Lorazepam induces multiple disturbances in selective attention: attentional overload, decrement in target processing efficiency, and shifts in perceptual discrimination and response bias

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*J Psychopharmacol* 2007; 21: 691 originally published online Jan 26, 2007; DOI: 10.1177/0269881106074011

The online version of this article can be found at: http://jop.sagepub.com/cgi/content/abstract/21/7/691
Lorazepam induces multiple disturbances in selective attention: attentional overload, decrement in target processing efficiency, and shifts in perceptual discrimination and response bias

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Abstract

There is a general consensus that benzodiazepines affect attentional processes, yet only few studies have tried to investigate these impairments in detail. The purpose of the present study was to investigate the effects of a single dose of lorazepam on performance in a target cancellation task with important time constraints. We measured correct target detections and correct distractor rejections, misses and false positives. The results show that lorazepam produces multiple kinds of shifts in performance, which suggests that it impairs multiple processes: (a) the evolution of performance over time was not the same between the placebo and the lorazepam groups, with the lorazepam affecting performance quite early after the beginning of the test. This is suggestive of a depletion of attentional resources during sequential attentional processing; (b) lorazepam affected differently target and distractor processing, with target detection being the most impaired; (c) misses were more frequent under lorazepam than under placebo, but no such difference was observed as far as false positives were concerned. Signal detection analyses showed that lorazepam (d) decreased perceptual discrimination, and (e) reliably increased response bias. Our results bring new insights on the multiple effects of lorazepam on selective attention which, when combined, may have deleterious effects on human performance.

Keywords
lorazepam, benzodiazepine, visual selective attention, cancellation task, signal detection

Introduction

Attentional selectivity is the basic mechanism through which only a limited amount of the flow of incoming visual information is adequately processed. It is involved in almost all everyday activities, ranging from scanning and the visual search for targets on maps to driving and machine control. Attentional failures are frequently responsible for human errors and have been reported even after acute benzodiazepine administration among other cognitive impairments such as memory, oculomotor control, visual spatial and perceptual abilities (Danion et al., 1989; Vidalhiet et al., 1994; Giersch et al., 1995, 1996; Masson et al., 2000; Beckers et al., 2001; Speeg-Schatz et al., 2001; see Buffett-Jerrott and Stewart, 2002 for a review). Even though benzodiazepines are widely prescribed for the treatment of disorders like anxiety and insomnia (Kaplan, 2005), little is known about the specific attentional disturbances they induce.

Using the Posner’s paradigm involving detection of a visual target presented on the right or left of fixation, two studies have shown that the benzodiazepine triazolam impairs spatial selectivity (Johnson et al., 1995; Carter et al., 1998). The location of the impeding target is briefly pre-cued with either peripheral increments in luminance (exogenous cues that drive attention involuntarily) or arrows presented at fixation (endogenous cues that direct
attention voluntarily). Both cueing modes result in shorter response times (RT) when the target appears at cued rather than uncued locations. Johnson and colleagues (1995) found that, compared with placebo-treated participants, RT following both exogenous and endogenous cues were slowed by triazolam. Most interestingly, the difference between cued and uncued targets in terms of detection speed was sharper in the case of triazolam than placebo. The authors suggested that rather than affecting attention allocation triazolam affected attentional disengagement. A second study conducted by Carter and colleagues (1998) showed that the detection benefits for targets appearing at cued locations were greater for triazolam-treated participants than for those who received the placebo. The authors suggested that triazolam might lead to an increase in facilitation or a reduction in inhibition for involuntary attention. The discrepancies between the two studies may be due to paradigm variations and/or the difference in the dose of triazolam used in the studies. Post and colleagues (1997) used a different paradigm to assess the effects of the benzodiazepine lorazepam on the spatial distribution of attention. Subjects were asked to detect changes (onsets or offsets) in the luminance of LEDs located near fixation or far from it. The authors reported that, in the onset task, lorazepam produced only a general slowing in detection wherever the signal was located, but that it produced a specific effect in the detection of offsets located far from fixation. They argued that this might reflect impairments in attentional disengagement. In light of more recent findings, an alternative account can be proposed. The detection of offsets is more difficult than that of onsets (as may be noticed in the performance of the detection account can be proposed. The detection of offsets is more difficult than that of onsets (as may be noticed in the performance of the detection account (LaBerge, 2002), visual selective attention operates by suppressing unwanted stimuli and enhancing the processing of attended ones. Thus, a proper investigation of attentional efficiency should consider the correct processing of both target and non-target items, as well as their respective attentional flaws, misses and false positives. To our knowledge, little is known about the effects of benzodiazepines on these measures, which are thought to reflect distinct and qualitatively different processes involved in selective attention.

The present study was designed to investigate the effects of a single dose of lorazepam on different measures of attention in a newly developed cancellation task (test of focused attention; TFA 2000) where subjects are required to find and cross out all complete circles among circles with small gaps (Fig. 1). Random search is prevented by the arrangement of the stimuli in ten rows of 30 items each, which subjects have to scan in a sequential manner, from left to right. Subjects may scan each row only for a very short time before moving on to the next row. This arrangement also allows performance to be analysed for individual rows and changes in performance to be investigated over time. The substantial time constraints of this task can induce more attentional flaws (misses and false positives), and, associated with the relatively large number of items in each row, they may lead to attentional overload and, therefore, can induce depletions in attentional resources. The discrepancies between the studies of Gorissen and Eling (1998) and Boucart et al. (2000) may be due to the kinds of tasks used and/or the sensitivity of the RSVP tasks. Another important source of information about the effects of benzodiazepines on selective attention is performance in clinical target cancellation tasks. In these commonly used tasks, subjects have to search for and mark predefined targets presented among distractors. Decreased performance has constantly been reported after acute benzodiazepine administration (Vidaillhet et al., 1994, 1996; Fluck et al., 2001; Buffet-Jerrott et al., 2002), and has been interpreted as evidence of attentional impairment. For instance, Vidaillhet and colleagues (1994) reported that both lorazepam and diazepam induced a decrement in the total number of symbols processed in a cancellation task, and a later study conducted by Vidaillhet et al. (1996) showed that these impairments were dose dependent for both treatments. Furthermore, the effects of lorazepam on performance were stronger than those induced by diazepam in both studies. Fluck and colleagues (2001) reported similar decrements in performance induced by high doses of lorazepam (2.5 mg). They furthermore showed that these changes were different from those resulting from normal ageing. There is a major problem with interpreting the results of cancellation tasks, however, since only the total number of correctly detected targets is examined. The question is whether decrements in performance really do represent attentional disturbances, or whether they reflect pure psychomotor slowing due to sedation. Providing a number of precautions are taken, cancellation tasks may offer more precise insights into attentional disturbances due to acute benzodiazepine administration. For instance, according to a widely accepted account (LaBerge, 2002), visual selective attention operates by suppressing unwanted stimuli and enhancing the processing of attended ones. Thus, a proper investigation of attentional efficiency should consider the correct processing of both target and non-target items, as well as their respective attentional flaws, misses and false positives. To our knowledge, little is known about the effects of benzodiazepines on these measures, which are thought to reflect distinct and qualitatively different processes involved in selective attention.
resources. Finally, more sophisticated performance analyses are possible, such as signal detection. On the basis of previous findings, we hypothesized that lorazepam would induce (a) a general psychomotor slowing as indexed through the general decrement of performance (Vidalhêt et al., 1994, 1996; Fluck et al., 2001), (b) decreased efficiency in sequential processing, most probably indexed by a larger number of misses (Boucart et al., 2000) and (c) a marked decrement of performance over time due to the depletion of attentional resources (Boucart et al., 2000; Boucart et al., in press).

Methods and materials

Subjects

Thirty-three healthy volunteers (14 men and 19 women; mean age: 22.7 ± 1.9 years; mean weight: 60 ± 11 kg) were recruited from the University of Strasbourg. They all reported normal or corrected-to-normal vision. They were randomly assigned to two distinct treatment groups, placebo (N = 17; nine females and eight males) and lorazepam (N = 16; ten females and six males), matched in age (placebo: 22.3 ± 1.6; lorazepam: 23.1 ± 2.1; t(31) = 0.11, p > 0.91), estimated IQ according to the AVB test (Beau Regards, 1971; placebo: 106 ± 8.8; lorazepam: 107 ± 8.1; t(31) = 0.77, p > 0.45) and weight (placebo: 60.4 ± 7.1 kg; lorazepam: 59.6 ± 14.3 kg; t(31) = 0.82, p > 0.41). All subjects gave their written informed consent and were paid for their participation. They had no medical illness or history of alcoholism, drug abuse or tobacco consumption in excess of ten cigarettes/day. Participants with a high consumption of coffee, tea (more than three cups a day) or cola-cola were not included in the study. Participants were not chronic users of benzodiazepines and had taken no medication for at least 15 days. They were instructed to refrain from drinking beverages containing caffeine or alcohol for the 24h immediately prior to the study. The protocol was approved by the Faculty Ethics Committee.

Drug administration

This was a double-blind study. The drug capsule (placebo or lorazepam 0.038 mg/kg) was administered orally in the morning (at 7.30 AM), after an overnight fast. The dose of lorazepam was specifically calculated and prepared for each participant. This dose corresponds to a commercial tablet of 2.5 mg for a person weighing 65 kg, and is commonly used for studies in experimental psychology (e.g. Bacon et al., 1998). The participants were fasting for the duration of the study and were not allowed to smoke during the whole day of the experiment. The plasmatic peak of lorazepam being attained approximately 90 min following intake, and its effects lasting approximately 2 hours (Harvey, 1980; Legrand et al., 1995), the test reported here was administered approximately 3 hours after the drug intake.

TFA 2000 stimuli

Stimuli consisted of small black circles (radius: 0.2 cm). Target items were complete circles, and distractors were circles comprising a 0.2 cm gap at one of eight different locations around the circumference: 0°, 45°, 90°, 135°, 180°, 225°, 270° and 315°. The test was presented on a white sheet of paper (29.7 × 21 cm) and consisted of ten numbered rows. Each row was 18 cm long (from the centre of the first item to the centre of the last) and 1 cm from the following row. An arrow signalled the starting point. Each row comprised 30 items equally spaced (0.6 cm centre-to-centre), including ten targets. In each row, each target was randomly separated from the next by one to four distractors. The first item of the first row was a target so as to encourage subjects to be prepared to cross it out and so that they were less inclined to search for the other targets before the beginning of the test. A single target was shown at the top of the page and was followed by a practice row. The stimuli were created on the basis of previous studies (Treisman and Gormican, 1988), which had shown that the detection of a complete circle among open circles requires serial, attentive visual search.

TFA 2000 procedure

The test was administered 3 hours after the drug intake (i.e. at 10.30 AM). Each participant was given a pen and one test page. He/she was shown the isolated target at the top of the page and asked to proceed from left to right and to mark all the targets in a practice row. The instructions were given again after the practice row in order to be sure that subjects had understood the purpose of the task, and then subjects were required to proceed with the first row (indicated by an arrow) in a similar way and as quickly as possible. They were told they had a limited amount of time for each row but were not informed of the precise time limits. The experimenter then gave the ‘start’ signal, and subjects were given only 7 s to scan the row and mark all the targets. At the end of this critical period, a ‘line change’ signal was given, and subjects had to pass immediately to the beginning of the next row and look for targets, and so on. If a subject reached the end of a row before the end of the 7-s period (this was generally not the case), he/she was asked not to go on to the next row until the examiner gave the ‘line change’ signal. Only the explored portions of each row were analysed, that is, the parts included between the first item of each row and the last item the subjects had marked before the ‘change line’ signal. Items included in the remaining not explored part of the row were not naturally analysed. Within the explored portions, different measures of performance were considered: (a) the

![Figure 1](https://example.com/figure1.png)

**Figure 1** Illustration of the TFA 2000 test. Subjects were asked to start scanning the first row and cross out all the targets (complete circles) for 7 s only, then instructed with a ‘line change’ signal to pass to the next row, and so forth. The test contained ten rows, made of ten targets and twenty distractors each. Stími are not shown in scale.
percentage of hits (i.e. correctly marked targets), (b) the percentage of correct rejections (i.e. avoided distractors), (c) the percentage of misses (i.e. omitted targets) and (d) the percentage of false positives (i.e. marked distractors). In addition, these four measures were used to compute two signal detection theory (SDT) parameters: the sensitivity index d' and the response bias β. Sensitivity index d' represents the state of the sensory system whilst β represents the subject’s decisional criterion.

Measure of sedation

Benzodiazepines have known sedative effects (see Stewart, 2005 for a review). Sedation was therefore evaluated using the Stanford Sleepiness Scale (Hoddes et al., 1973). Each subject had to self-evaluate the degree of sedation by marking one out of seven assertions, each representing a degree of sedation (1: no sedation, 7: high sedation). The score contained an eighth point that was completed by the examiner in cases where the subject was sleeping, but this point was never used. The scale was completed four times: once before (at 7.15 AM), and three times after the drug intake (at 10.00 AM, 11.30 AM and 2.00 PM).

Statistics

Three different measures of the TFA 2000 were submitted to different statistical analyses.

(a) The time course of performance was investigated by submitting the mean percentage of hits and the mean percentage of correct rejections for steps comprising two successive rows (step 1 = rows 1 + 2; step 2 = rows 3 + 4 etc.) to a three-way analysis of variance, with the response type (hit vs correct rejection) and steps (one to five) as the within-subjects factors, and the treatment group (placebo vs lorazepam) as the between-groups factor. Furthermore, the time course of performance was investigated by comparing the course trend index of each group to the zero value with paired t-tests in order to detect any changes in performance over time, and the comparison between the lorazepam and the placebo groups was done with unpaired t-tests.

(b) Attentional flaws (errors) were investigated by submitting the percentage of misses and the percentage of false positives to a two-way analysis of variance, with the error type (miss vs false positive) as the within-subjects factor and the treatment group (placebo vs lorazepam) as the between-groups factor. For the two previous measures, post hoc comparisons were carried out with the Newman-Keuls test.

(c) The state of the sensory and decisional processes were examined by comparing the performance (d' and β indexes) of the two treatment groups using unpaired t-tests.

(d) On the other hand, the evolution of sedation over time was examined by subjecting the scores obtained using the Stanford Sleepiness Scale to an analysis of variance, with the time of day (7.15 AM, 10.00 AM, 11.30 AM, 2.00 PM) as the within-subjects factor and the treatment group (placebo vs lorazepam) as the between-groups factor. The reported correlation analyses between the sedation scores and the measures in the TFA 2000 test were carried out with the Bravais-Pearson r-test. Even though recent studies have shown that males and females may react differently to benzodiazepines (Jackson et al., 2005), the statistical analyses did not include gender as a between-group factor for several reasons: first, the number of males and females in the lorazepam group was not equivalent; second, including the gender as a factor would divide each treatment group to two quite smaller groups. The bias introduced by each of these two factors would thus weaken the strength of any statistically significant result and would inevitably render interpretations less plausible.

Results

Time course of performance

The main effect of treatment reached significance (F(1,30) = 26.3, p < 0.00001), due to a lower percentage of correctly processed items for the lorazepam group (75.1%) than for the placebo group (91%). This reflects a general psychomotor slowing, closely associated with the sedative properties of the lorazepam. The treatment × step interaction was marginally significant (F(4,120) = 2, p < 0.09). This interaction was due to a decrement of performance for the lorazepam group after step one (all ps < 0.01), which contrasted with the stable performance of the placebo group over time (all ps > 0.57; Fig. 2 panel A). Despite the short duration of the test, it seems that lorazepam impairs continuous information processing quite soon after the beginning of the test. It is unlikely that this result reflects sedation, given that sedative effects are not expected to have multiple influences on attentional performance during as short a period as the one used here (the test lasted 70 s). Instead, the result probably reflects a depletion of attentional resources (Boucart et al., 2000), the effects of which may be manifested shortly after the beginning of the test. The analysis of the course trend index confirmed the previous results. As a point of fact, only the lorazepam group significantly moved away from the zero value (course trend index = −23; t(15) = 2.6, p < 0.02) whilst the placebo group presented with a virtually unchanged performance over time (course trend index = −1.3; t(16) = 0.2, p > 0.87). Furthermore, the course trend index of the two treatment groups differed significantly (t(31) = 2.14; p < 0.04). Most interestingly, there was a significant treatment group × item type interaction (F(1,30) = 9.55, p < 0.004), suggesting that the effects of treatment on target were not the same as on distractor processing. As a matter of fact, the placebo group processed targets (90.6%) and distractors (91.4%) equally well (p > 0.26), whilst the lorazepam group processed fewer targets (72.8%) than distractors (77.4%; p < 0.0001). This result suggests that, in addition to a possible depletion of attentional resources, lorazepam selectively impaired target processing processes. Another interesting result of fundamental importance was the significant item type × step interaction (F(4,120) = 11.2, p < 0.00001). As may be seen in Fig. 2 (panel B), the time course
of target processing was different from that of distractor processing. Target processing decreased sharply at the second step ($p < 0.0002$), then increased ($p < 0.04$) and reached an asymptotic level at the third step ($p > 0.71$). Conversely, the processing of distractors decreased only at the third step ($p < 0.0001$), then gradually increased in steps three ($p < 0.12$) and four ($p < 0.039$), until it reached the initial level at the fifth step ($p > 0.605$). This finding suggests there are indeed fundamental qualitative differences between the processing of targets and the processing of distractors. This is quite a valid reason for investigating the two measures separately. Finally, the three-way treatment $\times$ item type $\times$ step failed to reach significance ($F(4,120) = 1.14$, $p > 0.34$), suggesting that the previous target/distractor distinction was clearly not an effect of treatment.

**Errors**

The results are given in Fig. 3 (panel A). The main effect of treatment was significant ($F(1,31) = 6.36$, $p < 0.018$), due to more errors for the lorazepam (2.35%) than the placebo group (0.72%). The main effect of error type was also significant ($F(1,31) = 15.3$, $p < 0.0005$), with misses (2.72%) more frequent than false positives (0.36%). Finally, the treatment $\times$ error type interaction reached significance ($F(1,31) = 5.55$, $p < 0.025$). The lorazepam group omitted more targets than the placebo group (4.23% vs 1.19%; $p < 0.0013$), whilst no such difference was found in respect of the false positives (0.46% vs 0.25%; $p > 0.81$). Furthermore, for the lorazepam group, misses were more frequent than false positives ($p < 0.0004$), whilst no such difference was evidenced for the placebo group ($p > 0.52$).

**Signal detection analysis**

The lorazepam group had a significantly lower sensitivity index ($d' = 4.41$) than the placebo group ($d' = 4.96$, $t(31) = 2.88$, $p < 0.004$), and a higher response bias ($\beta = 7.11$ vs $\beta = 3.44$ for lorazepam and placebo, respectively; $t(31) = 1.76$, $p < 0.044$). These results (Fig. 3, panel B) intimate that the changes in performance caused by the intake of lorazepam concerned both the sensory processing of visual signals and the decisional stages responsible for setting a response criterion. More specifically, the lorazepam group showed decreased ability to differentiate between targets and distractors. In addition, lorazepam-treated subjects adopted a more conservative response criterion, meaning they were inclined to respond that the target was missing. This last result is in line with the analysis of the error pattern, which clearly showed the tendency of the lorazepam-treated subjects to miss targets.

**Sedation**

The results are given in Table 1. The main effects of treatment group reached significance ($F(1,31) = 8.41$, $p < 0.01$), with the lorazepam group scoring higher levels of sleepiness (3.53 vs 2.46). The treatment group $\times$ time of day interaction also reached significance ($F(3,93) = 3$, $p < 0.03$). Paired comparisons revealed similar scores for both groups at 7.15 AM (2.56 vs 2.65 for lorazepam and placebo, respectively; $t(31) = 0.14$, $p > 0.88$) and at 2.00 PM (4.31 vs 3.12 for lorazepam and placebo, respectively; $t(31) = 1.64$, $p > 0.11$), but the lorazepam group recorded higher levels (3.44) of sleepiness than the placebo group (2.18) at 10.00 AM ($t(31) = 2.9$, $p < 0.007$) and at 11.30 AM (3.81 vs 1.88 for lorazepam and placebo, respectively; $t(31) = 4.64$, $p < 0.0005$).
lorazepam and placebo, respectively; \( r(31) = 4.44, p < 0.0001 \). The unique value of the TFA 2000 which correlated with the sedation scores at moments of high sedation was the mean percentage of correctly processed items (targets and distractors) (at 11.30 AM \( r(31) = -0.344, p < 0.049 \)), a result that backs up the account that decrements observed for this value reflect sedation-related psychomotor slowing.

**Discussion**

A controlled clinical cancellation task with important attention-loading characteristics was used here to assess the effects of a single dose of lorazepam, a commonly prescribed benzodiazepine, on different aspects of selective attention. The results show that lorazepam induces specific and reliable shifts in multiple measures of performance, suggesting that it acts at multiple levels of attentional processing.

The findings can be summarized as follows. First, the percentage of correctly processed items (targets and distractors) decreased with lorazepam. Several previous studies have found similar effects after intake of lorazepam or other benzodiazepines (Vidalhét et al., 1994, 1996; Fluck et al., 2001) and were interpreted as a decrement in attentional efficiency. However, cancellation tasks have a strong motor component and such performance decrements can be attributed to sedation-related psychomotor slowing. This account is of course backed up by the significant correlation of this measure with sedation.

Second, the time course of correct performance was not the same for the placebo group as for the lorazepam-treated group. The performance of the placebo was unchanged throughout the five successive steps, whereas that of the lorazepam-treated group decreased sharply quite soon after the test had started. This was confirmed and extended by the results of the course trend index according to which only the lorazepam group exhibited diminished performance over time. It is unlikely that this result reflects impairments in sustained attention (Fluck et al., 2001) because of the very short duration of the test. It is also unlikely that the time course of performance be linked to sedation, and this is attested through the absence of significant correlation between the course trend index and the Stanford Sleepiness Scale. The absence of link

**Table 1** Mean scores (1SD) of sedation according to the Stanford Sleepiness Scale before (7.15AM) and after the drug intake

<table>
<thead>
<tr>
<th>Time of the day</th>
<th>7.15 AM</th>
<th>10.00 AM</th>
<th>11.30 AM</th>
<th>2.00 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.65 (1.27)</td>
<td>2.18 (1.13)</td>
<td>1.88 (0.99)</td>
<td>3.12 (1.73)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2.56 (2.06)</td>
<td>3.44 (1.36)</td>
<td>3.81 (1.47)</td>
<td>4.31 (2.41)</td>
</tr>
</tbody>
</table>

**Figure 3** Panel A depicts the mean (+1SE) percentage of misses and false positives for each treatment group. Panel B shows the results of the signal detection analysis for each treatment group with the mean \( d' \) (±1SE horizontal) being plotted as a function of the mean \( \beta \) (±1SE vertical). *\( p < 0.044 \), **\( p < 0.004 \), ***\( p < 0.0013 \), ****\( p < 0.0004 \).
with sedation, as is also the case for all other measures of the TFA 2000 (except general performance), is reminiscent of the effects of benzodiazepines on memory, which are usually considered as being independent of their sedative effects (Hurón et al., 2002; Mintzer and Griffith, 2003). Conversely, and as pointed out earlier, the TFA 2000 has attention-loading characteristics because it combines its important time limits with the requirement to process a relatively large number of items that are physically similar. It can thus lead to a depletion of attentional resources quite early on. Previous studies have shown that attention-loading tasks may have deleterious effects on performance after benzodiazepine intake. Furthermore, it has been shown that sequential processing of targets is quite impaired with these drugs (Boucart et al., 2000, in press). Of course, it is difficult to assess sequential processing in cancellation tasks, but one might think that it really occurs in the TFA 2000 because of the serial arrangement of the items to scan. In light of these studies, the sharp decrement in performance observed after lorazepam intake suggests a cognitive overload, leading to the depletion of attentional resources during sequential attentional processing.

Third, lorazepam affected correct target and distractor processing differently, with target detection being the most impaired. Fourth, misses were more frequent under lorazepam than under placebo, while false positives remained unchanged. Taken together, these two complementary findings suggest that lorazepam-treated subjects have difficulty detecting the target. Conversely, lorazepam has virtually no effect on the processing of distractors. Boucart et al. (2000) found no effects of lorazepam and diazepam on the detection of a single target presented among distractors in an RSVP stream, whereas detection was severely impaired if more than one target was present. This may suggest that the lower percentage of correct hits and the higher number of misses observed in the present study may be due to the presence of multiple targets in each row. In a more recent study, however, Boucart and colleagues (in press) found that higher doses of diazepam (0.3 mg/kg) do affect the detection of a single target in RSVP streams. This of course leads us to suggest that benzodiazepines impair the detection of targets presented among distractors, regardless of whether there is only one target or multiple targets. The differences found here in the processing of targets and distractors suggest that hits and misses, and correct distractor rejections and false positives assess qualitatively different processes (LaBerge, 2002). This assumption is strengthened by the different time course of hits and correct rejections reported earlier in this paper and leads us to conclude that each of these measures should be considered in cancellation tasks in clinical trials.

There might be multiple sources for the target processing impairment induced by benzodiazepines, such as failures in oculomotor control and spatial attention shifts during serial scanning, and/or failures in perceptual discrimination. For instance, several studies have shown that benzodiazepines affect oculomotor control, such as oculomotor balance (Speer-Schatz et al., 2001), saccades and smooth pursuit (e.g. Roy-Byrne et al., 1993; Masson et al., 2000). However, there is no clear evidence of the effects of lorazepam or other drugs in the benzodiazepine group on oculomotor control and behaviour during serial scanning of aligned items, such as those observed during reading or in tasks like the TFA 2000 presented here. In addition, some studies have shown that benzodiazepines impair shifts of attention in space (Johnson et al., 1995; Carter et al., 1998) and dramatically reduce the distribution of spatial attention (Post et al., 1997). The combination of such effects may indeed result in inefficient scanning, therefore allowing targets in explored portions of space to be disregarded. Even though research involving serial scanning of items without oculomotor components (Boucart et al., 2000, in press) showed that target processing is impaired under benzodiazepine treatment, future research should investigate this particular issue.

On the other hand, Pang and Fowler (1994) reported that triazolam has selective effects on perceptual processing by slowing early stages of visual processing, located before feature extraction. Furthermore, several studies have shown that benzodiazepines seriously impair visual integrative processes (Giersch et al., 1995, 1996; Beckers et al., 2001) and prolong visual information processing (Giersch and Herzog, 2004). Thus, impaired target processing may be closely linked to shifts in visual perceptual discrimination. The signal detection analysis we conducted showed, indeed, that lorazepam decreased perceptual discrimination. The differences in performance between the placebo and the lorazepam-treated groups can thus be attributed, at least in part, to shifts in the ability to differentiate between targets and distractors. Finally, lorazepam intake reliably increased response bias, causing subjects to respond more frequently that the target was absent. Shifts in the response criterion, at least as far as memory is concerned, have already been reported in psychopharmacology research. For instance, Mintzer and Griffiths (2000, 2003) used a paradigm in which subjects were required to recognize previously seen words among new ones. The authors reported that triazolam, but not lorazepam, induced a shift towards a liberal response bias, i.e., subjects tended to respond more often that new items were part of the list of the words they had seen. This is obviously a completely different task from the one used here, but it is interesting that both the Mintzer and Griffiths (2000) study and the present one have evidenced benzodiazepine-induced changes in response criteria.

In conclusion, the use of multiple measures of performance in a simple and brief cancellation task revealed that lorazepam induces important attention disturbances, and that these disturbances concern multiple processes. These findings show, once again, that benzodiazepine treatment, not only induces sedation and psychomotor slowing, but also produces early and acute attentional overload, alters the processing of relevant information, and induces shifts in visual perceptual discrimination and response bias. Such changes may have detrimental effects on everyday activities, such as driving, reading and the handling of machinery. The combined effects of these impairments may lead to severe attention lapses and errors.

Notes

1 The Signal Detection Theory (SDT) assumes that stimulus events are detected by a two-stage process: during an early
sensory stage, the detected signal generates an internal response, which depends on the state of the observer’s sensory system. The output of this system does not rely on strategies or motivational factors. A later decision process is influenced by strategic and pay-off factors. It represents the subject’s tendency to select one response rather than another. At this stage, a response criterion/bias is set and the system must determine whether the value it receives from the sensory system resulted from a trial in which the signal was present or absent. Importantly, the two processes—sensory and decisional—are independent: either can be changed or impaired without affecting the other. The output of the sensory stage, called selectivity index (d’), can be computed with the formula d’ = z(H) – z(FP), where z(H) represents the z value of the standard normal distribution corresponding to the probability of hits, and z(FP) to the z value corresponding to the probability of false positives. The decision criterion (β) is computed with the formula β = exp{–0.5[z(H)2 – z(FP)2]}. For instance, if a subject detected correctly 45 out of the 67 targets contained in the portion he/she explored (proportion of hits = 0.625), and marked 8 non-targets out of 215 (proportion of false positives = 0.037), then: d’ = z(0.625) – z(0.037) = 0.319 – (–1.784) = 2.10; and β = exp{–0.5[0.3192 – (–1.784)2]} = 4.67.

It can thus be noted that the computation of d’ and β is exclusively based on hits and false positives, and this is because the remaining two measures, misses and correct rejections, are complementary to the other two. As a point of fact, if the computations are carried out on misses and correct rejections, the results are the same.

2 The course trend index is a value that represents the global tendency of performance following the first step. This index is negative when the subject’s performance decreases over time, positive if it increases and zero if no change is observed. The course trend index can be derived as follows:

(a) the percentage of correctly processed items in the first ‘step’ is subtracted from the remaining four ‘steps’, resulting in four values. For example, if the percentages of correctly processed items were, respectively, step 1 = 90, step 2 = 75, step 3 = 91, step 4 = 82, step 5 = 78, then subtracting step 1 from the other four steps results in step 2 = −15, step 3 = +1, step 4 = −8, step 5 = −12. The four resulting values are averaged. In the example, the absolute average value is 8.5.

(b) The absolute average value is then multiplied by the number of positive values resulting from the subtractions in ‘a’, and by the number of negative values. The difference between these two scores is the course trend index. In the example, there are one positive and three negative values. Thus, 1 * 8.5 = 8.5 and 3 * 8.5 = 25.5. The difference is thus 8.5 – 25.5 = −17. The negative sign suggests that the subject’s performance tends to diminish over time. Furthermore, the more the value is distant from zero (which represents the no-change value), the more ‘steps’ had the same trend.

(c) If any zero values result from the computations in ‘a’, then they are not included in the computation of the difference, since they do not contribute to the difference with step 1. Zero values already contribute to the average derived in ‘a’ and regulate its amplitude.

Acknowledgements
We would like to thank the editor and the reviewers for their commitment to helping us to make this a valuable contribution to the literature.

References

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