GABAergic Involvement in Selective Attention

Kaja Faßbender[1], Philine M. Baumert[1], Maximilian W. M. Wintergerst[2], Jan H. Terheyden[2], Behrem Aslan[2], Wolf M. Harmening[2], and Ulrich Ettinger[1]

Abstract

■ Animals need to cope with abundant sensory information, and one strategy is to selectively direct attention to only the most relevant part of the environment. Although the cortical networks of selective attention have been studied extensively, its underlying neurotransmitter systems, especially the role of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), remain less well understood. Increased $GABA_A$ receptor activity because of administration of benzodiazepines such as lorazepam is known to slow reactions in cognitive tasks. However, there is limited knowledge about GABAergic involvement in selective attention. Particularly, it is unknown whether increased $GABA_A$ receptor activity slows the build-up of selectivity or generally widens attentional focus. To address this question, participants (n = 29) received 1 mg lorazepam and placebo (within-subjects, double-blind) and performed an extended version of the flanker task. The spatial distribution of selective attention was studied by systematically manipulating number and position of incongruent flankers; the temporal build-up was characterized using delta plots. An online task version was presented to an independent, unmedicated sample (n = 25) to verify task effects. Under placebo and in the unmedicated sample, only the number of incongruent flankers, but not their position, influenced RTs. Incongruent flankers impaired RTs more strongly under lorazepam than placebo, especially when adjacent to the target. Delta plot analyses of RT showed that this effect persisted even when participants reacted slowly, indicating that lorazepam-induced impairments in selective attention do not result from simply slowed down build-up of selectivity. Instead, our data indicate that increased $GABA_A$ receptor activity widens the attentional focus. ■

INTRODUCTION

Selective visual attention, the ability to favor goal-relevant stimuli and responses, is often characterized as a zoom lens with its focus sharpening over time (e.g., LaBerge, Brown, Carter, Bash, & Hartley, 1991; Eriksen & St. James, 1986). Despite its high relevance in daily life and its known impairments in neuropsychiatric disorders (Pattij & Schoffelmeer, 2015), the neurotransmitter mechanisms underlying selective attention are not fully characterized.

Understanding the neurotransmitter systems involved in selective attention is important not only for cognitive neuroscience research in healthy populations (Bari & Robbins, 2013), but also for better understanding deficits in neuropsychiatric disorders (e.g., Nigg, 2001) and developing possible treatments (e.g., Yang & Tsai, 2017). From neuroimaging and lesion studies, it is known that selective attention is mediated chiefly by fronto-posterior cortical networks (Corbetta & Shulman, 2002). Neurochemically, the excitatory neurotransmitter acetylcholine (ACh) enhances selective attention (Moore & Zirnsak, 2017; Noudoost & Moore, 2011; Coull, 1998). However, regarding inhibitory neurotransmitters, there is insufficient knowledge. Initial evidence suggests interactions between ACh and the most widespread human inhibitory neurotransmitter, γ-aminobutyric acid (GABA; Granger, Mulder, Saunders, & Sabatini, 2016). In addition, inhibitory neurotransmitters reduce ACh release in rats, thereby impairing attention (Burk, Blumenthal, & Maness, 2018). Importantly, the relationship between GABA and selective attention remains unclear.

One approach to studying GABAergic effects on attention is the administration of benzodiazepines such as lorazepam, which modulate $GABA_A$ receptors by increasing the hyperpolarizing effect of GABA, thus decreasing neuronal excitability (Knoflach & Bertrand, 2021; Uusi-Oukari & Korpi, 2010). Experimentally, benzodiazepines impair performance in simple psychomotor and cognitive tasks, including increased RTs and error rates (e.g., Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 2012; de Visser et al., 2003; Wittenborn, 1979). Clinically, benzodiazepines have arousal-reducing, sleep-promoting, muscle-relaxing, antispasmodic and anxiolytic effects (Baldwin et al., 2013). Given the anxiolytic effects of benzodiazepines, studies on anxiety and attention may also provide evidence as to whether benzodiazepines, and thus increased GABAergic activity, might influence attention. Interestingly, both state and trait anxiety have been found to narrow the central attentional focus (Wegbreit, Franconeri, & Beeman, 2015; Caparos

[1]University of Bonn, Germany, [2]University Hospital Bonn, Germany

& Linnell, 2012), suggesting that GABAergic-induced reductions of anxiety may widen the attentional focus.

Selective attention can be studied using flanker tasks (Eriksen & Eriksen, 1974). In such tasks, participants are typically instructed to react to a central target (e.g., an arrow symbol such as > or <), ignoring peripheral flankers associated with the correct (congruent, e.g., > > > > >) or incorrect response (incongruent, e.g., < < > < <). RTs and error rates are higher in incongruent than congruent conditions, termed *congruency effect*.

We recently studied lorazepam effects on performance in flanker, antisaccade, and Simon tasks (Faßbender et al., 2021). In all tasks, lorazepam increased the rate of erroneous responses, particularly in incongruent conditions, suggesting that the drug impaired the ability to resolve response conflicts. Notably, the flanker task was the only one that additionally revealed an increased congruency effect for RT under lorazepam, thereby implying GABAergic involvement in selective attention. Specifically, a widened attentional focus with lorazepam may increase the impact of incongruent flankers on RTs of responses to the target, and as incongruency in the flanker task delays the production of a correct response (Ridderinkhof, Wylie, van den Wildenberg, Bashore, & van der Molen, 2021), an increased congruency effect for RT could imply a widened attentional focus with lorazepam. One aim of the present study is to address this assumption.

A more fine-grained assessment of selective attention in the flanker task was put forward by White, Ratcliff, and Starns (2011). Their task considers both the number and the position of the flankers by additionally including outer incongruent (only the two outer flankers point in the opposite direction to the target, e.g., < > > > <) and inner incongruent conditions (only the two flankers next to the target point in the opposite direction to the target, e.g., > < > < >). In general, flankers that are more distant to the target are less in the focus of attention and have less influence on RT than flankers closer to the target (Eriksen & Eriksen, 1974). Under an optimal, very narrow attentional focus on the target, outer and inner flankers should only slightly influence responses to the target. Under a somewhat wider attentional focus, however, the influence of flankers should be increased, especially for inner conditions, which should be reflected in a stronger RT congruence effect for inner than outer incongruent conditions. Importantly, the effects of benzodiazepines on attentional mechanisms in this task have not yet been studied.

In addition, only considering mean RT dismisses that the narrowing of attentional focus is also subject to temporal dynamics (Eriksen & Eriksen, 1974). Generally, selective attention is low at stimulus onset, with responses strongly determined by both target and flankers (Ridderinkhof, 2002). Over time, controlled processes increase, and the influence of irrelevant flankers decreases. This build-up of selectivity is illustrated in delta plots where congruency effects are displayed as a function of RT quintiles. These delta plot analyses typically reveal large congruency effects for accuracy (percent correct) in quintiles with short RTs, indicating strong direct activation by irrelevant flankers before build-up of selectivity. For later quintiles, there are typically no differences in accuracy between congruent and incongruent conditions. Thus, participants are able to inhibit incorrect responses when reacting slowly. Delta plots for RT, on the other hand, reflect the build-up of selectivity over time. Fast compared with slow build-up of selectivity reduces the influence of irrelevant flankers and thus congruency effects for RT in later quintiles (Ridderinkhof, 2002).

Using delta plots in combination with the extended task version by White et al. (2011), it is possible to further characterize the build-up of selectivity over time. Specifically, a smaller difference between outer and inner incongruent RT on trials in which participants respond slowly may indicate that the influence of outer flankers decreased over time. Regarding possible lorazepam effects on selective attention, it is thus possible to investigate not only whether there is a general widening of selective attention but also whether such an effect is subject to temporal dynamics. For example, a compensation of potential impairments under lorazepam in slow RT trials could indicate that temporal build-up of selectivity was merely slowed-down by the drug. If, on the other hand, differences persist for slow RT trials, this would suggest that the attentional focus is generally widened, regardless of temporal dynamics.

Here, for the first time, we studied GABAergic influences on selective attention taking into account these issues. In a preregistered Experiment 1, participants performed the extended flanker task after 1 mg lorazepam and placebo (within-subject). Following previous findings, our preregistered hypotheses were that lorazepam would increase RT and error rates (1). In addition, we expected impaired selective attention under lorazepam, which should be reflected in higher congruency effects for RT under lorazepam compared with placebo. On the basis our previous study (Faßbender et al., 2021), we also expected an increased congruency effect in error rate with lorazepam (2). Regarding the extended version of the flanker task, we hypothesized that RT and error rate would increase from congruent to outer, inner, and incongruent conditions (3). Furthermore, we explored the influence of lorazepam on the spatial distribution of attention by comparing drug effects on the outer and inner incongruent conditions. In addition, we included delta plot analyses to investigate whether possible impairments under lorazepam reflect a slowing-down of the build-up of selectivity or a fundamental widening of the attentional focus independent of temporal dynamics. In Experiment 2, we applied the flanker task in an online setting to an independent sample without drug administration, to replicate placebo task effects from Experiment 1 and to provide comparative data for this task version.

EXPERIMENT 1

Methods

Sample

Thirty healthy students aged 18–40 years completed the study. Sample size was determined a priori to obtain ≈85% power with an effect size of $d = 0.5$ and an alpha level of .05 using G*Power (V 3.1).

Participants were recruited through online and local advertisements. After completing an online screening questionnaire, suitable participants were invited to an in-person screening. Participants meeting all inclusion criteria and none of the exclusion criteria were invited to the experimental sessions. Inclusion criteria were: right-handedness, normal or corrected-to-normal vision. Exclusion criteria were: medication consumption (except oral contraceptives in women); any current or history of psychiatric, neurological, or physical disorder; blood pressure below 100/60 or above 140/90; resting pulse < 60 or > 100 beats per minute; body mass index <18 or > 29 kg/m^2 for men or < 19 or > 30 kg/m^2 for women; a history of nicotine consumption (more than 10 cigarettes in lifetime); positive drug or alcohol test; earlier consumption of lorazepam or other benzodiazepines (lifetime); known allergic reactions to medications; and, for women, a positive pregnancy test (Cleartest Diagnostik HCG), breastfeeding, or not using effective contraceptives for the duration of at least one cycle.

All participants gave written informed consent. After completion of experimental sessions, participants were compensated with 100€ or course credits. The study was approved by the ethics committee of the Faculty of Medicine at the University of Bonn (Lfd. Nr. 240/19) and preregistered on OSF (Open Science Framework; https://osf.io/uhrjf/).

Design and Procedure

The study design was within-subject, double-blind, placebo-controlled, with counterbalanced order of drug administration. Participants completed two experimental sessions on separate occasions, 7 days apart, at the same time of day (difference between starting times in minutes: mean = 2.59, *SD* = 2.88, maximum = 10.00).

After confirming participants' well-being and performing a urine pregnancy test (Cleartest Diagnostik HCG) for women, participants received either placebo (mannitol) or 1 mg lorazepam (Tavor, Pfizer). Drugs were encapsulated identically; thus, they were visually indistinguishable and had no odor. Administration was oral, and capsules were served with a glass of water. After administration, there was a waiting period of 1:45 hr (Kyriakopoulos, Greenblatt, & Shader, 1978).

First, participants carried out other oculomotor tasks, which are not described in this study, lasting about 70 min. Subsequently, the flanker task was performed (approx. 3 hr after drug administration). Lastly, participants filled in an online questionnaire containing visual analogue rating scales (Bond & Lader, 1974), the NASA-Task Load Index (NASA-TLX) to assess subjective effects of drug administration and an item asking whether participants thought they received lorazepam or placebo that day. Because of the COVID-19 pandemic, participants wore facemasks during assessments.

Flanker Task

The visual stimulus and task procedure (Figure 1) was written in Presentation software (Version 19.0, Neurobehavioral Systems, Inc.) and presented on a flat-screen monitor (Sony 55XE8505, 55-in., height: 68 cm, width: 121 cm,

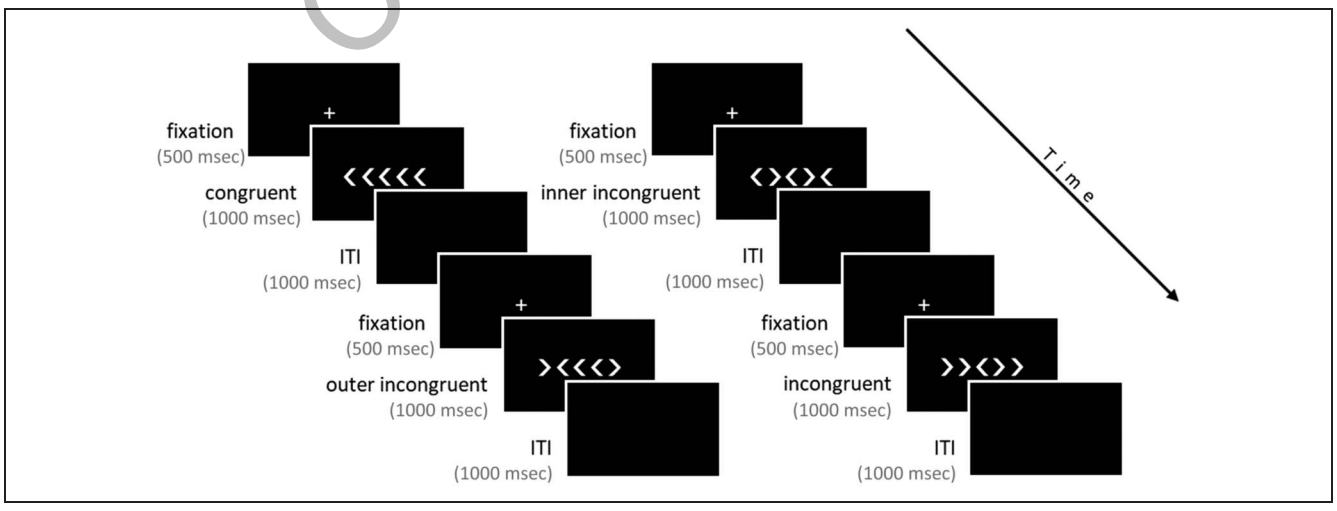

Figure 1. Flowchart of the flanker task. The figure shows four example trials of the flanker task used in Experiments 1 and 2. In all task conditions shown here, the left button should be pressed to indicate the correct response to the central target arrow. During the experiment, each condition also existed with mirror-inverted arrows that had to be reacted to by pressing the right button. Presentation order was randomized. ITI = intertrial interval.

resolution: 3840 × 2160 px, 59-Hz refresh rate). Eye-to-screen distance was about 220 cm. Stimuli were white (r, g, b: 255, 255, 255) on black (0, 0, 0) background. In each trial, a central fixation cross was shown for 500 msec, followed by five arrows (total horizontal size approx. 16.66° of visual angle, vertical size approx. 3.44°) shown for 1000 msec, and an intertrial interval (ITI) of 1000 msec before the next trial began.

Participants were instructed to respond quickly and accurately to the direction of the middle arrow (the target) by pressing a corresponding key on a QWERTZ keyboard, ignoring the flankers. The factor Task Condition comprised four conditions: congruent (all arrows in the same direction, e.g., "< < < < <"), incongruent (all flankers in opposite direction to target, e.g., "> > < > >"), outer (both outer flankers in opposite direction to target, e.g., "> < < < >"), and inner (both inner flankers in opposite direction to target, e.g., "< > < > <"). Participants did not receive feedback on their performance. For each condition, 100 trials (50 right, 50 left) were presented in pseudorandomized order, resulting in 400 trials for each participant. In the beginning, 20 practice trials were presented.

Raw data from all participants were combined and organized on trial level using MATLAB 2017b (The MathWorks). Data sets for statistical analyses on subject level were prepared in R (R Core Team, 2021). Outcome variables were RT for correct trials (msec) and error rate (%).

Subjective Effects

Computerized visual analogue rating scales (VAS; Bond & Lader, 1974) were applied in German to measure subjective effects after completing the flanker test. Participants submitted ratings on 16 continuous scales, each comprising two anchors and scored 0–100. Responses were made by moving a marker using mouse clicks. Variables were *alertness*, comprising "Alert/Drowsy" (1), "Strong/Feeble" (3), "Muzzy/Clear-headed" (4, R), "Well-coordinated/Clumsy" (5), "Lethargic/Energetic" (6, R), "Mentally slow/Quick-witted" (11, R), "Attentive/Dreamy" (13), "Interested/Bored" (14), "Incompetent/Proficient" (16, R); *contentedness*, comprising "Contented/Discontented" (7), "Troubled/Tranquil" (8, R), "Happy/Sad" (9), "Antagonistic/Amicable" (10, R), "Gregarious/Withdrawn (15, R)"; and *calmness*, comprising "Calm/Excited" (2), "Tense/Relaxed (12, R)." Numbers indicate questionnaire positions, and "R" indicates item recoding. Higher scores indicate less alertness, less contentedness, and less calmness.

The computerized NASA-TLX measured subjective workload (Hart & Staveland, 1988). Participants submitted ratings on six continuous scales ranging from "very low" to "very high" and scored 0–100. Items were "mental demand," "physical demand," "temporal demand," "overall performance," "effort," and "frustration level" (in German). All ratings were combined to the *overall task load score* (Bustamante & Spain, 2008).

Statistical Analyses

Statistical analyses were carried out in R (R Core Team, 2021) using the packages *apaTables* (Stanley, 2021), *dplyr* (Wickham, François, Henry, & Müller, 2021), *ez* (Lawrence, 2016), *ggplot2* (Wickham, 2016), and *rstatix* (Kassambara, 2021). Trials were counted as invalid when RT was < 150 msec or > 1200 msec. Participants with > 50% missing/invalid trials or > 80% incorrect in one condition were excluded.

Within-subject ANOVA with the factors Drug (placebo, lorazepam) and Task Condition (congruent, outer incongruent, inner incongruent, incongruent) was carried out for RT and error rate. Effect sizes were reported using partial eta-square and its 95% confidence interval (CI; Cohen, 1973). Significant effects were further explained using post hoc Bonferroni-corrected t tests and effect size d_{AV} (Lakens, 2013). If Mauchly's test indicated violation of sphericity, Greenhouse–Geisser correction was applied. We used a $p < .05$ significance criterion.

For delta plots, RTs of valid trials were rank-ordered separately for congruent, outer incongruent, inner incongruent, and incongruent conditions at subject level and each divided into five equal parts. For each quintile, RT for correct trials and accuracy (% correct) were determined. Delta plots show either the difference between congruent and incongruent conditions or between outer and inner incongruent conditions in RT and accuracy as a function of mean RT of both conditions per quintile. Within-subject ANOVAs, including the factor Drug (placebo, lorazepam), were performed to compare slopes between Quintiles 1 and 2, Quintiles 2 and 3, Quintiles 3 and 4, and Quintiles 4 and 5.

Finally, within-subject ANOVAs with the factor Drug (placebo, lorazepam) were carried out for VAS and NASA-TLX.

Results

Sample Description

The final sample consisted of $n = 29$ (14 female, 15 male) participants. According to preregistered exclusion criteria, none of the initially recruited 30 participants had to be excluded. However, we decided to exclude one participant with an average 69.95% error rate under placebo as outlier. The participant showing the next highest values had an error rate of 4.50%. Percentages of trials excluded as invalid were low (0.01% of all trials for RT < 150 msec; 3.37% of all trials for RT > 1200 msec). Mean age was 22.76 years ($SD = 3.35$ years). Table 1 contains descriptive results and internal consistencies of flanker task data.

Table 1. Descriptive Statistics and Internal Consistencies in Experiment 1

	Placebo		*Lorazepam*	
	M (SD)	*α [95% CI]*	*M (SD)*	*α [95% CI]*
RT con.	524.02 (41.17)	.97 [.95, .98]	577.49 (55.34)	.97 [.94, .98]
RT outer	546.39 (47.40)	.97 [.95, .98]	608.56 (67.98)	.97 [.95, .98]
RT inner	553.13 (49.70)	.97 [.96, .99]	623.49 (73.15)	.97 [.95, .98]
RT incon.	582.98 (46.64)	.97 [.95, .98]	648.59 (61.18)	.96 [.94, .98]
ER con.	0.41 (0.63)	−.05 [−.72, .44]	0.46 (0.89)	.44 [.09, .70]
ER outer	0.86 (1.16)	.37 [−.01, .66]	1.23 (1.88)	.65 [.44, .81]
ER inner	0.83 (1.29)	.51 [.22, .74]	1.50 (1.79)	.50 [.20, .73]
ER incon.	3.18 (3.16)	.70 [.52, .84]	3.56 (3.66)	.74 [.59, .86]

Numbers indicate the mean (standard deviation). RT = mean reaction time; con. = congruent; outer = outer incongruent; inner = inner incongruent; incon. = incongruent; ER = error rate in %; α = Cronbach's α; CI = confidence interval (Feldt procedure), $n = 29$.

Data sets, code, material, as well as all analyses with complete data sets, are provided on OSF (https://osf.io/y49a3/).

Flanker Task

In line with previous studies, we find that lorazepam slowed down RT across all participants in all task conditions. Interestingly, RT for outer and inner incongruent conditions decreased at different rates, offering insights into the mechanisms of selective attention. Specifically, for RT (Figure 2A), there was a main effect of Drug, $F(1, 28) = 63.34$, $p < .001$, $\eta_p^2 = .693$, CI [.462, .795], indicating longer RT under lorazepam than placebo, and a main effect of Task Condition, $F(3, 84) = 104.34$, $p < .001$, $\eta_p^2 = .788$, CI [.699, .833], $\epsilon = .78$. The main effect of Task Condition was because of an increase in RT from congruent via outer and inner incongruent to incongruent conditions. Importantly, there was also an interaction between Drug and Task Condition, $F(3, 84) = 5.52$, $p = .004$, $\eta_p^2 = .165$, CI [.029, .284], $\epsilon = .77$. This interaction arose because of significant differences in RT between outer and inner incongruent conditions under lorazepam, $t(28) = -3.74$, $p = .014$, $d = -0.053$, that did not exist under placebo, $t(28) = -2.63$, $p = .22$, $d = -0.035$. On the other hand, all other task conditions differed significantly within drug each condition (all $p < .001$), and RT was always higher under lorazepam than placebo within each task condition (all $p < .001$). Thus, the interaction essentially showed that although there was a significant linear trend from congruent, outer incongruent, inner incongruent, to incongruent under lorazepam ($t = 4.24$, $p < .001$) and placebo ($t = 4.77$, $p < .001$), there was a significant RT difference between outer and inner incongruent conditions only under lorazepam, but not placebo.

For error rate (Figure 2B), there was no main effect of Drug, $F(1, 28) = 2.36$, $p = .14$, $\eta_p^2 = .078$, CI [.000, .293], and no interaction between Drug and Task Condition, $F(3, 84) = 0.45$, $p = .64$, $\eta_p^2 = .016$, CI [.000, .067], $\epsilon = .67$. However, there was a main effect of Task Condition, $F(3, 84) = 25.24$, $p < .001$, $\eta_p^2 = .474$, CI [.303, .576], $\epsilon = .43$. t Tests following up that main effect revealed

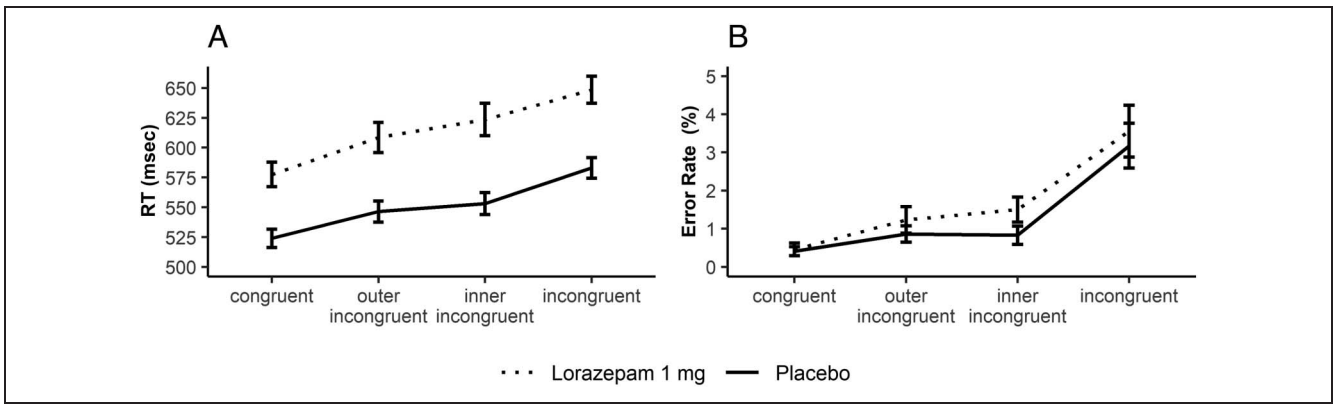

Figure 2. RT and error rate in Experiment 1. The figure illustrates the effects of lorazepam (1 mg) compared with placebo administration on (A) mean RT of correct trials and (B) mean error rate in Experiment 1. Error bars indicate the standard error of the mean, $n = 29$.

that there were significant differences in error rate between all conditions (all $p < .005$) except between outer and inner incongruent conditions, $t(57) = -0.47$, $p = 1.00$, $d = -0.019$, and a linear trend from congruent to incongruent conditions ($t = 7.35$, $p < .001$). Thus, error rate was unimpaired by drug, but increased from congruent to incongruent conditions, whereas there was no significant difference between outer and inner incongruent conditions.

To provide comparability with our previous study (Faßbender et al., 2021), we repeated the analyses excluding outer and inner incongruent conditions, that is, reducing the data set only to include fully congruent and incongruent conditions. Results replicate our previous findings for RT, with significant main effects of Drug and Task Condition as well as a significant interaction effect (Table 2).

Delta Plots

To examine whether lorazepam effects on flanker task performance may be because of effects on build-up of selectivity or direct activation (Ridderinkhof, 2002), we calculated delta plots for RT and accuracy, respectively.

Delta plots (Figure 3) for RT did not reveal significant drug effects for slopes of any quintile, neither when comparing outer and inner incongruent conditions nor when comparing congruent and incongruent conditions (all $p > .05$). Thus, the increased RT congruency effect under lorazepam was independent of mean RT and was sustained even in trials with higher RT. As expected from previous studies (Pratte, 2021), delta plots for RT were positive-going and visual inspection confirmed slower RT under lorazepam compared with placebo in all quintiles.

Delta plots of slopes for accuracy between Quintiles 4 and 5 revealed significant drug effects when comparing outer and inner incongruent, $F(1, 28) = 4.36$, $p = .046$, $\eta_p^2 = .135$, CI [.000, .360], and congruent and incongruent conditions, $F(1, 28) = 5.77$, $p = .023$, $\eta_p^2 = .171$, CI [.001, .397]. This is illustrated in the fact that there were negative slopes for accuracy under lorazepam for later quintiles, whereas they were positive for placebo. Importantly, those effects were because of lower accuracy in inner incongruent and incongruent conditions (Figure 4) and did not result from higher accuracy for congruent or outer incongruent conditions in later quintiles. This finding suggests that lorazepam lowers the accuracy of responding particularly for slow reactions, especially when inner or both flankers are incongruent.

Subjective Effects

Participants scored significantly higher on VAS alertness and contentedness with lorazepam than placebo. As higher scores indicate less alertness and contentedness, this result indicates that participants were less alert and less content under drug (Table 3). VAS calmness and NASA-TLX task load score were unaffected by lorazepam.

At assessment Session 1, participants could not reliably guess whether they had received placebo or lorazepam ($p > .05$). At assessment Session 2, the proportion of participants guessing correctly was significantly above chance level ($p = .002$).

Order Effects

In an exploratory analysis, the factor Order (placebo–lorazepam, lorazepam–placebo) was included in the ANOVA for RT to test whether drug effects depended on administration order. Main effects for Drug, $F(1, 27) = 95.73$, $p < .001$, $\eta_p^2 = .780$, CI [.593, .854], and Task Condition, $F(3, 81) = 104.38$, $p < .001$, $\eta_p^2 = .794$, CI [.705, .838], $\epsilon = .78$, as well as the interaction between Drug and Task Condition, $F(3, 81) = 7.42$, $p < .001$, $\eta_p^2 = .216$, CI [.059, .340], were confirmed.

In addition, there was an interaction between Drug and Order, $F(1, 27) = 12.62$, $p = .001$, $\eta_p^2 = .319$, CI [.059, .528], indicating that when lorazepam was given in Session 1, RT was significantly higher than when lorazepam was given in Session 2 ($p = .038$). RT under placebo did not differ as a

Table 2. Repeated-Measures ANOVA for Congruent and Incongruent Conditions Only

	Effect	df_n	df_d	F	p	η_p^2 *[95% CI]*
RT	Drug	1	28	71.97	< .001	.720 [.502, .813]
	Task Condition	1	28	338.20	< .001	.924 [.853, .949]
	Drug × Task Condition	1	28	8.24	.008	.227 [.018, .449]
Error rate	Drug	1	28	0.37	.545	.013 [.000, .179]
	Task Condition	1	28	32.89	< .001	.540 [.259, .690]
	Drug × Task Condition	1	28	0.41	.526	.015 [.000, .183]

Data from outer and inner incongruent conditions were excluded before the analysis to provide comparability with our previous study (Faßbender et al., 2021).

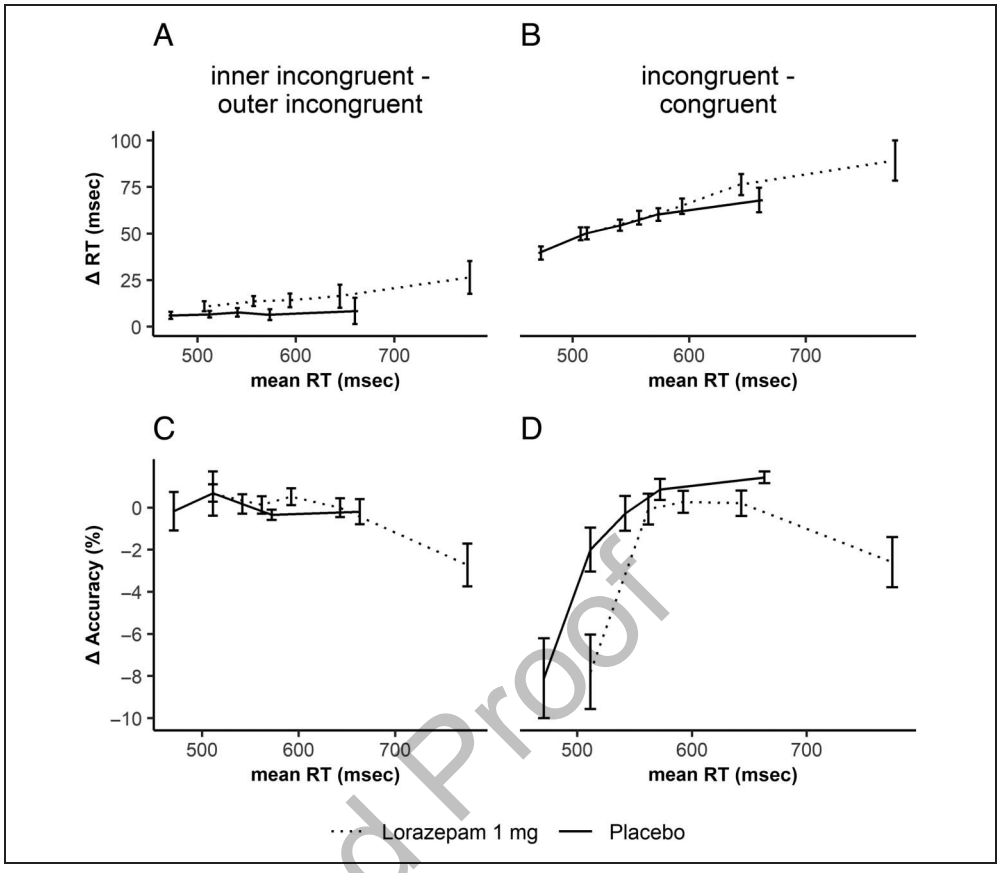

Figure 3. Delta plots in Experiment 1. The figure shows lorazepam effects compared with placebo in delta plots for mean RT of correct trials (A, B) and accuracy (percent correct) (C, D). In delta plots, RTs are rank-ordered and separated into quintiles. For each quintile, the difference (Δ) in RT or accuracy between outer and inner incongruent conditions (A, C) and between congruent and incongruent conditions (B, D) are plotted against the mean RT of both conditions in the respective quintile. Error bars indicate the standard error of the mean, $n = 29$.

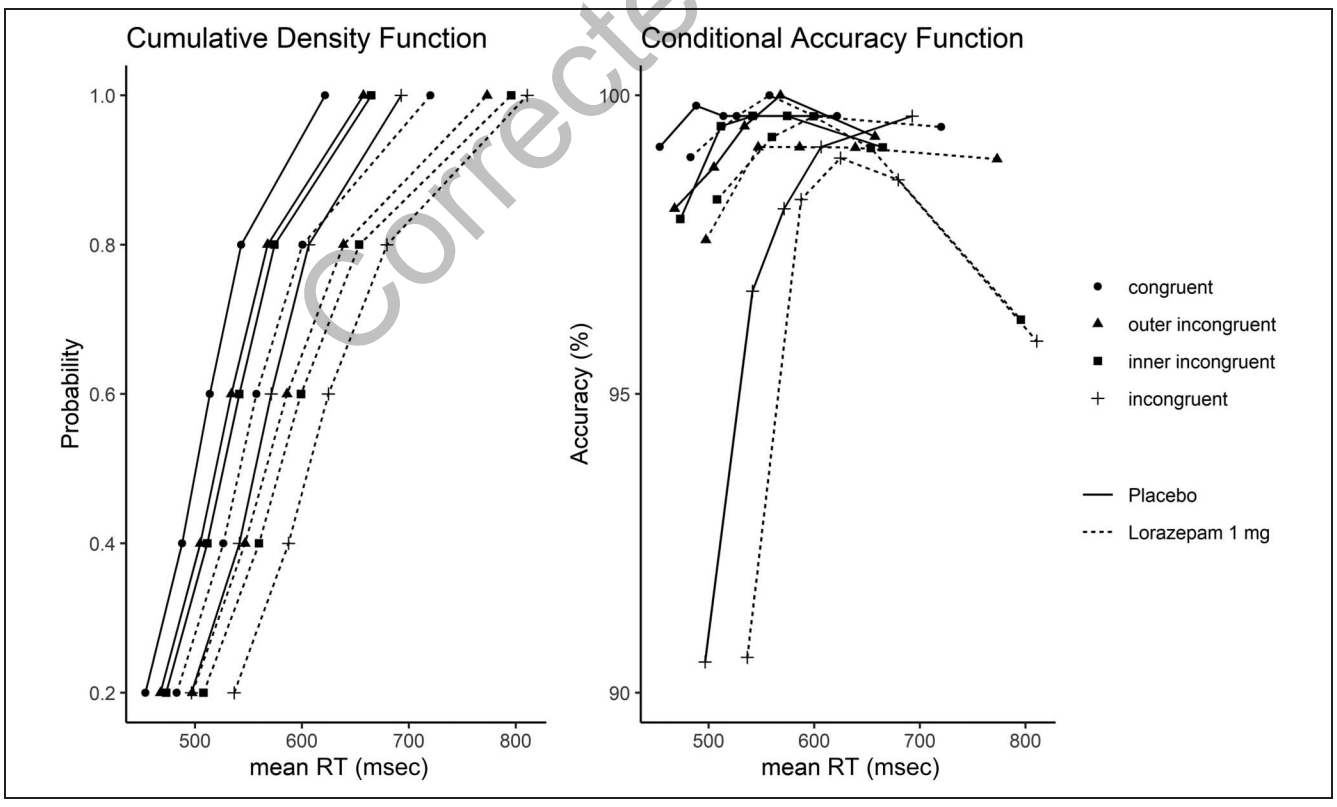

Figure 4. Cumulative density and conditional accuracy functions. Lorazepam effects across task conditions in comparison to placebo expressed in cumulative density function (CDF) and conditional accuracy function (CAF). RTs were first rank-ordered and separated into quintiles. In CDFs, for each condition separately, the cumulative RT probability is plotted against the mean RT for each quintile. In CAFs, for each condition separately, the accuracy is plotted against the mean RT for each quintile, $n = 29$.

Table 3. Descriptive Statistics and Lorazepam Effects on Visual Analogue Scales and NASA-TLX

	Placebo	*Lorazepam 1 mg*	*df*	*t*	*p*	*d*
VAS						
Alertness	37.33 (16.76)	55.36 (15.51)	28	−6.19	< .001	−.279
Contentedness	29.92 (10.87)	37.41 (13.02)	28	−3.66	< .001	−.157
Calmness	26.62 (14.09)	23.00 (13.60)	28	1.13	.27	.065
NASA-TLX						
Overall task load	39.76 (8.79)	42.13 (9.85)	28	−1.21	.24	−.064

The table includes descriptive statistics of the subjective scales under placebo and lorazepam (1 mg), where numbers indicate the mean (standard deviation) for each item in units from 1 to 100, as well as *t* test results testing for differences between both drug conditions. Higher numbers in visual analogue scales (VASs) indicate lower alertness, lower contentedness, and lower calmness. Higher numbers in NASA-TLX indicate a higher reported task load, $n = 29$.

function of administration order ($p = .51$). In addition, RT was higher for lorazepam than placebo in bother order groups (both $p < .001$). Thus, in our data, the overall increase in RT with lorazepam compared with placebo was more pronounced in participants who received lorazepam first.

Furthermore, there was a significant three-way interaction between Drug, Task Condition, and Order, $F(3, 81) = 5.24, p = .002, \eta_p^2 = .162$, CI [.025, .284], reflecting that the above described interaction between drug and task condition, which was the basis for our interpretation of lorazepam effects on in selective attention, was more pronounced when lorazepam was administered first ($p = .001$), than when placebo was given in Session 1 ($p = .272$). A possible explanation is that, in the second session of the placebo-first group, when the task was well practiced, inner flankers no longer had a stronger influence than outer flankers under lorazepam, as participants had practiced to narrow their attentional focus in this task under optimal conditions, that is, placebo, in the first session.

To ensure that the above reported interaction between Drug and Task Condition was not an artifact of order effects, we used data from Session 1 only and evaluated Drug as a between-subjects factor. Importantly, the interaction was still significant, $F(3, 81) = 4.16, p = .019, \eta_p^2 = .133$, CI [.010, .250], $\epsilon = .71$. Thus, we conclude that our key findings regarding the impairment of selective attention with lorazepam did not result from order effects.

For error rate, there was no significant main effect of Order, $F(1, 27) = 0.43, p = .52, \eta_p^2 = .016$, CI [.0000, .190]; no interaction between Drug and Order, $F(1, 27) = 0.64, p = .43, \eta_p^2 = .023$, CI [.0000, .208]; or between Task Condition and Order, $F(3, 81) = 0.02, p = .93, \eta_p^2 = .001$, CI [.0000, 1.000], $\epsilon = .43$; and no three-way interaction between Drug, Task Condition, and Order, $F(3, 81) = 2.37, p = .10, \eta_p^2 = .081$, CI [.0000, .184], $\epsilon = .68$.

EXPERIMENT 2

As this version of the flanker task had not been studied before and as we intended to substantiate our conclusions about lorazepam effects in comparison to the placebo condition, we applied the task in an independent sample without pharmacological manipulation.

Methods

Sample and Procedure

Twenty-seven healthy students aged 18–30 years were recruited by online and local advertisements. Inclusion criteria were: right-handed, normal or corrected-to-normal vision, no medication (except oral contraceptives in women), and no current diagnosis of physical, neurological, or psychiatric condition.

The online assessment started with a short demographic and screening questionnaire. Subsequently, all participants performed the experiment. However, only data from suitable participants were processed further. Participants carried out the flanker task and a Simon task, which is not part of this article. Task order was randomized between participants.

Participants provided informed consent by mouse click. After completion, participants were compensated with psychology course credits.

Flanker Task

The task (Figure 1) was implemented online using PsyToolkit (Stoet, 2010, 2017). Participants were instructed to carry out the experiment undisturbed in a quiet room, sitting comfortably and upright at a table. Mobile phones or tablets were disabled to ensure a sufficient screen resolution.

Task procedure was as in Experiment 1, except for the following variations owing to the online setting. First, participants were instructed to respond by pressing the right or left arrow key on their keyboard. Second, the size of the arrows was specified in pixels (total horizontal size = 720 px, vertical size = 154 px) instead of visual angle, as eye-to-screen distance likely varied. Third, during practice trials, immediate feedback was given after every trial to ensure participants understood the instructions.

Table 4. Descriptive Statistics and Internal Consistencies in Experiment 2

	M (SD)	*α [95% CI]*
RT con.	442.17 (63.38)	.99 [.98, .99]
RT outer	468.01 (69.62)	.99 [.98, .99]
RT inner	469.61 (67.23)	.98 [.97, .99]
RT incon.	503.37 (67.49)	.98 [.96, .99]
ER con.	0.36 (0.76)	.43 [.02, .71]
ER outer	1.81 (1.98)	.56 [.28, .78]
ER inner	2.82 (3.25)	.74 [.57, .87]
ER incon.	7.60 (6.95)	.86 [.77, .93]

Numbers indicate the mean (standard deviation). RT = mean reaction time; con. = congruent; outer = outer incongruent; inner = inner incongruent; incon. = incongruent; ER = error rate in %; α = Cronbach's α; CI = confidence interval (Feldt procedure), $n = 25$.

Data were preprocessed using R (R Core Team, 2021). Outcome variables were RT for correct trials (msec) and error rate (%).

Statistical Analyses

Statistical analyses of task data were as in Experiment 1, except that the within-subject ANOVA included only the factor Task Condition (congruent, outer, inner, incongruent).

Results

Sample Description

The final sample comprised $n = 25$ (17 female, 8 male) participants. Two of the initially 27 participants were excluded because of exclusion criteria (see Experiment 1). Percentages of trials excluded as invalid were low (0.08% of all trials for RT > 1200 msec). Mean age was 22.04 years ($SD = 2.98$ years). Table 4 contains descriptive results and internal consistencies of task performance data. Data sets, code, and material are provided on OSF (https://osf.io/y49a3).

Flanker Task

For RT (Figure 5A), there was a main effect of Task Condition, $F(3, 72) = 127.17, p < .001, \eta_p^2 = .841$, CI [.765, .876]. *t* Tests revealed significant differences between all conditions (all $p < .001$), except between outer and inner incongruent conditions, $t(24) = -0.55$, $p = 1.00$, $d = -0.006$, Similar to the pattern in Experiment 1, this indicates that RT was lowest in the congruent condition and highest in the incongruent condition, whereas RTs in outer and inner incongruent conditions were in between and comparable. Accordingly, the linear trend from congruent to incongruent condition was significant ($t = 3.09$, $p = .002$).

For error rate (Figure 5B), there was also a main effect of Task Condition, $F(3, 72) = 24.67, p < .001, \eta_p^2 = .507$, CI [.323, .610], $\epsilon = .46$. *t* Tests revealed significant differences between all conditions (all $p < .002$) except between outer and inner incongruent conditions, $t(24) = -2.13$, $p = .26$, $d = -0.097$. This pattern again indicates that error rate was lowest in the congruent condition and highest in the incongruent condition, whereas error rates in outer and inner incongruent conditions were in between. This finding was also reflected in a significant linear trend from congruent to incongruent condition ($t = 6.39$, $p < .001$).

Delta Plots

Based on visual inspection, delta plots (Figure 6) strongly resembled those from the placebo condition in Experiment 1 (Figure 3). As expected, there were no noticeable differences in RT and accuracy between outer and inner incongruent conditions for earlier or later quintiles. The difference in RT between congruent and incongruent

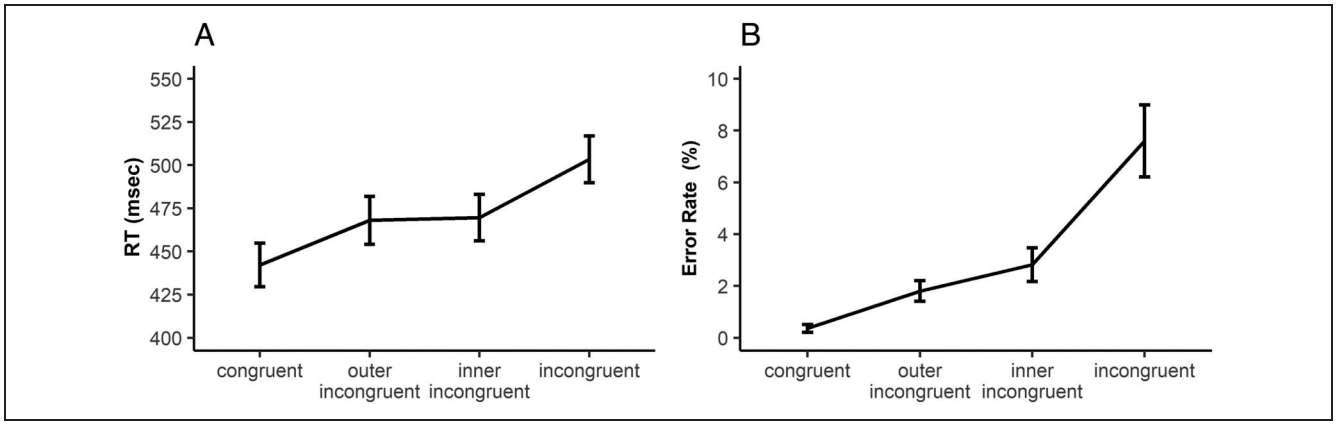

Figure 5. RT and error rate in Experiment 2. The figure illustrates the mean RTs of correct trials (A) and error rates (B) in the online version of the flanker task. Error bars indicate the standard error of the mean, $n = 25$.

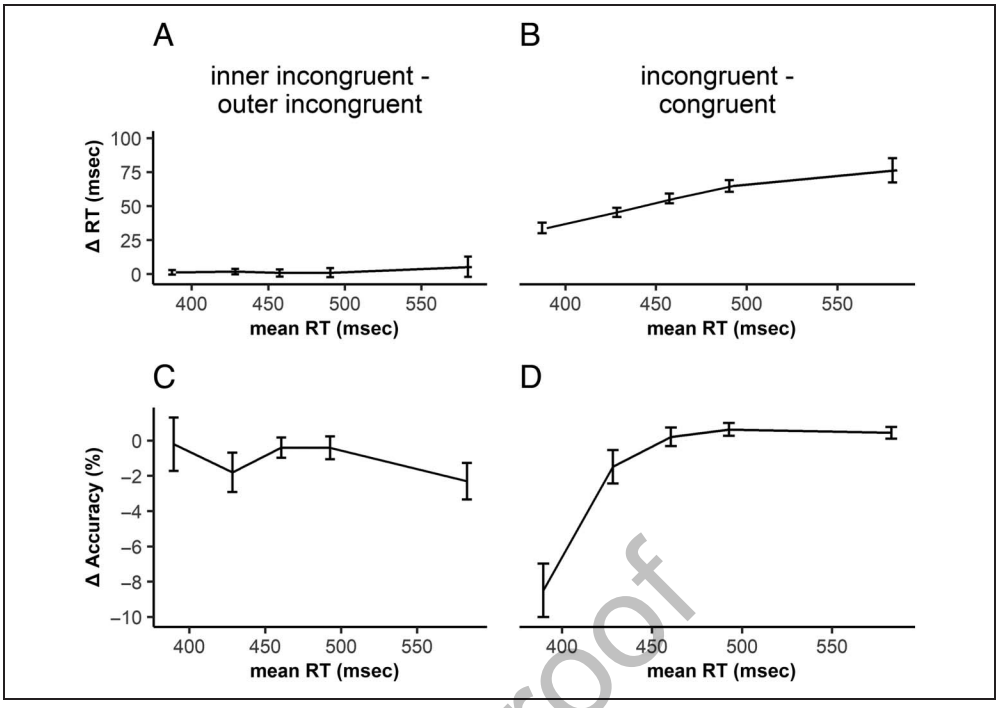

Figure 6. Delta plots in Experiment 2. The figure shows delta plots for the online version of the flanker task for mean RT of correct trials (A, B) and accuracy (percent correct) (C, D). In delta plots, RTs are rank-ordered and separated into quintiles. For each quintile, the difference (Δ) in RT or accuracy between outer and inner incongruent conditions (A, C) and the difference between congruent and incongruent conditions (B, D) are plotted against the mean RT of both conditions in the respective quintile. Error bars indicate the standard error of the mean, $n = 25$.

conditions increased over time, resulting in a positively sloped delta plot. The difference in accuracy decreased over time.

DISCUSSION

Lorazepam Effects on the Flanker Task (Experiment 1)

The present study significantly extends our knowledge of GABAergic involvement in cognition by demonstrating that benzodiazepine-induced increased GABAergic activity widens the attentional focus in a visual attention task. In the following, we first discuss the general worsening of selective attention under lorazepam and then further elaborate on the build-up of selectivity that emerged from delta plot analyses.

The statistically most pronounced effect of lorazepam in this study was an overall increase in RT with large effects size, confirming our hypothesis and previous research (Faßbender et al., 2021; Clariá et al., 2011; Riba, Rodríguez-Fornells, Münte, & Barbanoj, 2005; de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004), although there were no drug effects on error rates (Faßbender et al., 2021). Importantly, in addition to these general effects on response slowing under lorazepam that are likely not because of specific impairments in selective attention, there was a significant interaction between drug and task conditions. Thus, lorazepam did not increase RTs equally across task conditions.[1]

Crucially, we showed that the interaction was because of significantly higher RT with outer than inner incongruent flankers under lorazepam, a difference that did not exist under placebo. This critical comparison thus showed that under placebo (and in the absence of a pharmacological manipulation, Experiment 2), only the number of incongruent flankers impacts RT, whereas under lorazepam, their position is additionally relevant. A possible explanation of this result is a hypothetical distribution of selective attention and its modulation by lorazepam as suggested in Figure 7. Under placebo, the overall influence of inner and outer flankers was small but comparable. Under lorazepam, however, inner flankers had a stronger adverse influence on RT than outer flankers. Thus, when focusing on mean RT, it may be concluded that benzodiazepines broaden the spread of selective visual attention by flattening its distribution.

However, these results and their hypothetical model in Figure 7 do not explicate whether increased $GABA_A$ receptor activation simply slows down the build-up of selectivity over time, as it slows down other processes (cf. increased RT overall), or whether the spatial focus of attention is generally widened under lorazepam, reflecting a deficit that is not compensated in trials with high RT. Therefore, we drew upon delta plot analyses to further characterize the process of focusing on the central target over time (Ridderinkhof, 2002; Eriksen & St. James, 1986). Delta plots for RT increased over time in both drug conditions (cf. Ulrich, Schröter, Leuthold, & Birngruber, 2015; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005). The shift of the lorazepam data to the right (Figure 3) indicated the general slowing of responses under drug.

Crucially, if the increase in selective attention over time was simply slowed-down by lorazepam, the difference in RT between lorazepam and placebo should become smaller in later quintiles (Hübner & Töbel, 2012) as slower responses should provide more time for building

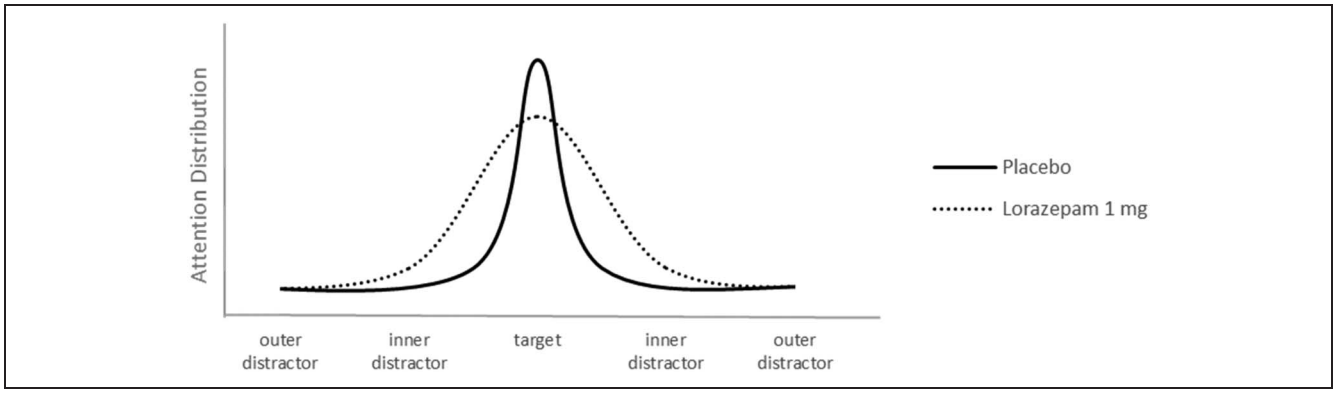

Figure 7. Model representation of a hypothetical distribution of selective attention in the flanker task. Representation of a hypothetical distribution of selective attention to account for the flanker task RT data from Experiment 1 under placebo and lorazepam (1 mg). Higher values on the *y* axis indicate stronger attentional processing. It should be noted that both lines do not flatten to zero.

up selectivity and thereby reducing impairments. White et al. (2011) reported significantly higher RT in inner compared with outer incongruent conditions when participants were instructed to respond quickly, that is, when there was little time to build up selectivity. Without this instruction, thus, at higher RT, there was enough time to build selectivity, and the difference was no longer present. However, delta plot analyses of our data showed that even for late quintiles, in trials with high RT, and despite overall higher RT under lorazepam, the difference in RT between placebo and lorazepam was still observed. Thus, it remained stable over time. Consequently, even slow reactions seemed to have no advantage in attentional focus, which we interpret to indicate that increased $GABA_A$ receptor activation generally widens the attentional focus.

Interestingly, and further disproving the hypothesis of lorazepam induced slowing of build-up of selectivity, delta plots for accuracy indicated even lower accuracy in later quintiles. That is, reacting slowly increased the adverse influence of incongruent flankers on response selection, especially the inner ones, thereby triggering more errors. Specifically, error rate in late quintiles significantly increased for inner compared with outer incongruent conditions and for incongruent compared with congruent conditions, resulting from a decline in inner incongruent and incongruent conditions. This finding was rather unexpected, given that delta plots for accuracy typically do not reveal differences in accuracy between congruent and incongruent conditions for later quintiles (Ridderinkhof, 2002). A possible explanation of this finding is that, with lorazepam, selectivity is initially built up and reduces the influence of the direct activation by irrelevant flankers. However, this suppression apparently cannot be maintained, and after some time, the influence of the irrelevant flankers again increases, and incorrect responses are no longer successfully suppressed. Although this is of course speculative, this pattern of findings further argues against a continuously yet slowed build-up of selectivity under lorazepam. It should be noted that because responses were generally faster under placebo than lorazepam, it is impossible to infer with certainty whether increased error rates in late quintiles is specific to increased $GABA_A$ receptor activity or the result of very slow reactions that did not occur under placebo.

Overall, we conclude that not only simple psychomotor responses and their underlying cognitive processes are slowed down by increased $GABA_A$ receptor activation (e.g., Tannenbaum et al., 2012; de Visser et al., 2003; Wittenborn, 1979), but that the focus of visual attentional is additionally widened.

Further evidence for GABAergic involvement in selective visual attention comes, for example, from research on anxiety. Anxiety has been shown to be associated with narrowed attentional focus (Wegbreit et al., 2015; Caparos & Linnell, 2012). Because lorazepam has known anxiolytic effects, those previous findings are consistent with our interpretation of the drug widening the attentional focus.

Functional neuroimaging studies have identified the neuronal correlates of a gradual decrease in the spatial distribution of attentional focus. For example, BOLD signal in visual cortex is reduced for locations nearby the target compared with the target itself. In higher extrastriate regions, the BOLD signal gradually decreases from the target outward (Hopf et al., 2006; Müller & Kleinschmidt, 2004). This finding indicates stronger neural processing of the target and reduced processing of flankers, the latter suggesting a role of inhibitory local projections using GABA. However, to what extent benzodiazepine-induced alterations in $GABA_A$ receptor activity influence neural processing of targets and flankers remains to be investigated.

Subjective Effects of Lorazepam

As expected, lorazepam reduced self-ratings of alertness. Against our hypotheses, there was no significant effect on calmness, and contentedness even decreased. The latter finding may suggest that participants perceived participation under lorazepam as more negative, perhaps

because of increased fatigue, although there was no effect on perceived workload.

Online Task Assessment (Experiment 2)

The online assessment closely replicated task effects from the placebo condition. Specifically, there were differences in RTs between all conditions except the outer and inner incongruent conditions, as under placebo in Experiment 1. Although this result does not correspond to our previously formulated expectations, it clearly shows that participants were able to direct their selective attention very specifically to the central stimulus in our version of the flanker task. With an increasing number of incongruent flankers, RTs and error rates increased, but the position of the incongruent flankers did not seem to be decisive.

Previous studies have typically manipulated either the proportion of incongruent flankers or the distance from flankers to target. It has been shown that larger distances between target and incongruent flankers reduce RT and error rate (Danielmeier, Wessel, Steinhauser, & Ullsperger, 2009; Eriksen & Eriksen, 1974) and, consistent with our results, a larger proportion of incongruent flankers increases RT and error rate (Forster, Carter, Cohen, & Cho, 2011). To our knowledge, simultaneous manipulation of distance and proportion of incongruent stimuli to the target has only been reported by White and colleagues (2011). In contrast to our results, they found a significant difference between outer and inner incongruent conditions. However, that difference only existed when participants were given feedback to respond more quickly after slow reactions. That instruction, like a short response stimulus interval (RSI), may have led to a lack of preparation for the next response and, thus, comparable to the lorazepam-induced impairments, may have influenced the narrowing of attention in unmedicated participants as well.

Compared with Experiment 1, RTs were faster overall, and error rates were slightly higher, which may be because of the online assessment where we were not able to control the type of device or interruptions during the assessment. This interpretation also fits with the fact that the standard deviations in the online assessment were consistently higher compared with the placebo condition in the laboratory.

Limitations

A number of limitations should be raised.

First, for Experiment 1, it should be noted that the specific effect of lorazepam on selective attention was rather small compared with the general drug-induced increase in RT.

Furthermore, in our task design, presentation times and ITIs were fixed. Therefore, the RSI varied depending on RT and the later the response in the current trial, the less time there was between response and the appearance of the next stimulus. A short RSI may not have provided enough time to sufficiently prepare for the next response resulting in a refractory phase (Hübner & Töbel, 2012). The general lorazepam-induced slowing may thus have affected the build-up of selectivity in the subsequent trial. To ensure that slowing in the previous trial does not affect performance in the current one, future studies could start the ITI immediately after the response by stopping the presentation of the stimuli.

An additional limitation relates to effects of repeated exposure to the tasks and measures in this study. Specifically, participants were better than chance at guessing the drug administered only in assessment Session 2, and there were effects of order of drug administration on RT suggesting that the two-way interaction between task condition and drug was weakened when lorazepam was given second.

Next, in Experiment 1, the flanker task was performed after a series of oculomotor tasks, which may have resulted in fatigue. However, the drug effect should not have been affected as the peak plasma concentration of lorazepam is reached after 1–4 hr. The main metabolite of lorazepam, glucuronide, also reaches its peak concentration after about 4 hr (Elliott, 1976). However, because it has low pharmacological activity (Greenblatt, 1981), we do not assume it influenced the results.

A final limitation is that Experiment 2 was not preregistered. However, assessments took place parallel to Experiment 1 without knowledge of any results.

Conclusion

The present study makes an important contribution to our understanding of the role of the GABAergic system in cognition. Although it was previously known that increased $GABA_A$ receptor activity slows down responses, we now showed that it also causes a generally widened attentional focus. Because benzodiazepine-induced neuronal inhibition occurs across a variety of brain areas, it would next be important to investigate in more detail in which areas neuronal inhibition contributes to widening the focus of attention.

Acknowledgments

We thank Lisa Urfei, Anna Schippers, and Johanne Wiepking for their valuable support in data collection.

Reprint requests should be sent to Ulrich Ettinger, Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9, 53111 Bonn, Germany, or via e-mail: ulrich.ettinger@uni-bonn.de.

Data Availability Statement

Data sets, code, and material are provided on OSF (https://osf.io/y49a3/).

Author Contributions

Kaja Faßbender: Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—

Original draft. Philine M. Baumert: Investigation; Validation; Writing—Review & editing. Maximilian W. M. Wintergerst: Investigation; Writing—Review & editing. Jan H. Terheyden: Investigation; Writing—Review & editing. Behrem Aslan: Investigation; Writing—Review & editing. Wolf M. Harmening: Conceptualization; Project administration; Resources; Supervision; Writing—Review & editing. Ulrich Ettinger: Conceptualization; Project administration; Resources; Supervision; Writing—Review & editing.

Funding Information

Wolf M. Harmening: Emmy Noether Program of the German Research foundation (Ha5323/5-1).

Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance. The authors of this article report its proportions of citations by gender category to be as follows: M/M = .649, W/M = .243, M/W = .108, and W/W = 0.

Note

1. Note that additional analyses, excluding the newly established outer and inner incongruent conditions to make the data comparable to our previous study, confirmed the previously observed increased congruency effect for RT under lorazepam (Faßbender et al., 2021).

REFERENCES

Baldwin, D. S., Aitchison, K., Bateson, A., Curran, H. V., Davies, S., Leonard, B., et al. (2013). Benzodiazepines: Risks and benefits. A reconsideration. *Journal of Psychopharmacology*, *27*, 967–971. https://doi.org/10.1177/0269881113503509, PubMed: 24067791

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology*, *108*, 44–79. https://doi.org/10.1016/j.pneurobio.2013.06.005, PubMed: 23856628

Bond, A., & Lader, M. H. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology*, *47*, 211–218. https://doi.org/10.1111/j.2044-8341.1974.tb02285.x

Burk, J. A., Blumenthal, S. A., & Maness, E. B. (2018). Neuropharmacology of attention. *European Journal of Pharmacology*, *835*, 162–168. https://doi.org/10.1016/j.ejphar.2018.08.008, PubMed: 30092180

Bustamante, E. A., & Spain, R. D. (2008). Measurement invariance of the NASA TLX. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, *52*, 1522–1526. https://doi.org/10.1177/154193120805201946

Caparos, S., & Linnell, K. J. (2012). Trait anxiety focuses spatial attention. *Emotion*, *12*, 8–12. https://doi.org/10.1037/a0026310, PubMed: 22148993

Clariá, F., Vallverdú, M., Riba, J., Romero, S., Barbanoj, M. J., & Caminal, P. (2011). Characterization of the cerebral activity by time-frequency representation of evoked EEG potentials. *Physiological Measurement*, *32*, 1327–1346. https://doi.org/10.1088/0967-3334/32/8/021, PubMed: 21765206

Cohen, J. (1973). Eta-squared and partial eta-squared in fixed factor ANOVA designs. *Educational and Psychological Measurement*, *33*, 107–112. https://doi.org/10.1177/001316447303300111

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*, 201–215. https://doi.org/10.1038/nrn755, PubMed: 11994752

Coull, J. (1998). Neural correlates of attention and arousal: Insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress in Neurobiology*, *55*, 343–361. https://doi.org/10.1016/S0301-0082(98)00011-2, PubMed: 9654384

Danielmeier, C., Wessel, J. R., Steinhauser, M., & Ullsperger, M. (2009). Modulation of the error-related negativity by response conflict. *Psychophysiology*, *46*, 1288–1298. https://doi.org/10.1111/j.1469-8986.2009.00860.x, PubMed: 19572907

de Bruijn, E. R. A., Hulstijn, W., Verkes, R. J., Ruigt, G. S. F., & Sabbe, B. G. C. (2004). Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology*, *177*, 151–160. https://doi.org/10.1007/s00213-004-1915-6, PubMed: 15578258

de Visser, S. J., van der Post, J. P., de Waal, P. P., Cornet, F., Cohen, A. F., & van Gerven, J. M. A. (2003). Biomarkers for the effects of benzodiazepines in healthy volunteers. *British Journal of Clinical Pharmacology*, *55*, 39–50. https://doi.org/10.1046/j.1365-2125.2002.t01-10-01714.x, PubMed: 12534639

Elliott, H. W. (1976). Metabolism of lorazepam. *British Journal of Anaesthesia*, *48*, 1017–1023. https://doi.org/10.1093/bja/48.10.1017, PubMed: 10938

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*, 143–149. https://doi.org/10.3758/BF03203267

Eriksen, C. W., & St. James, J. D. (1986). Visual attention within and around the field of focal attention: A zoom lens model. *Perception & Psychophysics*, *40*, 225–240. https://doi.org/10.3758/BF03211502, PubMed: 3786090

Faßbender, K., Bey, K., Lippold, J. V., Aslan, B., Hurlemann, R., & Ettinger, U. (2021). GABAergic modulation of performance in response inhibition and interference control tasks. *Journal of Psychopharmacology*, *35*, 1496–1509. https://doi.org/10.1177/02698811211032440, PubMed: 34278874

Forster, S. E., Carter, C. S., Cohen, J. D., & Cho, R. Y. (2011). Parametric manipulation of the conflict signal and control-state adaptation. *Journal of Cognitive Neuroscience*, *23*, 923–935. https://doi.org/10.1162/jocn.2010.21458, PubMed: 20146615

Granger, A. J., Mulder, N., Saunders, A., & Sabatini, B. L. (2016). Cotransmission of acetylcholine and GABA. *Neuropharmacology*, *100*, 40–46. https://doi.org/10.1016/j.neuropharm.2015.07.031, PubMed: 26220313

Greenblatt, D. J. (1981). Clinical pharmacokinetics of oxazepam and lorazepam. *Clinical Pharmacokinetics*, *6*, 89–105. https://doi.org/10.2165/00003088-198106020-00001, PubMed: 6111408

Hart, S. G., & Staveland, L. E. (1988). Development of NASA-TLX (task load index): Results of empirical and

theoretical research. In P. A. Hancock & N. Meshkati (Eds.), *Advances in psychology: Human mental workload* (Vol. 52, pp. 139–183). Elsevier. https://doi.org/10.1016/S0166-4115(08)62386-9

Hopf, J.-M., Boehler, C. N., Luck, S. J., Tsotsos, J. K., Heinze, H.-J., & Schoenfeld, M. A. (2006). Direct neurophysiological evidence for spatial suppression surrounding the focus of attention in vision. *Proceedings of the National Academy of Sciences, U.S.A.*, *103*, 1053–1058. https://doi.org/10.1073/pnas.0507746103, PubMed: 16410356

Hübner, R., & Töbel, L. (2012). Does attentional selectivity in the flanker task improve discretely or gradually? *Frontiers in Psychology*, *3*, 434. https://doi.org/10.3389/fpsyg.2012.00434, PubMed: 23112779

Kassambara, A. (2021). *Rstatix: Pipe-friendly framework for basic statistical tests* (Version 0.7.0) [R Package]. CRAN. https://CRAN.R-project.org/package=rstatix

Knoflach, F., & Bertrand, D. (2021). Pharmacological modulation of $GABA_A$ receptors. *Current Opinion in Pharmacology*, *59*, 3–10. https://doi.org/10.1016/j.coph.2021.04.003, PubMed: 34020139

Kyriakopoulos, A. A., Greenblatt, D. J., & Shader, R. I. (1978). Clinical pharmacokinetics of lorazepam: A review. *Journal of Clinical Psychiatry*, *39*, 16–23. PubMed: 30762

LaBerge, D., Brown, V., Carter, M., Bash, D., & Hartley, A. (1991). Reducing the effects of adjacent distractors by narrowing attention. *Journal of Experimental Psychology: Human Perception and Performance*, *17*, 65–76. https://doi.org/10.1037/0096-1523.17.1.65, PubMed: 1826323

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for *t* tests and ANOVAs. *Frontiers in Psychology*, *4*, 863. https://doi.org/10.3389/fpsyg.2013.00863, PubMed: 24324449

Lawrence, M. A. (2016). *Ez: Easy analysis and visualization of factorial experiments* (Version 4.4-0) [R Package]. CRAN. https://CRAN.R-project.org/package=ez

Moore, T., & Zirnsak, M. (2017). Neural mechanisms of selective visual attention. *Annual Review of Psychology*, *68*, 47–72. https://doi.org/10.1146/annurev-psych-122414-033400, PubMed: 28051934

Müller, N. G., & Kleinschmidt, A. (2004). The attentional 'spotlight's' penumbra: Center-surround modulation in striate cortex. *NeuroReport*, *15*, 977–980. https://doi.org/10.1097/00001756-200404290-00009, PubMed: 15076718

Nigg, J. T. (2001). Is ADHD a disinhibitory disorder? *Psychological Bulletin*, *127*, 571–598. https://doi.org/10.1037/0033-2909.127.5.571, PubMed: 11548968

Noudoost, B., & Moore, T. (2011). The role of neuromodulators in selective attention. *Trends in Cognitive Sciences*, *15*, 585–591. https://doi.org/10.1016/j.tics.2011.10.006, PubMed: 22074811

Pattij, T., & Schoffelmeer, A. N. M. (2015). Serotonin and inhibitory response control: Focusing on the role of $5\text{-}HT_{1A}$ receptors. *European Journal of Pharmacology*, *753*, 140–145. https://doi.org/10.1016/j.ejphar.2014.05.064, PubMed: 25094037

Pratte, M. S. (2021). Eriksen flanker delta plot shapes depend on the stimulus. *Attention, Perception, & Psychophysics*, *83*, 685–699. https://doi.org/10.3758/s13414-020-02166-0, PubMed: 33155124

R Core Team. (2021). *R: A language and environment for statistical computing* [Computer Software]. https://www.R-project.org/

Riba, J., Rodríguez-Fornells, A., Münte, T. F., & Barbanoj, M. J. (2005). A neurophysiological study of the detrimental effects of alprazolam on human action monitoring. *Cognitive Brain Research*, *25*, 554–565. https://doi.org/10.1016/j.cogbrainres.2005.08.009, PubMed: 16168630

Ridderinkhof, K. R. (2002). Activation and suppression in conflict tasks: Empirical clarification through distributional analyses. In W. Prinz & B. Hommel (Eds.), *Common mechanisms in perception and action: Attention and performance XIX* (pp. 494–519). Oxford University Press. https://hdl.handle.net/11245/1.419995

Ridderinkhof, K. R., Scheres, A., Oosterlaan, J., & Sergeant, J. A. (2005). Delta plots in the study of individual differences: New tools reveal response inhibition deficits in AD/HD that are eliminated by methylphenidate treatment. *Journal of Abnormal Psychology*, *114*, 197–215. https://doi.org/10.1037/0021-843X.114.2.197, PubMed: 15869351

Ridderinkhof, K. R., Wylie, S. A., van den Wildenberg, W. P. M., Bashore, T. R., & van der Molen, M. W. (2021). The arrow of time: Advancing insights into action control from the arrow version of the Eriksen flanker task. *Attention, Perception, & Psychophysics*, *83*, 700–721. https://doi.org/10.3758/s13414-020-02167-z, PubMed: 33099719

Stanley, D. (2021). *apaTables: Create American Psychological Association (APA) style tables* (Version 2.0.8) [R Package]. CRAN. https://CRAN.R-project.org/package=apaTables

Stoet, G. (2010). PsyToolkit: A software package for programming psychological experiments using Linux. *Behavior Research Methods*, *42*, 1096–1104. https://doi.org/10.3758/BRM.42.4.1096, PubMed: 21139177

Stoet, G. (2017). PsyToolkit: A novel web-based method for running online questionnaires and reaction-time experiments. *Teaching of Psychology*, *44*, 24–31. https://doi.org/10.1177/0098628316677643

Tannenbaum, C., Paquette, A., Hilmer, S., Holroyd-Leduc, J., & Carnahan, R. (2012). A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs & Aging*, *29*, 639–658. https://doi.org/10.1007/BF03262280, PubMed: 22812538

Ulrich, R., Schröter, H., Leuthold, H., & Birngruber, T. (2015). Automatic and controlled stimulus processing in conflict tasks: Superimposed diffusion processes and delta functions. *Cognitive Psychology*, *78*, 148–174. https://doi.org/10.1016/j.cogpsych.2015.02.005, PubMed: 25909766

Uusi-Oukari, M., & Korpi, E. R. (2010). Regulation of $GABA_A$ receptor subunit expression by pharmacological agents. *Pharmacological Reviews*, *62*, 97–135. https://doi.org/10.1124/pr.109.002063, PubMed: 20123953

Wegbreit, E., Franconeri, S., & Beeman, M. (2015). Anxious mood narrows attention in feature space. *Cognition & Emotion*, *29*, 668–677. https://doi.org/10.1080/02699931.2014.922933, PubMed: 24901246

White, C. N., Ratcliff, R., & Starns, J. J. (2011). Diffusion models of the flanker task: Discrete versus gradual attentional selection. *Cognitive Psychology*, *63*, 210–238. https://doi.org/10.1016/j.cogpsych.2011.08.001, PubMed: 21964663

Wickham, H. (2016). *ggplot2: Elegant graphics for data analysis* (Version 3.3.6) [R Package]. New York: Springer-Verlag. https://ggplot2.org. https://doi.org/10.1007/978-3-319-24277-4

Wickham, H., François, R., Henry, L., & Müller, K. (2021). *dplyr: A grammar of data manipulation* (Version 1.0.9) [R Package]. CRAN. https://CRAN.R-project.org/package=dplyr

Wittenborn, J. R. (1979). Effects of benzodiazepines on psychomotor performance. *British Journal of Clinical Pharmacology*, *7(Suppl. 1)*, 61S–67S. https://doi.org/10.1111/j.1365-2125.1979.tb04667.x, PubMed: 35207

Yang, A. C., & Tsai, S.-J. (2017). New targets for schizophrenia treatment beyond the dopamine hypothesis. *International Journal of Molecular Sciences*, *18*, 1689. https://doi.org/10.3390/ijms18081689, PubMed: 28771182