Original Article

Effects of lorazepam on saccadic eye movements: the role of sex, task characteristics and baseline traits

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Abstract

Background: Saccadic eye movements are controlled by a network of parietal, frontal, striatal, cerebellar and brainstem regions. The saccadic peak velocity is an established biomarker of benzodiazepine effects, with benzodiazepines reliably reducing the peak velocity.

Aims: In this study, we aimed to replicate the effects of benzodiazepines on peak velocity and we investigated effects on previously less studied measures of saccades. We also explored the roles of sex, task characteristics and the baseline variables age, intelligence and trait anxiety in these effects.

Method: Healthy adults (N = 34) performed a horizontal step prosaccade task under 1 mg lorazepam, 2 mg lorazepam and placebo in a double-blind, within-subjects design.

Results: We replicated the dose-dependent reduction in peak velocity with lorazepam and showed that this effect is stronger for saccades to targets at smaller eccentricities. We also demonstrated that this effect is independent of sex and other baseline variables. Lorazepam effects were widespread, however, occurring on mean and variability measures of most saccadic variables. Additionally, there were sex-dependent lorazepam effects on spatial consistency of saccades, indicating more adverse effects in females.

Conclusions: We conclude that saccadic peak velocity is a sensitive and robust biomarker of benzodiazepine effects. However, lorazepam has pronounced effects also on other parameters of horizontal saccades. Sex-dependent drug effects on spatial consistency may reflect cerebellar mechanisms, given the role of the cerebellum in saccadic spatial accuracy.

Keywords

Lorazepam, benzodiazepine, saccadic eye movements, oculography, biomarker, sex differences, anxiety

Introduction

The peak velocity of saccadic eye movements is an established biomarker of GABAergic benzodiazepine effects (Atack, 2008; Chen et al., 2012; De Visser et al., 2003). However, despite the widespread use of this measure in drug studies, there are a number of gaps in our knowledge of benzodiazepine effects on saccadic peak velocity. These concern primarily the role of baseline trait variables that may explain variance in benzodiazepine effects, such as sex, age, intelligence or anxiety; the effects of benzodiazepines on intra-individual variability of peak velocity; and the role of experimental task factors in these effects. Additionally, whilst saccadic peak velocity is frequently studied, there are other saccadic measures whose modulation by benzodiazepines has not yet been investigated. To address these questions, we carried out a comprehensive examination of the effects of lorazepam on peak velocity and other saccadic variables. Our aims were as follows.

First, we aimed to replicate the previously reported reduction of peak velocity by benzodiazepines (De Visser et al., 2003) using a horizontal, centrifugal, step saccade paradigm (Study Aim 1). We chose lorazepam as it is a widely prescribed drug for anxiety and a frequently used comparator compound in the examination of novel compounds (e.g. Atack, 2008; De Haas et al., 2009). We applied multiple doses of lorazepam (1 mg, 2 mg) in order to assess the dose-dependency of any effects.

Second, we aimed to characterise lorazepam effects on other saccadic variables, in addition to peak velocity (Study Aim 2). Whilst peak velocity is a well-established biomarker of benzodiazepine effects (De Visser et al., 2003), saccadic tasks yield a rich array of performance measures (Holmqvist et al., 2011; Leigh and Zee, 2015). The widespread expression of $GABA_A$ receptors in brain (Uusi-Oukari and Korpi, 2010), especially the α1 subunit thought to be responsible for the sedative effects of

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benzodiazepines (Chen et al., 2012), suggests that lorazepam influences likely manifest themselves throughout the neural network underlying saccades (Leigh and Zee, 2015), thereby affecting diverse performance measures.

For example, detailed analysis of the temporal waveform of saccades yields measures of average velocity, Q and skewness. Average velocity is calculated as the ratio of amplitude and duration and has been found to be reduced by lorazepam (Harron et al., 1995). Q refers to the ratio of peak and average velocity (Leigh and Zee, 2015). Benzodiazepine effects on Q have, to our knowledge, not been investigated. This is important, as a reduction in Q would be indicative of a more pronounced effect on peak than average velocity, buttressing the primacy of peak velocity as a benzodiazepine biomarker. Skewness refers to the ratio between time to reach peak velocity (acceleration phase) and the total saccade duration (combining acceleration and deceleration phases) (Collewijn et al., 1988). Benzodiazepine effects on skewness have, to our knowledge, not been reported. Whilst two previous studies observed a reduction in acceleration/deceleration ratio with midazolam (Ball et al., 1991) and lorazepam (King et al., 1995), another study observed increased acceleration phase with diazepam (Roy-Byrne et al., 1993). However, these measures differ from skewness, as they do not take into account saccade duration (Leigh and Zee, 2015).

Another measure that has not been investigated in relation to benzodiazepine effects is saccadic curvature. The trajectories of horizontal saccades are rarely entirely straight but typically show some degree of curvature (Smit and Van Gisbergen, 1990; Yarbus, 1967). Curvature is influenced by attentional factors (Sheliga et al., 1994) and is related to neuronal activity in frontal eye fields and superior colliculus (Port and Wurtz, 2003), suggesting that exogenous GABAergic modulation of these neurons may affect this metric. However, to our knowledge, no previous study has investigated benzodiazepine influences on saccadic curvature in humans.

We also investigated saccade latency and measures of spatial accuracy. Latency reflects the speed of visual information processing, decision making and response execution processed in subcortical and cortical areas (Carpenter, 2004). Spatial accuracy is a function of sensorimotor transformations which involve dorsal stream cortical areas, but is also sensitive to cerebellar integrity (Robinson and Fuchs, 2001). Previous studies have found lorazepam to increase latency (Chen et al., 2014, 2015; De Haas et al., 2007, 2008, 2009; Green et al., 2000; Masson et al., 2000; Tedeschi et al., 1983) and reduce spatial accuracy (Chen et al., 2014, 2015; De Haas et al., 2007, 2008, 2009; King et al., 1995; Masson et al., 2000).

Third, we wished to assess lorazepam effects not merely on mean performance measures, but also on measures of the intra-individual variability of performance (Study Aim 3). Intra-individual variability is an important phenomenon in studies of drug effects (Coghill et al., 2014) and psychopathology (Kuntsi and Klein, 2012). While one previous study showed that 1 mg lorazepam increases the variance in saccadic latency (Masson et al., 2000), it is unknown whether lorazepam systematically affects intra-individual variability across saccadic measures.

Fourth, we aimed to investigate the role of sex in the effects of lorazepam on saccadic variables (Study Aim 4).[1] Sex is a primary domain of variation in biomedical research (Brooks and Clayton, 2017; Tannenbaum et al., 2016). However, much preclinical and clinical research includes only male humans or animals or fails to identify the subjects' sex (Brooks and Clayton, 2017). Studying sex differences is particularly relevant in the investigation of treatments for disorders that differ in their prevalence between males and females. Specifically, whilst females have an approximately two-fold higher risk for anxiety disorders than males (Kessler et al., 2011; Tolin and Foa, 2006), not enough is known about the role of sex in the pharmacological treatment of these disorders (Bekker and van Mens-Verhulst, 2007). Similarly, most previous studies of benzodiazepine effects on saccades were performed in males, and no study, to our knowledge, has considered the role of sex in the reported effects.

Fifth, we investigated the role of experimental task factors such as stimulus direction (right, left) and distance (near, far) in lorazepam effects (Study Aim 5). Such task factors, especially stimulus distance from centre, are known to affect saccadic performance (Leigh and Zee, 2015) but have not, to our knowledge, been investigated in relation to benzodiazepine effects.

Sixth, we explored the role of other relevant baseline trait variables along which individuals differ and which may relate to lorazepam effects, such as age, intelligence and trait anxiety (Study Aim 6). Inter-individual variation contributes significantly towards the heterogeneity of brain structure and function (Brooks and Clayton, 2017) and the ability to predict treatment response using such baseline measures remains a formidable challenge (Owen et al., 2013). The roles of age, intelligence and trait anxiety have, to our knowledge, not been considered in benzodiazepine effects on saccades.

Finally, we investigated whether the internal consistency of performance is affected by lorazepam (Study Aim 7). Reduced internal consistency of a measure, e.g. Cronbach's alpha, would be indicative of less consistent responding, possibly due to increased intra-individual variability.

On the basis of the previous literature, our hypotheses were that lorazepam would have adverse effects on peak and average velocity, latency and duration. Further, we aimed to characterise lorazepam effects on mean and variability measures not previously considered and explore the roles of sex, age, intelligence, trait anxiety and task-related factors in lorazepam effects.

Method

Participants

Forty healthy volunteers were recruited via circular emails to staff and students of King's College London, UK. Participants underwent a thorough physical and psychiatric assessment by the study doctor before admission to the study to ensure they were in good physical and mental health. All participants had normal or corrected-to-normal vision.

The study was approved by King's College Hospital Research Ethics Committee. Participants gave written informed consent before participating.

Design and procedure

The study employed a double-blind, placebo-controlled, within-subjects design with order of drug administration randomised. Each participant was assessed three times, under placebo (50mg

ascorbic acid), 1 mg lorazepam and 2 mg lorazepam. Sessions were separated by at least a week to allow for adequate drug washout. Assessments took place in the afternoon, between 1.30 p.m. and 6.30 p.m., with the time of assessment kept the same for each participant as closely as possible.

On study days, participants' current health was first verified by study staff. A capsule containing the drug or placebo was then administered p.o. with 300 mL of water. After a 120 min wait for the drug to reach peak concentrations in blood (Kyriakopoulos et al., 1978), participants completed cognitive tasks lasting approximately 40 min, followed by the saccade task. The cognitive tasks have been described in detail elsewhere (Perkins et al., 2013a, 2013b).

Saccade task

The saccade task was written using ExperimentBuilder (SR Research Ltd., Ontario, Canada). Participants were seated with their eyes 57 cm from a 19-in monitor (visible screen area 360 mm × 270 mm, 1024 × 768 pixels, 60 Hz refresh rate), with the head on a chinrest. They were shown a stimulus on the monitor and were asked to follow it with their eyes as fast and accurately as possible without moving the head. The stimulus was a black circle (0.3°), presented on white background. Before each trial, a drift correction procedure was carried out. A trial began with the stimulus shown in the central position of the monitor for a random duration of 500–1500 ms, before it stepped to one of four horizontal positions (right far (RF): +14.5°, right near (RN): +7.25°, left near (LN): −7.25°, left far (LF): −14.5°), where it remained for 1000 ms. Each peripheral location was used 15 times in a random order, resulting in a total of 60 trials. Four practice trials were carried out before the task.

Movements of the right eye were recorded using a video-based corneal reflection and pupil tracker (Eyelink 1000, SR Research Ltd.) at 1000 Hz sampling rate. A nine-point calibration was carried out before the beginning of the task.

Saccade data were processed blind to drug group using EyeLink DataViewer (SR Research Ltd.) and Matlab (The Mathworks, Natick, MA, USA). For each trial, the first saccade following onset of the peripheral stimulus was included in analysis if (i) it was made in the direction of the peripheral stimulus, (ii) it had a minimum amplitude of 1°, (iii) it had a minimum latency to stimulus of 70 ms, (iv) there was no blink or saccade in the window from 100 ms before to onset of peripheral stimulus, (v) there was no blink within the saccade, and (vi) the saccade start position did not deviate from the central stimulus position by more than 50 pixels horizontally or vertically.

The following dependent variables were extracted for included saccades at each peripheral stimulus position (±7.25°, ±14.5°).

- Latency: the time from peripheral stimulus onset to saccade onset (ms).
- Amplitude gain: the ratio of saccade amplitude divided by desired amplitude. A saccade with perfect spatial accuracy thus has a score of 1. Smaller scores indicate hypometric (undershooting) saccades and larger scores indicate hypermetric (overshooting) saccades.
- Spatial error: the residual position error. This measure was obtained by subtracting the desired saccade amplitude (±7.25° or ±14.5°, depending on peripheral stimulus location) from the actual saccade amplitude and dividing the result by the desired saccade amplitude. The absolute value of this term reflects the residual error; this was then averaged across all saccades. A saccade with perfect spatial accuracy thus has a score of 0, and higher scores indicate greater spatial error, irrespective of saccadic overshoot or undershoot.
- Peak velocity: the maximal velocity of the saccade (°/s).
- Average velocity: the mean velocity of the saccade (°/s).
- Duration: the time from saccade onset to offset (ms).
- Curvature: the maximal deviation of vertical eye position during a saccade adjusted for the final vertical eye position in the saccade. This measure is calculated by subtracting the final eye position in the saccade from the maximal deviation of eye position during the saccade.
- Skewness: the ratio of acceleration and deceleration phases. This measure is calculated as the time (ms) from saccade onset to peak velocity divided by the time (ms) from peak velocity to saccade offset. A perfectly symmetrical saccadic waveform thus has a score of 0.5. Smaller scores indicate a shorter acceleration than deceleration phase, and larger scores indicate a shorter deceleration than acceleration phase.
- Q: the relationship between peak velocity and average velocity. This measure is calculated by dividing the peak velocity by the average velocity.

For each variable, each participant's mean score was calculated. Additionally, for latency, amplitude gain, spatial error, peak and average velocity, duration as well as curvature, the intra-individual coefficient of variation (ICV) was calculated as a measure of variability by dividing a participant's intra-individual standard deviation by his/her mean score. Only participants who had at least 5 correct trials at each peripheral stimulus position were included in statistical analysis.

Psychometric assessment

Age and sex were measured using a self-report questionnaire.

Intelligence was estimated using the 16PF reasoning ability scale (Cattell et al., 1970). This 13-item test is a validated short scale measure of intelligence (Abel and Brown, 1998). The possible score range is 0–13, with higher scores indicating better performance.

Trait anxiety was measured using the State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). This 20-item questionnaire is a well-established measure of trait anxiety. Higher scores indicate higher levels of anxiety.

Statistical analysis

Statistical analysis was carried out using SPSS 22.0 (IBM, Armonk, NY, USA) unless otherwise noted.

To assess effects of lorazepam, mixed-model analyse of variance (ANOVA) were carried out for each dependent variable with the within-subjects factors drug (placebo, 1 mg lorazepam, 2 mg lorazepam), direction (right, left) and distance (near, far) and the between-subjects factor sex (male, female). Significant interactions were followed up with t-tests using Bonferroni correction of the alpha level.

Table 1. Sample characteristics.

	Sample characteristics[a]
N male/female	18/16
Age (years)	25.06 (4.09)
16PF Reasoning Scale score	9.47 (1.71)
STAI trait anxiety score	35.21 (9.01)

[a]Data are given as mean (SD) unless otherwise stated. The 16PF Reasoning Scale was used as a measure of intelligence (Cattell et al., 1970). The STAI was used to measure trait anxiety (Spielberger et al., 1983). *N* = 34.

To assess the role of demographic variables in lorazepam effects, change scores (placebo – drug) were calculated for each variable, separately for 1 mg and 2 mg doses. These change scores were correlated with age, STAI trait anxiety and 16PF reasoning score, using Bonferroni correction of the alpha level (0.05/128 = 0.0004).

To assess internal consistency, Cronbach's alpha was calculated over the individual trials for each variable in each drug condition (1 mg, 2 mg, placebo), independent of direction and distance. To assess effects of lorazepam on internal consistency, Cronbach's alphas were compared across drug conditions using the Cran R package cocron (Diedenhofen and Musch, 2016).

Results

Descriptive statistics

A total of $N = 40$ participants completed the study. Six participants were excluded from analyses as they did not meet the minimum number criterion of five trials per peripheral stimulus position, leaving a final sample of $N = 34$ (Table 1).

Spatial error, Q, curvature and the ICVs of gain, peak velocity, duration, latency and curvature were positively skewed and, therefore, log-transformed. Descriptive statistics of all variables are in Table 2 (males) and Table 3 (females). ANOVA results are in Table 4.

Drug and task effects on performance

Study aims 1–3. Replicating previous studies, there was a significant main effect of drug on saccadic peak velocity (Study Aim 1).

In addition, there were significant main effects of drug on all other variables, both mean (Study Aim 2) and variability (Study Aim 3) measures, except duration ($p = 0.87$), curvature ($p = 0.82$) and ICV of spatial error ($p = 0.55$). These results indicate negative effects of lorazepam: increased latency, reduced amplitude gain, increased spatial error, reduced peak velocity, reduced average velocity, increased skewness, reduced Q and increased ICV of latency, amplitude gain, peak velocity, average velocity, duration and curvature.

For explanatory purposes, note that increased skewness scores due to lorazepam reflect a relative increase in acceleration time and a relative decrease in deceleration time. Reduced Q due to lorazepam indicates a reduction in the ratio between peak and average velocity, suggesting that the reduction in peak velocity due to lorazepam was more pronounced than the reduction in average velocity.

Effects on velocity and duration have to be interpreted by considering the known relationships of these variables with saccadic amplitude (Bahill et al., 1975; Westheimer, 1954), given that lorazepam caused reduced saccadic amplitudes in our data. Therefore, we calculated the ratios of peak and average velocities as well as duration over saccade amplitude (Sweeney et al., 1997). For the amplitude-corrected measure of peak velocity (log transformed due to positive skew), there was a main effect of drug ($F[2,64] = 7.46$, $p = 0.001$, $\eta_p^2 = 0.19$), confirming above finding. However, there was no main effect of drug on amplitude-corrected average velocity ($F[2,64] = 0.93$, $p = 0.40$, $\eta_p^2 = 0.03$). For amplitude-corrected duration, a main effect of drug emerged ($F[2,64] = 18.36$, $p < 0.001$, $\eta_p^2 = 0.37$), suggesting that lorazepam increased saccade duration when correcting for amplitude.

Simple contrasts to follow up main effects of drug revealed that all pairwise differences between placebo, 1 mg and 2 mg lorazepam were significant (all $p < 0.05$), with the exceptions of the contrast placebo vs. 1 mg for latency ($p = 0.50$), skewness ($p = 0.29$), latency ICV ($p = 0.08$), duration ICV ($p = 0.09$), curvature ICV ($p = 0.30$) and the contrast 1 mg vs. 2 mg for amplitude-corrected peak velocity ($p = 0.34$), Q ($p = 0.40$) and latency ICV ($p = 0.19$).

Study aim 4. Before considering the role of sex in the effects of drug (Study Aim 4), main effects of sex were investigated. These revealed that males had greater spatial error, higher skewness and greater ICV of gain than females. For explanatory purposes, higher skewness in males indicates that the onset of peak velocity in the saccade occurred later than in females.

Drug by sex interactions (Study Aim 4) were observed for spatial error and ICV of gain, indicating stronger negative responses to lorazepam in females than males on both variables (Figure 1). The comparison of 2 mg vs. placebo was significant in both males and females for both variables ($p < 0.003$), but the comparison of 2 mg vs. 1 mg was significant only in females for both variables ($p < 0.001$) but not in males for either variable ($p > 0.12$). The effect of 1 mg vs. placebo was significant in females for both variables ($p \leq 0.005$) but not in males for either variable ($p > 0.05$). Males had higher spatial error and ICV of gain than females only on placebo (both $p \leq 0.001$), but not on lorazepam (all $p > 0.007$, not surviving Bonferroni corrected alpha level of $p = 0.0056$).

Study aim 5. Study Aim 5 concerns interactions of drug with the task factors direction and distance.

Drug by direction interactions were observed for average velocity, skewness and Q. For amplitude-corrected average velocity, the interaction became non-significant ($p = 0.09$). For amplitude-corrected duration, an interaction arose ($F[2,64] = 3.20$, $p = 0.047$, $\eta_p^2 = 0.09$).

For average velocity, the interaction indicated stronger reductions with lorazepam for saccades to the right (all $p < 0.002$) than the left (all $p > 0.01$; not significant at Bonferroni corrected alpha level of 0.0056). Effects of direction were significant for placebo ($p < 0.001$), but not lorazepam conditions ($p > 0.02$).

For skewness, the interaction indicated stronger increases with lorazepam for saccades to the left ($p < 0.001$ for 2 mg vs.

Table 2. Descriptive statistics of prosaccade variables – males.

	Placebo				Lorazepam 1 mg				Lorazepam 2 mg			
	Right, far (14.5°)	Right, near (7.25°)	Left, near (–7.25°)	Left, far (–14.5°)	Right, far (14.5°)	Right, near (7.25°)	Left, near (–7.25°)	Left, far (–14.5°)	Right, far (14.5°)	Right, near (7.25°)	Left, near (–7.25°)	Left, far (–14.5°)
Latency (M)	176.85 (24.56)	155.69 (21.79)	156.88 (22.29)	180.45 (39.87)	175.44 (21.63)	157.58 (19.72)	158.84 (21.52)	173.91 (25.95)	188.00 (20.36)	164.30 (18.79)	160.88 (25.62)	189.28 (28.50)
Amplitude gain (M)	0.91 (0.05)	0.96 (0.10)	0.92 (0.07)	0.86 (0.06)	0.88 (0.08)	0.92 (0.12)	0.88 (0.10)	0.85 (0.12)	0.85 (0.11)	0.86 (0.12)	0.85 (0.10)	0.81 (0.10)
Spatial error (M)	0.10 (0.04)	0.11 (0.05)	0.11 (0.05)	0.14 (0.05)	0.13 (0.07)	0.14 (0.08)	0.15 (0.08)	0.17 (0.10)	0.16 (0.10)	0.18 (0.11)	0.18 (0.09)	0.19 (0.10)
Peak velocity (M)	413.42 (68.96)	322.45 (63.29)	286.84 (42.97)	370.99 (53.91)	383.29 (68.32)	301.68 (53.45)	269.43 (39.54)	342.25 (44.46)	374.95 (71.75)	277.40 (52.62)	252.18 (47.36)	326.61 (50.01)
Average velocity (M)	219.51 (20.81)	157.87 (20.49)	147.61 (15.98)	203.92 (19.73)	209.07 (27.23)	154.17 (21.61)	146.31 (19.23)	204.17 (27.75)	201.61 (24.58)	141.87 (21.38)	138.83 (20.67)	194.40 (27.66)
Duration (M)	60.95 (4.83)	44.53 (5.17)	45.79 (3.90)	62.03 (3.87)	61.31 (4.89)	43.24 (4.21)	43.87 (3.86)	61.06 (6.13)	61.97 (5.41)	44.38 (6.05)	46.18 (7.16)	62.51 (6.29)
Curvature (M)	0.02 (0.01)	0.03 (0.02)	0.02 (0.02)	0.01 (0.01)	0.02 (0.01)	0.03 (0.02)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.03 (0.02)	0.02 (0.02)	0.02 (0.01)
Skewness	0.35 (0.06)	0.39 (0.05)	0.39 (0.06)	0.37 (0.07)	0.35 (0.06)	0.39 (0.05)	0.39 (0.06)	0.38 (0.06)	0.35 (0.06)	0.40 (0.05)	0.41 (0.07)	0.41 (0.05)
Q	1.89 (0.31)	2.07 (0.49)	1.96 (0.37)	1.82 (0.22)	1.84 (0.27)	1.97 (0.33)	1.86 (0.30)	1.68 (0.18)	1.86 (0.26)	1.97 (0.32)	1.82 (0.25)	1.68 (0.14)
Latency (ICV)	0.16 (0.07)	0.15 (0.06)	0.15 (0.05)	0.21 (0.14)	0.17 (0.06)	0.18 (0.08)	0.21 (0.10)	0.18 (0.06)	0.21 (0.12)	0.19 (0.12)	0.19 (0.10)	0.25 (0.18)
Amplitude gain (ICV)	0.09 (0.06)	0.13 (0.08)	0.13 (0.08)	0.14 (0.10)	0.14 (0.09)	0.17 (0.11)	0.17 (0.11)	0.15 (0.11)	0.18 (0.12)	0.21 (0.13)	0.20 (0.12)	0.17 (0.12)
Spatial error (ICV)	0.80 (0.35)	0.85 (0.23)	0.87 (0.26)	0.78 (0.43)	0.83 (0.30)	0.84 (0.22)	0.85 (0.29)	0.70 (0.31)	0.81 (0.22)	0.85 (0.26)	0.79 (0.18)	0.67 (0.31)
Peak velocity (ICV)	0.11 (0.08)	0.14 (0.11)	0.15 (0.10)	0.16 (0.11)	0.17 (0.12)	0.18 (0.11)	0.19 (0.09)	0.19 (0.11)	0.23 (0.12)	0.25 (0.15)	0.22 (0.12)	0.25 (0.13)
Average velocity (ICV)	0.12 (0.06)	0.13 (0.05)	0.13 (0.06)	0.16 (0.09)	0.15 (0.07)	0.16 (0.07)	0.14 (0.06)	0.17 (0.10)	0.21 (0.09)	0.20 (0.08)	0.21 (0.11)	0.21 (0.11)
Duration (ICV)	0.11 (0.07)	0.12 (0.06)	0.12 (0.04)	0.16 (0.11)	0.12 (0.06)	0.13 (0.06)	0.13 (0.07)	0.16 (0.09)	0.18 (0.08)	0.17 (0.09)	0.20 (0.19)	0.18 (0.10)
Curvature (ICV)	1.00 (0.61)	0.83 (0.45)	1.21 (0.80)	1.04 (0.54)	1.08 (0.59)	0.90 (0.46)	0.97 (0.36)	1.06 (0.46)	1.19 (0.56)	1.12 (0.57)	1.21 (0.53)	1.25 (0.62)

Numbers reflect means (standard deviations); ICV: intra-individual coefficient of variation; M: mean. $N = 18$.

placebo; other $p > 0.007$, n.s. at Bonferroni corrected alpha level of $p = 0.0056$) than to the right (all $p > 0.22$). There were no significant effects of direction at each level of drug (all $p > 0.01$, n.s.).

For Q, the interaction suggested stronger reductions with lorazepam for saccades to the left ($p < 0.001$ for 1 mg vs. placebo and for 2 mg vs. placebo; other $p = 0.19$) than to the right (all $p > 0.13$). There was a significant effect of direction only for 2 mg ($p = 0.003$; other $p > 0.01$, n.s. at Bonferroni corrected alpha level of $p = 0.0056$).

For amplitude-corrected duration, the interaction indicated stronger increases with lorazepam for saccades to the right (all $p < 0.002$) than the left (1 mg vs. placebo: $p = 0.60$; 1 mg vs. 2 mg: $p = 0.002$; 2 mg vs. placebo: $p = 0.004$). Effects of direction were significant for placebo ($p < 0.001$), but not lorazepam conditions ($p > 0.03$).

Drug by distance interactions were observed for gain, peak velocity and Q. Drug by distance interactions similarly were found for amplitude-corrected average velocity ($F[2,64] = 4.38$, $p = 0.02$, $\eta_p^2 = 0.12$) and amplitude-corrected duration ($F[2,64] = 3.35$, $p = 0.04$, $\eta_p^2 = 0.10$).

For gain, the interaction indicated stronger reductions with lorazepam for near (all $p<0.004$) than far stimuli, and only the comparison of 2 mg vs. placebo reached Bonferroni corrected significance ($p < 0.001$; all other $p > 0.009$ and n.s. at corrected alpha level $p = 0.0056$). Effects of distance were observed for placebo ($p < 0.001$) and 1 mg ($p = 0.004$), but not 2 mg ($p = 0.86$).

For peak velocity, the interaction similarly indicated that reductions due to lorazepam were more pronounced for near than far stimuli, with all pairwise comparisons significant for near stimuli (all $p \leq 0.001$), whereas for far stimuli the comparison of 1 mg vs. 2 mg was not significant ($p = 0.11$; all other $p<0.001$). Effects of distance were significant for all drug conditions (all $p < 0.001$) (Figure 2).

For Q, the interaction suggested a stronger reduction with lorazepam for near than far stimuli. Pairwise comparisons were

Table 3. Descriptive statistics of prosaccade variables – females.

	Placebo				Lorazepam 1 mg				Lorazepam 2 mg			
	Right, far (14.5°)	Right, near (7.25°)	Left, near (–7.25°)	Left, far (–14.5°)	Right, far (14.5°)	Right, near (7.25°)	Left, near (–7.25°)	Left, far (–14.5°)	Right, far (14.5°)	Right, near (7.25°)	Left, near (–7.25°)	Left, far (–14.5°)
Latency (M)	178.63 (19.08)	160.76 (14.66)	161.42 (20.44)	179.32 (23.36)	183.53 (15.91)	166.16 (19.97)	165.01 (19.60)	185.14 (27.19)	202.23 (28.43)	181.19 (24.46)	180.14 (28.79)	196.27 (28.77)
Amplitude gain (M)	0.94 (0.04)	0.98 (0.06)	0.95 (0.07)	0.93 (0.05)	0.92 (0.05)	0.92 (0.05)	0.93 (0.07)	0.90 (0.06)	0.86 (0.08)	0.84 (0.14)	0.86 (0.14)	0.87 (0.12)
Spatial error (M)	0.07 (0.03)	0.07 (0.03)	0.08 (0.04)	0.08 (0.04)	0.09 (0.05)	0.10 (0.05)	0.10 (0.04)	0.11 (0.05)	0.14 (0.07)	0.19 (0.12)	0.19 (0.09)	0.17 (0.09)
Peak velocity (M)	403.22 (48.70)	316.30 (33.78)	298.97 (35.45)	393.65 (42.63)	380.34 (57.78)	294.12 (54.21)	285.61 (46.60)	364.02 (61.85)	372.02 (88.78)	262.47 (54.92)	254.32 (59.78)	352.38 (69.25)
Average velocity (M)	220.67 (17.26)	157.55 (16.55)	145.60 (16.36)	208.67 (22.75)	209.19 (19.81)	145.32 (12.11)	146.18 (10.88)	202.32 (20.23)	196.15 (22.13)	137.62 (15.44)	136.41 (16.85)	195.67 (26.04)
Duration (M)	62.81 (5.45)	45.98 (4.22)	48.16 (5.01)	66.10 (7.45)	64.78 (5.32)	46.73 (3.89)	46.71 (2.95)	66.19 (6.57)	64.79 (4.79)	44.02 (6.55)	46.01 (5.46)	65.84 (6.93)
Curvature (M)	0.01 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.02)	0.01 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)
Skewness	0.32 (0.05)	0.36 (0.04)	0.34 (0.04)	0.31 (0.06)	0.31 (0.04)	0.37 (0.04)	0.36 (0.03)	0.32 (0.05)	0.32 (0.05)	0.38 (0.05)	0.38 (0.06)	0.34 (0.06)
Q	1.83 (0.20)	2.03 (0.30)	2.07 (0.28)	1.90 (0.20)	1.82 (0.23)	2.03 (0.35)	1.95 (0.28)	1.80 (0.22)	1.89 (0.40)	1.90 (0.27)	1.85 (0.28)	1.79 (0.20)
Latency (ICV)	0.17 (0.06)	0.15 (0.07)	0.17 (0.07)	0.17 (0.08)	0.15 (0.05)	0.18 (0.07)	0.19 (0.06)	0.19 (0.08)	0.18 (0.07)	0.20 (0.08)	0.21 (0.14)	0.23 (0.16)
Amplitude gain (ICV)	0.06 (0.06)	0.07 (0.02)	0.08 (0.04)	0.06 (0.03)	0.08 (0.06)	0.12 (0.06)	0.11 (0.04)	0.08 (0.04)	0.11 (0.05)	0.21 (0.15)	0.21 (0.11)	0.16 (0.11)
Spatial error (ICV)	0.71 (0.45)	0.72 (0.16)	0.69 (0.22)	0.62 (0.23)	0.71 (0.28)	0.85 (0.21)	0.90 (0.36)	0.65 (0.21)	0.72 (0.37)	0.81 (0.27)	0.85 (0.32)	0.76 (0.33)
Peak velocity (ICV)	0.10 (0.05)	0.09 (0.04)	0.11 (0.05)	0.10 (0.06)	0.15 (0.08)	0.16 (0.08)	0.13 (0.06)	0.14 (0.09)	0.26 (0.34)	0.23 (0.12)	0.22 (0.09)	0.21 (0.09)
Average velocity (ICV)	0.11 (0.05)	0.10 (0.04)	0.13 (0.05)	0.10 (0.05)	0.13 (0.07)	0.16 (0.06)	0.14 (0.05)	0.12 (0.05)	0.14 (0.06)	0.18 (0.09)	0.19 (0.05)	0.19 (0.09)
Duration (ICV)	0.13 (0.08)	0.10 (0.04)	0.12 (0.06)	0.10 (0.07)	0.12 (0.06)	0.14 (0.07)	0.13 (0.05)	0.13 (0.06)	0.12 (0.05)	0.20 (0.11)	0.17 (0.07)	0.19 (0.14)
Curvature (ICV)	1.08 (0.36)	1.03 (0.55)	1.01 (0.50)	0.92 (0.44)	1.40 (0.53)	0.96 (0.40)	0.99 (0.38)	1.00 (0.52)	1.02 (0.49)	1.06 (0.28)	1.16 (0.56)	1.15 (0.41)

Numbers reflect means (standard deviations); ICV: intra-individual coefficient of variation, M: mean. $N = 16$.

significant for near stimuli at 2 mg vs. placebo ($p = 0.001$) and 1 mg vs. placebo (but not surviving Bonferroni corrected alpha level of $p = 0.0056$; $p = 0.02$) but not 1 mg vs. 2 mg ($p = 0.07$). For far stimuli only the comparison of 2 mg vs. placebo was significant ($p = 0.001$; other $p > 0.05$). Effects of distance were observed for placebo and 1 mg (both $p < 0.001$), but not 2 mg ($p = 0.01$; not surviving Bonferroni corrected alpha level of $p = 0.0056$).

For amplitude-corrected average velocity, the interaction indicated that reductions due to lorazepam occurred for near (1 mg vs. placebo, $p = 0.04$, not surviving Bonferroni corrected alpha level of $p = 0.0056$) but not far stimuli (all $p > 0.58$). Effects of distance were significant for all drug conditions (all $p < 0.001$).

For amplitude-corrected duration, effects of drug were observed at both near and far stimuli (all $p < 0.001$) with the exception of 1 mg vs. placebo (both $p > 0.04$, not surviving Bonferroni corrected alpha level of $p = 0.0056$). Effects of distance were significant for all drug conditions (all $p < 0.001$).

Finally, there were a number of main effects and interactions involving direction, distance and sex, but not drug.

Main effects of direction indicated that saccades to stimuli in the right hemifield had lower spatial error, higher average and peak velocity (also amplitude-corrected), shorter duration (also amplitude-corrected), and higher Q than saccades to stimuli in the left hemifield.

Main effects of distance indicated that saccades to near stimuli had higher gain, lower average and peak velocity (also amplitude-corrected), shorter duration (also amplitude-corrected), shorter latency, higher skewness, higher Q, higher curvature and higher ICVs of gain, spatial error and peak velocity than saccades to far stimuli.

Table 4. ANOVA results.

	Drug	Direction	Distance	Sex	Drug × Direction	Drug × Distance	Drug × Sex	Direction × Distance	Direction × Sex	Distance × Sex	Drug × Direction × Distance	Drug × Direction × Sex	Drug × Distance × Sex	Direction × Distance × Sex	Drug × Direction × Distance × Sex
Latency (M)	F[2,64] = 14.52, p < .001, η_p^2 = 0.31	F[1,32] = 0.01, p = 0.95, η_p^2< 0.005	F[1,32] = 115.45, p < .001, η_p^2 = 0.78	F[1,32] = 2.49, p = 0.12, η_p^2 = 0.07	F[1.56,49.95] = 0.61, p = 0.61, η_p^2 = 0.02	F[2,64] = 1.34, p = 0.27, η_p^2 = 0.04	F[2,64] = 2.18, p = 0.12, η_p^2 = 0.06	F[1,32] = 0.01, p = 0.92, η_p^2< 0.005	F[1,32] = 0.03, p = 0.86, η_p^2< 0.005	F[1,32] = 0.75, p = 39, η_p^2 = 0.02	F[2,64] = 0.03, p = 0.97, η_p^2 < 0.005	F[2,64] = 0.09, p .92, η_p^2< 0.005	F[2,64] = 1.50, p .23, η_p^2 = 0.05	F[1,32] = 0.09, p = 0.77, η_p^2< 0.005	F[2,64] = 0.85, p = 0.43, η_p^2 = 0.03
Amplitude gain (M)	F[2,64] = 15.59, p < 0.001, η_p^2 = 0.33	F[1,32] = 2.53, p = 0.12, η_p^2 = 0.07	F[1,32] = 9.41, p = 0.004, η_p^2 = 0.23	F[1,32] = 2.28, p = 0.14, η_p^2 = 0.07	F[1.48,47.39] = 2.17, p = 0.14, η_p^2 = 0.06	F[1.64,52.48] = 6.97, p = 0.004, η_p^2 = 0.18	F[2,64] = 0.37, p = 0.69, η_p^2 = 0.01	F[1,32] = 0.72, p = 0.40, η_p^2 = 0.02	F[1,32] = 2.10, p = 0.16, η_p^2 = 0.62	F[1,32] = 4.05, p = 0.05, η_p^2 = 0.11	F[2,64] = 1.11, p = 0.34, η_p^2 = 0.03	F[2,64] = 0.31, p = 0.74, η_p^2 = 0.01	F[2,64] = 0.24, p = 0.79, η_p^2 = 0.01	F[1,32] = 0.20, p = 0.66, η_p^2 = 0.01	F[2,64] = 1.50, p = 0.23, η_p^2 = 0.05
Spatial error (M)	F[2.64] = 32.90, p < 0.001, η_p^2 = 0.51	F[1,32] = 6.44, p = 0.02, η_p^2 = 0.17	F[1,32] = 0.84, p = 0.37, η_p^2 = 0.03	F[1,32] = 5.97, p = 0.02, η_p^2 = 0.16	F[2,64] = 0.64, p = 0.53, η_p^2 = 0.02	F[2,64] = 1.86, p = 0.16, η_p^2 = 0.06	F[2,64] = 4.31, p = 0.02, η_p^2 = 0.12	F[1,32] = 2.38, p = 0.13, η_p^2 = 0.07	F[1,32] = 0.16, p = 0.70, η_p^2 = 0.01	F[1,32] = 1.13, p = 0.30, η_p^2 = 0.03	F[2,64] = 0.24, p = 0.79, η_p^2 = 0.01	F[2,64] = 0.02, p = 0.98, η_p^2<0.005	F[2,64] = 0.41, p = 0.67, η_p^2 = 0.01	F[1,32] = 0.87, p = 0.36, η_p^2 = 0.03	F[2,64] = 1.17, p = 0.32, η_p^2 = 0.04
Peak velocity (M)	F[2,64] = 21.13, p < 0.001, η_p^2 = 0.40	F[1,32] = 21.04, p < 0.001, η_p^2 = 0.40	F[1,32] = 733.49, p < 0.001, η_p^2 = 0.96	F[1,32] = 0.10, p = 0.76, ηp²< 0.005	F[1.34,42.83] = 0.03, p = 0.93, η_p^2 < 0.005	F[1.52,48.52] = 3.25, p = 0.06, η_p^2 = 0.09	F[2,64] = 0.06, p = 0.94, η_p^2< 0.005	F[1,32] = 2.78, p = 0.11, η_p^2 = 0.08	F[1,32] = 4.80, p = 0.04, η_p^2 = 0.13	F[1,32] = 1.80, p = 0.19, η_p^2 = 0.05	F[1.37,43.79] = 1.13, p = 0.31, η_p^2 = 0.03	F[2,64] = 0.02, p = 0.99, η_p^2< 0.005	F[2,64] = 0.88, p = 0.42, η_p^2 = 0.03	F[1,32] = 81, p = 0.37, η_p^2 = 0.26	F[2,64] = 0.18, p = 0.83, η_p^2 = 0.01
Average velocity (M)	F[2,64] = 14.88, p < 0.001, η_p^2 = 0.32	F[1,32] = 11.61, p = 0.002, η_p^2 = 0.27	F[1,32] = 1852.56, p < 0.001, η_p^2 = 0.98	F[1,32] = 08, p = 0.78, η_p^2<0.005	F[1.68,53.60] = 7.68, p = 0.002, η_p^2 = 0.19	F[2,64] = 0.82, p = 0.45, η_p^2 = 0.03	F[2,64] = 0.29, p = 0.75, η_p^2 = 0.01	F[1,32] = 0.66, p = 0.42, η_p^2 = 0.02	F[1,32] = 0.53, p = 0.47, η_p^2 = 0.02	F[1,32] = 1.18, p = 0.29, η_p^2 = 0.04	F[2,64] = 0.03, p = 0.98, η_p^2 < 0.005	F[2,64] = 0.22, p = 0.80, η_p^2 = 0.01	F[2,64] = 0.19, p = 0.83, η_p^2 = 0.01	F[1,32]<0.005, p = 0.98, η_p^2 < 0.005	F[2,64] = 2.19, p = 0.12, η_p^2 = 0.06
Duration (M)	F[2,64] = 0.15, p = 0.87, η_p^2 = 0.01	F[1,32] = 5.53, p = 0.26, η_p^2 = 0.15	F[1,32] = 1059.58, p < 0.001, η_p^2 = 0.97	F[1,32] = 3.97, p = 0.06, η_p^2 = 0.11	F[2,64] = 1.77, p = 0.18, η_p^2 = 0.05	F[1.64,52.41] = 2.34, p = 0.11, η_p^2 = 0.07	F[2,64] = 1.97, p = 0.15, η_p^2 = 0.06	F[1,32] = 0.02, p = 0.88, η_p^2<0.005	F[1,32] = 0.58, p = 0.45, η_p^2 = 0.02	F[1,32] = 2.80, p = 0.10, η_p^2 = 0.08	F[2,64] = 0.76, p = 0.47, η_p^2 = 0.02	F[2,64] = 0.34, p = 0.71, η_p^2 = 0.01	F[2,64] = 1.16, p = 0.32, η_p^2 = 0.04	F[1,32] = 0.68, p = 0.42, η_p^2 = 0.02	F[2,64] = 0.26, p = 0.77, η_p^2 = 0.01
Curvature (M)	F[1.67,53.36] = 0.20, p = 0.78, η_p^2 = 0.01	F[1,32] = 0.58, p = 0.45, η_p^2 = 0.02	F[1,32] = 28.56, p < 0.001, η_p^2 = 0.47	F[1,32] = 1.11, p = 0.30, η_p^2 = 0.03	F[2,64] = 0.34, p = 0.71, η_p^2 = 0.01	F[2,64] = 0.10, p = 0.91, η_p^2<0.005	F[2,64] = 2.67, p = 0.08, η_p^2 = 0.08	F[1,32] = 3.45, p = 0.07, η_p^2 = 0.10	F[1,32] = 5.06, p = 0.03, η_p^2 = 0.14	F[1,32]<0.005, p = 0.96, η_p^2 < 0.005	F[2,64] = 0.321, p = 0.73, η_p^2 = 0.01	F[2,64] = 0.28, p = 0.75, η_p^2 = 0.01	F[2,64] = 1.28, p = 0.29, η_p^2 = 0.04	F[1,32] = 1.81, p = 0.19, η_p^2 = 0.05	F[2,64] = 0.07, p = 0.93, η_p^2<0.005
Skewness	F[2,64] = 6.85, p = 0.002, η_p^2 = 0.18	F[1,32] = 4.05, p = 0.05, η_p^2 = 0.11	F[1,32] = 67.60, p < 0.001, η_p^2 = 0.68	F[1,32] = 8.43, p = 0.01, η_p^2 = 0.21	F[2,64] = 3.45, p = 0.04, η_p^2 = 0.10	F[2,64] = 0.06, p = 0.94, η_p^2 < 0.005	F[2,64] = 0.01, p = 0.99, η_p^2<0.005	F[1,32] = 11.93, p = 0.002, η_p^2 = 0.27	F[1,32] = 7.88, p = 0.01, η_p^2 = 0.20	F[1,32] = 3.32, p = 0.08, η_p^2 = 0.09	F[2,64] = 2.13, p = 0.13, η_p^2 = 0.06	F[2,64] = 0.32, p = 0.73, η_p^2 = 0.01	F[2,64] = 0.66, p = 0.52, η_p^2 = 0.02	F[1,32] = 1.10, p = 0.03, η_p^2 = 0.03	F[2,64] = 0.26, p = 0.78, η_p^2 = 0.01
Q	F[2,64] = 7.94, p = 0.001, η_p^2 = 0.20	F[1,32] = 6.31, p = 0.02, η_p^2 = 0.17	F[1,32] = 47.74, p < 0.001, η_p^2 = 0.60	F[1,32] = 0.29, p = 0.60, η_p^2 = 0.01	F[2,64] = 7.05, p = 0.002, η_p^2 = 0.18	F[1.65,52.91] = 4.60, p = 0.02, η_p^2 = 0.13	F[2,64] = 0.37, p = 0.69, η_p^2 = 0.01	F[1,32] = 04, p = 0.84, ηp²<0.005	F[1,32] = 3.48, p = 0.07, η_p^2 = 0.10	F[1,32] = 0.07, p = 0.79, η_p^2 < 0.005	F[2,64] = 0.82, p = 0.44, η_p^2 = 0.03	F[2,64] = 0.28, p = 0.76, η_p^2 = 0.01	F[2,64] = 2.55, p = 0.09, η_p^2 = 0.07	F[1,32] = 47, p = 0.50, η_p^2 = 0.02	F[2,64] = 0.48, p = 0.62, η_p^2 = 0.02
Latency (ICV)	F[2,64] = 4.64, p = 0.01, η_p^2 = 0.13	F[1,32] = 2.72, p = 0.11, η_p^2 = 0.08	F[1,32] = 0.85, p = 0.37, η_p^2 = 0.03	F[1,32] = 0.03, p = 0.86, η_p^2< 0.005	F[2,64] = 0.62, p = 0.54, η_p^2 = 0.02	F[2,64] = 1.76, p = 0.18, η_p^2 = 0.05	F[2,64] = 0.06, p = 0.94, η_p^2<0.005	F[1,32] = 1.70, p = 0.20, η_p^2 = 0.05	F[1,32] = 0.05, p = 0.83, η_p^2<0.005	F[1,32] = 0.58, p = 0.45, η_p^2 = 0.02	F[2,64] = 0.50, p = 0.61, η_p^2 = 0.02	F[2,64] = 0.03, p = 0.97, η_p^2<0.005	F[2,64] = 0.29, p = 0.75, η_p^2 = 0.01	F[1,32] = 0.27, p = 0.61, η_p^2 = 0.01	F[2,64] = 1.64, p = 0.20, η_p^2 = 0.05

(Continued)

Table 4. (Continued)

	Drug	Direction	Distance	Sex	Drug × Direction	Drug × Distance	Drug × Sex	Direction × Distance	Direction × Sex	Distance × Sex	Drug × Direction × Distance	Drug × Direction × Sex	Drug × Distance × Sex	Direction × Distance × Sex	Drug × Direction × Distance × Sex
Amplitude gain (ICV)	F[2,64] = 31.93, $p < 0.001$, $\eta_p^2 = 0.50$	F[1,32] = 2.21, $p = 0.15$, $\eta_p^2 = 0.07$	F[1,32] = 30.26, $p < 0.001$, $\eta_p^2 = 0.49$	F[1,32] = 10.72, $p = 0.003$, $\eta_p^2 = 0.25$	F[2,64] = 0.32, $p = 0.73$, $\eta_p^2 = 0.01$	F[2,64] = 0.93, $p = 0.40$, $\eta_p^2 = 0.03$	F[2,64] = 4.25, $p = 0.02$, $\eta_p^2 = 0.12$	F[1,32] = 0.20, $p = 0.66$, $\eta_p^2 = 0.01$	F[2,64] = 0.06, $p = 0.81$, $\eta_p^2 < 0.005$	F[1,32] = 2.80, $p = 0.10$, $\eta_p^2 = 0.08$	F[2,64] = 0.13, $p = 0.88$, $\eta_p^2 < 0.005$	F[2,64] = 1,51, $p = 0.23$, $\eta_p^2 = 0.05$	F[2,64] = 0.23, $p = 0.80$, $\eta_p^2 = 0.01$	F[1,32]<0.005, $p = 0.99$, $\eta_p^2 < 0.005$	F[1,32] = 1.31, $p = 0.28$, $\eta_p^2 = 0.04$
Spatial error (ICV)	F[2,64] = 0.60, $p = 0.55$, $\eta_p^2 = 0.02$	F[1,32] = 1.3, $p = 0.26$, $\eta_p^2 = 0.04$	F[1,32] = 16.53, $p < 0.001$, $\eta_p^2 = 0.34$	F[1,32] = 1.21, $p = 0.28$, $\eta_p^2 = 0.04$	F[2,64]<0.005, $p = 0.10$, $\eta_p^2 < 0.005$	F[2,64] = 0.74, $p = 0.48$, $\eta_p^2 = 0.02$	F[2,64] = 2.29, $p = 0.11$, $\eta_p^2 = 0.07$	F[1,32] = 2.36, $p = 0.14$, $\eta_p^2 = 0.07$	F[1,32] = 0.76, $p = 0.39$, $\eta_p^2 = 0.02$	F[1,32] = 0.41, $p = 0.53$, $\eta_p^2 = 0.01$	F[2,64] = 0.21, $p = 0.81$, $\eta_p^2 = 0.01$	F[2,64] = 1.27, $p = 0.29$, $\eta_p^2 = 0.04$	F[2,64] = 58, $p = 0.56$, $\eta_p^2 = 0.02$	F[1,32] = 0.10, $p = 0.75$, $\eta_p^2 < 0.005$	F[2,64] = 0.08, $p = 0.92$, $\eta_p^2 < 0.005$
Peak velocity (ICV)	F[2,64] = 26.27, $p < 0.001$, $\eta_p^2 = 0.45$	F[1,32] = 0.75, $p = 0.39$, $\eta_p^2 = 0.02$	F[1,32] = 4.30, $p = 0.05$, $\eta_p^2 = 0.12$	F[1,32] = 1.46, $p = 0.24$, $\eta_p^2 = 0.04$	F[2,64] = 2.22, $p = 0.12$, $\eta_p^2 = 0.07$	F[2,64] = 0.15, $p = 0.86$, $\eta_p^2 = 0.01$	F[2,64] = 0.66, $p = 0.52$, $\eta_p^2 = 0.02$	F[1,32] = 0.42, $p = 0.52$, $\eta_p^2 = 0.01$	F[1,32] = 1.51, $p = 0.23$, $\eta_p^2 = 0.05$	F[1,32] = 0.20, $p = 0.66$, $\eta_p^2 = 0.01$	F[2,64] = 0.21, $p = 0.81$, $\eta_p^2 = 0.01$	F[2,64] = 0.94, $p = 0.40$, $\eta_p^2 = 0.03$	F[2,64] = 0.41, $p = 0.67$, $\eta_p^2 = 0.01$	F[1,32] = 2.64, $p = 0.11$, $\eta_p^2 = 0.08$	F[2,64] = 0.21, $p = 0.81$, $\eta_p^2 = 0.01$
Average velocity (ICV)	F[2,64] = 0.60, $p = 0.55$, $\eta_p^2 = 0.02$	F[1,32] = 1.30, $p = 0.26$, $\eta_p^2 = 0.04$	F[1,32] = 16.53, $p < 0.001$, $\eta_p^2 = 0.34$	F[1,32] = 1.21, $p = 0.28$, $\eta_p^2 = 0.04$	F[2,64]<0.005, $p = 0.10$, $\eta_p^2 < 0.005$	F[2,64] = 0.74, $p = 0.48$, $\eta_p^2 = 0.02$	F[2.64] = 2.29, $p = 0.11$, $\eta_p^2 = 0.07$	F[1,32] = 2.36, p = 0.14, $\eta_p^2 = 0.07$	F[1,32] = 0.76, $p = 0.39$, $\eta_p^2 = 0.02$	F[1,32] = 0.41, $p = 0.53$, $\eta_p^2 = 0.01$	F[1,32] = 0.21, $p = 0.81$, $\eta_p^2 = 0.01$	F[2,64] = 1.27, $p = 0.29$, $\eta_p^2 = 0.04$	F[2,64] = 0.58, $p = 0.56$, $\eta_p^2 = 0.02$	F[1,32] = 0.10, $p = 0.75$, $\eta_p^2 < 0.005$	F[1,32] = 0.08, $p = 0.92$, $\eta_p^2 < 0.005$
Duration (ICV)	F[2,64] = 12.83, $p < 0.001$, $\eta_p^2 = 0.29$	F[1,32] = 1.68, $p = 0.21$, $\eta_p^2 = 0.05$	F[1,32] = 0.21, $p = 0.65$, $\eta_p^2 = 0.01$	F[1,32] = 0.52, p = 0.48, $\eta_p^2 = 0.02$	F[2,64] = 0.09, $p = 0.92$, $\eta_p^2 < 0.005$	F[2,64] = 0.38, $p = 0.69$, $\eta_p^2 = 0.01$	F[2,64] = 0.66, $p = 0.52$, $\eta_p^2 = 0.02$	F[1,32] = 2.06, $p = 0.16$, $\eta_p^2 = 0.06$	F[1,32] = 0.29, $p = 0.59$, $\eta_p^2 = 0.01$	F[1,32] = 1.97, $p = 0.17$, $\eta_p^2 = 0.06$	F[2,64] = 0.96, $p = 0.39$, $\eta_p^2 = 0.03$	F[2,64] = 1.71, $p = 0.19$, $\eta_p^2 = 0.05$	F[2,64] = 0.20, $p = 0.82$, $\eta_p^2 = 0.01$	F[1,32] = 0.30, $p = 0.59$, $\eta_p^2 = 0.01$	F[2,64] = 2.65, $p = 0.08$, $\eta_p^2 = 0.08$
Curvature (ICV)	F[2,64] = 5.44, $p = 0.01$, $\eta_p^2 = 0.15$	F[1,32] = 0.18, $p = 0.68$, $\eta_p^2 = 0.01$	F[1,32] = 2.28, $p = 0.14$, $\eta_p^2 = 0.07$	F[1,32] = 0.12, $p = 0.73$, $\eta_p^2 < 0.005$	F[1.65,52.88] = 0.90, $p = 0.40$, $\eta p^2 = 0.03$	F[2,64] = 2.05, $p = 0.14$, $\eta_p^2 = 0.06$	F[2,64] = 1.52, $p = 0.23$, $\eta_p^2 = 0.05$	F[1,32] = 3.44, $p = 0.07$, $\eta_p^2 = 0.10$	F[1,32] = 2.34, $p = 0.14$, $\eta_p^2 = 0.07$	F[1,32] = 0.06, $p = 0.81$, $\eta_p^2 < 0.005$	F[2,64] = 2.22, $p = 0.12$, $\eta_p^2 = 0.07$	F[2,64] = 1.65, $p = 0.20$, $\eta_p^2 = 0.05$	F[2,64] = 0.34, $p = 0.71$, $\eta_p^2 = 0.01$	F[1,32] = 0.02, $p = 0.89$, $\eta_p^2 < 0.005$	F[2,64] = 1.17, $p = 0.32$, $\eta_p^2 = 0.04$

ICV: intra-individual coefficient of variation; M: mean. $N = 34$.

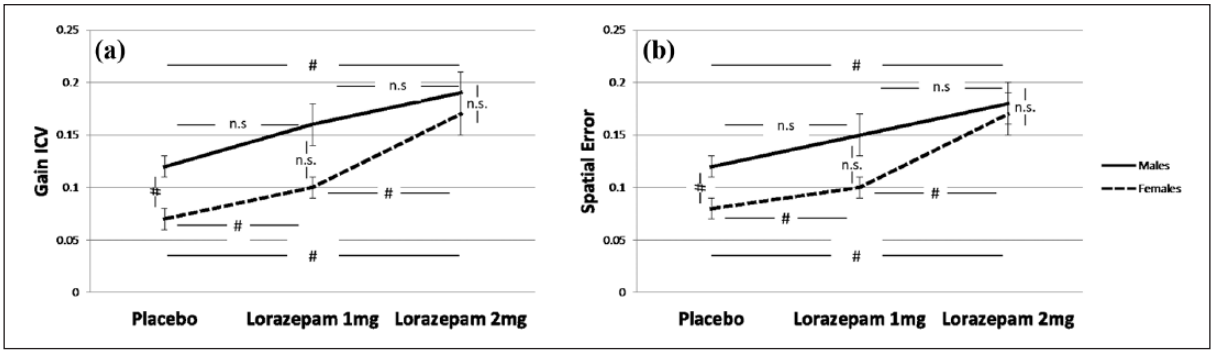

Figure 1. Effects of lorazepam on spatial accuracy measures in males and females. The diagram shows the effects of lorazepam, sex (male, female) and their interaction on (a) variability of amplitude gain and (b) mean spatial error. Data are means; error bars reflect ±1 standard error. For illustration purposes, untransformed data are shown but statistical analyses were performed on transformed data (see main text).
ICV: intra-individual coefficient of variation. *N* = 18 males, *N* = 16 females. # indicates statistical significance following Bonferroni correction and n.s. indicates not significant (see main text for details).

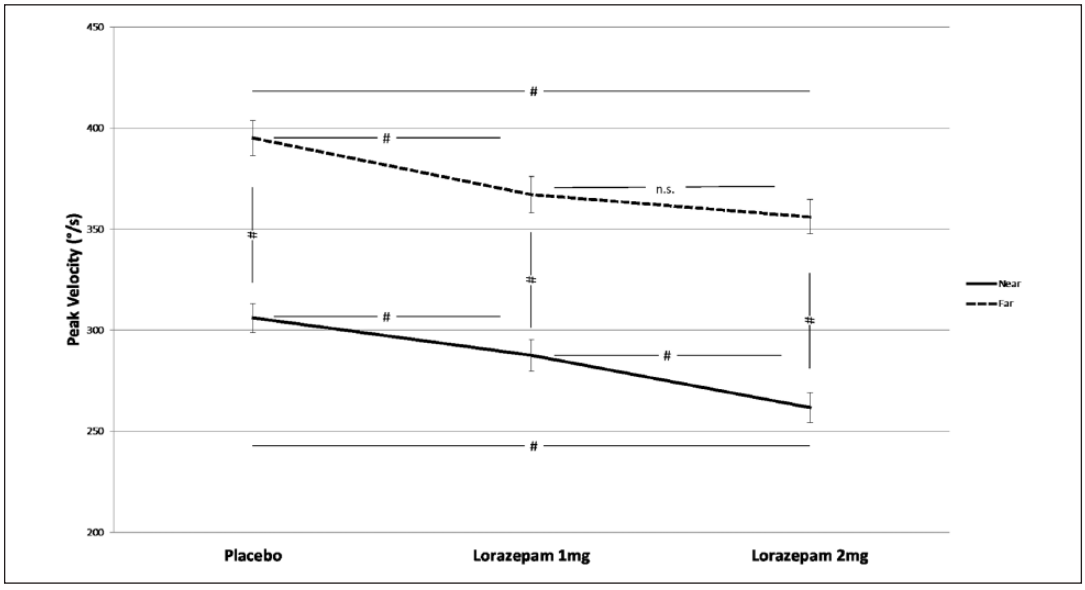

Figure 2. Effects of lorazepam on peak velocity as a function of stimulus position. The diagram shows the effects of lorazepam and stimulus position (near (7.25°), far (14.5°)) as well as their interaction on saccadic peak velocity (in degrees per second). Data are means; error bars reflect ±1 standard error. *N* = 34.
# indicates statistical significance following Bonferroni correction and n.s. indicates not significant (see main text for details).

A direction by distance interaction for skewness indicated that greater skewness for saccades to the left than to the right was observed for far (p = 0.002) but not near (p = 0.75) stimuli. Effects of Distance were observed for saccades both to the right and to the left (both $p \leq 0.001$).

Direction by sex interactions were observed for peak velocity, skewness and curvature. For amplitude-corrected peak velocity, however, the interaction was non-significant (p = 0.26).

For peak velocity, the interaction indicated higher peak velocity for right than left saccades for males ($p < 0.001$) but not females (p = 0.10). Sex differences were not significant for either direction (both $p > 0.25$).

For skewness, the interaction indicated greater skewness for left than right saccades for males (p = 0.001) but not females (p = 0.63). Sex differences were observed for saccades to the left (p = 0.001) but not to the right (p = 0.08).

For curvature, there were no significant post-hoc tests (all $p > 0.30$).

A distance by sex interaction was observed for average velocity ICV, indicating that the effects of distance was stronger for females (p = 0.02; but not surviving Bonferroni corrected alpha level of 0.0125) than for males (p = 0.15). Males had greater ICV than females for far (p = 0.03; not surviving Bonferroni corrected level of 0.0125) but not for near (p = 0.52) stimuli.

Correlations of baseline trait variables with change scores

Study aim 6. There were no significant correlations of age, intelligence and trait anxiety with change scores from placebo for performance under either 1 mg or 2 mg lorazepam (all $r < 0.49$,

Table 5. Cronbach's alpha results.

	Placebo	Lorazepam 1 mg	Lorazepam 2 mg	Statistical comparison
Latency	0.83	0.85	0.80	Pla = 1 mg, $p = 0.62$ Pla = 2 mg, $p = 0.75$ 1 mg = 2 mg, $p = 0.42$
Amplitude gain	0.81	0.87	0.86	Pla = 1 mg, $p = 0.29$ Pla = 2 mg, $p = 0.46$ 1 mg = 2 mg, $p = 0.74$
Spatial error	0.78	0.84	0.81	Pla = 1 mg, $p = 0.36$ Pla = 2 mg, $p = 0.70$ 1 mg = 2 mg, $p = 0.60$
Peak velocity	0.94	0.93	0.91	Pla = 1 mg, $p = 0.60$ Pla = 2 mg, $p = 0.26$ 1 mg = 2 mg, $p = 0.55$
Average velocity	0.89	0.90	0.87	Pla = 1 mg, $p = 0.98$ Pla = 2 mg, $p = 0.51$ 1 mg = 2 mg, $p = 0.49$
Duration	0.82	0.83	0.81	Pla = 1 mg, $p = 0.86$ Pla = 2 mg, $p = 0.82$ 1 mg = 2 mg, $p = 0.69$
Curvature	0.73	0.60	0.59	Pla = 1 mg, $p = 0.26$ Pla = 2 mg, $p = 0.23$ 1 mg = 2 mg, $p = 0.95$
Skewness	0.88	0.82	0.75	Pla = 1 mg, $p = 0.27$ Pla = 2 mg, $p = 0.04$ 1 mg = 2 mg, $p = 0.32$
Q	0.94	0.93	0.87	Pla = 1 mg, $p = 0.60$ Pla = 2 mg, $p = 0.03$ 1 mg = 2 mg, $p = 0.09$

No comparison reached significance at Bonferroni corrected level of $p = 0.0167$.
Pla = placebo. $N = 34$.

all $p > 0.003$, n.s. at Bonferroni corrected alpha level of 0.0003) (see Supplementary Table 1 online).

Drug effects on internal consistency

Study aim 7. Cronbach's alphas were high for most saccade variables (ranging from 0.75 to 0.94), with the exception of somewhat lower alphas for curvature (ranging from 0.59 to 0.73) (Table 5). There were no significant differences between the Drug conditions in internal consistency of any variables (all $p > 0.02$, n.s. at Bonferroni corrected alpha level of 0.0167).

Discussion

The key findings from this study are as follows. First, we confirmed that lorazepam reduces saccadic peak velocity and we demonstrated that this effect is both sensitive to dose and independent of age, sex, intelligence and trait anxiety. The sensitivity of peak velocity was further underscored by the effect of lorazepam on Q, a measure of the ratio between peak and average velocity, showing that the drug effect was more pronounced on peak than average velocity. Second, lorazepam effects on saccades were widespread, with deteriorations observed on most mean and variability measures. Notably, however, the internal reliability of performance (Cronbach's alpha) was not affected. Third, lorazepam effects interacted with sex on consistency measures of spatial accuracy, indicating more pronounced adverse effects in females. Fourth, there was evidence that lorazepam effects depend on task factors. Effects on peak velocity, gain and Q were more pronounced for near than far stimuli. Effects on average velocity were more pronounced for saccades to the right, whereas effects on skewness and Q were stronger for saccades to the left. Fifth, analysis of dose-dependency showed that most variables were sensitive to both 1 mg lorazepam compared to placebo and an increase from 1 mg to 2 mg. Exceptions were latency, skewness and the variabilities of latency, duration and curvature, which showed deterioration from placebo only with 2 mg, suggesting these measures are less suited to detecting low-dose lorazepam effects.

Lorazepam effects

Using a multi-dose, within-subjects design, we replicated the well-established finding of reduced saccadic peak velocity following benzodiazepine administration (Study Aim 1). Considering the magnitude of the effect observed in this study and the consistency of this finding across numerous studies using various benzodiazepine compounds (De Visser et al., 2003), we argue that this effect is likely to be one of the most consistent findings in experimental psychopharmacology.

The current study advances this literature in a number of ways. First, we confirmed that the effect on peak velocity is independent of sex, age, intelligence and trait anxiety (Study Aims 4 and 6). The reason for investigating these possible predictor variables lies in the known variability in pharmacological response across individuals and the importance of developing individualised treatment strategies, e.g. by taking into account patients' baseline measurements (Owen et al., 2013). We can thus conclude that the effect of lorazepam on saccadic peak velocity is fundamental, i.e. independent of the participant variables studied here, at least within the range of scores observed in this carefully selected, healthy sample.

Second, we extend previous studies by demonstrating that lorazepam effects on saccades are pronounced, affecting almost all measured aspects of mean and variability of performance (Study Aims 2 and 3). Most previous studies have focussed on peak velocity, and no previous study has investigated a spectrum of variables as comprehensive as that reported here. Therefore, and because our study included multiple doses and a larger sample than most other studies in the field (De Visser et al., 2003), our findings provide an important archive of lorazepam effects across saccadic performance measures. To summarise, lorazepam led to increased latency, reduced spatial accuracy, reduced average velocity, reduced peak/average velocity ratio (Q), increased skewness, increased curvature and increased intra-individual variabilities of all measures except spatial error. Most variables showed evidence of dose-dependency, except mean latency, mean skewness, latency variability, duration variability and curvature variability for the comparison of placebo vs. 1 mg, as well as Q, amplitude-corrected peak velocity and latency variability for the comparison of 1 mg vs. 2 mg.

Taken together, and comparing these data to the often much more subtle and specific effects of other substances on oculomotor measures (Ettinger and Kumari, 2003; Reilly et al., 2008), the picture that emerges is that benzodiazepines cause a fundamental,

nonspecific destabilisation of the neural system controlling saccadic eye movements. The macroscopic neural mechanisms underlying this effect remain unknown, necessitating functional neuroimaging studies (Minzenberg, 2012; Nathan et al., 2014). The distribution of $GABA_A$ receptors in brain and the observed pattern of lorazepam effects suggest that various structures in the neural network underlying saccades are affected, from cortical eye fields to brainstem.

Specifically, peak velocity is related to activity of burst neurons in the pontine reticular formation (Fuchs et al., 1985), suggesting that the robust reduction of peak velocity in this and other studies is a result of GABAergic effects on brainstem neurons. Saccadic latency, on the other hand, is a composite measure that reflects perceptual processes, attention, target selection, decision making and programming premotor commands and is subject to both top-down and bottom-up influences (Carpenter, 2004; Hutton, 2008). Benzodiazepine effects on saccadic latency have been observed previously (Chen et al., 2014, 2015; De Haas et al., 2007, 2008, 2009; Green et al., 2000; Masson et al., 2000; Tedeschi et al., 1983). The increase in latency could reflect a delay in the programming of the saccadic command (Masson et al., 2000) and may stem from GABAergic effects in frontal or parietal eye fields (Roy-Byrne et al., 1993; Sommer and Tehovnik, 1997). Reduced spatial accuracy following benzodiazepines has also been observed previously (Chen et al., 2014, 2015; De Haas et al., 2007, 2008, 2009; King et al., 1995; Masson et al., 2000), and might reflect lorazepam's action in frontal eye fields or cerebellum (Glue, 1991; Robinson and Fuchs, 2001; Sommer and Tehovnik, 1997). Effects on curvature may arise in the brainstem (Leigh and Zee, 2015).

Some lorazepam effects interacted with the saccade task factors direction (right/left stimuli) and distance (near/far stimulus positions) (Study Aim 5). Specifically, effects on average velocity were more pronounced for saccades to the right, whereas effects on skewness and Q were stronger for saccades to the left. Effects on gain, peak velocity and Q were more pronounced for near than far stimuli. An important implication of these findings for future drug screening studies using saccadic biomarkers is to include multiple stimulus positions, in order to be able to detect adverse drug effects with maximal sensitivity, especially for comparisons between different drug doses.

Finally, an interesting observation of this study was that the internal reliability (Cronbach's alpha) of performance was not significantly altered by lorazepam (Study Aim 7). This finding suggests that despite the observed increases in intra-individual variability of some measures, performance remained consistent across individuals. An important corollary of this finding is that lorazepam does not reduce the internal reliability with which saccadic performance is measured, even at a dose of 2 mg.

Sex-dependent effects of lorazepam

In addition to these primary effects of lorazepam, there was evidence of sex-dependent effects (Study Aim 4) on two saccadic measures, viz. the intra-individual variability of spatial error and amplitude gain. These findings indicated that adverse effects of lorazepam on these variables were stronger in females than in males. The spatial accuracy of saccades reflects basic sensorimotor transformation processes that rely on cerebellar integrity (Ettinger et al., 2002, 2005; Robinson and Fuchs, 2001).

The finding of sex-dependent lorazepam effects on spatial accuracy may be explained via the drug's action in the cerebellum and sex differences in mediating these effects. Support for this hypothesis comes from a positron emission tomography (PET) study demonstrating sex differences in glucose metabolism in brain following administration of lorazepam (Wang et al., 1998). In that study, bodyweight-adjusted, intravenous administration of lorazepam (30 μg/kg) led to similar reductions in overall brain metabolic activity in both females and males. However, a sex effect was observed in cerebellum, where lorazepam-induced reductions tended to be more pronounced in females (−5.9 ±6%) than in males (−1.1 ±6.6%) (Wang et al., 1998). Whilst Wang et al. (1998) did not observe sex-dependent lorazepam effects on motor or cognitive tasks, we agree with their conclusion that 'more specific cerebellar tests may have been able to disclose differences between the genders in sensitivity to lorazepam's motor effects' (Wang et al., 1998: 43) given that we succeeded in showing such effects on saccadic spatial accuracy in our study. It should be noted that men also have larger cerebellar volume than females, even when adjusted for whole-brain volume (Giedd et al., 2012), suggesting they may need a higher dosage to achieve the same occupancy. Interestingly, male>female differences in volume are particularly pronounced in motor-related cerebellar areas such as lobule VIIIB (Steele and Chakravarty, 2017), an area whose volume we have previously found to be related to saccadic spatial accuracy in healthy humans (Ettinger et al., 2005).

These findings of sex-dependent lorazepam effects suggest that anxiolytic treatment effects may generally differ by sex, an issue that has previously been raised (Bekker and van Mens-Verhulst, 2007; Yonkers et al., 1992). Here, the effects of lorazepam were not observed on a measure of anxiety, of course, but on an oculomotor measure. Two issues should be raised in this context. First, it is unclear whether sex-dependent drug effects on this measure translate to sex differences in the anxiolytic response in patients with anxiety disorders. Second, it should be noted that males in this study showed worse performance on these measures than females, suggesting that the observed drug by sex interaction may reflect a difference in baseline performance, perhaps compatible with sex differences in cerebellar metabolism in the absence of pharmacological challenges (Volkow et al., 1997). Thus, further studies are needed to investigate whether genuine sex differences in drug response are observed, even in the absence of baseline performance differences.

Limitations

The following limitations should be noted. First, we did not measure lorazepam concentrations. These may have been helpful in further characterising pharmacodynamics effects, especially as they may be affected by age or sex. A second limitation is that we did not obtain weight measures of our participants; therefore, it is not possible to relate inter-individual differences in the magnitude of drug effects to body weight.

Conclusions and implications

To conclude, we confirm that lorazepam dose-dependently reduces saccadic peak velocity. This effect is both robust, not being related to various baseline variables, and sensitive, given

that effects on peak velocity were greater than those on average velocity. An important additional conclusion from this study is that lorazepam effects on saccades are pronounced, leading to deteriorations in most measures of saccadic performance investigated here. An implication of this pattern of findings is that studies aiming to detect (adverse) effects of benzodiazepine compounds should include saccadic parameters other than just the peak velocity in order to obtain a full picture of the drug's effects. Additionally, task factors interacted with lorazepam effects, suggesting that the drug exerts negative influences especially at smaller-amplitude saccades. Future studies should thus include multiple target positions in order to optimally probe for benzodiazepine effects. Finally, a noteworthy finding was that effects of lorazepam on measures of spatial consistency were more pronounced for females than males. Whilst this finding of course needs to be replicated, it underscores the importance of including both male and female participants in pharmacological studies.

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Declaration of conflicting interest

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Note

1. In this study, we use the term "sex" to denote biological sex, as indicated by participants' self-report. We acknowledge that in humans the term biological "sex" is confounded with, and difficult to separate from, the more psychosocial concept "gender" (Brooks and Clayton, 2017).

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