 2 s (Fig. 1a).

Stereo stimuli

A total of 120 pairs of random-dot stereograms that were cycled through in sequence depicted the stereo stimuli. The elements of each random-dot image were white (30 cd m^{-2}) and black (0.01 cd m^{-2}) dots. Each dot was a 3×3 min arc and the dot density was 50%. Each pair of stereograms was composed of two successive frames of random-dot patterns. Odd frames were for the left eye and even frames for the right. When viewed monocularly, there were only patterns of dynamic noise without any recognizable features. But when viewed dichoptically with the crystal shutter glasses, a depth square (1°×1°, crossed disparity 24 min) was vividly perceived in front of a background of random-dots (shown schematically in Fig.1b). At the beginning of each trial, the square was perceived at the center of the screen. After a variable interval of 2–4 s, the square was shifted randomly to the left or right with displacement of 4° or 8° for 2 s (Fig.1b). Note that the disparity of the square remained the same after the target displacement.

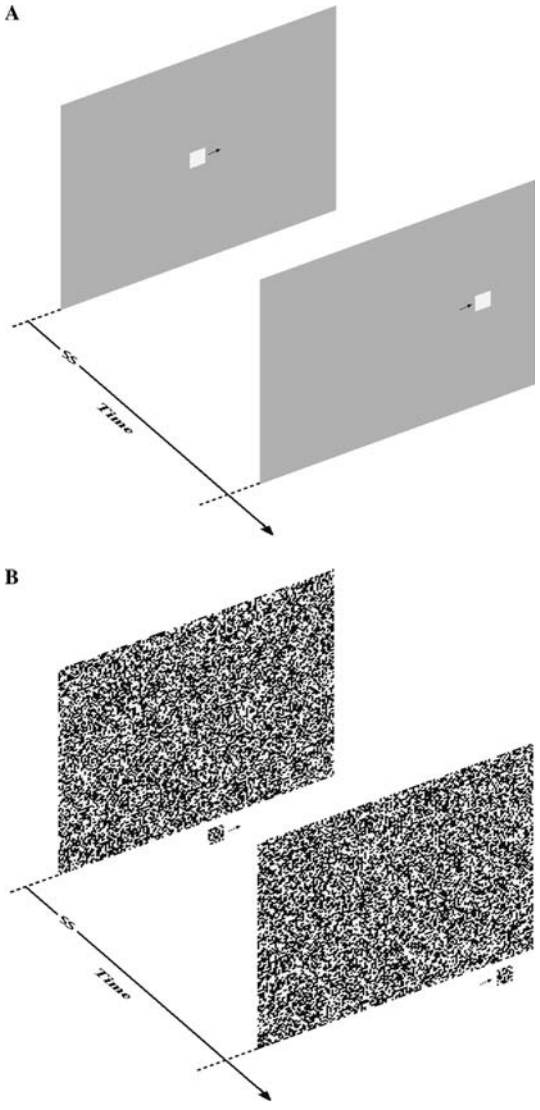

Fig. 1 Schematic representations of luminance and stereo stimuli. **A** Luminance stimuli: a bright square (1°×1°, luminance 30 cd m^{-2}) was presented on the screen against a gray background (15 cd m^{-2}). During experiments, the bright square shifted to left or right from the center. **B** Stereo stimuli: through the crystal shutter glasses for dichoptically viewing, a depth square (1°×1°, crossed disparity 24 min arc) was vividly perceived in front of the background, which shifted randomly to left or right during experiments

Experimental procedure

For each subject, 10 mg diazepam or placebo (Vitamin B_1) was administrated orally in a double-blind, randomized fashion. On each test day, the saccade experiments started about 75 min after the drug intake. Each subject returned for a second day after an interval of at least 1-week.

Subject sat in a dimly lit room with the head stabilized by a chin rest. He/she was instructed to keep gaze on the center of the fixation square and move the eyes as quickly as possible to the new location of the square. Each block consisted of six trials in any stimulus conditions. And the block order of two stimulus conditions was randomized and counterbalanced across subjects and drugs. Calibration was performed carefully at the beginning of each block. At least 20 blocks were performed for each stimulus condition, thus 60 successive peripheral saccades were measured for each target displacement.

Eye movement measurement

Eye movements were mainly measured with the magnetic scleral search coil technique (Collewijn et al. 1975; Robinson 1963). The electro-oculographic (EOG) technique was adopted for only two subjects (Tong et al. 2002). An annulus of silicone rubber with an induction coil (Skalar Medical BV, Netherlands) was placed on the subject's right eye after topical anesthesia with oxybuprocaine hydrochloride 0.4%. Eye movement signals were sampled at 1,000 Hz and stored on a computer for off-line analysis. Simultaneously, eye movements were displayed on another screen for online monitoring (Wei and Sun 1998; Yang et al. 2000).

Data analysis

The latency, peak velocity and amplitude of primary saccades were calculated by means of a computer program (Tian et al. 2003). Saccade initiation was defined as the time when eye velocity exceeded 5% of saccadic peak velocity. Saccade termination was determined as the time when eye velocity dropped below 10° s^{-1}. Saccadic latency was defined as the time difference between stimulus onset and saccade beginning. Saccades in the wrong direction, contaminated by blinks, or with latency less than 100 ms or more than 1,000 ms were excluded (Yang et al. 2002; Leigh and Zee 1999).

The changes of mean saccadic latency, peak velocity and amplitude for all subjects were analyzed by a multiway factorial analysis of variance (ANOVA) with stimulus type (disparity versus luminance defined), target displacement (4° vs. 8°) and treatment (diazepam versus placebo) as fixed factors, and subjects as random factor. The planned comparisons were further used to compare the effects of diazepam for each stimulus condition.

Results

Changes in saccadic latency

Mean saccadic latencies for all subjects after diazepam were plotted against those after placebo, for two stimulus types, in Fig. 2a. The diagonal line represented no difference in saccadic latency after diazepam administration compared with placebo.

The ANOVA showed that there was a significant effect of diazepam administration on saccadic latency ($F_{(1,9)} = 311.7$, $P < 0.001$). On further analysis by means of the planned comparisons, we found that for all subjects after diazepam intake, for target displacement of 4°, the average saccadic latency significantly increased from 142.4 ms (SD ±24.4) to 164.1 ms (SD ±31.5) for luminance ($F_{(1,9)} = 20.8$, $P = 0.001$), and from 266.3 ms (SD ±35.8) to 369.6 ms (SD ±39.1) for stereo stimuli ($F_{(1,9)} = 137.6$, $P < 0.001$), respectively. Similarly, significant increases were also found for target displacement of 8°. The average saccadic latency significantly increased from 140.0 ms (SD ±21.4) to 158.0 ms (SD ±25.3) for luminance ($F_{(1,9)} = 46.6$, $P < 0.001$), and from 287.7 ms (SD ±28.1) to 415.4 ms (SD ±54.4) for stereo stimuli ($F_{(1,9)} = 111.8$, $P < 0.001$), respectively. The interaction between treatment (diazepam versus placebo) and target displacement (4° vs. 8°) was not significant ($F_{(1,9)} = 1.9$, $P = 0.2$), which means the increases of latency were independent of target displacements. But the interaction between treatment and stimulus type (disparity versus luminance defined) was significant ($F_{(1,9)} = 86.9$, $P < 0.001$), which indicated that the increases of saccadic latency were dependent on stimulus conditions.

The percentage changes of saccadic latency induced by diazepam for the two stimuli are shown in Fig. 2b. The mean percentage increases in saccadic latency were +15.17% (SD ±10.74) and +13.02% (SD ±5.75) for luminance, and +39.52% (SD ±12.37) and +44.38% (SD ±12.39) for stereo stimuli, for 4° and 8°, respectively. The increases in saccadic latency for stereo stimuli were significantly greater than those for luminance stimuli ($F_{(1,9)} = 36.7$, $P < 0.001$).

Changes in saccadic peak velocity and amplitude

Mean saccadic peak velocities and amplitudes for all subjects after diazepam are plotted against those after placebo, for two stimulus types, in Fig. 2c and Fig. 2e. The diagonal line represents no difference in saccadic peak velocity or amplitude after diazepam administration compared to placebo.

The ANOVA showed that both saccadic peak velocity and primary amplitude were significantly affected by diazepam ($F_{(1,9)} = 116.6$, $P < 0.001$, and $F_{(1,9)} = 27.8$, $P < 0.001$, respectively). On further analysis

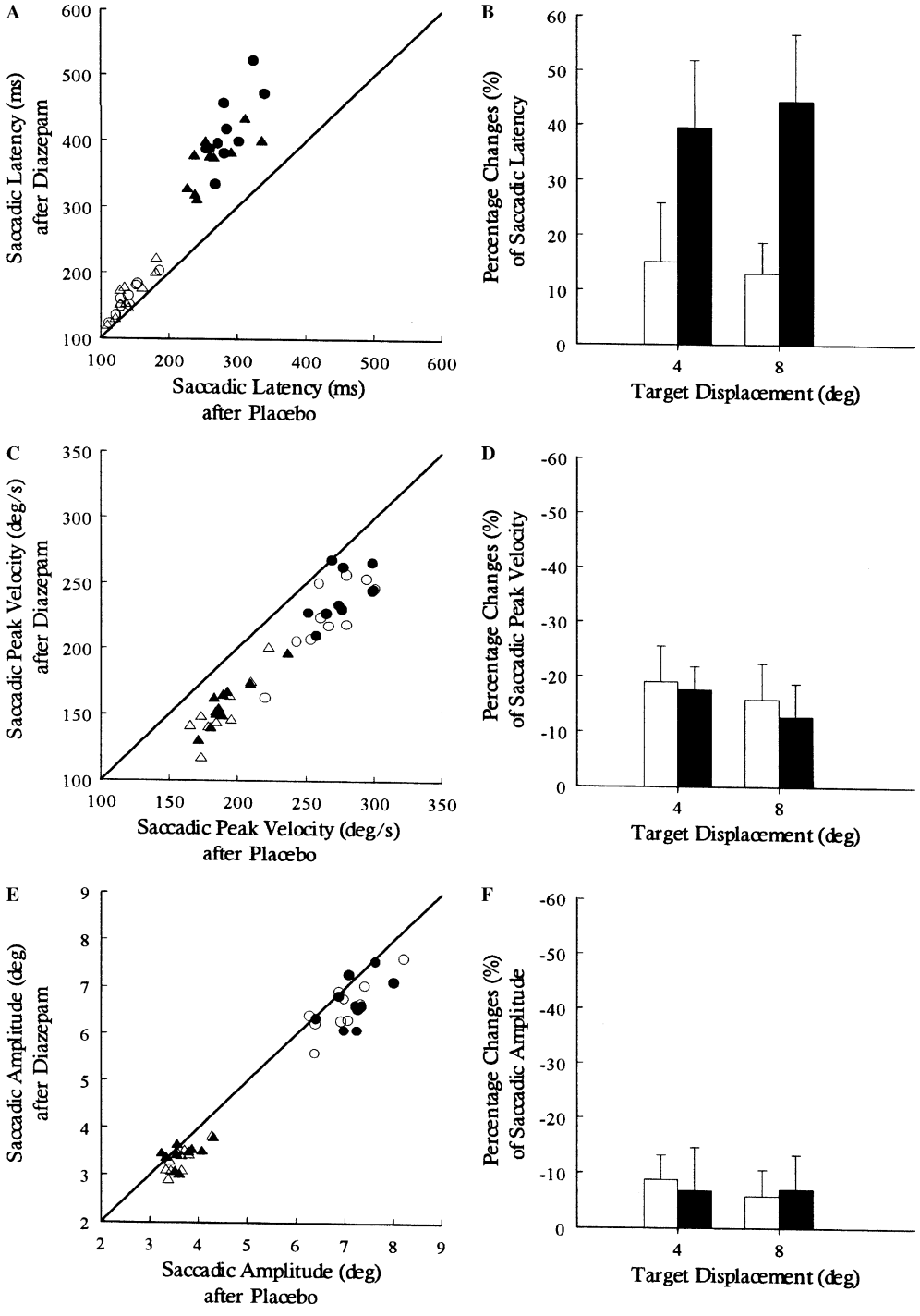

Fig. 2 Saccadic latency, peak velocity, and amplitude after diazepam or placebo, and their diazepam-induced percentage changes for both luminance (*empty symbols*) and stereo stimuli (*solid symbols*) for target displacements of 4° (*triangles*) and 8° (*circles*) for all subjects ($n = 10$). The *diagonal line* represents no difference between the diazepam and placebo. **A** Saccadic latency significantly increased after diazepam ($F_{(1,9)} = 311.7$, $P < 0.001$). *Each symbol* represents one subject. **B** The percentage changes in saccadic latency for stereo stimuli, *solid bars*, were significantly larger than those for luminance stimuli, *empty bars* ($F_{(1,9)} = 36.7$, $P < 0.001$). *Error bars* are standard deviations across subjects. **C** Saccadic peak velocity significantly decreased after diazepam ($F_{(1,9)} = 116.6$, $P < 0.001$). **D** No significant decrease differences between the two stimulus conditions for saccadic peak velocity ($F_{(1,9)} = 2.6$, $P = 0.14$). **E** Saccadic amplitude significantly decreased after diazepam ($F_{(1,9)} = 27.8$, $P < 0.001$). **F** No significant differences between the two stimulus conditions for saccadic amplitude ($F_{(1,9)} = 0.1$, $P = 0.79$)

by means of the planned comparisons, we found that for all subjects after diazepam, for target displacement of 4°, the average peak velocity of saccades significantly reduced from 188.4° s^{-1} (SD ±17.7) to 152.8° s^{-1} (SD ±22.6) for luminance ($F_{(1,9)} = 101.9$, $P < 0.001$), and from 192.4° s^{-1} (SD ±18.3) to 158.7° s^{-1} (SD ±18.5) for stereo stimuli ($F_{(1,9)} = 205.1$, $P < 0.001$), respectively. And the average saccadic amplitude significantly decreased from 3.62° (SD ±0.28) to 3.30° (SD ±0.27) for luminance ($F_{(1,9)} = 38.2$, $P < 0.001$), and from 3.69° (SD ±0.33) to 3.42° (SD ±0.24) for stereo stimuli ($F_{(1,9)} = 8.45$, $P < 0.05$), respectively. Similarly, significant decreases were also found for target displacement of 8°. The average peak velocity of saccades significantly decreased from 266.3° s^{-1} (SD ±24.2) to 224.3° s^{-1} (SD ±29.1) for luminance ($F_{(1,9)} = 68.4$, $P < 0.001$), and from 277.3° s^{-1} (SD ±17.4) to 241.6° s^{-1} (SD ±19.3) for stereo stimuli ($F_{(1,9)} = 42.3$, $P < 0.001$), respectively. And the average saccadic amplitude significantly decreased from 6.99° (SD ±0.58) to 6.58° (SD ±0.55) for luminance ($F_{(1,9)} = 15.9$, $P < 0.01$), and from 7.21° (SD ±0.43) to 6.70° (SD ±0.50) for

stereo stimuli ($F_{(1,9)}=12.5$, $P<0.01$), respectively. Both the interaction between treatment (diazepam versus placebo) and target displacement (4° vs. 8°) and the interaction between treatment and stimulus type (disparity versus luminance defined) were not significant for saccadic peak velocity ($F_{(1,9)}=1.6$, $P=0.24$, and $F_{(1,9)}=1.5$, $P=0.26$, respectively) and saccadic amplitude ($F_{(1,9)}=3.1$, $P=0.11$, and $F_{(1,9)}=0.1$, $P=0.74$, respectively).

The mean percentage decreases in saccadic peak velocity after diazepam, for 4° and 8°, were −19.09% (SD ±6.48) and −15.93% (SD ±6.46) for luminance stimuli and −17.64% (SD ±4.15) and −12.81% (SD ±6.04) for stereo stimuli (Fig. 2d). And the mean percentage decreases in saccadic amplitude, for 4° and 8°, were −8.80% (SD ±4.42) and −5.84% (SD ±4.77) for luminance stimuli and −6.86% (SD ±7.76) and −7.04% (SD ±6.29) for stereo stimuli (Fig. 2f). Between the luminance and stereo stimulus conditions the changes of saccadic peak velocity were not significantly different ($F_{(1,9)}=2.6$, $P=0.14$), neither was saccadic amplitude ($F_{(1,9)}=0.1$, $P=0.79$).

Discussion

With the luminance contrast defined stimuli, a Bz-induced increase in saccadic latency was found in previous studies and present experiments, which reflected a specific pharmacological effect of the drugs on pathways concerned with saccadic latency (Fafrowicz et al. 1995; Masson et al. 2000; Roy-Byrne et al. 1993). Neurophysiological studies indicated that at least two pathways are involved in the visually-guided saccades. One is the cortical pathway from striate and posterior parietal cortices to the superior colliculus, and the other is the direct projection from retinal ganglion cells to the superficial layers of the superior colliculus, i.e. the subcortical pathway (Gaymard et al. 1998; Isa and Kobayashi 2004; Munoz 2002; Robinson and McClurkin 1989). For saccades to disparity defined random-dot stimuli without any monocular location cues (Julesz 1960, 1971), substantial sensory processing is likely to occur in the striate cortex. This is because the primary visual cortex is the earliest location in the visual pathway where disparity sensitivity neurons are found (e.g., Poggio et al. 1985; for reviews, see DeAngelis 2000; Gonzalez and Perez 1998). Recent investigations have showed that disparity-sensitive neurons also exist in extrastriate visual cortices, and in lateral intraparietal cortex (area LIP) and frontal eye field (FEF) (e.g., Ferraina et al. 2000; Gnadt and Mays 1995; for reviews, see DeAngelis 2000; Gonzalez and Perez 1998). In our experiments, the greater increase in saccadic latency for stereo stimuli compared with luminance stimuli when diazepam was administered is consistent with a greater involvement of cortical areas in saccades to stereo compared to luminance stimuli. This is because the density of Bz binding sites is substantially higher in cortical compared with sub-cortical areas (Braestrup et al. 1977; Carlson et al. 1993; Möhler and Okada 1978; Speth et al. 1978).

In the present study all subjects demonstrated a significant decrease in saccadic peak velocity for both stereo and luminance stimuli after diazepam. However, the decrease differences between the stereo and luminance stimulus conditions were not significant. This result suggests that saccadic peak velocity is more closely related to the brainstem activity and is less influenced by a depression in cortical activity (Keller 1974; Luschei and Fuchs 1972; Roy-Byrne et al. 1993; Tedeschi et al. 1986). After diazepam, although a small decrease in saccadic amplitude was found, the decrease differences between the two stimulus conditions were not significant, either.

Previous literature indicated that the depth perception is independent of sizable vergence error when large suprathreshold disparity was employed (Erkelens and Collewijn 1985a, b). In our experiments, both the central fixation and eccentric targets possessed the equal disparity, about 24 min of arc, and it was substantially larger than the stereothreshold (Heron et al. 1985). Therefore, the possible changes of vergence state occurring after diazepam might be small and only have minor effects on the saccadic latency. However, to precisely examine the effects of vergence state on the latency of saccades, the eye movements should be recorded by means of a binocular search coil method.

In summary, we have investigated a new approach for examining the effects of Bzs on cortical brain areas. We found that, the diazepam treatment produced a substantially larger change in saccadic latency when binocular disparity defined random-dot stimuli, compared with luminance contrast defined stimuli, was utilized. Our results suggest that the latency of saccades to binocular disparity defined random-dot stimuli could more sensitively reflect the effects of Bzs on cerebral cortex.

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