Short Report

Effects of lorazepam on prosaccades and saccadic adaptation

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Abstract

Background: Benzodiazepines have reliable adverse effects on saccadic eye movements, but the impact of sex as a potential modulator of these effects is less clear. A recent study reported stronger adverse effects on the spatial consistency of saccades in females, which may reflect sex differences in cerebellar mechanisms.

Aims: We aimed to further examine the role of sex as a potential modulator of benzodiazepine effects by employing the saccadic adaptation paradigm, which is known to be sensitive to cerebellar functioning.

Methods: A total of n=50 healthy adults performed a horizontal step prosaccade task and a saccadic adaptation task under 0.5 mg lorazepam, 1 mg lorazepam and placebo in a double-blind, within-subjects design.

Results: In the prosaccade task, lorazepam had adverse effects on measures of peak velocity, latency and spatial consistency. The administration of 0.5 mg lorazepam led to significant reductions in gain-decrease adaptation, while a dose of 1 mg did not impair adaptation learning. Gain-increase adaptation was generally less pronounced, and unaffected by the drug. There were no significant drug×sex interactions in either task.

Conclusions: We conclude that a low dose of lorazepam impairs gain-decrease adaptation independent of sex. At higher doses, however, increasing fatigue may facilitate adaptation and thus counteract the adverse effects observed at lower doses. With regards to prosaccades, our findings confirm peak velocity as well as latency and spatial measures as sensitive biomarkers of GABAergic effects.

Keywords
Saccadic adaptation, prosaccades, benzodiazepines, lorazepam, cerebellum

Introduction

Benzodiazepines such as lorazepam are among the most commonly prescribed psychotropic medications. By acting as gamma-aminobutyric acid (GABA) positive allosteric modulators, they have sedative and anxiolytic properties, but also exhibit adverse effects on motor functions and cognition. Specifically, even small doses of lorazepam impair saccadic eye movements, resulting in reduced peak velocity, increased latencies and lower and less consistent spatial accuracy (Ettinger et al., 2018; Masson et al., 2000). While mounting evidence supports the role of saccadic functioning as a biomarker of GABAergic benzodiazepine effects, the impact of sex as a potential modulator of these effects is less clear. Given that women are twice as likely to consume benzodiazepines (Ashton, 1991; Habraken and Soenen, 1993; Koenig et al., 1987), more detailed investigation of sex effects is of major concern.

Recently, Ettinger et al. (2018) found that lorazepam has sex-dependent negative effects on the spatial consistency of saccades, with more adverse effects in females. Given the role of the cerebellum in saccadic spatial accuracy (Ettinger et al., 2002, 2005; Robinson and Fuchs, 2001), this effect may reflect sex differences in cerebellar sensitivity to benzodiazepines. In line with this hypothesis, lorazepam-induced reductions in cerebellar glucose metabolism have been reported to be more pronounced in females than in males (Wang et al., 1998). While Wang et al. did not find sex-dependent lorazepam effects on behavioural outcomes (i.e. balance and coordination), the authors acknowledge that more specific tests of cerebellar functioning may be able to disclose interaction effects between sex and lorazepam.

In this regard, the investigation of implicit motor learning mechanisms in the cerebellum, such as saccadic adaptation, may be instructive. Saccadic adaption is a process for maintaining saccade accuracy based on evaluating the accuracy of past saccades and appropriately correcting the motor commands for subsequent saccades (Scudder, 2009). It can be experimentally induced by the double-step target paradigm, in which a target steps away from the fixation point, and while the saccade is in flight, the target is displaced so that the otherwise accurate saccade will not land on the target (McLaughlin, 1967). Backward intra-saccadic target steps in the direction opposite to the primary saccade induce progressive shortening of saccadic amplitude; forward intra-saccadic target steps in the same direction as the primary saccade result in lengthening of saccadic amplitude (Lemoine-Lardennois et al., 2016).

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Backward and forward adaptation may rely on separate mechanisms (Catz et al., 2008; Ethier et al., 2008; Golla et al., 2008; Kojima et al., 2004; Panouillères et al., 2009). While backward, i.e. gain-decrease, adaptation is established by alterations of the saccadic trajectory midflight, forward, i.e. gain-increase, adaptation is induced via target remapping (Ethier et al., 2008). Saccadic adaptation is facilitated by the cerebellum (Hopp and Fuchs, 2004; Karnath and Thier, 2006; Kojima et al., 2011), but frontal cortex, supplementary eye fields, posterior insula and posterior intraparietal sulcus are also involved (Blurton et al., 2012; Gerardin et al., 2012; Panouillères et al., 2014).

GABA is the main fast-acting inhibitory neurotransmitter in the brain. It acts via $GABA_A$, $GABA_B$ and $GABA_C$ receptors, which are widely distributed throughout cortical and subcortical regions (Uusi-Oukari and Korpi, 2010; Waldvogel and Faull, 2015). Local-circuit interneurons that constitute 15–20% of all cortical neurons predominantly use GABA as neurotransmitter (Jazvinscak Jembrek and Vlainic, 2015). Benzodiazepines target $GABA_A$ receptors, which are the most abundant subtype and play a crucial role in motor control in basal ganglia and cerebellum (Prsa and Thier, 2011; Waldvogel and Faull, 2015). Notably, Purkinje cells are the only output element of the cerebellar cortex, and their axons terminate in deep cerebellar and vestibular nuclei where they form GABAergic synapses. Changes in firing properties of Purkinje cells during acquisition of a motor response may underlie saccadic adaptation (Prsa and Thier, 2011; Soetedjo et al., 2019).

Considering the widespread distribution of $GABA_A$ receptors in brain regions associated with saccadic adaptation, most notably the cerebellum, it is of major interest to characterize the impact of benzodiazepines on this learning mechanism as well as its putative sex dependency. In rhesus monkeys, injection of the GABA agonist muscimol, which substantially deactivated the oculomotor vermis (OMV) of the cerebellum, reduced saccadic forward adaptation, but did not impair backward adaptation (Kojima et al., 2011). However, benzodiazepine effects on saccadic adaptation have not been investigated.

The aims of this study were twofold. First, we aimed to confirm findings of stronger adverse lorazepam effects on consistency of saccadic accuracy in females than males (Ettinger et al., 2018) in a larger, independent sample, and extend the results into the lower dose range. Second, we aimed to investigate effects of lorazepam and sex on saccadic adaptation. Two doses of lorazepam (0.5 mg, 1 mg) were applied to assess the dose-dependency of any effects. We hypothesized that lorazepam would have dose-dependent adverse effects on peak velocity, amplitude gain, spatial error and latency of prosaccades as well as on saccadic adaptation. As gain-decrease adaptation is generally more pronounced than gain-increase adaptation (Bahcall and Kowler, 2000; Noto et al., 1999; Panouillères et al., 2009), we hypothesized that drug effects would be better measurable in the former than in the latter. Furthermore, we expected that adverse effects on adaptation learning would be more pronounced in females.

Materials and methods

Participants

A-priori power analysis in G*Power (Version 3.1.9.7, Faul et al., 2009) indicated that n=50 would be adequate to detect a small effect of f=0.2 with 85% power at α=0.05. Thus, a total of 50 healthy volunteers aged 18–35 years were recruited via public advertisement. Participants underwent thorough screening before admission to the study to ensure they were in good physical and mental health. Exclusion criteria comprised any current medication (except for oral contraceptives and thyroid drugs), consumption of nicotine or other psychoactive drugs, previous consumption of lorazepam or other benzodiazepines, presence of physical, neurological or psychiatric disorders as assessed by the Mini International Neuropsychiatric Interview (M.I.N.I.; Ackenheil et al., 1999; Sheehan et al., 1998), hyper- or hypotonia, obesity (body mass index (BMI)>30) or underweight (BMI<18), pregnancy, colour blindness and deafness. Participants were right-handed, non-smokers and had normal or corrected-to-normal vision.

Written informed consent was obtained and participants were compensated for their time with 90€. The study was conducted in accordance with the revised Declaration of Helsinki and approved by the research ethics committee of the Faculty of Medicine at the University of Bonn.

Study design and procedure

The study employed a double-blind, placebo-controlled, within-subjects design with order of drug administration randomized using the Latin square method. Each participant was assessed three times, i.e. under placebo (mannitol), 0.5 mg lorazepam and 1 mg lorazepam. Assessment days were separated by a week to allow for adequate drug washout. Assessments were conducted at the University Hospital Bonn between 08:00–18:00, with weekday and time of assessment kept the same for each participant as closely as possible. A study physician was available throughout.

On assessment days, participants' current health was first verified. For female participants, nonpregnancy was confirmed by urine tests (CleartestDiagnostik HCG). Then, a capsule containing drug or placebo was administered per os with water. After a 120 min wait for the drug to reach peak concentrations in blood (Kyriakopoulos et al., 1978), participants completed a joystick task lasting 17 min, followed by the saccade tasks. At the end of each assessment day, participants completed 10 computerized visual analogue scales (VASs; Costa et al., 2013).

Saccade tasks

Saccade tasks were written using ExperimentBuilder Version 2.1.140 (SR Research Ltd, Ontario, Canada) and presented using a standard Workstation Host PC (SR Research Ltd, Ontario, Canada) on a 22-inch liquid crystal display monitor (Viewsonic; height: 29.5 cm; width: 47.5 cm; resolution: 1680×1050 pixels; 60 Hz refresh rate) at a distance of 70 cm from participants' eyes. A chinrest was used to minimize head movements. Movements of the right eye were recorded using video-based corneal reflection and pupil tracking (EyeLink 1000, SR Research Ltd., Ottawa, Canada) at 1000 Hz. Before the beginning of each saccade task, a horizontal-vertical five-point calibration was carried out (stimulus positions: (0°, 0°); (0°, +9.9°); (0°, −9.9°); (+16.6°, 0°); (−16.6°, 0°)).

First, a horizontal prosaccade task was presented. Participants were instructed to follow a target, a white circle (15 pixels diameter, stroke width 5 pixels; 0.35°) on a black background, with their eyes as fast and accurately as possible without moving the

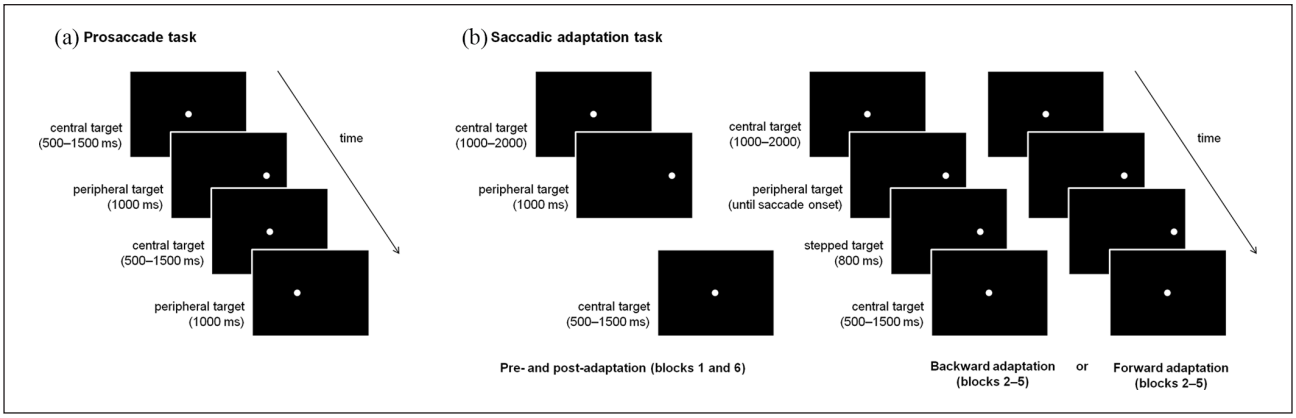

Figure 1. Task design of (a) the prosaccade task and (b) the saccadic adaptation task.

head. Central drift checking/correction (0°, 0°) was carried out at the beginning of each trial. After a variable interval of 500–1500 ms, the target stepped to one of four 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 (Figure 1(a)). Each peripheral location was used 15 times in random order, resulting in 60 trials.

Second, participants completed a saccadic adaptation task (McLaughlin, 1967). Target and background were identical to the prosaccade task. Participants were instructed to keep their eyes on the target without moving the head. They were not informed of the target displacement during the saccade. Central drift checking/correction was carried out at the beginning of each trial. After a variable interval of 1000–2000 ms, the target stepped 10° to the right. There were six blocks. In block 1 (pre-adaptation), the target did not change position after the step. In blocks 2–5, saccadic adaptation was induced by repositioning of the target. As soon as the subject initiated a saccade towards the target, it stepped 2.5° backward or forward, respectively, from its original peripheral position and remained there for 800 ms (Figure 1(b)). The direction condition (backward/forward) varied between subjects, i.e. half of the participants completed the backward condition and the other half completed the forward condition at all three sessions. Finally, block 6 (post-adaptation) was identical to block 1, i.e. the peripheral target position remained constant after saccade initiation. Pre- and post-adaptation blocks comprised 20 trials each, while each adaptation block included 50 trials.

Eye movement data processing

Saccades were identified using EyeLink DataViewer Version 3.2.48 (SR Research Ltd., Ottawa, Canada) and resultant data were processed blind to drug condition. For each trial, the first saccade following peripheral target onset was included if (a) it was made in the direction of the peripheral target, (b) it had a minimum amplitude of 1°, (c) it had a minimum latency to target stimulus of 70 ms and a maximum latency of 1000 ms (prosaccade task) or 500 ms (adaptation task), respectively, (d) there was no blink or saccade in the window from 100 ms before onset of the peripheral target to beginning of the included saccade, (e) there was no blink within the saccade, and (f) gaze location at saccade start did not deviate from central target position (0°, 0°) by more than 100 pixels horizontally or vertically.

For each participant, mean peak velocity, gain, spatial error and latency of prosaccades as well as mean gain of saccades in the adaptation task were computed (see Supplemental Material for detailed definition of outcome measures). For prosaccades, we also calculated the intra-individual coefficient of variation (ICV) of peak velocity, gain, spatial error and latency, by dividing a participant's intra-individual standard deviation (*SD*) by his/her mean score (Ettinger et al., 2018).

Only participants with at least three (out of 15) valid prosaccade trials at each peripheral target position were included in data analysis, resulting in n=45. For saccadic adaptation, participants were included in analyses if they had at least five (out of 20/50) valid trials per block, leaving n=46.

To quantify the amount of adaptation, the mean relative change in saccadic gain (gain change (GC)) was calculated by subtracting mean gain at pre-adaptation (block 1) from mean gain in the last adaptation block (block 5) and dividing the difference by mean gain at pre-adaptation.

$$GC_{adapt} = \left(G_{last\_adapt} - G_{pre\_adapt}\right)/G_{pre\_adapt}$$

Similarly, a post-adaptation score was calculated by standardizing mean gain in the post-adaptation block (block 6) by mean gain in the pre-adaptation block (block 1).

$$GC_{post\_adapt} = \left(G_{post\_adapt} - G_{pre\_adapt}\right)/G_{pre\_adapt}$$

GC_{adapt} and GC_{post_adapt} thus denote changes in gain at the end of the adaptation phase and post-adaptation, respectively. This method has been used previously (Gaymard et al., 2001; Hopp and Fuchs, 2002; Lemoine-Lardennois et al., 2016; Salman et al., 2006; Wallman and Fuchs, 1998).

Visual analogue scales (VASs)

Computerized VASs were applied to measure subjective cognitive and affective effects of the drug (see Supplemental Material).

Statistical analyses

Statistical analyses were conducted using SPSS 24 (IBM, Armonk, New York, USA). To assess the effects of lorazepam

and sex on prosaccades (Ettinger et al., 2018), repeated measures analyses of variance (ANOVAs) were carried out with drug (placebo, 0.5 mg lorazepam, 1 mg lorazepam), direction (left, right) and distance (near, far) as within-subjects factors and sex (male, female) as between-subjects factor.

For saccadic adaptation, two repeated measures ANOVAs were computed with drug (placebo, 0.5 mg lorazepam, 1 mg lorazepam) as within-subjects factor, sex (male, female) and direction (backward, forward) as between-subjects factors, and GC_{adapt} and GC_{post_adapt} as dependent variables, respectively.

Analyses of VASs are described in the Supplemental Material.

Partial eta squared (ηp^2) was used to calculate effect sizes in ANOVAs (Cohen, 1973). Mauchly's test of sphericity was performed for each variable and Greenhouse-Geisser correction was applied if necessary. Significant main and interaction effects were followed up with post-hoc *t*-tests and ANOVAs, respectively. The significance level was 0.05. Considering the ordinal scale and interdependence (within-subjects factor) of the drug conditions, we computed least significant difference (LSD) post-hoc *t*-tests.

Pearson correlations to investigate whether drug effects across task parameters were associated with each other are described in the Supplemental Material.

Sex and gender

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).

Results

Sample characteristics

A total of n=50 participants (23 males, 27 females) with mean age 22.4 years (SD=3.68) completed the study. Males and females did not differ in age ($t_{(48)}$=1.14, p=0.26) or their allocation to backward and forward adaptation conditions ($\chi^2_{(1)}$=0.30, p=0.59). Descriptive statistics are presented in Tables 1 and 2. Physical characteristics of males and females can be found in Supplementary Material Table S1. Figure 2 depicts the trajectory of saccadic gain across blocks. The dataset is available online (https://osf.io/9ws2e/).

Prosaccade task

For mean peak velocity, we observed significant effects of drug ($F_{(2,86)}$=12.39, $p<0.001$, ηp^2=0.22), direction ($F_{(1,43)}$=67.75, $p<0.001$, ηp^2=0.61; larger peak velocity for rightward saccades) and distance ($F_{(1,43)}$=618.35, $p<0.001$, ηp^2=0.94; larger peak velocity for far saccades). Post-hoc *t*-test yielded significantly reduced peak velocity under both doses of lorazepam compared to placebo (0.5 mg: p=0.001; 1 mg: $p<0.001$), while there was no substantial difference between 0.5 mg and 1 mg (p=0.16). Effects of sex and the drug×sex interaction did not reach significance and there were no further interactions.

For ICV of peak velocity, there was a significant effect of drug ($F_{(2,86)}$=4.66, p=0.012, ηp^2=0.10), indicating increased ICV under 0.5 mg (p=0.011) and 1 mg lorazepam (p=0.012) compared to placebo. The difference between 0.5 mg and 1 mg was not significant (p=0.89). No other main or interaction effects reached significance.

For mean gain, we observed significant effects of direction ($F_{(1,43)}$=38.70, $p<0.001$, ηp^2=0.47) and distance ($F_{(1,43)}$=6.06, p=0.018, ηp^2=0.12), indicating larger gain for rightward saccades and near saccades, respectively. There was no significant effect of drug ($F_{(1.63,70.07)}$=0.59, p=0.53, ηp^2=0.013). Effects of sex ($F_{(1,43)}$=3.14, p=0.084, ηp^2=0.068) and the sex×drug interaction ($F_{(1.63,70.07)}$=2.65, p=0.088, ηp^2=0.058) also did not achieve significance.

For ICV of gain, there were significant effects of drug ($F_{(1.68,72.28)}$=5.20, p=0.011, ηp^2=0.11) and distance ($F_{(1,43)}$=17.59, $p<0.001$, ηp^2=0.29; larger ICV for near saccades). Post-hoc *t*-tests indicated an increased ICV of gain under both 0.5 mg (p=0.008) and 1 mg lorazepam (p=0.007) compared to placebo; the difference between 0.5 mg and 1 mg was not significant (p=0.32). No other main or interaction effects reached significance.

For spatial error, we observed significant effects of drug ($F_{(1.71,73.30)}$=3.71, p=0.036, ηp^2=0.079), direction ($F_{(1,43)}$=10.82, p=0.002, ηp^2=0.20; larger spatial error in leftward saccades), distance ($F_{(1,43)}$=6.93, p=0.012, ηp^2=0.14; larger spatial error in near saccades) and the drug×distance interaction ($F_{(1.56,66.99)}$=4.24, p=0.027, ηp^2=0.090). Post-hoc *t*-tests showed that spatial error was significantly increased under both 0.5 mg (p=0.010) and 1 mg lorazepam (p=0.030) compared to placebo, whereas the difference between the two doses was not significant (p=0.65). As indicated by follow-up ANOVAs stratified by direction, the drug effect was only significant for near ($F_{(1.55,68.22)}$=5.27, p=0.013, ηp^2=0.11), but not far saccades ($F_{(2,86)}$=1.91, p=0.15, ηp^2=0.043). No other main or interaction effects reached significance.

For ICV of spatial error, there were significant effects of direction ($F_{(1,43)}$=23.98, $p<0.001$, ηp^2=0.36) and distance ($F_{(1,43)}$=8.15, p=0.007, ηp^2=0.16), indicating larger ICV in rightward and near saccades, respectively. Furthermore, we found a significant sex×distance interaction ($F_{(1,43)}$=5.86, p=0.020, ηp^2=0.12). Subsequent ANOVAs separated by sex yielded a significant effect of distance in males ($F_{(1,18)}$=18.49, $p<0.001$, ηp^2=0.51) but not in females ($F_{(1,25)}$=0.09, p=0.77, ηp^2=0.004), indicating that the observed main effect of a larger ICV of spatial error for near saccades was driven by males. No other main and interaction effects reached significance.

For mean latency, we observed significant effects of drug ($F_{(1.69,72.58)}$=5.35, p=0.010, ηp^2=0.11), sex ($F_{(1,43)}$=4.30, p=0.044, ηp^2=0.091; higher latency in females) and distance ($F_{(1,43)}$=4.66, $p<0.001$, ηp^2=0.65; higher latency for far saccades). As indicated by post-hoc *t*-tests, latency was significantly increased under 1 mg lorazepam compared to placebo (p=0.005) and 0.5 mg lorazepam (p=0.004). There was no substantial difference between placebo and 0.5 mg (p=0.46). No other main or interaction effects reached significance.

For ICV of latency, there also was a significant effect of drug $F_{(1.63,70.11)}$=3.89, p=0.033, ηp^2=0.11). Specifically, we observed increased ICV under 1 mg compared to 0.5 mg, while differences between placebo and both drug doses did not reach significance (0.5 mg: p=0.64; 1 mg: p=0.067). No other main or interaction effects reached significance.

Main effects of drug on all prosaccade parameters are depicted in the Supplemental Material Figure S1.

Table 1. Descriptive statistics of saccadic parameters in the prosaccade task.

	Placebo				Lorazepam 0.5 mg				Lorazepam 1 mg			
	LN	LF	RN	RF	LN	LF	RN	RF	LN	LF	RN	RF
Males												
Peak velocity (*M*)	280.75 (36.38)	367.87 (48.72)	315.19 (36.81)	415.62 (61.49)	260.40 (38.99)	342.00 (50.68)	302.49 (50.26)	386.24 (68.49)	258.34 (45.65)	345.09 (50.19)	309.03 (57.42)	386.83 (62.13)
Gain (*M*)	0.90 (0.07)	0.89 (0.05)	0.95 (0.05)	0.92 (0.05)	0.88 (0.08)	0.86 (0.05)	0.93 (0.09)	0.92 (0.06)	0.89 (0.09)	0.88 (0.04)	0.96 (0.10)	0.93 (0.07)
Spatial accuracy (*M*)	0.12 (0.05)	0.11 (0.05)	0.09 (0.03)	0.09 (0.04)	0.14 (0.08)	0.14 (0.05)	0.12 (0.07)	0.10 (0.05)	0.14 (0.09)	0.12 (0.04)	0.12 (0.06)	0.09 (0.06)
Latency (*M*)	156.39 (16.57)	174.39 (24.30)	153.55 (11.72)	173.19 (16.75)	158.08 (15.77)	172.99 (17.24)	154.71 (17.21)	175.37 (24.03)	162.90 (15.81)	177.53 (19.31)	161.73 (11.89)	180.09 (18.54)
Peak velocity (ICV)	0.11 (0.08)	0.09 (0.04)	0.12 (0.09)	0.12 (0.12)	0.14 (0.10)	0.15 (0.11)	0.15 (0.12)	0.16 (0.11)	0.13 (0.09)	0.13 (0.08)	0.16 (0.13)	0.15 (0.13)
Gain (ICV)	0.11 (0.07)	0.07 (0.05)	0.11 (0.07)	0.08 (0.09)	0.13 (0.08)	0.09 (0.07)	0.14 (0.11)	0.10 (0.06)	0.14 (0.11)	0.07 (0.03)	0.14 (0.08)	0.11 (0.09)
Spatial accuracy (ICV)	0.72 (0.32)	0.53 (0.19)	0.86 (0.43)	0.66 (0.23)	0.71 (0.30)	0.54 (0.25)	0.74 (0.24)	0.71 (0.36)	0.72 (0.24)	0.52 (0.17)	0.83 (0.27)	0.79 (0.27)
Latency (ICV)	0.15 (0.08)	0.14 (0.05)	0.14 (0.06)	0.15 (0.09)	0.14 (0.06)	0.15 (0.05)	0.12 (0.03)	0.15 (0.10)	0.17 (0.07)	0.18 (0.10)	0.17 (0.07)	0.16 (0.06)
Females												
Peak velocity (*M*)	276.28 (32.38)	364.41 (51.44)	296.05 (47.92)	396.44 (55.46)	265.32 (42.66)	356.60 (52.09)	290.74 (49.50)	389.35 (73.81)	252.99 (41.25)	338.65 (52.84)	277.58 (59.92)	378.12 (62.64)
Gain (*M*)	0.93 (0.08)	0.92 (0.06)	0.97 (0.09)	0.95 (0.08)	0.94 (0.07)	0.93 (0.06)	0.98 (0.11)	0.95 (0.09)	0.91 (0.10)	0.90 (0.08)	0.95 (0.15)	0.94 (0.07)
Spatial accuracy (*M*)	0.09 (0.06)	0.09 (0.05)	0.09 (0.05)	0.07 (0.06)	0.10 (0.06)	0.09 (0.05)	0.10 (0.07)	0.09 (0.07)	0.12 (0.08)	0.11 (0.07)	0.12 (0.12)	0.08 (0.06)
Latency (*M*)	165.63 (20.07)	181.56 (28.22)	165.01 (14.87)	179.35 (23.38)	172.42 (26.93)	182.95 (29.96)	166.89 (15.99)	180.61 (22.83)	170.98 (24.44)	193.16 (32.54)	170.09 (23.11)	188.21 (26.13)
Peak velocity (ICV)	0.11 (0.12)	0.08 (0.06)	0.09 (0.04)	0.08 (0.06)	0.10 (0.06)	0.10 (0.08)	0.11 (0.09)	0.11 (0.07)	0.13 (0.09)	0.10 (0.11)	0.13 (0.12)	0.11 (0.08)
Gain (ICV)	0.06 (0.03)	0.07 (0.06)	0.08 (0.05)	0.06 (0.05)	0.09 (0.06)	0.08 (0.09)	0.09 (0.06)	0.09 (0.08)	0.12 (0.08)	0.10 (0.12)	0.13 (0.14)	0.09 (0.11)
Spatial accuracy (ICV)	0.61 (0.20)	0.58 (0.38)	0.75 (0.33)	0.76 (0.44)	0.68 (0.19)	0.66 (0.33)	0.74 (0.41)	0.73 (0.41)	0.70 (0.23)	0.61 (0.27)	0.70 (0.17)	0.77 (0.40)
Latency (ICV)	0.17 (0.09)	0.16 (0.09)	0.17 (0.09)	0.15 (0.08)	0.17 (0.08)	0.15 (0.06)	0.15 (0.07)	0.16 (0.08)	0.18 (0.09)	0.19 (0.08)	0.18 (0.08)	0.18 (0.08)

ICV: intra-individual coefficient of variation; LF: left far; LN: left near; *M*: mean; RF: right far; RN: right near.

Table 2. Descriptive statistics of mean amplitude gain in the saccadic adaptation task.

	Placebo			Lorazepam 0.5 mg			Lorazepam 1 mg		
	Pre	Adapt.	Post	Pre	Adapt.	Post	Pre	Adapt.	Post
Backward									
Males	0.93 (0.06)	0.84 (0.05)	0.86 (0.06)	0.87 (0.16)	0.84 (0.04)	0.88 (0.05)	0.91 (0.09)	0.79 (0.09)	0.79 (0.18)
Females	0.97 (0.07)	0.81 (0.07)	0.86 (0.06)	0.94 (0.10)	0.85 (0.06)	0.89 (0.05)	0.95 (0.10)	0.84 (0.05)	0.87 (0.08)
Forward									
Males	0.97 (0.06)	1.00 (0.08)	0.99 (0.07)	0.92 (0.09)	0.98 (0.07)	0.98 (0.09)	0.91 (0.16)	0.96 (0.10)	0.96 (0.09)
Females	1.01 (0.07)	1.06 (0.07)	1.04 (0.08)	1.03 (0.05)	1.04 (0.06)	1.03 (0.07)	1.02 (0.08)	1.05 (0.07)	1.03 (0.08)

Adapt. indicates the last adaptation block, i.e. block 5.

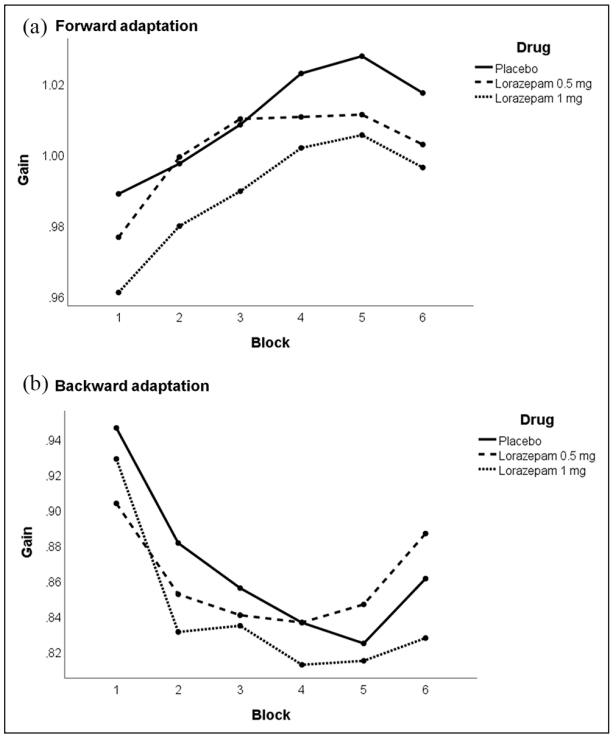

Figure 2. Saccadic adaptation of amplitude gain across blocks. Block 1 denotes the pre-adaptation phase, blocks 2–5 are adaptation blocks, and block 6 is post-adaptation.

Additionally, in order to replicate the sex-dependent lorazepam effect on ICV of gain and spatial error that were reported by Ettinger et al. (2018) with doses of 1 mg and 2 mg, we re-ran analyses of these parameters for placebo versus 1 mg lorazepam only in the present data. Furthermore, we re-ran the analyses reported in Ettinger et al. (2018) excluding the 2 mg condition, thus also for 1 mg only, to facilitate cross-study comparison. The results of these analyses are presented in the Supplemental Material. Overall, the pattern of results was similar between the two studies; however, the sex×drug interaction was more pronounced in the Ettinger et al. (2018) study.

Saccadic adaptation task

For GC_{adapt}, we observed a significant effect of direction ($F_{(1,44)}$=44.12, p<0.001, ηp^2=0.50), reflecting negative gain change in the backward condition and positive gain change in the forward condition. Furthermore, there was a significant drug×direction (backward/forward) interaction ($F_{(2,88)}$=3.42, p=0.037, ηp^2=0.072; Figure 3) and a trend-level effect of sex ($F_{(1,44)}$=3.86, p=0.056, ηp^2=0.081). All other main and interaction effects did not reach significance. Subsequent ANOVAs, where backward and forward conditions were analysed separately to further investigate the drug×direction interaction, revealed a significant effect of drug in the backward ($F_{(2,44)}$=4.21, p=0.021, ηp^2=0.16) but not the forward condition ($F_{(1.42,31.20)}$=0.15, p=0.78, ηp^2=0.007). Post-hoc t-tests in the backward condition showed that GC_{adapt} was significantly smaller, i.e. more negative, under placebo compared to 0.5 mg lorazepam (p=0.020), indicating worse adaptation under 0.5 mg lorazepam. Differences between 1 mg and placebo (p=0.61) and between 0.5 mg and 1 mg (p=0.058) were not significant.

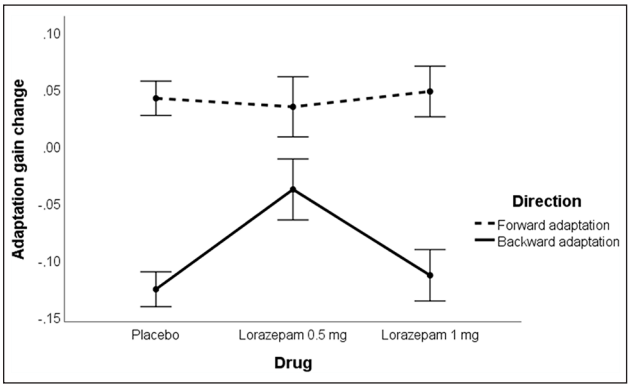

Figure 3. Adaptation gain change in backward and forward conditions. Values <0 indicate decreased gain compared to pre-adaptation; values >0 indicate increased gain compared to pre-adaptation. There was a significant interaction effect between drug and condition (p<0.05). Error bars indicate standard errors.

For GC_{post_adapt}, there was also a significant effect of direction ($F_{(1,42)}$=25.21, p<0.001, ηp^2=0.38), indicating negative gain change in the backward condition and positive gain change in the forward condition. Again, the drug×direction (backward/forward) interaction was significant ($F_{(2,84)}$=3.42, p=0.037, ηp^2=0.075), while all other main effects and interactions were not. Subsequent ANOVAs for backward and forward conditions indicated a trend-level effect of drug in the backward condition ($F_{(1.36,28.48)}$=3.58, p=0.057, ηp^2=0.15) but no substantial effect in the forward condition ($F_{(1.36,28.70)}$=0.39, p=0.68, ηp^2=0.018). Post-hoc t-tests in the backward condition yielded significantly smaller, i.e. more negative, scores under placebo compared to 0.5 mg

(p=0.028), while differences between placebo and 1 mg (p=0.57) and between 0.5 mg and 1 mg (p=0.067) were not significant.

Supplementary analyses

Analyses involving VAS, correlations amongst task parameters and effects on gain change across all four adaptation blocks are presented in the Supplemental Material. Furthermore, we examined the potential impact of circadian rhythm and order effects.

Discussion

The present study examined sex-dependent effects of lorazepam on prosaccades and saccadic adaptation. There were substantial and partially dose-dependent effects of lorazepam across almost all prosaccade parameters. Drug effects on saccadic adaptation depended on direction of adaptation. Gain-decrease adaptation was significantly reduced under 0.5 mg of lorazepam, but unaffected under 1 mg. Gain-increase adaptation, on the other hand, was not impaired by lorazepam. Unexpectedly, we did not observe any significant drug×sex interactions.

Lorazepam effects on prosaccades

For prosaccades, mean peak velocity was reduced and mean spatial error as well as mean latency were increased under both doses. Most ICVs significantly increased with lorazepam.

The findings regarding peak velocity support the role of this measure as a sensitive biomarker of GABAergic effects (Atack, 2008; Chen et al., 2012; De Visser et al., 2003). Impaired latency (M and ICV), spatial error (M) and gain (ICV) is in line with previous findings (Ettinger et al., 2018). While peak velocity (M and ICV), spatial error (M) and gain (ICV) were impaired under both doses, latency (M and ICV) was only affected by 1 mg lorazepam. This suggests that different saccadic parameters are associated with different neural processes that vary in their sensitivity to GABAergic effects. While peak velocity is closely related to activity of burst neurons in pontine reticular formation (Fuchs et al., 1985), latency reflects a composite measure of higher-level functions including perceptual processes, attention, target selection, decision-making and programming premotor commands (Carpenter, 2004; Hutton, 2008). Adverse lorazepam effects on latency may result from delayed programming of the saccadic command (Masson et al., 2000) through GABAergic effects in frontal or parietal eye fields (Roy-Byrne et al., 1993; Sommer and Tehovnik, 1997).

We thus conclude that latency is less sensitive to low doses of lorazepam than peak velocity. Furthermore, significant drug effects on mean spatial error and ICV of gain but not on mean gain indicate that lorazepam does not systematically decrease or increase saccadic amplitude, but rather reduces overall accuracy by increasing saccade residual position error on a trial-by-trial basis, irrespective of overshoot or undershoot. This is an important basis for interpreting lorazepam effects on saccadic adaptation.

Lorazepam effects on saccadic adaptation

As expected, saccadic adaptation was more pronounced in the backward than the forward condition (Bahcall and Kowler, 2000; Noto et al., 1999; Panouillères et al., 2009). For gain changes between pre-adaptation (block 1) and the last adaptation block (block 5; GC_{adapt}), we observed a significant drug effect in the backward condition, indicating reduced adaptation under 0.5 mg lorazepam, whereas the effect of 1 mg was not significant. For post-adaptation gain change (GC_{post_adapt}), there was a trend-level drug effect in the backward condition, with less negative scores under 0.5 mg lorazepam compared to placebo. Given the results reported for GC_{adapt}, this effect appears to be driven by impaired adaptation rather than reflecting improved post-adaptation, i.e. extinction of learned adaptation. In the forward condition, there were no significant drug effects, potentially because forward adaptation was too small to be modulated by drug.

Descriptively, adverse effects on backward adaptation following 0.5 mg lorazepam were driven by pre-adaptation differences as well as early saturation of adaptation (Figure 2). It is unclear, however, why this trajectory is only observed under 0.5 mg but not under 1 mg. So far, research on GABAergic effects on saccadic adaptation is scarce. In rhesus monkeys, injections of GABA agonist muscimol into OMV led to impaired gain-increase adaptation, whereas gain-decrease adaptation was unaffected or, in some experiments, even improved by the drug (Kojima et al., 2011). The latter finding is consistent with our observation that 1 mg lorazepam did not impair backward adaptation and even showed a tendency to initially improve adaptation learning. The other results, however, contrast with our findings. Inconsistencies may be due to differences in compound (GABA agonist vs allosteric modulation of GABA receptors), administration method (injection into the OMV vs oral administration) and pharmacodynamic properties.

The differences in saccadic adaptation under 0.5 mg and 1 mg may be explained by the existence of distinct underlying mechanisms. We observed that the effect of 0.5 mg lorazepam on ICV of gain in prosaccades (LF) was significantly associated with drug effects on GC_{adapt} and GC_{post_adapt} in the backward condition, indicating that more adverse effects of 0.5 mg lorazepam on the intra-individual variability of prosaccadic gain were associated with more adverse drug effects on saccadic adaptation and post-adaptation (see Supplemental Material). However, these effects were largely driven by an outlier and should be interpreted with caution. Examining correlations for drug effects under 1 mg lorazepam, we found significant negative correlations between prosaccade gain (LN, LF, RF) and backward GC_{adapt} as well as significant positive correlations between spatial error (LN, LF) and backward GC_{adapt}. Thus, more adverse effects of 1 mg lorazepam on spatial error, i.e. increments, tended to go along with more adverse drug effects on backward adaptation. Likewise, decrements in prosaccadic gain were related to more adverse drug effects on backward adaptation. Interestingly, this strong association (r=−0.74 for LN, r=−0.69 for LF, and r=−0.69 for RF saccades) was observed in the absence of significant drug effects of 1 mg lorazepam on prosaccadic gain and GC_{adapt}.

Our findings suggest that impaired adaptation learning with 0.5 mg lorazepam may be driven by the same neural processes that underlie an increased intra-individual variability of saccadic accuracy, whereas different mechanisms may have contributed to the apparent maintenance of adaptation under 1 mg lorazepam. In fact, the missing impairment of adaptation observed under 1 mg lorazepam may be due to more general processes facilitating adaptation under higher drug doses, such as fatigue. Prsa and Thier (2011) propose that fatigue effects on movement trajectories can be exploited by cerebellar mechanisms that establish saccadic adaptation. As subjective fatigue was significantly increased under 1 mg

lorazepam but not under 0.5 mg (see Supplemental Material), this may explain diverging adaptation effects between the two doses. However, it should be noted that drug effects on fatigue as assessed by VAS and drug effects on saccadic adaptation were not significantly correlated (see Supplemental Material).

Compensation of both natural error in saccadic spatial accuracy and error induced by the McLaughlin paradigm is established primarily by the cerebellum (Karnath and Thier, 2006; Kojima et al., 2011). Specifically, OMV is involved in saccadic adaptation learning, and OMV lesions result in loss of saccadic adaptation (Karnath and Thier, 2006). Optican and Robinson (1980) showed that in rhesus monkeys, cerebellectomies as well as lesions to OMV led to highly hypermetric saccades, which did not recover for the rest of the monkeys' lives (maximum 4 months), supporting the notion that cerebellar functioning is crucial for backward adaptation. In addition to cerebellum, cortical parietal and frontal areas have been implicated in saccadic adaptation, resulting in an extended brain network supporting this sensorimotor learning mechanism (Blurton et al., 2012; Gaymard et al., 2001; Gerardin et al., 2012; Zimmermann et al., 2015). Both the cerebellum and the cerebral regions associated with saccadic adaptation are prominently innervated by GABAergic neurons (Uusi-Oukari and Korpi, 2010). Whilst this is the first study in humans to directly implicate the GABAergic system in saccadic adaptation, further research will need to clarify the roles of different cortical and cerebellar regions in the observed effects.

Sex effects

Saccadic latencies were higher in females than males, and females showed a tendency for increased gain. These effects are consistent with a recent study in n=1058 healthy young adults reporting that regardless of saccade task, females tended to be slower than males at initiating saccades and exhibited increased dynamic overshoots in prosaccades (Bargary et al., 2017).

Contrary to our hypotheses, we did not observe significant drug×sex interactions. First, the sex-dependent lorazepam effects on spatial error and ICV of gain reported by Ettinger et al. (2018) did not replicate in this independent, larger sample. This inconsistency may be explained by differences in drug doses. In the previous study, the interaction effect was mainly driven by increased impairments in females under 2 mg lorazepam compared to 1 mg. Here, however, we administered doses of 0.5 mg and 1 mg lorazepam, which were less sensitive to drug×sex interactions. In line with Ettinger et al. (2018), additional post-hoc analyses (see Supplemental Material) indicated a significant difference between placebo and 1 mg lorazepam in females, but not in males. Still, this effect should be interpreted with caution as the interaction in ANOVA did not reach significance.

Second, we did not find a significant drug×sex interaction on saccadic adaptation gain change. There was a trend-level main effect of sex, indicating an overall tendency for smaller (i.e. more negative) saccadic gain change scores (GC_{adapt}) in females. However, we did not observe substantial differences between males and females when backward and forward conditions were examined separately. These findings are inconsistent with our initial hypothesis of more adverse drug effects on saccadic adaptation learning in females compared to males. A possible explanation may be that the task was insensitive to sex effects at the low dose of 0.5 mg lorazepam, whereas at the higher dose of 1 mg, potential sex effects may have been overshadowed by fatigue mechanisms, as discussed above.

Limitations

The study is not without limitations. First, although the sample is larger than previous studies of benzodiazepine effects on eye movements (e.g. Ettinger et al., 2018), the examination of backward and forward adaptation in a between-subjects design led to reductions in group sizes and thus test power. Second, we did not measure lorazepam concentrations in blood, which may have been helpful in further characterizing pharmacodynamic effects and their relation to performance, especially given that male and female participants differed with respect to physical characteristics that might have affected drug response. Third, we only administered low doses of lorazepam, thus it remains unknown whether effects may have been more pronounced at higher doses.

Conclusions and implications

This is the first study to demonstrate adverse effects of lorazepam on saccadic adaptation in humans, thereby implicating the GABAergic system in this fundamental sensorimotor learning mechanism. Specifically, administration of 0.5 mg but not 1 mg lorazepam led to reductions in gain-decrease adaptation. Gain-increase adaptation was generally less pronounced and remained unaffected by the drug. Furthermore, we replicated the well-established finding of reduced peak velocity following the administration of lorazepam, even at a low dose of 0.5 mg. Adverse effects of lorazepam affected most saccadic parameters. Future studies may employ other motor learning tasks as well as neuroimaging techniques to extend the knowledge of sex-dependent effects of lorazepam and their neurofunctional mechanisms. Although we did not observe significant drug×sex interactions, our study makes an important contribution to the field by addressing the major issue of a paucity of sex-based analyses in biomedical research (Beery and Zucker, 2011; Woitowich et al., 2020).

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Supplemental material

Supplemental material for this article is available online.

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