Original Paper

GABAergic modulation of performance in response inhibition and interference control tasks

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Abstract

Background: Inhibitory control is a crucial executive function with high relevance to mental and physical well-being. However, there are still unanswered questions regarding its neural mechanisms, including the role of the major inhibitory neurotransmitter, γ-aminobutyric acid (GABA).
Aims: This study examined the effects of lorazepam (0.5 mg and 1 mg), a positive allosteric modulator at the $GABA_A$ receptor, on response inhibition and interference control. We also explored the heterogeneity of inhibitory control and calculated delta plots to explore whether lorazepam affects the gradual build-up of inhibition and activation over time.
Methods: $N=50$ healthy participants performed antisaccade, Eriksen flanker and Simon tasks in a within-subjects, placebo-controlled, double-blind randomized design.
Results: Lorazepam increased reaction time (RT) and error rates dose dependently in all tasks ($p \leqslant 0.005$). In the antisaccade and Simon tasks, lorazepam increased congruency effects for error rate ($p \leqslant 0.029$) but not RT ($p \geqslant 0.587$). In the Eriksen flanker task, both congruency effects were increased by the drug ($p \leqslant 0.031$). Delta plots did not reflect drug-induced changes in inhibition and activation over time. Delta plots for RT in the Simon task were negative-going, as expected, whereas those for the antisaccade and flanker tasks were positive-going.
Conclusions: This study provides evidence for GABAergic involvement in performance on response inhibition and interference control tasks. Furthermore, our findings highlight the diversity of the broader construct of inhibitory control while also pointing out similarities between different inhibitory control tasks. In contrast to RT and error rates, the cognitive processes indexed by delta plots may not be sensitive to GABAergic modulation.

Keywords

Lorazepam, benzodiazepine, response inhibition, interference control, delta functions

Introduction

Inhibitory control, a major dimension of cognitive control, plays an important role in goal-directed behavior. Countless situations require the inhibition of inappropriate reactions, thoughts, impulses, or feelings, and inhibitory impairments that are observed in various neuropsychiatric patient populations (Chamberlain et al., 2006; Ettinger et al., 2018a; Schachar et al., 1993). Inhibitory control is a heterogeneous construct (Aron, 2007; Harnishfeger, 1995) and comprises the ability to suppress the execution of inappropriate responses, termed response inhibition (Friedman and Miyake, 2004), and the capacity to reduce the processing of task-irrelevant stimuli or stimulus features, termed interference control (Friedman and Miyake, 2004).

For this study, we selected three frequently implemented paradigms. The antisaccade task, a measure of response inhibition, requires the inhibition of a prepotent saccade toward a sudden-onset stimulus and the generation, instead, of a saccade in opposite direction (Hutton and Ettinger, 2006). Theoretical models (Aponte et al., 2017; Noorani and Carpenter, 2016) differ with regard to the underlying cognitive processes; some assume a distinct stop unit, whereas others propose that automatic prosaccades and voluntary antisaccades are programmed in parallel, and the inhibition is achieved when the voluntary response is programmed fast enough (Hutton, 2008; Massen, 2004). The Eriksen flanker task requires a reaction to a central stimulus while ignoring peripheral distractors. This task is not only a measure of resistance to distractor interference but also places demands on selective attention (Eriksen and Eriksen, 1974; Friedman and Miyake, 2004; LaBerge et al., 1991). It has been employed in tests of the variable zoom lens theory of attention, where a broader attentional focus is linked to greater difficulty in ignoring the distractors. The Simon task induces conflict between stimulus location and response location in incongruent trials (Hommel, 2011). This task has also been interpreted as a measure of interference control (Proctor, 2011; Simon and Small, 1969).

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Inhibitory control in these tasks is commonly measured as the difference in mean reaction time (RT) or error rate (percent incorrect) between incongruent and congruent trials called congruency effect. Larger congruency effects indicate weaker inhibitory control.

On a neural level, inhibitory control is associated with prefrontal, frontoparietal, and subcortical activation (Aron and Poldrack, 2006; Friedman and Miyake, 2017). Underlying neurotransmitter systems include dopamine, noradrenalin, and acetylcholine (Bari and Robbins, 2013; Ettinger and Kumari, 2019). The role of inhibitory neurotransmitters, however, is less well characterized.

GABA is the primary inhibitory neurotransmitter (Uusi-Oukari and Korpi, 2010). Approximately 10%–40% of cerebral cortex is innervated by GABAergic neurons, which are also widespread in subcortical regions (Fonnum, 1987; Rubenstein and Merzenich, 2003; Uusi-Oukari and Korpi, 2010). There are two classes of GABA receptors, $GABA_A$ and $GABA_B$ (Owens and Kriegstein, 2002). GABAergic influences on human cognition are frequently studied via administration of benzodiazepines. Benzodiazepines are positive allosteric modulators of $GABA_A$ receptors, thus enhancing the agonist's effect (Uusi-Oukari and Korpi, 2010) and decreasing the neuron's excitability. Clinically, benzodiazepines have anxiolytic, arousal-reducing, sleep-promoting, muscle relaxing, and anticonvulsive effects. Negative effects, include sedation, mental slowing, and drowsiness (Baldwin et al., 2013).

In line with these properties, benzodiazepines adversely affect basic sensorimotor functions, including increased RT, reduced saccadic peak velocity, and increased saccadic latency (Ettinger et al., 2018b; Haas et al., 2007; Masson et al., 2000; Visser et al., 2003). Effects on attention include impaired vigilance, choice RT, visual information processing, and encoding mechanisms (Duka et al., 1995; Giersch and Herzog, 2004; Jalava et al., 1995; Wesnes et al., 1997). Furthermore, benzodiazepines may decrease the ability to differentiate between distractor and target (Michael et al., 2007) and impair attentional switching (Post et al., 1997). Effects on attentional processes are relevant in the context of inhibitory control, given the close link between inhibition and attention (Barkley, 1997; Moorselaar and Slagter, 2020; Verbruggen et al., 2008).

However, only little is known about benzodiazepine influences on performance in inhibitory control paradigms. Previous studies have consistently shown increased RT and error rates for both inhibitory and non-inhibitory conditions. Antisaccade latencies and directional error rates are increased by lorazepam, but prosaccade latencies may also be increased (Chen et al., 2015; Ettinger et al., 2018b; Green and King, 1998; Green et al., 2000; Haas et al., 2009; Masson et al., 2000; McCartan et al., 2001). However, specific effects on inhibitory performance, that is, interactions between task (prosaccade vs. antisaccade) and drug conditions, or benzodiazepine effects on the congruency effect, have not been reported.

Regarding flanker tasks, it has been shown that benzodiazepines increase both congruent and incongruent RT dose dependently (Bruijn et al., 2004; Clariá et al., 2011; Riba et al., 2005). Error rates were not affected by lorazepam (Bruijn et al., 2004) or alprazolam (Riba et al., 2005), but alprazolam increased error rates depending on dose (Clariá et al., 2011). However, sample sizes were small ($N \leqslant 12$) and again, benzodiazepine effects on specific measures of inhibitory control were either nonsignificant (Bruijn et al., 2004; Riba et al., 2005) or not reported (Clariá et al., 2011).

To our knowledge, effects of benzodiazepines on Simon task performance have not yet been studied.

Regarding the widely used stop signal and go/no-go response inhibition tasks, some studies failed to observe significant drug effects on stop or go processes (Reynolds et al., 2004; Shadli et al., 2016). Others showed inhibition to stop-signals and estimated time to inhibit the reaction to be impaired under triazolam (Fillmore et al., 2001).

Altogether, these findings do not allow drawing clear conclusions about the impact of benzodiazepines on inhibitory control.

In addition to studying RT and error rates, GABAergic effects on cognitive processes may also be studied by considering how congruency effects change as a function of RT. This approach, called distributional analysis, may reveal distinct patterns not reflected in simple comparisons of RT between congruent and incongruent trials across the entire task (Burle et al., 2005; Pratte et al., 2010). A common tool in distributional analysis is the delta plot, in which trials are binned in quantiles and congruency effects for RT or error rate are plotted against the RT of each quantile.

Applying this approach, Ridderinkhof (2002) proposed a dual-process model, including direct activation and selective inhibition processes. In this model, the build-up of selective inhibition is reflected in delta plots for RT: efficient inhibition leads to a reduction of congruency effects, thus decreasing the delta plot for slower segments. Direct activation is expressed in plots for accuracy (percent correct): stronger direct activation produces a greater congruency effect for faster segments. A common finding is a pattern of negative-going delta plots for RT in the Simon task, where congruency effects at higher RT approach zero or become negative, compared to positive-going delta plots for the Eriksen flanker task, where congruency effects for accuracies grow with increasing RT (Wildenberg et al., 2010b). These patterns may be due to differences in onset and strength of active suppression (Burle et al., 2005; Pratte et al., 2010; Ulrich et al., 2015). Delta plots for the antisaccade task have not been characterized in detail. Including distributional analysis in our study may thus allow characterizing lorazepam effects on specific processes underlying inhibitory control.

Therefore, we comprehensively assessed benzodiazepine effects on response inhibition and interference control task performance using antisaccade, Eriksen flanker, and Simon tasks. Previous studies typically did not use more than one task, thereby failing to provide a systematic characterization of GABAergic effects on inhibitory control. This is an important omission given the heterogeneity of inhibitory control (Aichert et al., 2012; Stahl et al., 2014). Accordingly, we investigated the specificity and generality of lorazepam effects on inhibitory control via systematic investigation of drug effects in congruent and incongruent conditions across tasks. An additional weakness of previous studies is that they often used small ($N < 20$) samples and single drug doses (Visser et al., 2003), thereby suffering from low power and failing to provide estimates of dose–response relations. Therefore, we applied multiple doses (placebo, 0.5 mg lorazepam and 1 mg lorazepam) to a large sample ($N = 50$) in a within-subject design.

We hypothesized increased RT and error rates as a function of dose for all tasks. We also expected incongruent trials to be slower and more error-prone than congruent trials. Due to heterogeneous and insufficient previous studies, analyses concerning

interactions between congruency and drug are labelled exploratory. Nevertheless, since benzodiazepines impair various features of information processing, it is reasonable to assume that inhibitory control is also negatively affected. To further explore the heterogeneity of inhibitory control, we studied correlations between drug-induced changes in congruency effects between tasks. We hypothesized delta plots for response speed to be positive-going for the Eriksen flanker task and negative-going for the Simon task. Analyses of delta plots from the antisaccade task as well as drug effects on delta plots across tasks are exploratory. Finally, we included measures of subjective states, which we expected to reflect lorazepam-induced sedating effects.

Method

Sample

Healthy participants aged 18–35 years were recruited via ads placed around the university campus and online. We aimed for $N=50$ participants to achieve enough power to detect small effects, which may be expected in the lower dose range of lorazepam applied here. We had approximately 99% power to detect an effect of $\eta_p^2=0.10$ ($\alpha=0.05$). Before admission to the study, potential participants were screened for the following exclusion criteria: any current or history of psychiatric, neurological, or physical disorder; any current medication intake (except contraceptives or thyroid medicines); hypertension (blood pressure >140/90) or hypotension (blood pressure <100/60); body mass index (BMI) <18 or >30; current or recent (within last 12 months) consumption of any drugs including nicotine; former intake of any benzodiazepines; and, for women, a positive pregnancy test. Further requirements were that participants had normal or corrected sight, were right-handed and non-smokers. Participants provided written informed consent and were compensated with 90 € or course credits. The study was approved by the ethics committee of the Faculty of Medicine at the University of Bonn (Lfd. Nr. 292/17).

Design and procedure

The design was within-subject, double-blind, and placebo-controlled with counterbalanced order of drug conditions (Latin square design). Participants took part in a screening session and three assessment sessions.

In the screening session, exclusion criteria were checked in a detailed interview and weight, height, and blood pressure were measured. Assessment sessions took place in three subsequent weeks, with day of the week and time of assessment kept the same for each participant as closely as possible (difference between days: mean = 7.12, SD = 0.92, maximum = 14; difference between starting times in minutes: mean = 4.34, SD = 19.85, maximum = 180).

At the beginning of each assessment session, participants' well-being was confirmed and female participants performed a urine pregnancy test (Cleartest® Diagnostik HCG, Wesel, Germany). Then, a capsule containing either placebo (mannitol), 0.5 mg or 1 mg lorazepam (Tavor™, Pfizer, Berlin, Germany) was administered with a glass of still water. After a waiting period of 120 min (Kyriakopoulos et al., 1978), participants completed psychomotor tasks lasting approximately 35 min (not reported here). Subsequently, participants performed the antisaccade, Eriksen flanker, and Simon tasks. Task order was randomized between participants but kept constant for each participant across assessment sessions. After finishing the tasks, participants completed 10 computerized visual analog scale (VAS) (Costa et al., 2013) and the computerized NASA task load index (NASA-TLX) (Hart and Staveland, 1988).

Finally, at the end of each assessment session, participants were asked to guess whether they had received placebo, 0.5 mg lorazepam or 1 mg lorazepam.

Inhibitory control tasks

The antisaccade task (Supplemental Figure S1) was written using the SR Research ExperimentBuilder software (SR Research Ltd., Ottawa, ON, Canada). A chinrest was used to minimize head movements. Each trial started with a central fixation stimulus for 1000–2000 ms (random duration) in either yellow (225, 225, 0) or blue (0, 150, 255). The fixation stimulus was a circle of approximately 0.34° in diameter and stroke width of 0.12°. Subsequent to the fixation stimulus, the peripheral stimulus, a white circle of the same dimensions, was shown for 1000 ms randomly on the left or right side of the screen at 10.32° amplitude from the center. Depending on the color of the central fixation stimulus, participants were instructed to look at the peripheral stimulus (prosaccade) or directly to the exact opposite position of the stimulus (antisaccade). Color-instruction mapping was counterbalanced across participants, but kept the same within each participant. A desktop-mounted video-based, combined pupil and corneal reflection tracker (EyeLink 1000, SR Research Ltd.) registered movements of the right eye at a sampling rate of 1000 Hz. Saccade detection was based on criteria of minimum amplitude (1°), and starting point (±100 pixels horizontally from central stimulus position). Trials in which no saccade could be detected, as well as responses with latencies to stimulus onset of <80 ms or >1000 ms, were counted as invalid and excluded.

The Eriksen flanker task (Supplemental Figure S2) was written in Presentation (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, USA). In each trial, five white (255, 255, 255) arrows (total horizontal size approximately 16.66°, vertical size approximately 3.44°) appeared in the center of the screen. Participants were instructed to respond to the middle arrow, which pointed to the right ">" or to the left "<," by pressing the "," or "X" key, respectively, on a QWERTZ keyboard. The two flankers on each side were either congruent (e.g., "<<<<<") or incongruent (e.g., "<<><<"). Each trial started with a central fixation cross shown for 500 ms. Then the arrows were presented for 1000 ms followed by a black screen interstimulus interval of 1000 ms. Trials in which no response could be recorded as well as responses with RT of <150 ms or >1200 ms were counted as invalid and excluded.

The Simon task (Supplemental Figure S3) also was written in Presentation (Neurobehavioral Systems, Inc.). The target consisted of a green (0, 255, 150) or blue (0, 150, 255) point of approximately 3.03° in diameter appearing on the right or left side of the screen at 8.99° amplitude from the center. Each color was assigned to either the "," or "X" keys on a QWERTZ keyboard. Color-instruction mapping was counterbalanced across participants, but kept the same across assessments within each participant. Participants were instructed to press the key corresponding

to the color, regardless of target position. In congruent trials, the assigned key was on the same side of the keyboard as the target position (e.g., target on the left and key located on the left side); in incongruent trials, the assigned key was on the opposite side of the stimulus (e.g., target on the right and key located on the left side). Each trial started with a central fixation cross shown for 500 ms. Then the stimulus was presented for 1500 ms. Trials, in which no response could be recorded as well as responses with RT of $<$150 ms or $>$1200 ms, were counted as invalid and excluded.

All tasks were presented on a 22-inch LCD monitor (ViewSonic Corp., Brea, CA, USA; height: 29.5 cm; width: 47.5 cm; resolution: 1680 $\times$ 1050 pixels; 60 Hz refresh rate) at a distance of 70 cm from participants' eyes. Stimuli were presented on a black (0, 0, 0) screen and each task consisted of 100 congruent/prosaccade and 100 incongruent/antisaccade trials, presented in randomized order. Eye movement data analysis as well as data preprocessing in all tasks was conducted using the MATLAB 2017b (The MathWorks, Natick, MA, USA).

Dependent variables in the antisaccade task were mean latency of directionally correct saccades (ms) and directional error rate (% incorrect, valid reactions) for antisaccade and prosaccade conditions. Congruency effects for latency and error rate were computed as the difference between antisaccade and prosaccade conditions. Dependent variables in the Eriksen flanker and Simon tasks were RT of correct trials (ms) and error rate (% incorrect, valid reactions) for congruent and incongruent conditions. Congruency effects for RT and error rate were computed as the difference between incongruent and congruent conditions.

Rating scales measuring subjective effects

VAS consisted of 10 continuous horizontal scales with the anchors *not at all* and *very*. A marker could be moved by mouse click to indicate the extent of agreement with each item. Items were "anxious," "attentive," "restless," "tired," "carefree," "my thoughts are racing," "I have self-control," "elevated mood," "energetic," and "irritable" (Supplemental Table S1; Costa et al., 2013). Items were scored from 0 to 100, with higher scores representing stronger expressions of the relevant statement.

The NASA-TLX was used to measure subjective workload (Hart and Staveland, 1988). It consisted of computerized, continuous rating scales that ranged from "very low" to "very high" and related to the expressions "mental demand," "physical demand," "temporal demand," "overall performance," "effort," and "frustration level" (in German language, Supplemental Table S2). Items were scored from 0 to 100, with higher scores representing stronger endorsements of the item. Ratings from NASA-TLX were combined to an overall task load score (Bustamante and Spain, 2008).

Statistical analysis

Statistical analyses were carried out in (R Core Team, 2019), using the packages *ez* (Lawrence, 2016), *e1071* (Meyer et al., 2019), *lsr* (Navarro, 2015), and *pastecs* (Grosjean et al., 2018). Participants were excluded from all variables in a particular task if they failed to follow task instructions in at least one assessment session, indicated by $>$80% error rates or $>$50% missing trials. In the antisaccade task, one participant who produced more than 80% invalid trials in congruent and incongruent conditions (e.g., eyeblinks or artifact) was excluded. In the Eriksen flanker task, two participants with high error rates in the incongruent condition were excluded. In the Simon task, three participants were excluded due to high error rates in congruent and incongruent conditions and one due to a large number of missing trials in both conditions.

Dependent variables from each task were analyzed separately using analysis of variance (ANOVA). For each task and each dependent variable (RT and error rate), the ANOVA comprised the within-subjects factors drug (placebo, 0.5 mg and 1 mg) and task condition (congruent and incongruent for Eriksen flanker and Simon, prosaccades and antisaccades for the antisaccade task). To investigate whether effects of lorazepam on inhibitory processes differ across tasks, we carried out two further ANOVAs with congruency effects for RT and error rate as dependent variables. The ANOVA comprised the within-subject factors drug (placebo, 0.5 mg and 1 mg) and task (antisaccade, Eriksen flanker, and Simon task).

Partial eta-square including its 95% confidence interval (CI) was used for calculating effect sizes of ANOVAs (Cohen, 1973). We used post hoc *t*-tests (Bonferroni-corrected *p*-values) to clarify ANOVA results with Cohen's *d* (Cohen, 1988) as measure of effect size. The Mauchly's test of sphericity was performed for each variable and if the condition of sphericity was violated, the Greenhouse–Geisser procedure was applied. Significance level was set to 5% a priori.

In addition, we examined whether there is a relation between lorazepam-induced deficits in inhibitory control across different tasks. Therefore, change scores were calculated reflecting the difference in the congruency effect (RT and error rate) between placebo and 1 mg lorazepam, the dose at which strongest effects are expected. The Pearson correlations (Bonferroni-corrected) tested for associations between drug-induced changes in congruency effects between different tasks.

Delta plots were constructed following Ridderinkhof et al. (2005). First, individual RT of correct and incorrect responses from all participants were rank ordered separately for congruent and incongruent trials. Next, RT was split into five equal-sized parts (quintiles), and RT and error rate were determined for each quintile. Delta plots were then constructed, plotting the congruency effect for RT or accuracy as a function of RT per quintile (including both congruent and incongruent trials). A comparison between different shapes of delta plots across drug conditions was provided by analyzing the slopes that result when data points between two quintiles are connected. In order to analyze delta plots for RT, ANOVAs were conducted comparing slopes between quintiles 1 and 2, quintiles 2 and 3, quintiles 3 and 4, and quintiles 4 and 5. For error rate, only segments 1 and 2 were analyzed, as direct activation processes are only expected to be seen in the first segments (Ridderinkhof, 2002). All delta plot ANOVAs included the within-subjects factor drug (placebo, 0.5 mg and 1 mg).

VAS and NASA-TLX were analyzed using ANOVA with the within-subject factor drug (placebo, 0.5 mg and 1 mg).

Results

Sample description

A sample of N = 50 participants (27 females and 23 males) completed the study. Mean age was 22.4 years (SD = 3.68). Dataset and code are available online (https://osf.io/ts5b9/). Descriptive results are in Table 1.

Table 1. Descriptive statistics of inhibitory control variables.

	Placebo	Lorazepam 0.5 mg	Lorazepam 1 mg
Antisaccades (*N*=49)			
Latency PS	165.41 (17.65)	170.17 (21.25)	174.62 (21.24)
Latency AS	236.33 (33.78)	241.21 (37.94)	243.44 (35.35)
Error rate PS (%)	1.30 (1.45)	1.68 (2.01)	1.81 (2.13)
Error rate AS (%)	24.18 (16.32)	26.14 (15.25)	30.01 (14.38)
Flanker (*N*=48)			
RT congruent	433.77 (49.26)	455.36 (55.68)	473.37 (61.39)
RT incongruent	495.13 (53.73)	523.11 (63.89)	547.13 (70.56)
Error rate congruent (%)	0.61 (0.97)	1.21 (1.41)	1.29 (1.62)
Error rate incongruent (%)	5.56 (4.45)	5.72 (3.78)	7.41 (5.05)
Simon (*N*=46)			
RT congruent	455.50 (56.82)	474.09 (66.70)	493.87 (65.59)
RT incongruent	474.07 (56.99)	494.05 (69.44)	512.17 (68.66)
Error rate congruent (%)	1.84 (1.95)	2.73 (3.53)	2.68 (2.08)
Error rate incongruent (%)	2.95 (3.05)	4.77 (4.18)	5.25 (4.08)

Numbers indicate the mean (standard deviation).
AS: antisaccades; PS: prosaccades; RT: reaction time.

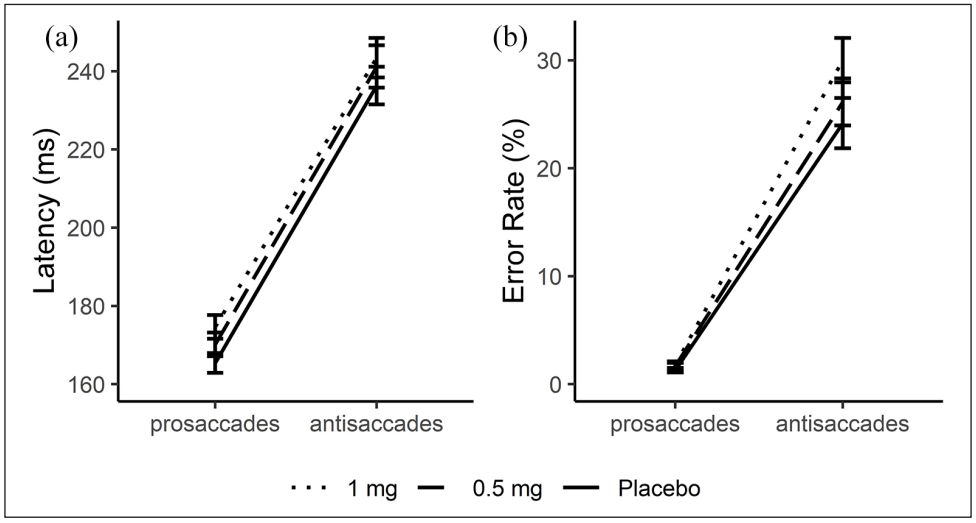

Figure 1. Lorazepam effects on the antisaccade task: (a) effects of lorazepam on prosaccades and antisaccades latency and (b) effects of lorazepam on prosaccades and antisaccades error rate. Error bars indicate the standard error. *N*=49.

Antisaccade task

For latency there were main effects of drug ($F_{(2, 96)}=5.70$, $p=0.005$, $\eta_p^2=0.106$, CI [0.012, 0.219]), indicating longer latencies with increasing drug dose, and task condition ($F_{(1, 48)}=308.40$, $p<0.001$, $\eta_p^2=0.865$, CI [0.785, 0.903]), indicating longer latencies in antisaccades than in prosaccades (Figure 1(a)). The *t*-tests did not reveal significant differences between the three drug conditions (all $p>0.05$) and there was no interaction between drug and task condition ($F_{(2, 96)}=0.54$, $p=0.587$, $\eta_p^2=0.011$, CI [0.0000, 0.068]).

The ANOVA for error rate revealed main effects of drug ($F_{(2, 96)}=6.87$, $p=0.002$, $\eta_p^2=0.125$, CI [0.021, 0.242]), suggesting higher error rate with increasing dose, and task condition ($F_{(1, 48)}=171.22$, $p<0.001$, $\eta_p^2=0.781$, CI [0.657, 0.842]), suggesting fewer errors for prosaccades than for antisaccades (Figure 1(b)). The *t*-tests did not show significant differences between the three drug conditions (all $p>0.05$). In addition, there was an interaction between drug and task condition ($F_{(2, 96)}=6.46$, $p=0.002$, $\eta_p^2=0.119$, CI [0.018, 0.234]). Qualitatively, the interaction suggests that congruency effects increased with increasing drug dose (Figure 1(b)). The *t*-tests revealed that participants made fewer errors in prosaccades than antisaccades at each level of drug (all $p<0.001$). Error rate did not differ significantly between drug conditions in neither of the two task conditions (all $p>0.05$).

Eriksen flanker task

For RT of correct responses, there were main effects of drug ($F_{(2, 94)}=33.95$, $p<0.001$, $\eta_p^2=0.419$, CI [0.262, 0.530]), suggesting higher RT with increasing dose, and task condition

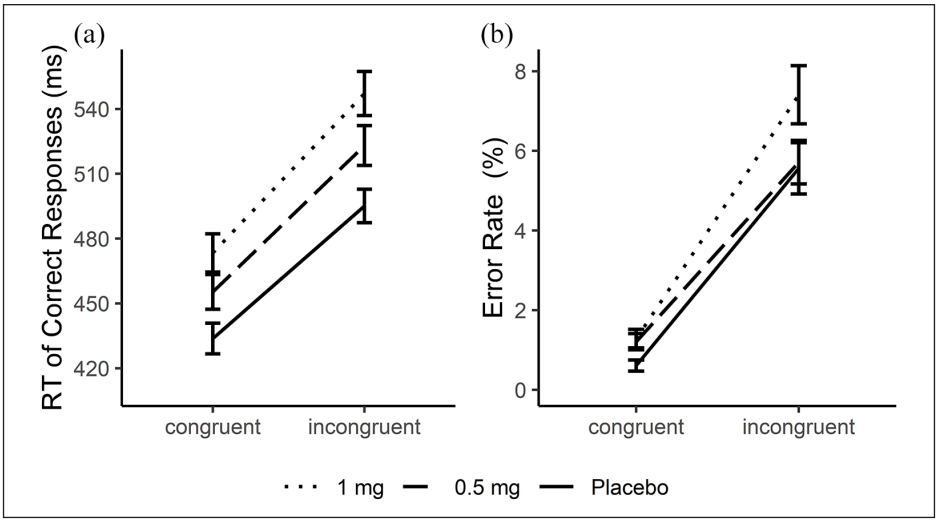

Figure 2. Lorazepam effects on the Eriksen flanker task: (a) effects of lorazepam on congruent and incongruent reaction time (RT) of correct trials and (b) effects of lorazepam on congruent and incongruent error rate. Error bars indicate the standard error. $N=48$.

($F_{(1, 47)}=923.69$, $p<0.001$, $\eta_p^2=0.952$, CI [0.921, 0.965]), indicating higher RTs for the incongruent than the congruent condition (Figure 2(a)). The *t*-tests showed that RT was shorter in the placebo condition compared to 0.5 mg lorazepam ($p=0.037$, $d=0.723$) and compared to 1 mg lorazepam ($p<0.001$, $d=1.028$). RT under 0.5 mg and 1 mg lorazepam was not significantly different ($p=0.102$, $d=0.504$). In addition, there was an interaction between drug and task condition ($F_{(2, 94)}=6.36$, $p=0.003$, $\eta_p^2=0.119$, CI [0.017, 0.236]). Qualitatively, the interaction suggests that congruency effects increased with increasing drug dose (Figure 2(a)). The *t*-tests revealed that RTs were higher in the incongruent than the congruent condition at each level of drug (all $p<0.001$). In the congruent condition, RTs under placebo were significantly shorter than under 1 mg lorazepam ($p=0.011$, $d=1.022$), an effect that was more pronounced in the incongruent condition ($p<0.001$, $d=1.054$). Comparing 0.5 mg lorazepam with placebo or 1 mg lorazepam, RT did not differ significantly in neither of the two task conditions (all $p>0.05$).

The ANOVA for error rate found main effects of drug ($F_{(2, 94)}=6.96$, $p=0.002$, $\eta_p^2=0.129$, CI [0.022, 0.247]), indicating higher error rates with increasing dose, and task condition ($F_{(1, 47)}=108.21$, $p<0.001$, $\eta_p^2=0.697$, CI [0.535, 0.782]), indicating higher error rates in the incongruent than the congruent condition (Figure 2(b)). The *t*-tests did not show significant differences between drug conditions (all $p>0.05$). In addition, there was an interaction between drug and task condition ($F_{(2, 94)}=3.86$, $p=0.031$, $\eta_p^2=0.076$, CI [0.0000, 0.181], $\varepsilon=0.84$). Qualitatively, the interaction suggests that congruency effects increased with increasing drug dose (Figure 2(b)). The *t*-tests revealed that participants made more errors in the incongruent compared to the congruent condition at each level of drug (all $p<0.001$). Error rates did not differ significantly between placebo, 0.5 mg or 1 mg lorazepam in neither of the two task conditions (all $p>0.05$).

Simon task

For RT of correct responses, there were main effects of task condition ($F_{(1, 45)}=56.73$, $p<0.001$, $\eta_p^2=0.558$, CI [0.348, 0.680]), indicating higher RTs for the incongruent condition than the congruent condition, and drug ($F_{(2, 90)}=24.16$, $p<0.001$, $\eta_p^2=0.349$, CI [0.188, 0.470]), indicating increasing RT with increasing drug dose. The *t*-tests revealed that RT was lower in the placebo condition compared to 1 mg lorazepam ($p<0.001$, $d=0.999$). For the other comparisons, there were no significant differences (all $p>0.05$) (Figure 3(a)). There was no significant interaction between drug and task condition ($F_{(2, 90)}=0.16$, $p=0.853$, $\eta_p^2=0.004$, CI [0.0000, 0.040]).

The ANOVA for error rate revealed main effects of drug ($F_{(2, 90)}=8.44$, $p<0.001$, $\eta_p^2=0.158$, CI [0.036, 0.282]), suggesting higher error rates with increasing drug dose, and task condition ($F_{(1, 45)}=24.18$, $p<0.001$, $\eta_p^2=0.350$, CI [0.133, 0.518]), suggesting more errors for the incongruent than the congruent condition (Figure 3(b)). The *t*-tests showed significant differences between placebo and 0.5 mg lorazepam ($p=0.022$, $d=0.384$) as well as placebo and 1 mg lorazepam ($p=0.006$, $d=0.497$). Error rate did not differ between 0.5 and 1 mg lorazepam ($p>0.05$). In addition, there was an interaction between drug and task condition ($F_{(2, 90)}=3.67$, $p=0.029$, $\eta_p^2=0.075$, CI [0.0000, 0.183]). Qualitatively, the interaction suggests that congruency effects increased with increasing drug dose (Figure 3(b)). The *t*-tests revealed that participants made fewer errors in the congruent compared to the incongruent condition under 0.5 mg ($p=0.027$, $d=0.554$) and under 1 mg lorazepam ($p=0.002$, $d=0.801$) but not under placebo ($p=0.937$, $d=0.340$). In the congruent condition, error rate did not differ significantly between placebo, 0.5 mg or 1 mg lorazepam (all $p>0.05$), whereas in the incongruent condition error rate was significantly higher under 1 mg lorazepam compared to placebo ($p=0.008$, $d=0.632$). Comparing 0.5 mg with placebo or 1 mg lorazepam, RT did not differ significantly in neither of the two task conditions (all $p>0.05$).

Lorazepam effects across tasks

Analyses of the congruency effect for RT/latency across tasks and drug revealed a main effect of task ($F_{(2, 84)}=107.90$, $p<0.001$, $\eta_p^2=0.720$, CI [0.610, 0.781]). The congruency effect for RT

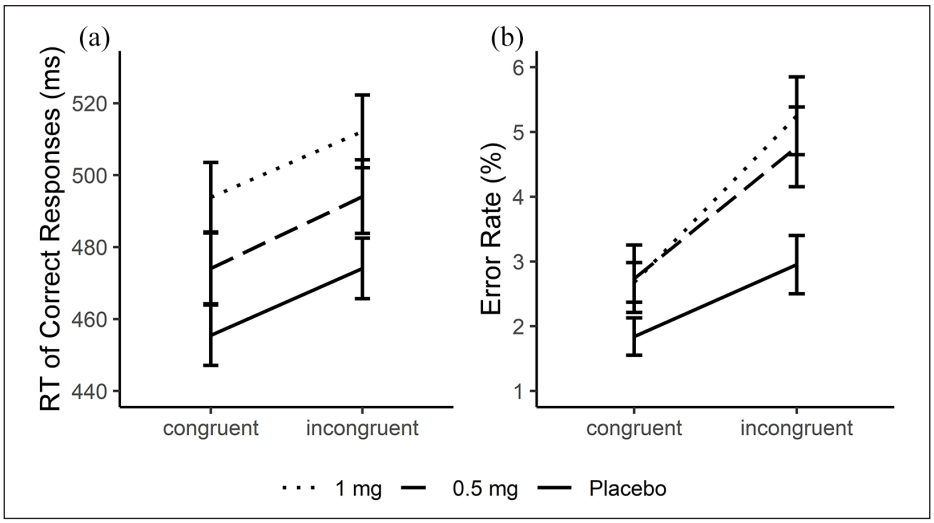

Figure 3. Lorazepam effects on the Simon task: (a) effects of lorazepam on congruent and incongruent reaction time (RT) of correct trials and (b) effects of lorazepam on congruent and incongruent error rate. Error bars indicate the standard error. $N=46$.

differed significantly between the Simon and Eriksen flanker tasks ($p<0.001$, $d=1.774$), between the Simon and antisaccade tasks ($p<0.001$, $d=1.646$) but not between the Eriksen flanker and antisaccade tasks ($p=0.614$, $d=0.121$) (Figure 4(a)). There was no main effect of drug ($F_{(2, 84)}=0.41$, $p=0.664$, $\eta_p^2=0.010$, CI [0.0000, 0.068]), but there was an interaction between drug and task ($F_{(4, 168)}=2.55$, $p=0.041$, $\eta_p^2=0.057$, CI [0.0000, 0.117]). Qualitatively, the interaction suggests that the congruency effect increased with increasing drug dose only in the Eriksen flanker task (Figure 4(a)). The *t*-tests revealed smaller congruency effects for all drug conditions in the Simon task compared to the Eriksen flanker (all $p<0.001$) and antisaccade tasks (all $p<0.001$). Congruency effects did not differ between the Eriksen flanker and antisaccade tasks for any drug condition (all $p>0.05$). In addition, within each task, *t*-tests did not reveal significant differences in the congruency effect for RT between the three drug conditions (all $p>0.05$).

Analyses of the congruency effect for error rate across tasks and drug revealed a main effect of task ($F_{(2, 84)}=110.82$, $p<0.001$, $\eta_p^2=0.725$, CI [0.617, 0.785], $\varepsilon=0.57$), due to greater congruency effects in the antisaccade task compared to the Eriksen flanker ($p<0.001$, $d=1.351$) and Simon tasks ($p<0.001$, $d=1.590$) (Figure 4(b)). Also, the congruency effect for error rate was significantly smaller for the Simon task compared to the Eriksen flanker task ($p=0.033$, $d=0.572$). There was a main effect of drug ($F_{(2, 84)}=10.64$, $p<0.001$, $\eta_p^2=0.202$, CI [0.060, 0.333]), which qualitatively suggests increasing error rates with increasing drug dose, but the *t*-tests did not reveal significant differences between the three drug conditions (all $p>0.05$). In addition, there was an interaction between drug and task ($F_{(4, 168)}=3.46$, $p=0.020$, $\eta_p^2=0.076$, CI [0.005, 0.144], $\varepsilon=0.67$). Qualitatively, the interaction suggests that the drug-induced increase of the congruency effect is more pronounced in the antisaccade task than the other tasks (Figure 4(b)). The *t*-tests revealed stronger congruency effects for all drug conditions in the antisaccade task compared to the Eriksen flanker task (all $p<0.001$) and the Simon task (all $p<0.001$). Congruency effects did not differ between Eriksen flanker and Simon tasks for any drug condition (all $p>0.05$). Also, within each task, *t*-tests did not reveal significant differences in the congruency effect for error rate between the three drug conditions (all $p>0.05$).

Change score correlations

Change scores between performance under placebo and 1 mg lorazepam for congruency (error rate) were significantly correlated between the antisaccade and Simon tasks ($r=0.407$, $p=0.020$). Other correlations were not significant ($p>0.05$).

Delta plots

For delta plots for RT, there was no significant drug effect for any segment in any of the tasks (all $p>0.05$). Also, delta plots for accuracy in the earliest segment were not significantly influenced by drug in any of the tasks (all $p>0.05$).

Visual inspection shows that delta plots for RT were positive-going for the antisaccade and Eriksen flanker tasks and negative-going for the Simon task (Figure 5). For the Simon task, negative-going delta functions extend even below zero; thus, congruency effects are reversed for higher quintiles.

Subjective effects

Results for subjective measures are in Table 2. For VAS, there were main effects of drug for "attentive" ($F_{(2, 98)}=7.82$, $p<0.001$, $\eta_p^2=0.138$, CI [0.028, 0.255]), "tired" ($F_{(2, 98)}=5.81$, $p=0.004$, $\eta_p^2=0.106$, CI [0.012, 0.218]) and "I have self-control" ($F_{(2, 98)}=9.20$, $p<0.001$, $\eta_p^2=0.158$, CI [0.040, 0.278]), indicating participants were less attentive ($p=0.003$, $d=0.534$), more tired ($p=0.008$, $d=0.441$) and less self-controlled ($p=0.003$, $d=0.602$) under 1 mg lorazepam compared to placebo. The *t*-tests did not show significant differences between 0.5 mg lorazepam and placebo or 1 mg lorazepam (all $p>0.05$). There were no main effects of drug for any other variables (all $p>0.05$).

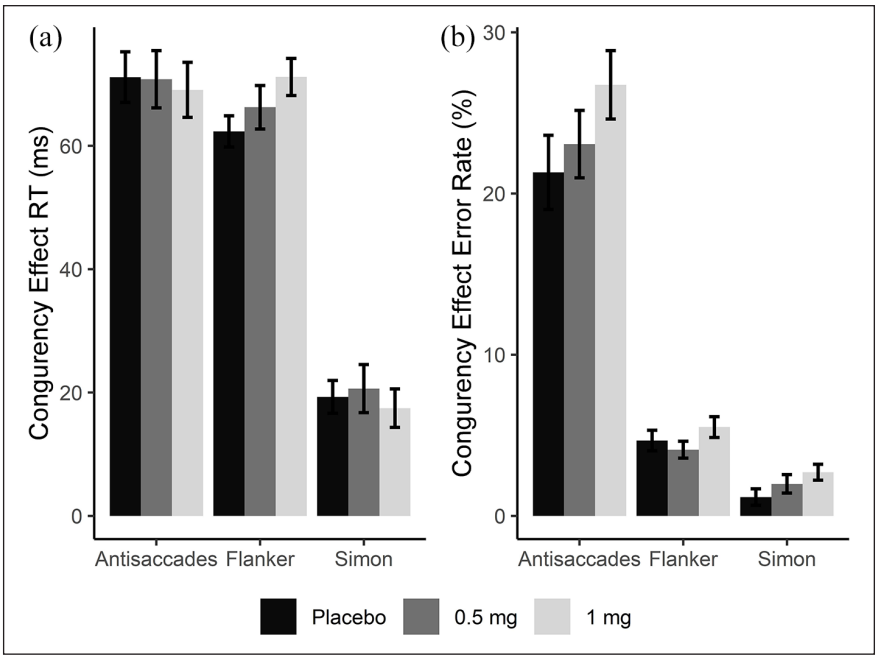

Figure 4. Lorazepam effects on congruency effects in antisaccade task, Eriksen flanker task and Simon task: (a) effects of lorazepam on congruency for reaction time (RT) of correct trials (latency, respectively) and (b) effects of lorazepam on congruency for error rate. Error bars indicate the standard error.

For NASA-TLX, there was no main effect of drug for the overall task load score ($p > 0.05$).

At assessment session 1 and 3, participants could not reliably guess whether they had received placebo, 0.5 mg lorazepam or 1 mg lorazepam (both $p > 0.05$). At assessment session 2, the proportion of participants guessing correctly the drug they had received was significantly above chance level ($p = 0.019$).

Discussion

The key finding is that the benzodiazepine lorazepam reduced performance in all tasks and across task conditions. With regard to inhibitory control measures, however, the drug did not affect performance indices in the same manner across tasks. While lorazepam increased congruency effects in RT and error rate for the Eriksen flanker task, for the antisaccade and Simon tasks the drug increased the congruency effect for error rate but not RT. These differential effects are in agreement with the previously demonstrated heterogeneity of the concept of inhibition (Friedman and Miyake, 2004; Rey-Mermet et al., 2018; Stahl et al., 2014). Generally, it should be noted that main effects of drug were larger than interactions of drug and task condition.

Antisaccade task

In line with previous research, we find negative effects of lorazepam on prosaccade latency (Chen et al., 2015; Ettinger et al., 2018b; Green and King, 1998; Green et al., 2000; Haas et al., 2009; Masson et al., 2000; McCartan et al., 2001) as well as antisaccade latency and error rate (Green and King, 1998; Green et al., 2000; McCartan et al., 2001). The applied doses are lower than those of most previous studies (usually 2 mg). Green et al. (2000) also examined the effect of lorazepam doses below 2 mg on an antisaccade task. Like us, they showed effects to be dose-dependent. Importantly, we also report, for the first time, an interaction between task condition (prosaccade vs. antisaccade) and drug for error rates, but not latencies. This finding, which indicates greater impact of the drug on performance accuracy for antisaccades than prosaccades, might help understanding the precise mechanisms of inhibitory control in this task.

Specifically, there is disagreement in the literature on how to explain successful antisaccade generation (Hutton, 2008). In parallel programming models (Massen, 2004), an erroneous prosaccade is cancelled if the antisaccade response is generated fast enough. Thus, no separate stop or inhibition process is necessary. According to this type of model, comparable increases in both antisaccade and prosaccade latencies should not lead to a selective increase in rate of direction errors in antisaccades compared to prosaccades (Massen, 2004). Thus, our findings of (i) comparable increases in antisaccade and prosaccade latency and (ii) a significantly greater increase in direction errors in the antisaccade than the prosaccade condition question these assumptions. Instead, our findings are in line with the assumption that an additional process may be necessary, as postulated by the LATER (linear approach to threshold with ergodic rate) or SERIA (stochastic, early reaction, inhibition, and late action) models. The Linear approach to threshold with ergodic rate (LATER) model (Noorani and Carpenter, 2013, 2016) involves a go unit for the prosaccade, a go unit for the antisaccade and a stop unit. Transforming the stimulus position to the opposite goal position takes some time and, therefore, the activation of the antisaccade unit is delayed. The stop unit inhibits the erroneous prosaccade. The stochastic early reaction, inhibition, and late action (SERIA)

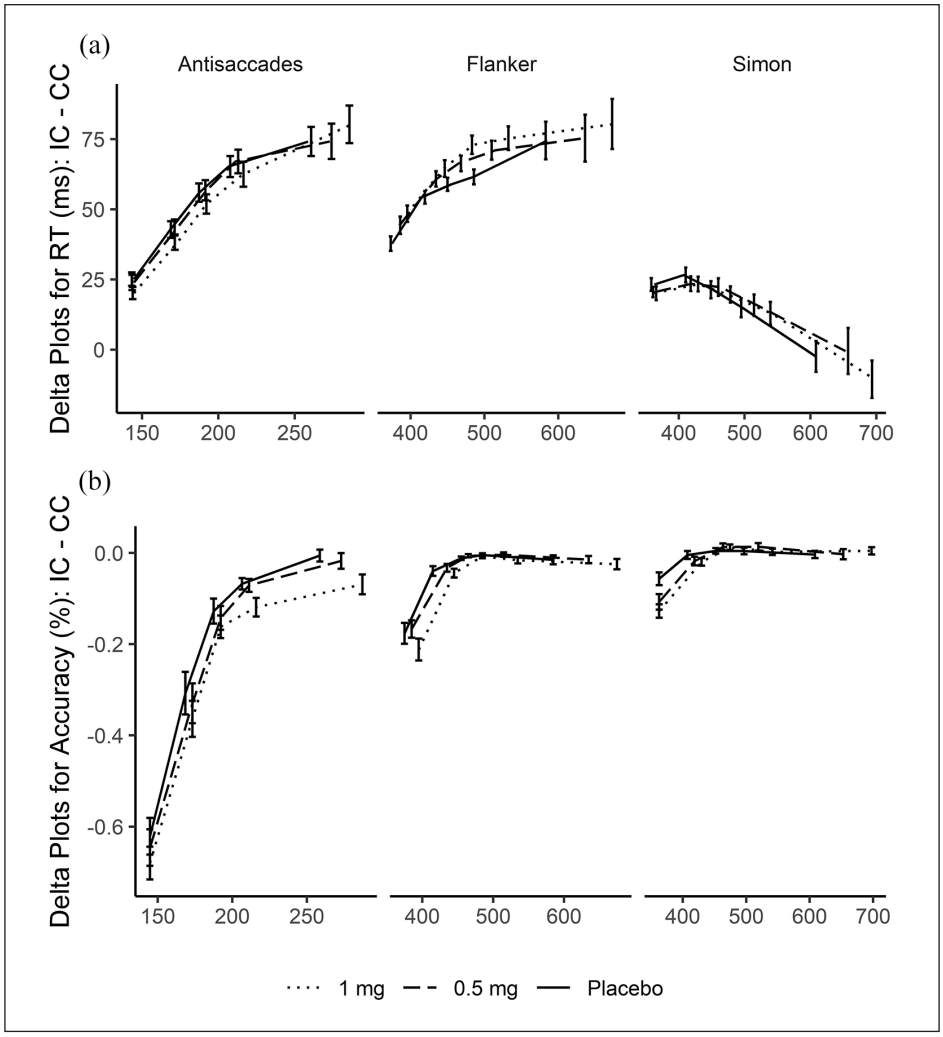

Figure 5. Lorazepam effects in delta plots: (a) delta plots for reaction time (RT) of correct trials (latency, respectively) and (b) delta plots for accuracy (percent correct). In delta plots, congruency effects of each quantile are plotted against the respective RT. Error bars indicate the standard error.
CC: congruent condition; IC: incongruent condition.

Table 2. Descriptive statistics of VAS and NASA-TLX.

	Placebo	Lorazepam 0.5 mg	Lorazepam 1 mg
VAS ($N=50$)			
Anxious	5.78 (9.89)	2.82 (4.18)	3.94 (6.12)
Attentive	49.4 (25.24)	42.12 (26.83)	31.7 (26.76)
Restless	17.98 (22.54)	12.02 (16.97)	18.24 (24.61)
Tired	52.5 (29.6)	57.48 (27.43)	69.7 (27.04)
Carefree	51.36 (33.49)	60.56 (29.52)	56.36 (30.62)
My thoughts are racing	16.88 (20.52)	13.04 (20.18)	11.24 (13.77)
I have self-control	75.7 (22.2)	64.6 (30.38)	57.14 (29.08)
Elevated mood	46.62 (26.44)	42.46 (25.06)	38.84 (27.17)
Energetic	35.92 (25.47)	32.04 (26.17)	28.42 (25.69)
Irritable	11.88 (18.46)	11.06 (18.1)	12.34 (17.35)
NASA-TLX ($N=50$)			
Overall task load	39.41 (15.7)	40.89 (15.56)	42.53 (13.75)

Numbers indicate the mean (standard deviation) for each item in arbitrary units from 1 to 100. Higher numbers indicate stronger agreement on the respective scale.
NASA-TLX: NASA task load index; VAS: visual analog scales.

model (Aponte et al., 2017) extends the LATER model by adding a further process that can account for late pro- and antisaccades. Early errors are explained as a failure of inhibition and late errors as the result of a late race between both saccade types. Regarding our data, both models accommodate the interpretation that lorazepam may have had an impact on a dedicated stop process, while also equally affecting saccade generating units of both antisaccades and prosaccades.

Eriksen flanker task

Benzodiazepine effects on RT and error rates in congruent and incongruent flanker task conditions have been shown previously (Bruijn et al., 2004; Clariá et al., 2011; Riba et al., 2005). We replicate this finding and extend it into a lower dose range. In addition, we find an interaction between task condition and drug, both for RT and error rates, suggesting specifically impaired inhibitory control under lorazepam. In previous studies, these interactions were either not significant (Bruijn et al., 2004; Riba et al., 2005) or not reported (Clariá et al., 2011).

The Eriksen flanker task measures the ability to solve the conflict arising between a central target and peripheral distractors. The task is used not only to measure distractor interference, but also for selective visual attention (Eriksen and Eriksen, 1974; LaBerge et al., 1991). Both processes are closely related, since selective attention is required to identify relevant stimuli and to ignore irrelevant distractors (Moorselaar and Slagter, 2020; Treisman, 1969).

Solving conflicts that arise from interference is thought to involve different stages of processing (Kornblum et al., 1990; Stahl et al., 2014). At the early-stage level of response selection, there are influences of both stimulus-related interference and response interference. In the Eriksen flanker task, those are considered to be particularly important (Stahl et al., 2014). At a later processing stage, the initiated response is stopped (response inhibition). This is thought to be particularly relevant, for example, in the antisaccade task.

Other authors highlight similarities between response inhibition and distractor interference tasks, arguing that both processes are related (Friedman and Miyake, 2004). Possible explanations on the one hand are shared requirements of maintaining a task goal facing distracting stimuli or prepotent but inappropriate response tendencies (Friedman and Miyake, 2004). On the other hand, the Eriksen flanker task may require suppressing incorrect responses in incongruent trials, which might be linked to response inhibition (Ridderinkhof et al., 1999; Verbruggen et al., 2005).

As for the antisaccade and Simon tasks, lorazepam increased the congruency effect for error rate in the Eriksen flanker task, showing that lorazepam impairs the cancellation of incorrect responses. However, there was no correlation between lorazepam-induced changes in the Eriksen flanker effect and antisaccade or Simon tasks. Furthermore, lorazepam significantly increased the congruency effect for RT only in the Eriksen flanker task. This indicates that in the flanker task, processes take place that are distinguishable from other inhibitory control tasks and, furthermore, that these processes have a GABAergic basis. As elaborated above, the task places special demands on stimulus interference and selective visual attention. Lorazepam might impair the ability to focus on relevant details, causing irrelevant features to be processed more strongly (Duka et al., 1995; Giersch and Herzog, 2004; Michael et al., 2007). Drawing upon the zoom lens theory of visual attention (Eriksen and St. James, 1986), lorazepam could either slowdown the adjustment or widen the zoom lens. Our results suggest the latter, since otherwise effects on the delta plots for accuracy would be expected.

Generally, the precise inhibitory or attentional effects of lorazepam in the flanker task remain to be investigated further.

Simon task

In the Simon task, RT and error rate were increased under drug compared to placebo and there was an interaction between task condition and drug for error rate but not RT, similar to the results in the antisaccade task.

The Simon task is suggested to be a measure of interference control (Proctor, 2011; Simon and Small, 1969). The requested response is indicated by the relevant stimulus feature, in this case color. The location of the stimulus is an irrelevant stimulus feature, which causes a conflict between stimulus location and response location in the incongruent condition. Assuming that stimulus and response interference take place during response selection (Kornblum et al., 1990; Stahl et al., 2014), differences between the Eriksen flanker and Simon tasks become apparent. In the Simon task, interference is not caused by distracting stimuli but by the irrelevant stimulus feature location. Therefore, it can be assumed that there is, if any, only little stimulus conflict.

This would make the processes that unfold in the Simon task more similar to those that occur in the antisaccade task: an automatically generated response in one direction must be suppressed. This apparent similarity is also reflected in our results. As in the antisaccade task, lorazepam significantly increased the congruency effect for error rate but not RT. Furthermore, the change in congruency effect for error rate from placebo to 1 mg lorazepam correlated between the two tasks. Lorazepam may, therefore, reduce inhibitory control in both tasks in a similar manner. Previous literature also supports the presence of an active inhibition mechanism in the Simon task. Specifically, Verbruggen et al. (2005) observed an interaction between stopping an initiated response in a stop-signal task and resolving interference control in the Simon task.

Overall, the precise cognitive processes that are affected by lorazepam in the Simon task remain to be investigated further.

Delta plot analysis

It might have been expected that lorazepam effects on inhibitory control would also be reflected in the delta plots, extending previous work of dopaminergic influences (Ridderinkhof, 2002). However, this was not the case. Lorazepam did not significantly alter the slopes for RT or accuracy. This indicates that lorazepam had comparable effects on RT and error rates in early and later segments of the response time distribution. Thus, we conclude that delta plots provide measures of cognitive processes that are not sensitive to GABAergic effects, at least not in these tasks and at the studied doses. Assuming that delta plots for RT reflect the gradual build-up of selective inhibition and delta plots for accuracy reflect direct activation, neither of these processes appears to have been selectively impaired by lorazepam or, otherwise, the model does not seem to represent the processes that are impaired. It is important to note that selective inhibition is not identical

with the broader construct of inhibitory control. However, as there were effects of lorazepam on the suppression of incorrect responses in the incongruent conditions of all tasks, it can be hypothesized that inhibitory control under lorazepam is not built up more slowly, but is simply less effective.

Delta plot analysis also provided evidence of differences in the mechanisms underlying performance on the three inhibitory control tasks in this study. Delta plots for RT were positive in slope for the Eriksen flanker and antisaccade tasks. For the Simon task, delta plots for RT were negatively sloped and for later segments congruency effects were even reversed. According to Ridderinkhof (2002), delta functions extending below zero may indicate the build-up of an active suppression mechanism over time. This suppression is stronger for slow responses and can therefore even lead to an overshoot, reflected in negative congruency effects. Generally, a reason for different shapes in delta plots might be the temporal lag between task relevant and irrelevant activations (Hübner and Töbel, 2019; Jong et al., 1994). As stimulus location in the Simon task is processed faster than the relevant feature (color), the temporal overlap of different activations is smaller than in the Eriksen flanker task where target and distractors are processed similarly fast. Overall, these differences lead to a lower conflict in the Simon task, especially for slow responses.

In accordance with these considerations, the Simon effect was significantly smaller overall than both other congruency effects, for RT and accuracy.

Neural mechanisms

The neural mechanisms that mediate the negative impact of lorazepam on inhibitory control remain unknown and should be further investigated.

In rodents, different subtypes of $GABA_A$ receptors were shown to be responsible for sedative effects, anxiolytic effects, and cognitive functions (Chen et al., 2012; Uusi-Oukari and Korpi, 2010). The use of selective $GABA_A$ agonists in future could further clarify whether the drug-induced impairments in inhibitory control observed here are more likely due to cognitive or sedative effects.

A large cortical network is involved in the neural mechanisms of inhibitory control (Aron and Poldrack, 2006; Friedman and Miyake, 2017) and although GABA receptors are distributed throughout the entire brain (Fonnum, 1987), there are only few studies directly investigating the role of GABA in response inhibition and interference control.

Magnetic resonance spectroscopy (MRS) and transcranial magnetic stimulation (TMS) studies suggest higher GABA concentrations in primary motor cortex (Sohn et al., 2002; Wessel et al., 2013; Wildenberg et al., 2010a), pre-supplementary motor area (Hermans et al., 2018), and basal ganglia (Haag et al., 2015; Quetscher et al., 2014) to be associated with better performance in inhibitory control tasks.

However, TMS manipulations do not provide data on natural GABA release, uptake, and concentration (Sumner et al., 2010) and are, therefore, complementary to our approach of direct GABAergic modulation. Likewise, MRS studies are difficult to reconcile with our findings, given that lorazepam does not selectively affect specific areas. Instead, our results implicate that increased GABA activity in many brain areas may be harmful for successful performance.

An often-studied drug, which is associated with GABA release, is alcohol (Kelm et al., 2011). Besides somewhat comparable phenomenology, alcohol has also been shown to have negative effects on inhibitory control (Day et al., 2015), suggesting that direct comparisons between benzodiazepines and alcohol may be of value in this line of research.

A further lead with regard to the neural mechanisms of these effects comes from the hypothesis that variation in levels of arousal may critically modulate inhibitory control (Hasher et al., 2007). The idea that reduced activity in brain arousal systems may be an explanation of reduced inhibitory control is supported both by studies of time-of-day effects (Hasher et al., 2007) and by our own findings of lorazepam, a drug that has sedative, arousal-reducing effects (Brignell et al., 2007).

Subjective effects

Benzodiazepines are used in the treatment of anxious and agitated states and have pronounced and fast-acting effects in relevant patient groups (Ashton, 1994). An expected finding was that our sample of healthy participants reported they were less attentive and more tired with lorazepam, confirming sedative effects of the drug (Baldwin et al., 2013). In addition, participants described themselves as less in control under lorazepam, a self-report that corroborates our findings from the inhibitory control tasks.

Contrary to the clinical use of lorazepam, however, there were no effects on subjectively perceived anxiety. This may be due to the fact that state anxiety levels in this healthy sample in an affectively rather neutral environment were relatively low overall.

Limitations

A general caveat in the interpretation of our findings is that lorazepam induced performance decline across tasks and conditions and impairments on the subjective level. This might indicate general cognitive and physiological effects, limiting our ability to draw conclusions regarding specific effects on inhibitory control.

A further limitation of the study is that we did not measure lorazepam concentrations in blood. These may have been helpful to provide a more comprehensive understanding of the drug's effects and their relation with performance.

Additionally, resulting from a lack of extensive previous studies, most of our analyses were exploratory. Therefore, confirmatory analyses as well as replications are required. Furthermore, the neural mechanisms of the effects reported in this study remain unknown. Accordingly, it would be of considerable interest to apply inhibitory tasks with concurrent measures of brain function in order to obtain a fuller understanding of GABAergic effects. Finally, future work may also elaborate mathematical modeling approaches to data from inhibitory control tasks, such as drift diffusion models (Voss et al., 2013; White et al., 2011).

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Data availability statement

Data and code can be found online (https://osf.io/ts5b9/).

Supplemental material

Supplemental material for this article is available online.

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