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Research report

Lorazepam-induced modifications of saccadic and smooth-pursuit eye movements in humans: attentional and motor factors

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Abstract

In a placebo-controlled, double-blind study, we measured the effects of low dose lorazepam on attentional and motor factors involved in saccadic and smooth pursuit eye movements. We manipulated the temporal interval between the extinction of the central fixation target and the appearance of a second eccentric target (gap/overlap step paradigm). The second target was either stationary (saccade trial) or moving in a direction opposite to the step (pursuit trial). Gap/overlap effects on the latency of saccadic and smooth pursuit eye movements were measured before and after oral intake of either lorazepam or placebo. Pharmacological effects on the dynamics and the accuracy of both types of eye movements were also investigated. In 14 healthy volunteers, we found that the temporal interval between fixation target offset and eccentric target onset modulates the latency of saccadic and smooth pursuit eye movements in a similar way. As compared to placebo, lorazepam significantly increased the latency of both types of eye movements, but did not modify the gap/overlap effect. Moreover, lorazepam significantly decreased the peak velocity of the first saccade towards the eccentric stationary target, as well as the gain of tracking towards the eccentric moving target. However, the overall accuracy of both behaviors was not significantly affected, indicating that systematic errors in foveating or tracking were detected and corrected by appropriate corrective or catch-up saccades, respectively. Results are discussed in terms of shared/different mechanisms for saccadic and pursuit systems in primates.

Keywords: Lorazepam; GABA; Smooth pursuit; Saccades; Humans; Oculomotor system

1. Introduction

Human vision relies extensively on the ability to make both saccadic and smooth tracking eye movements. Saccadic eye movements rapidly shift the images of visual targets from eccentric location in the visual field towards the fovea. When the retinal image of a target moves, smooth pursuit eye movements restore a nearly stationary retinal image, by producing a slow rotation that keeps the eyes aligned with the target. Neural structures and systems responsible for saccades and pursuit have been extensively studied in primates [1–3]. Overall, saccadic and smooth eye movements are controlled by different mechanisms and different neural structures. However, they also share some similar behavioral dependencies as well as some neural substrates [4–6]. Therefore, studying functional similarities and/or differences between both types of eye movements can provide insights into the nature of their shared inputs as well as into the way primate motor systems coordinate the use of a single effector by different neural systems.

Although the properties and mechanisms underlying saccadic and smooth pursuit eye movements are quite

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different, their initiation always requires a break from fixation [1,3,6]. For saccades, the gap paradigm has been used to investigate cognitive and neural processes preceding the initiation of eye movements. The basic aspect of the gap paradigm is to manipulate the timing in which visual stimuli are presented. A first visual fixation target is presented in a central, straight-ahead location. If a second target is presented at an eccentric position as the initial fixated target is extinguished, saccadic eye movements are elicited towards the second target with latencies of 150–200 ms. Saslow [7] first noticed that if the second target appears after the first has been turned off (therefore introducing a temporal gap between targets), saccadic latency is significantly reduced. This reduction depends on the exact duration of the gap, with maximal reductions (i.e. latencies in the range 90–130 ms) occurring for gaps >200 ms in humans [4,7,8]. On the contrary, when the second target appears before the first target is turned off (introducing a temporal overlap between targets), saccadic latency is significantly increased [9].

Recent studies have suggested a similar gap-effect for smooth pursuit eye movements in primates [4,5,10,11]. In humans, Krauzlis and Miles [4] reported that the latency of both smooth pursuit and saccades show similar dependencies upon gap duration. However, no express pursuits (latencies below 90 ms) were observed (but see [11]) and changes in pursuit latency reduction were independent of the second target eccentricity, two clear differences with saccadic eye movements. From those results, they suggested that both oculomotor systems share a common class of inputs, that are necessary, but not sufficient, to initiate movements. These inputs are related to the target selection process, and are involved in the release of fixation and the gating between the initiation of either saccadic or smooth pursuit eye movements. One advantage of a shared mechanism might be that this gating processes would be involved in the coordination of motor sequences for voluntary movements. The purpose of the present study is to further investigate the relationships between saccadic and pursuit eye movements by administrating a benzodiazepine (BZD) in healthy volunteers. After BZD intake, saccadic peak velocity is decreased [12–14]. That saccadic latency increases is more controversial [15]. Most of these studies used high doses of BZD and did not try to distinguish between specific effects on oculomotor behavior and more general, sedative effects [12]. Furthermore, few data are available on the effects on smooth pursuit eye movements [16,17] and outcomes are unclear. In the present study, we investigated whether low doses of lorazepam (1 mg) induces in healthy volunteers similar or different effects on saccadic and smooth pursuit eye movements when probed with a gap/overlap task in an interleaved paradigm. We carefully analyzed both latency and metrics of ocular responses to either stationary or a moving eccentric targets to disentangle attentional from motor effects of BZD on both types of eye movements.

2. Material and methods

2.1. Subjects

Fourteen healthy volunteers of both sexes (7 females; 7 males) participated in the study. Mean ($\pm$SD) age was 26 ± 3 years; mean height ($\pm$SD) was 168 ± 6 cm; mean weight ($\pm$SD) was 60 ± 8 kg; visual acuity was in the normal range, without correction ($>8/10$, Snellen test). The population was drawn from students at the Medical School. Subjects were excluded from the study if they had a history of head injury, alcohol abuse, epilepsy or any other neurological or ophthalmological illness. Subjects with a history of drug-misuse or psychiatric illness were excluded as well as heavy smokers. Subjects were asked not to drink coffee, tea or alcohol during the study and driving was prohibited. Tobacco was prohibited within 12 h before the drug intake. The study was approved by the local Ethic Committee and written informed consent was obtained from all subjects.

2.2. Apparatus and eye movement recording

Eye movements were recorded using a high resolution infrared scleral reflectance technique (IRIS Skalar). Subjects were seated in a darkened room with head firmly stabilized by a biting bar. Visual stimuli were presented on a video screen (BARCO PCD21, resolution 0.03 deg/pixel) with a refresh rate of 60 Hz. Viewing distance was 0.8 m. Vision was binocular but only the horizontal right eye movements were recorded. Analog signals were low-pass filtered (DC-100 Hz, -3 dB), digitized at 250 Hz (DT2801 board, 12 bits resolution) and stored for off-line analysis. Stimuli were white square targets (0.3×0.3 deg, luminance 0.35 cd/m^2, contrast: 97%) projected on a dark-grey background. Because of the mesopic luminance condition, 5 min of dark adaptation were allowed before each block. Stimuli were generated by a PC computer expanded with a graphic card (Matrox SM1281). The same PC collected eye movement data and controlled the experiment.

We examined the effects of changing the temporal interval between the disappearance of the first target and the appearance of the second. The temporal interval (δ) were of 0, -200 (gap) or 200 (overlap) ms. Eccentricity of the second target was always 5 deg, either rightward or leftward (random). Saccade and pursuit trials were randomly interleaved. For saccade trials, the second target stayed stationary for the rest of the trial. For pursuit trials, the second target appeared

at the same eccentricity (± 5 deg) and started to move in the opposite direction at a constant velocity of 14.5 deg/s (16 pixel/frame). To avoid anticipatory responses, the presentations of the first and second targets were randomly varied: the first target remained stationary for 500 ± 200 ms and the second target was displayed, either moving or stationary for 700 ± 200 ms. We interleaved pursuit and saccade trials because we wanted to be certain that the differences between pharmacological modulations of saccadic and pursuit eye movements were not caused by collecting the data in separate blocks and therefore at different times after the drug administration. Two blocks of 240 trials were completed for each experimental session, such that 40 trials were recorded for each condition. To ensure that subjects clearly understood the task and that no oculomotor abnormalities were present at baseline, subjects performed two training blocks during the week before the beginning of the study.

2.3. Pharmacological procedure

The study was a double-blind, cross-over, placebo-controlled study. That is, both subjects and investigators that run the experiments and analyzed the data were blinded regarding the order of treatment administration. A single dose of 1 mg was used for all subjects, corresponding to a dose of 0.017 mg/kg on average. The order of placebo versus lorazepam administration was randomly distributed over the 14 subjects, in two sessions, separated by a wash-out of 1 month. During each session, two blocks of eye movement trials were performed before (T0) and 2 h after (T2) oral intake of either lorazepam or placebo. Recording sessions always started (T0) at 08:00 h. Blood pressure and cardiac pulse were systematically assessed during each session, before (T0) dosing, 2 h (T2) and 8 h (T8) after dosing. Sedation was assessed with a Visual Analogic Scale (VARS) (Hindmarch, 1980) at T0, T2 and T8.

2.4. Eye movement analysis and statistical tests

At the beginning of each experimental session, the eye recording device was calibrated by having the subjects fixating different targets located at known positions (from $+15$ to $-15°$, 5° spaced). A first, quick check of the calibration was done by fitting a linear regression to the data and regression coefficient had to be better than 0.99 to continue the session. Otherwise, the apparatus was repositioned and a new calibration was performed. All data were stored on disk during the experiment and later transferred to a Unix-based system for subsequent analysis. Off-line, the horizontal eye position data obtained during the calibration procedure were fitted with a 5th-order polynomial which was then used to linearize the eye position recorded during the experiment. Eye position data were then smoothed with a cubic spline of weight 10^6, selected by means of a cross-correlation procedure. Horizontal eye velocity and acceleration data were obtained by a two-point digital differentiation. An interactive analysis software was used to display and take measurements from the data. For saccadic eye movements, quantitative measures were latency, peak velocity of the first saccade, amplitude of the first saccade and amplitude of the second, corrective saccade if present. For smooth pursuit eye movements, quantitative measures were latency, velocity of slow phases and displacement gain which is the ratio between the total target displacement and the total eye displacement. Notice that this latter index takes into account both smooth tracking and catch-up saccades during pursuit. Estimates of the saccadic and smooth pursuit latencies were obtained with objective method using an algorithm adapted from Carl and Gellman [18]. The experimental design interleaved saccade and pursuit trials and therefore one complication in analyzing the data from pursuit trials was that the initial change in smooth eye velocity was sometimes interrupted by early saccades. Instead of deleting all smooth pursuit trial containing an early catch-up saccade, we applied two criteria. First, if oculomotor responses were initiated by a saccadic eye movement, the trial was discarded. Second, when a saccadic eye movement was found within the response interval, data points within the saccadic segment were excluded from the computation of the response regression line. Pursuit latency was computed as described earlier but if measured latency of pursuit preceded the saccadic onset by less than 20 ms, the measure was discarded. Following this procedure, we excluded about 10% of the trials from the analysis.

Statistical analysis was performed on the statistical analysis system (SAS). The parameters were compared using an analysis of variance (ANOVA). The frequency distribution of saccadic and pursuit latencies were fitted with a simple gaussian function, for each subject and condition so that best-fit parameters can be compared across conditions.

3. Results

The study was designed to assess the effects of an acute low dose of lorazepam on both latency and metrics of saccadic and pursuit eye movements. We first present the data gathered before drugs (either lorazepam or placebo) administration and then we describe the effects of lorazepam versus placebo for each type of eye movement, separately.

3.1. Gap-effects on saccadic and smooth pursuit eye movements

Fig. 1A illustrates for one subject the distribution of saccadic latency for the three temporal delay conditions. No significant differences in latency were observed between rightward and leftward saccades. Furthermore, because there was no significant differences between the different baseline sessions, data were pooled across sessions for each subject in order to increase the number of trials and improve the significance of fitting the distribution with a gaussian function. For all subjects, saccadic latency distributions for all three temporal delays conditions were best fitted with an unimodal gaussian distribution, indicating that there was no evidence for a separate sub-population of express saccades. As illustrated in Fig. 1A, gaussian distributions became broader from gap to overlap conditions. Best fit σ (standard deviation) parameter of the gaussian function was significantly larger for an overlap of 200 ms as compared with the no-delay condition (39.98 ± 18.78 and 17.69 ± 6.20, $t(26) = 4.28$, $P < 0.03$, Buonferroni corrected). However, best fit σ parameters were not different between gap and no-delay conditions, while the mean value was different. This is further supported by the significant increase in the mean saccadic reaction time from a gap of 200 ms to an overlap of 200 ms ($F(154,2) = 126$, $P < 0.0001$), as illustrated by Fig. 1B. Mean saccadic latency across subjects were of 164 ± 17, of 137 ± 15 and of 201 ± 32 ms for temporal intervals (δ) of 0, -200 (gap) and 200 (overlap) ms, respectively.

While the temporal delay between the first and second target significantly affected the latency of saccadic eye movements, no significant effect was found on the dynamics of saccades. Mean saccadic peak velocity was

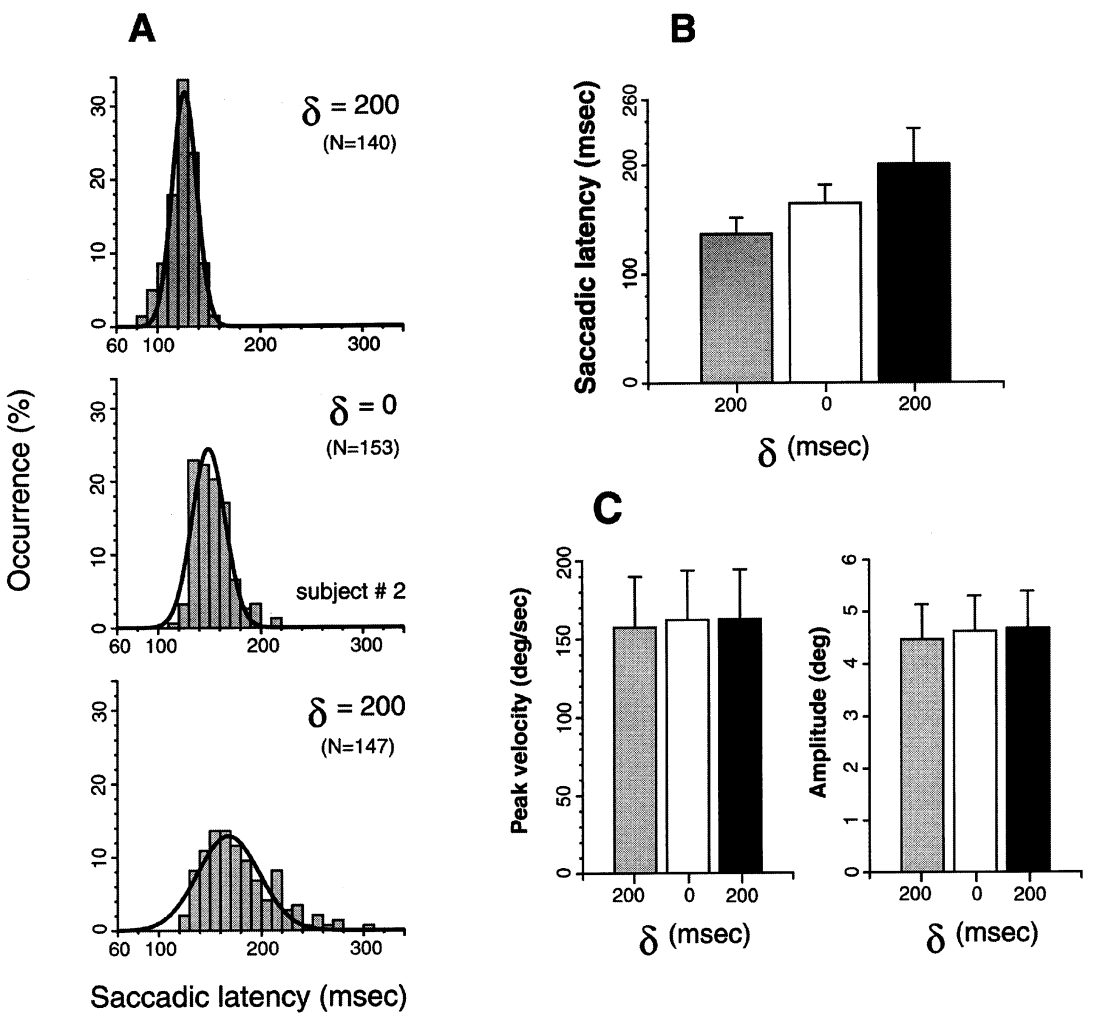

Fig. 1. Summary of the effects of a temporal gap/overlap between the disappearance of the fixated target and the appearance of the second, 5 deg eccentric, target. (A) Distribution of latencies obtained in subject # 2 in the three interval conditions, for both rightward and leftward saccadic eye movements, before any drug intake. (B) Mean $\pm$ SD saccadic reaction times across subjects for a gap of 200 ms ($\delta = -200$), a 0 ms delay ($\delta = 0$) and an overlap of 200 ms ($\delta = 200$). (C) Mean ($\pm$ SD) peak velocity (left panel) and amplitude (right panel) of the first saccadic eye movement after the appearance of the second, eccentric target, for each temporal interval.

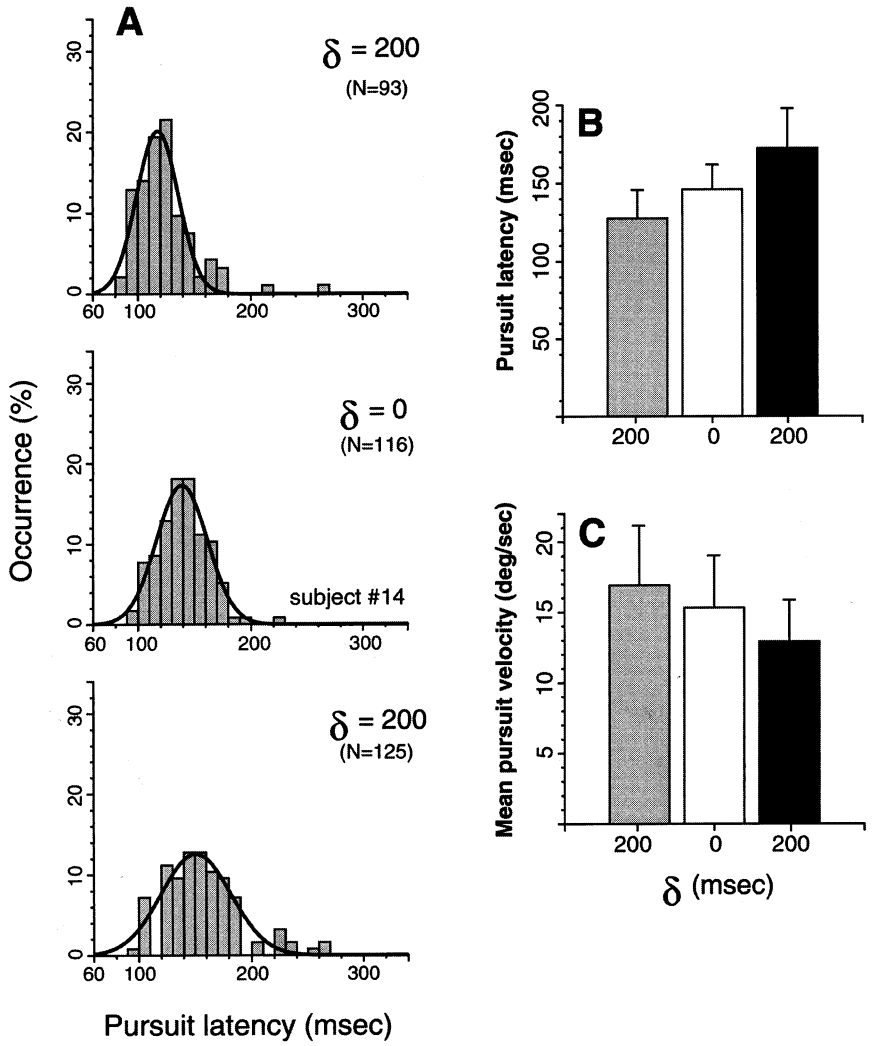

Fig. 2. Summary of the effects of a temporal gap/overlap between the disappearance of the fixated target and the appearance of the second moving target at an eccentric location. (A) Distribution of latencies obtained in subject #14 in the three interval conditions, for both rightward and leftward pursuit eye movements, before the drug intake. (B) Mean ($\pm$SD) smooth pursuit reaction times across subjects for a gap of 200 ms ($\delta = -200$), a 0 ms delay ($\delta = 0$) and an overlap of 200 ms ($\delta = 200$). (C) Mean ($\pm$SD) steady-state velocity of the smooth pursuit eye movement over an time window between 200 and 600 ms after the appearance of the second, eccentric, moving target, for each temporal interval.

of 160 ± 32 deg/s, mean amplitude of the first saccade was of 4.6 ± 0.7 deg and the systematic error was compensated by appropriate corrective saccade of mean amplitude 0.6 ± 0.3 deg (Fig. 1C).

Fig. 2 illustrates the effect of the delay between the first and the second target on smooth pursuit eye movements. Since no significant difference was found between the two baseline sessions, data were pooled across them. Moreover, data for rightward and leftward target motions were also pooled together since no statistically significant effect of target motion direction upon smooth pursuit latency or velocity was found. Fig. 2A illustrates for one subject the distribution of smooth pursuit latencies in the three temporal delay conditions. Distributions were always unimodal, for all conditions and subjects, and therefore data were fitted with a single gaussian function. Best-fit are shown with continuous lines. Introducing a delay between the first and second target shifted the distribution to the left, that is toward shorter latencies, while introducing an overlap shifted the distribution to the right, that is toward longer latencies. However, this latency shift was smaller than that observed with saccadic latency and the distributions were also narrower. While no significant difference was observed between best-fit σ parameters for a delay of -200 (gap) and 0 ms, significant differences were observed for this parameter between a delay of 0 and 200 (overlap) ms ($t(26) = 3.27$, $P < 0.02$) and a delay of -200 and 200 ms ($t(26) = 6.73$, $P < 0.0001$). For each baseline session, the timing of the stimulus sequence has a significant effect on smooth pursuit latency ($F(154,2) = 73.3$; $P < 0.0001$). Mean pursuit latencies were of 128 ± 18, 146 ± 16 and of 172 ± 25 ms for the gap, no-delay and overlap condi-

tions, respectively (Fig. 2B). Finally, we found significant differences between speeds of tracking eye movements initiated with different temporal delays ($F(154,2) = 20.81$, $P < 0.001$). Hence, mean tracking velocity over the time period 120–420 ms was increased when a gap was introduced between fixation point offset and target onset (16.83 ± 3.86 deg/s) but was decreased when there was a temporal overlap between fixation point offset and target onset (mean across subjects, 12.90 ± 2.93 deg/s), as compared to the no-delay condition (mean across subjects: 15.29 ± 3.58 deg/s) (Fig. 2C). These changes in mean tracking speed were largely compensated by appropriate catch-up saccades, irrespective of the temporal delay condition, as evidenced by the lack of significant gap-effect on the displacement gain ($F(154,2) = 1.98$; $P = 0.14$).

3.2. Effects of an acute dose of lorazepam (1 mg) on saccadic eye movements

Administration of 1 mg of lorazepam did not induce large changes in the behavior of healthy volunteers. We used a moderate dose of lorazepam to avoid strong side effects, with regard to the goals of the present study. Hence, no significant difference between placebo and lorazepam were found for the scores of the visual analog scale, evaluating sedation and drowsiness.

The histograms in Fig. 3 show the frequency distribution of saccade latencies for one subject, 2 h after administration of placebo and lorazepam. Leftward and rightward saccadic eye movements have been pooled together and latency distributions have been fitted with a simple gaussian function plotted, for each gap condition, with thick lines. A direct comparison can be made with baseline histograms plotted in Fig. 1A, for the same subject. As illustrated, 1 mg of lorazepam had severe effects on the latency distribution when the central and peripheral targets overlapped temporally for 200 ms, but had minor effects for the two other conditions (a temporal delay of either 200 or 0 ms). In the overlap condition, the main effects consistently found across subjects was an increased number of slow saccades (i.e. eye movements with latencies longer than 250 ms). These delayed saccades were barely observed in the other sessions, before or after placebo administration. This differential effect is further demonstrated when comparing best fit σ parameters, for each condition. Two hours after lorazepam intake, mean σ was significantly increased for the overlap condition ($t(26) = 2$, $P < 0.03$), while no significant effect was observed for the two other temporal delay conditions ($t(26) < 1.45$; $P > 0.08$). Administration of placebo had no effect on the variance of the saccadic latencies distribution.

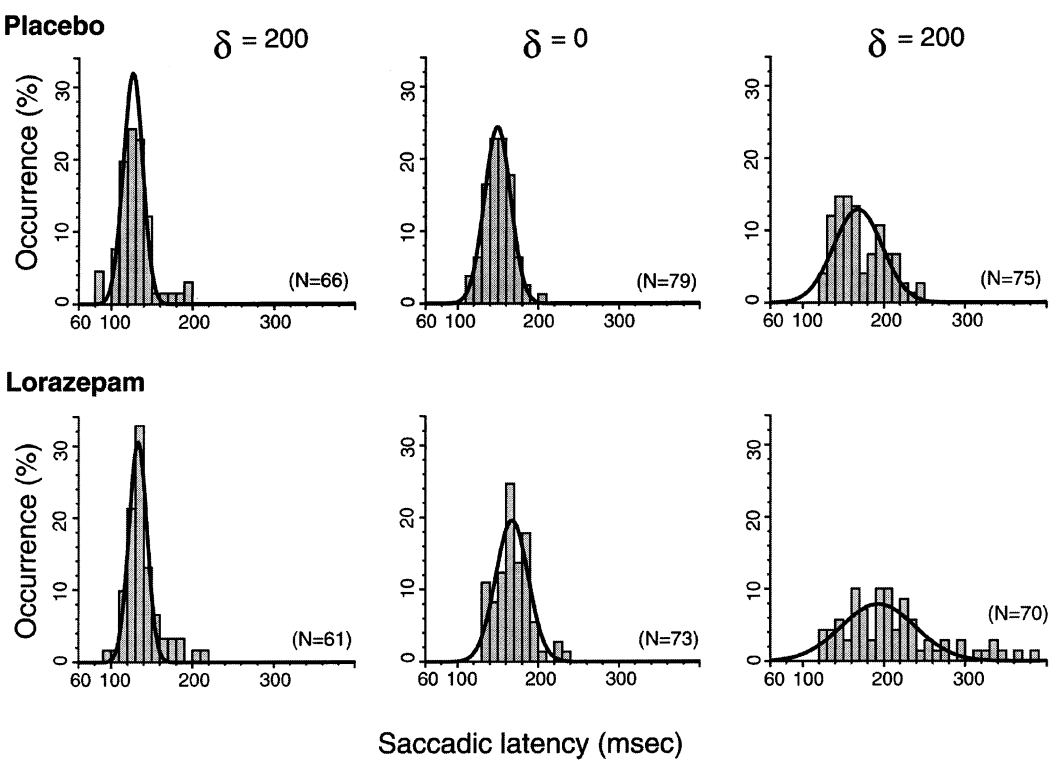

Fig. 3. Distribution of latencies obtained in subject 2 in the three interval conditions, for both rightward and leftward saccadic eye movements, 2 h after administration of either placebo (upper panels) or lorazepam (lower panels).

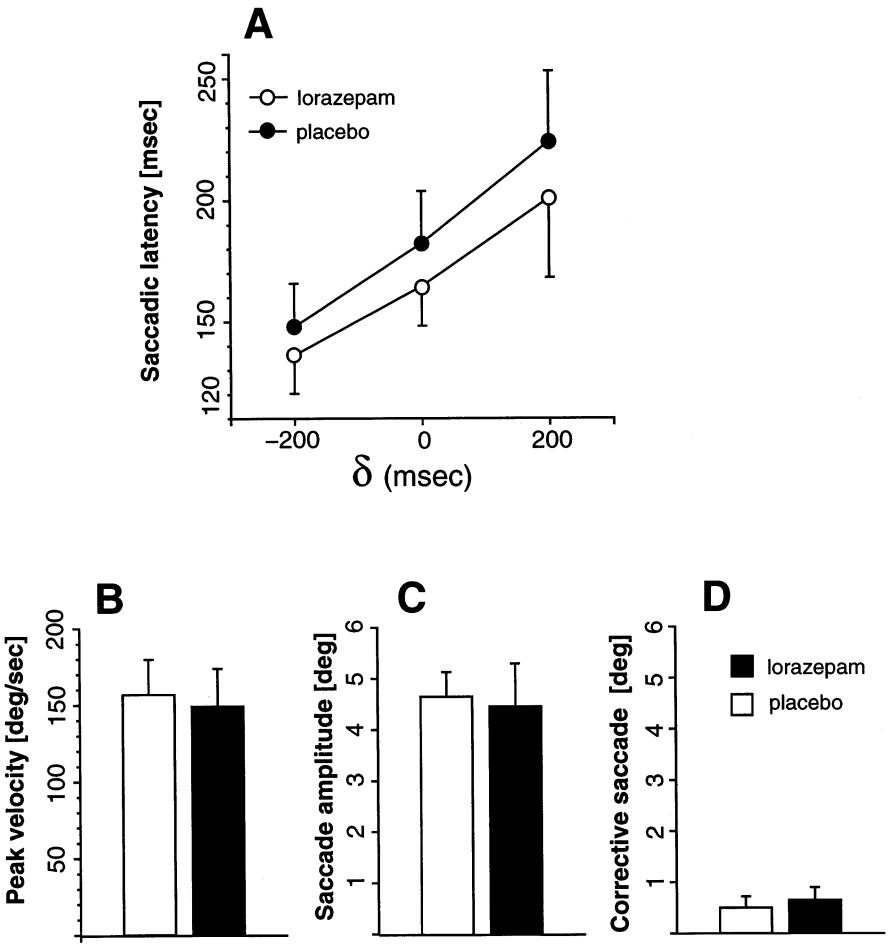

Fig. 4. Summary of the effects of placebo (open symbols) vs. lorazepam 1 mg (closed symbols) 2 h after intake. (A) Effects upon mean ($\pm$SD) saccadic reaction times, for each temporal interval conditions. Effects upon mean ($\pm$SD) peak velocity (B) and amplitude (C) of the first saccadic eye movements, and upon the amplitude of the second, corrective saccadic eye movements toward the target (D).

The second main effect of lorazepam was a rightward shift of the saccadic latency distribution, indicating a slower mean reaction time. Fig. 4A plots the average saccade latency as a function of stimulus sequence. Mean saccadic reaction times were globally increased after lorazepam administration, as compared to placebo, irrespective of the gap ($F(154,1) = 7.4$, $P = 0.007$). Furthermore, the magnitude of changes between before and after drug intake was stronger for lorazepam than for placebo ($F(154,1) = 22$, $P < 0.0001$). These effects indicate that lorazepam significantly increased saccadic reaction times (means of 185 and 177 ms for lorazepam and placebo, respectively). The temporal delay significantly changed saccadic reaction times, both after placebo or lorazepam administration (Fig. 4A). However, there was no significant interaction between treatment (placebo versus lorazepam) and temporal delay, indicating that gap-effects on saccadic reaction times were not sensitive to low doses of lorazepam ($F(154,2) = 0.4$, $P = 0.3$).

Fig. 4B–D illustrate the effects of lorazepam versus placebo on metrics of saccadic eye movements. Since there was no significant effects of either saccade direction or temporal delay on saccadic peak velocity and saccadic amplitude, data across those conditions were plotted together as mean ($\pm$SD) across subjects. Fig. 4B illustrates that saccadic peak velocity is significantly decreased after lorazepam administration, as compared to placebo ($F(154,1) = 19$; $P = 0.01$). The mean peak velocities for a 5 degree saccadic eye movement were of 149 ± 25 and of 158 ± 23 deg/s for lorazepam and placebo, respectively. As shown in Fig. 4C, the amplitude of the first saccadic eye movement towards the target was significantly decreased after lorazepam administration, as compared to placebo (4.5 ± 0.8 and 4.7 ± 0.5 deg, respectively; $F(154,1) = 5.9$; $P = 0.016$). Therefore, although highly significant, the effects of 1 mg of lorazepam where only moderate (around 5%), as compared to placebo. Such reduced amplitude of the first saccade was almost always compensated by an appropriate second, corrective saccade. This is illustrated in Fig. 4D, which shows that the mean amplitude of the corrective saccade was significantly increased after lorazepam administration, as compared to placebo ($F(154,1) = 19$; $P < 0.0001$).

3.3. Effects of an acute dose of lorazepam on pursuit eye movements

Fig. 5 illustrates the effects of placebo (upper panels) and lorazepam (lower panels) on the distribution of smooth pursuit latencies for one subject. Best-fit functions have been plotted for each condition. Lorazepam induced a small rightward shift of the curves, indicating a longer average reaction time, and a broader distribution of the smooth pursuit latencies. This latter effect was more noticeable for both the gap and the overlap conditions. Lorazepam increased the number of slow tracking responses. However, no significant differences between conditions were found for the best-fit σ parameters of the gaussian function.

Fig. 6 shows the effects of lorazepam versus placebo on both the mean smooth pursuit reaction times and the dynamics of tracking responses. As indicated in Fig. 6A, lorazepam induced an overall increase in pursuit latencies. As compared to the placebo, this increase was small but significant ($F(154,1) = 29.49$, $P < 0.0001$). Mean pursuit latencies were of 136 ± 13, 164 ± 17 and 200 ± 32 ms after lorazepam intake and of 129 ± 15, 148 ± 16 and 173 ± 24 ms after placebo administration, for gap, no-delay and overlap conditions, respectively. Therefore, mean latency changes induced by lorazepam were between 5 and 10%. Latency changes were smaller for the gap condition, but there was no significant interaction between the temporal interval and the drug factors, indicating that administration of lorazepam did not significantly change the effect of a temporal interval on the initiation of tracking responses. We found a significant linear relationships between the lorazepam-induced changes in saccadic and smooth pursuit latencies, across conditions ($r = 0.51$, $n = 42$, $P < 0.01$): subjects that showed the largest effects on saccade latency also showed the biggest effects on pursuit latency.

Fig. 5C shows the effect of lorazepam versus placebo on mean tracking velocity. Lorazepam significantly reduced mean tracking eye speed, as compared to the placebo ($F(154,1) = 8.18$; $P < 0.0048$). Mean eye speed was of 13 ± 3.8 and of 14.4 ± 2.9 deg/s, respectively. Significant effects of the target motion direction ($F(154,1) > 25$, $P < 0.0001$), the rightward pursuit being faster, and of the temporal interval upon the mean pursuit eye speed ($F(154,2) > 12$, $P < 0.001$) were found both before and after drug administration. However, no significant interaction between the treatment and both target motion direction or temporal interval were found, indicating that these dependencies of pursuit speed were insensitive to the administration of lorazepam. Finally, Fig. 5B plots the mean displacement gain after administration of either lorazepam or placebo. The displacement gain is the ratio between the total displacement of the target and the total displace-

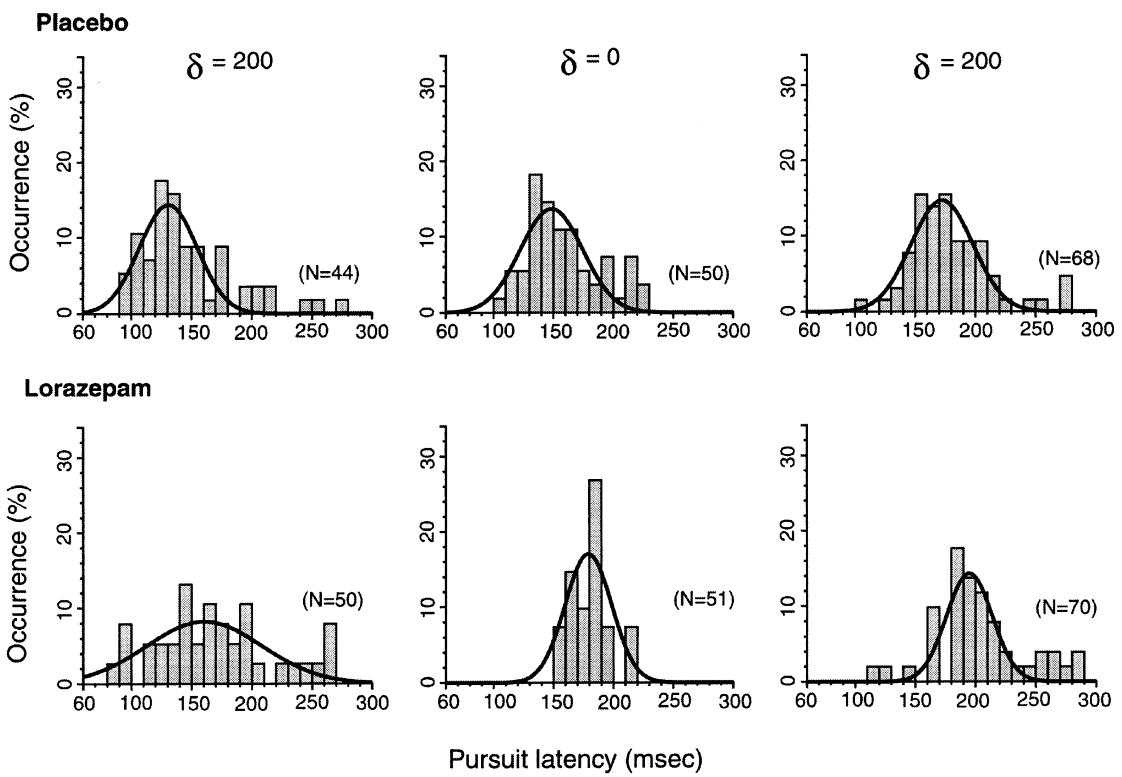

Fig. 5. Distribution of latencies obtained in subject 14 in the three interval conditions, for both rightward and leftward smooth pursuit eye movements, 2 h after administration of either placebo (upper panels) or lorazepam (lower panels).

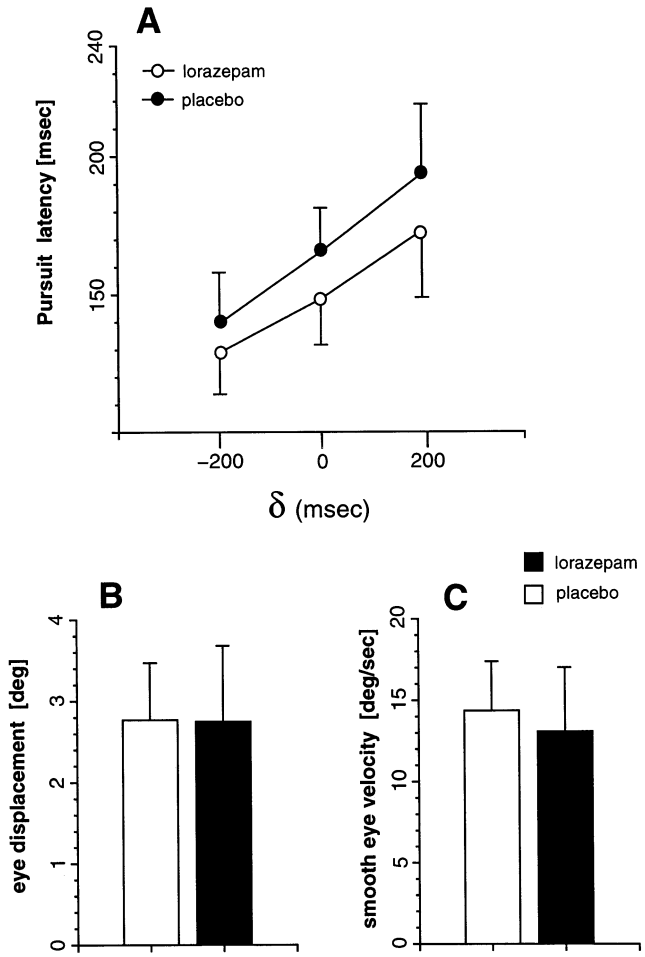

Fig. 6. Summary of the effects of placebo (open symbols) vs. lorazepam 1 mg (closed symbols) 2 h after intake. (A) Effects upon mean ($\pm$SD) smooth pursuit reaction times, for each temporal interval conditions. Effects upon mean ($\pm$SD) total eye displacement (B) and smooth eye velocity (C) of the tracking eye movements over the time period 200–600 ms after the stimulus onset.

ment of the eye during a given period of time (from 120 to 520 ms after the target onset). Therefore, it includes both smooth pursuit and saccadic components of the tracking response. As illustrated in Fig. 5B, administration of lorazepam did not significantly change the displacement gain ($F(154,1) = 0.17$, $P > 0.68$) as compared to placebo. This result indicates that tracking errors induced by lorazepam were compensated by appropriate catch-up saccades during the pursuit responses.

4. Discussion

In a double-blind, cross-over, placebo-controlled study, we investigated the effects of an acute dose of lorazepam (1 mg) on both saccadic and smooth pursuit eye movements. We will discuss first the effects of visual stimuli timing on both the initiation and the completion of both types of eye movements. Second, we will discuss specific effects of a low dose of lorazepam.

4.1. Effects of a temporal interval on initiation and execution of foveating eye movements

We found a significant effect of the temporal delay between the offset of the fixation target and the onset of the target on the latency of both saccadic and smooth pursuit eye movements. As reported by previous studies, a gap of 200 ms reduces the mean saccadic reaction time by about 20 ms while an overlap of 200 ms increases it by about 30 ms [7,8,19–21]. Moreover, as previously reported a 200 ms gap between the fixation target offset and the moving target onset significantly reduced the mean pursuit reaction time by about 40 ms [4,5,10,11]. We here confirm these results. Therefore, when saccadic and smooth pursuit eye movements are randomly interleaved, saccadic and pursuit eye movements exhibit similar dependencies on the timing of visual targets onset and offset [4,5].

We found no evidence for separate sub-populations of express saccades or express pursuits. The occurrence of express saccades is sensitive to numerous experimental conditions such as target uncertainty, practice, target eccentricity and so on [9,21,22] and we did not attempt to optimize the experimental setup in order to produce express saccades. On the contrary, since we interleaved saccadic and tracking trials and therefore introduce uncertainty about the type of eye movements to be produced. With a similar interleaved design, Krauzlis and Miles [4,5] also did not observe neither express saccades or express pursuit to targets appearing at an eccentricity similar to that used in the present study.

Error rates and movement accuracy have typically been ignored in studies on the gap effect. Express saccades have smaller amplitudes than the regular saccades and are more often followed by corrective saccades [9,23]. In the same vein, error rates are higher with express saccades than with regular saccades [24]. Moreover, the scatter of saccadic amplitudes toward targets of 4 degrees eccentricity decreases as the latency of regular saccades increases in the gap paradigm [9]. In the present study, the error rate was very low ($< 2\%$) and we did not find any significant effect of the temporal delay on motor performance (saccadic amplitude or saccadic peak velocity). On the contrary, there was a significant effect of the temporal delay on the mean tracking velocity of smooth eye movements (Fig. 2C). Tracking eye movement were faster when initiated with a temporal gap between the fixation point offset and the moving target onset, but slower in the overlap condition. Others reported that, in monkeys, the presence of a distracting moving target changes the latency of smooth pursuit [25]. Furthermore, in conditions where tracking latency was longer, initial eye acceleration tended to increase, perhaps because of integration of velocity signal over the latent period. The fact that,

in our condition, acceleration gets faster as latency gets shorter suggest that such integration cannot explain the relationships found between latency and initial tracking speed. Previous studies have shown that the presence of a stationary background reduces the initial eye speed of tracking eye movements in both monkeys [26] and humans [27]. These results suggest that, when a second, stationary, competing visual input is present in the visual field, initial eye acceleration is lowered.

4.2. Effects of a low dose of lorazepam on the latency of eye movements

As compared to placebo, we found that acute administration of a low dose of lorazepam (1 mg) induces a significant increase in both smooth pursuit and saccadic latencies. There was also a broader distribution of latencies for both types of eye movements. However, these two main effects were independent of the temporal delay between the fixation target offset and the eccentric target onset. Therefore, lorazepam induces a global increase in motor reaction times but does not modulate the 'gap effect' for both types of eye movements. Many studies have investigated the effects of benzodiazepines on saccadic eye movements. However, effects on saccade latency are controversial. Some studies failed to demonstrate an increase in saccadic reaction time [28,29,14]. However, others reported a significant increase in saccadic reaction time after administration of diazepam [30]. In a recent study, Fafrowicz and co-workers [31] investigated the effects of 5 mg of diazepam on saccades initiated towards 5 or 10 deg eccentric targets with either a gap or an overlap. Diazepam reduced saccadic reaction time by about 10%, decreased the number of fast saccades and increased the number of slow saccades. However, similar changes were observed in both the gap and overlap conditions. Our results are consistent with these previous observations in several ways. Thus, low or moderate doses of benzodiazepines induce small but significant increases in saccadic reaction times but do not modulate the gap effect. Furthermore, we demonstrated similar effects for smooth pursuit eye movements. Lorazepam induces a small (about 10%) but significant increase in smooth pursuit reaction times. While smaller changes were observed for the gap condition and a larger increase in the number of slow responses was evident only for the overlap condition, there was no clear relationships between the temporal delay and drug-induced changes in reaction times. To our knowledge, our study is the first demonstration, in a double-blind cross-over study, that a low dose of lorazepam induces a significant increase in smooth pursuit latency in humans.

For both smooth pursuit and saccadic eye movements, our results suggest that the gap/overlap effect is not modulated by a low dose of benzodiazepine. However, lorazepam induced an overall delay in oculomotor responses. This is further supported by the significant linear relationship found between lorazepam-induced changes in saccadic and smooth pursuit latencies. These results are consistent with the idea that low doses of benzodiazepine in humans do not specifically modify the release of fixation and/or the mechanism responsible for attentional shifts [9]. Otherwise, the gap effect would have been modified by administrating a low dose of lorazepam. From the present results, we suggest that benzodiazepines delay the programmation of an appropriate motor-command and its forwarding to the oculomotor centers once the target selection processes have been completed. The fact that similar changes are observed for smooth pursuit and saccadic eye movements suggest that such drive mechanism is shared by both oculomotor systems. Krauzlis and Miles [4,5] showed that both types of eye movements are coordinated through a common preparatory input acting on different neural substrates. Such shared preparatory input might explain why smooth pursuit and saccadic eye movements have a common dependency on gap duration. Moreover, we suggest that such shared input is modulated by drugs acting on the GABA-benzodiazepine receptor complex. In primates, the frontal eye fields trigger both saccadic and smooth pursuit eye movements [32,33] and pharmacological inactivation of this cortical area with GABA-related drugs result in both a slightly increased latency and a decreased accuracy for both saccadic [34] and tracking eye movements [35]. Thus, present results suggest that low doses of lorazepam alter the cortical control of the oculomotor behavior.

Previous studies have suggested that the effects of benzodiazepine upon eye movements latencies can be used as an objective measure of sedation [12,15]. Here, we assessed the effects of lorazepam on vigilance with visual analog scales. Indexes of drowsiness and sedation were not significantly changed 2 h after drug administration, as compared to placebo. This is consistent with previous results [36] showing that VARS alterness score was not significantly changed with 1mg of lorazepam. Therefore, motor responses can exhibit small but significant changes after benzodiazepine administration, at doses for which subjects do not self-report changes. Since higher doses of lorazepam do change VARS scores [36], further study will investigate whether or not changes in VARS and eye movements behavior are correlated in a dose-dependent way.

4.3. Effects of a low dose of lorazepam on the metacs of eye movements

We also measured the effects of lorazepam on the metrics (accuracy and dynamics) oculomotor responses.

As previously reported in the literature, lorazepam, like other benzodiazepines reduces both smooth pursuit velocity [16,17,37] and saccadic peak velocity [14,28,36]. In most of these studies, drug-induced variations were of small magnitude (about 10%) as found in the present study with a similar dose. Jurgens et al. [14] suggested that the drug-induced changes in saccadic velocity and duration were due to a change in a local feedback loop that compares a non-visual eye position signal to the perceived target eccentricity. Similarly, changes in smooth pursuit eye movements suggest that the local feedback loop comparing the eye velocity signal with the retinal target motion is altered by the administration of lorazepam. We did not attempt to investigate changes in the time course of eye velocity but many subjects showed a slower initial increase of tracking eye velocity with lorazepam, as compared to placebo. As a consequence, we suggest that, with lorazepam, it takes longer for the closed-loop system to reach the steady-state, accurate tracking speed. In conclusion, similar drug-induced changes in the dynamics of both saccades and pursuit eye movements suggest that their respective feedback-loops are altered.

Finally, while most studies report a lack of effect of benzodiazepine upon saccadic amplitude [14,29], we found a small but significant effect of lorazepam on the amplitude of initial saccades towards a 5 degrees eccentric target. The aforementioned hypothesis of a drug-induced change in a local feedback loop is correct only if the amplitude of the saccades remains unchanged with BZD. Jurgens et al. [14] found two subjects that performed accordingly. However, a third subject also showed small but significant changes in saccadic amplitude. They attributed such changes to a drug-induced impairment of processes 'upstream' of the pulse generator which determine the amplitude to be executed by the saccadic system. However, observed changes in saccadic amplitude cannot be attributed to alteration of the perceived location (or motion) of the target, since hypometria of the first saccade (or lowered tracking velocity) were fully compensated by appropriate corrective eye movements. Therefore, if the neural signal which determines the saccadic amplitude is changed by lorazepam, we suggest this does not occur at the level of visual encoding, but at the level of the sensorimotor transformation leading to the encoding of the desired movement amplitude.

4.4. Conclusion

In summary, we demonstrated that both smooth pursuit and saccadic eye movements exhibit similar changes induced by a low dose of lorazepam, a drug acting at the GABA benzodiazepine receptor complex. Similar changes in saccadic and pursuit latency suggest that a common preparatory signal is slowed down by treatment. This slowness was observed while no significant changes in VARS score were observed. Moreover, changes in both saccadic peak velocity and smooth pursuit tracking velocity suggest that local feedback-loops and sensorimotor transformations are altered by the administration of benzodiazepine in humans.

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