Psychopharmacology (2000) 152:249–255
DOI 10.1007/s002130000525

ORIGINAL INVESTIGATION

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Effect of benzodiazepine on temporal integration in object perception

Received: 9 June 1999 / Accepted: 17 May 2000 / Published online: 19 August 2000

Abstract *Rationale:* Though various psychometrical tests indicate that benzodiazepines affect vigilance, few studies have been conducted to assess the effect of benzodiazepines on attentional processes. *Objective:* We used a RSVP (Rapid Serial Visual Presentation) procedure to investigate the effect of benzodiazepines on the attentional blink effect. It refers to the difficulty in detecting a probe following identification of a target within a temporal window of 500 ms. *Method:* Three experimental groups were tested (placebo, lorazepam and diazepam). Sequences of 15 pictures were centrally displayed for 50 ms each. In a dual-task condition, observers were instructed (1) to identify the target (the single picture on a blue background) and (2) to detect the presence of a probe. In the single-task condition, subjects were asked to detect the probe. The serial position of the probe relative to the target was varied. *Results:* Performance was equivalent for the three groups in the single-task condition. In the dual-task condition, the attentional blink was increased in magnitude and duration for benzodiazepine-treated subjects, especially diazepam, than for placebo-treated subjects. A large number of intrusions (a tendency to report as target the name of a picture preceding the target) were observed in the benzodiazepine-treated groups. *Conclusion:* The results indicate that benzodiazepines impair visual integration in the temporal domain. This extends previous findings that benzodiazepine impairs visual integration in the spatial domain. The results also suggest that benzodiazepine increase time to disengage attention from a first to a second target.

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Key words Benzodiazepines · Lorazepam · Diazepam · Object recognition · Selective attention · Attentional blink

Introduction

Benzodiazepines have been shown to impair various cognitive processes. The most extensively studied impairment is that of human memory, where, in addition, a pharmacological dissociation of the effects of two benzodiazepines (lorazepam and diazepam) on implicit and explicit memory has been established (Danion et al. 1989a, 1989b; Sellal et al. 1992; Vidhailhet et al. 1994; Legrand et al. 1995). In addition to its deleterious effect on memory, one benzodiazepine (lorazepam) has recently been shown to impair visual information processing, especially perceptual integration of local contour elements into a visual shape or "Gestalt" (Giersch et al. 1995, 1996; Wagemans et al. 1998, Beckers et al., submitted). Though various psychometrical tests indicate that benzodiazepines affect vigilance, increasing response times and errors in sustained attention tasks (Kleinknecht and Donaldson 1975; Preston et al. 1989; van Leuwen et al. 1994), few studies have been conducted to assess the effect of benzodiazepines on attentional processes directly. Johnson et al. (1995) reported a study in which the effect of a benzodiazepine (triazolam) on spatial attention was investigated with a cueing paradigm. Central cues (arrows) and peripheral cues (the brightening of a box) were used to examine controlled (central cueing) and automatic (peripheral cueing) attention allocation mechanisms. Subjects were instructed to indicate which of two target letters was present in a display composed of four letters. The authors found that the cost in response times and accuracy for invalid cues, relative to valid cues, was larger in the triazolam treatment group than in placebo-treated subjects, indicating that triazolam affects the operation of disengagement of attention from the cue to the target.

We were interested in the effect of benzodiazepines on visual attention in the temporal domain. A method

that has become widely used to examine the time course of attentional processes is the rapid serial visual presentation (RSVP) paradigm. This technique involves the presentation of a sequence of stimuli in rapid succession usually at the same spatial location. Subjects are asked to report one or more pre-defined targets. In the classical paradigm, attention is engaged on a first target (e.g., the single white letter in a sequence of black letters) by requiring its identification. At varying intervals following the presentation of the first target, a second target (the probe) is presented for detection. Response is given at the end of the sequence. A result consistently found is that subjects experience difficulties in reporting a second target if it occurs in a temporal window of about 500 ms following the first target. This phenomenon has been called the "attentional blink" effect (Raymond et al. 1992).

Two main classes of explanations have been proposed for this effect: a memory account (Chun and Potter 1995; Raymond et al. 1995; Giesbrecht and Di Lollo 1998; Vogel et al. 1998) and a dual-task interference account (Ward et al. 1996, 1997; Jolicoeur 1999). The memory account states that the operation of transferring a first target into visual working memory (Vogel et al. 1998) or the operation of consolidation of a first target in short-term memory (Chun and Potter 1995) to be reported at the end of the sequence monopolizes attentional resources for some time (about 500 ms) thus reducing the processing of subsequent stimuli due to capacity limitations (Neuman 1987). The interference account is based on the idea that attention to an object for the purpose of identification produces a pattern of long lasting interference (called the "dwell time", about 500 ms) on the processing of subsequent stimuli. Consistent with this account, neuropsychological data on neglect patients (Husain et al. 1997) show that the blink is about 4 times longer in patients who have difficulties to disengage their attention from the first target to the probe (see also Di Pellegrino et al. 1997, 1998).

In our study, we tested the effect of two different benzodiazepines (lorazepam and diazepam) on the magnitude and the duration of the attentional blink effect. A longer attentional blink can reflect either increased time of attentional disengagement (Husain et al. 1997; Ward et al. 1997), increased time to consolidate or to transfer the target from short-term conceptual memory into working memory (Chun and Potter 1995; Vogel et al. 1998) or impaired temporal integration, since the target's identity and the physical feature defining the target have to be integrated. A way to dissociate between these accounts is to check for intrusions. Indeed, a major problem with the dwell time account of the attentional blink effect (Ward et al. 1997) is that it neither predicts nor explains the presence of intrusions (i.e., the tendency to report the name of distractors present in the sequence instead of the target's name), whereas intrusions can be anticipated from both the Chun and Potter (1995) model and the revised version (Vogel et al. 1998) of the Raymond et al. (1995) model because items temporally close to the target are included during the operation of consolidation or transfer. These accounts predict a pattern of *post-target* intrusions.

A higher number of intrusions is also expected if temporal binding is impaired. For instance, Intraub (1985, 1989) used outline drawings of objects in RSVP sequences. Subjects were asked to identify the picture surrounded by a frame. Intraub reported frequent migrations of the frame, i.e., subjects displayed a tendency to report the name of the picture preceding that surrounded by the frame. She argued that the frame is erroneously linked to the previous picture that is still in the buffer being processed. Given that the target was defined by the color of its background in the present study, impaired temporal binding should result in a high number of *pre-target* intrusions.

Materials and methods

Subjects

The study was approved by the Ethical Committee of Alsace. Fifty-four healthy volunteers (18–35 years of age) were recruited from the Faculty of Medicine of the University Louis Pasteur in Strasbourg. They were native French speakers. They had no medical illness or history of alcoholism, drug abuse or tobacco consumption of more than ten cigarettes per day. They were not chronic users of benzodiazepines and had not taken any concomitant medication for at least 21 days. Subjects were instructed to abstain from beverages containing caffeine or alcohol for the 24 h prior to the study. All subjects were tested in the morning after an overnight fast. They all had normal or corrected-to-normal vision. Written informed consent was obtained from all volunteers before they entered the study. Subjects were paid 1000 Francs for their participation.

Stimuli

The stimuli were 120 colored pictures of objects taken from children books ("L'imagier du Père Castor" Flammarion and "Des images et des mots" Nathan). Eight semantic categories were represented: four natural categories (four-legged animals, birds, fruits and vegetables) and four categories of non-living things (vehicles, furniture, tools and clothes). Each semantic category contained 15 different objects. The pictures were digitized in PCX format. The mean size was 130×130 pixels in a matrix of 200×200 pixels. Each of the 120 pictures was displayed as target (T1) on a blue background and as distractor on a grey background. The probe (T2) was an item belonging to none of the eight semantic categories. It was a globe (see Fig. 1).

Apparatus

The stimuli were centrally displayed on the color screen (14 inch) of a Pentium II 166 MHz PC computer equipped with a VGA graphic card. Viewing distance was not fixed but subjects viewed the display from a distance of approximately 35 cm. The screen resolution was 640×480 pixels spatially, and stimuli were displayed using 256 colors. The refresh rate of the screen was 60 Hz.

Experimental procedure and drugs

Subjects were randomly assigned to one of three parallel groups of 18 subjects each: a placebo (lactose 190 mg) group, a lorazepam

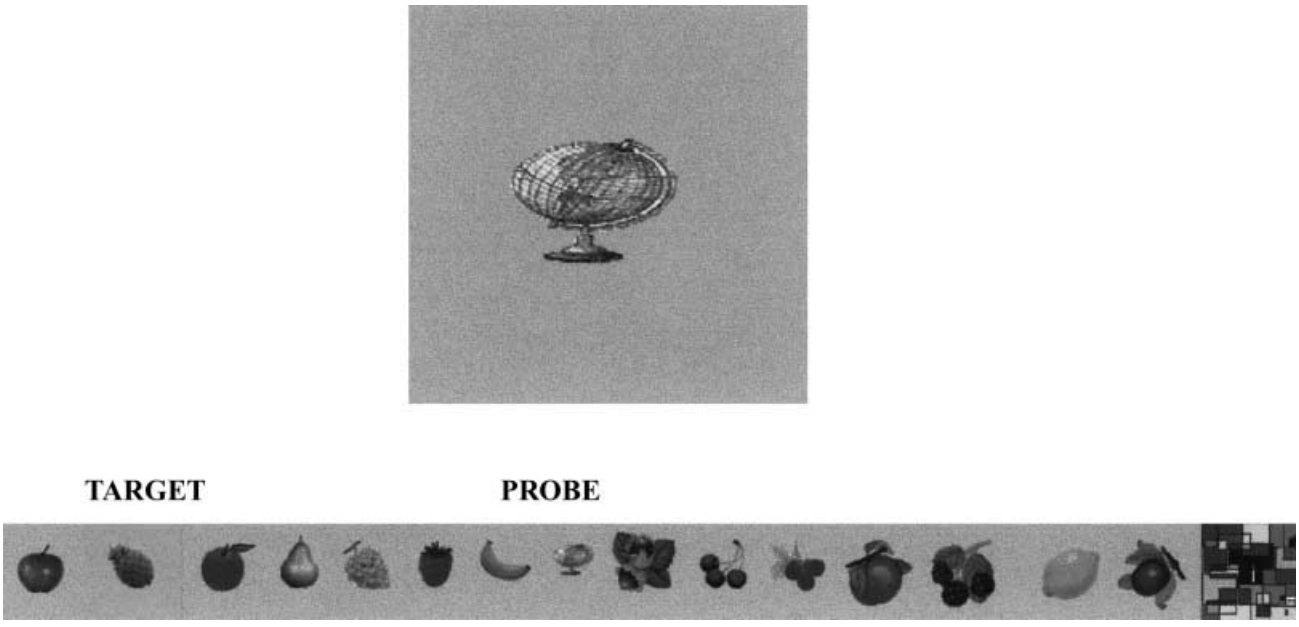


Fig. 1 An example of a sequence in which the target (*T1* on a blue background) is embedded in semantically related distractors. The probe (*T2*) is the globe

0.038 mg/kg group and a diazepam 0.3 mg/kg group. The diazepam and lorazepam doses were equally sedative. Drugs were administered orally using a double-blind procedure. In order to evaluate the effects of each drug at its peak plasma concentration, which is usually attained within 60 min after oral administration for diazepam and within 120 min for lorazepam (Mandelli et al. 1978; Greenblatt et al. 1993), a double-placebo procedure was used. Subjects in the diazepam group received placebo at 7.30 a.m. and diazepam at 8.30 a.m.; subjects in the lorazepam group received lorazepam at 7.30 a.m. and placebo at 8.30 a.m.; subjects in the placebo group received placebo at both times. Two subjects were tested per day, the first one starting at 9.00 a.m., the second one starting at 10.20 a.m.

A fixation dot was displayed centrally for 500 ms and followed by a sequence of 15 pictures which were centrally displayed. Each picture in the sequence was displayed for 50 ms separated by a 17-ms blank interval. Each picture appeared on a grey background except one (the target, T1) which appeared on a blue background. T1 appeared randomly at positions 2, 3 or 4 in the sequence. The probe T2 (the globe) appeared randomly at positions 2 (134 ms), 4 (251 ms), 6 (385 ms), 8 (519 ms) or 10 (653 ms) after T1. A mask composed of randomly distributed colored rectangles was presented at the end of each sequence. The target and the distractors were semantically related. An example of a sequence is displayed in Fig. 1.

Performance was compared in two conditions: a dual-task was used as the experimental condition. Participants were asked (1) to identify the single picture displayed on a blue background, and (2) to detect the presence of a globe. In the control single-task condition, participants were asked to detect the presence of a globe and to ignore the picture on a blue background. Participants were presented with 240 sequences in each condition: 120 sequences contained a globe. There were 24 trials for each position of T2 (2, 4, 6, 8 and 10). Responses were given verbally. The name of the picture on a blue background and the detected presence/absence of a globe, were typed by the experimenter on the keyboard of the computer at the end of each sequence. Participants were instructed to give the exact name of the target picture and to respond "nothing" if they did not identify the picture. All subjects started with the dual-task condition.

On the day before the experiment, participants were presented with an example of a picture on a blue background, the same picture on a grey background and the globe on a sheet of paper. Participants were then shown the whole set of pictures on paper and asked to name each picture. This test was designed to ensure that all pictures could be identified and given the same name. Following the identification task participants were given 20 trials as practice on the dual-task.

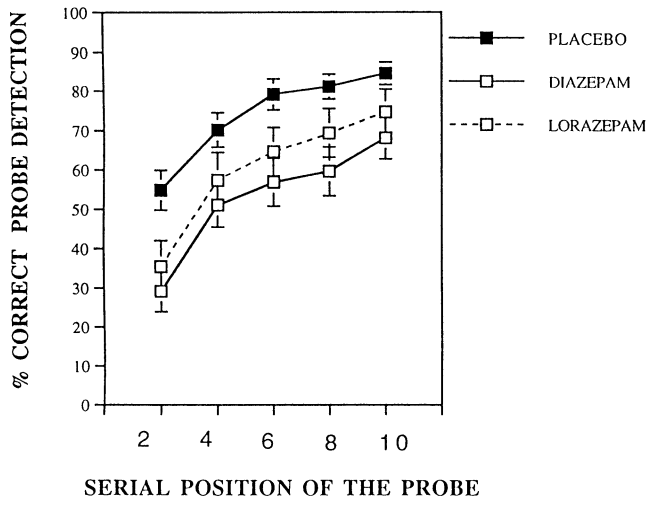
Results

One subject was discarded in the placebo-treated group because of a high false alarm rate on the probe (above 50%). The percentage of false alarms on the probe was higher in benzodiazepine-treated subjects than in the placebo group (diazepam: 8.3%, lorazepam: 7.1%, placebo: 4.3%) but the difference did not reach statistical significance [$F(2,50)=1.35$, NS].

Figure 2 shows the mean percentage of trials in which the probe was detected correctly for each treatment group as a function of the serial position of the probe relative to the target. An ANOVA (using SYSTAT 6.0) was conducted. The between-subject factor was the group determined by the treatment (placebo, diazepam, lorazepam). The within-subject factors were the task condition (dual-task versus single-task) and the serial position of the probe relative to the target (2, 4, 6, 8, 10).

Probe detection

A significant main effect of group was found [$F(2,50)=4.79$, $P<0.012$]. Accuracy in probe detection was higher in the placebo group than in the benzodiazepine groups (see Fig. 2). There was also a significant main effect of task condition [$F(1,50)=158$, $P<0.001$]: accuracy was higher in the single-task than in the dual-task condition. The main effect of probe serial position was also signifi-



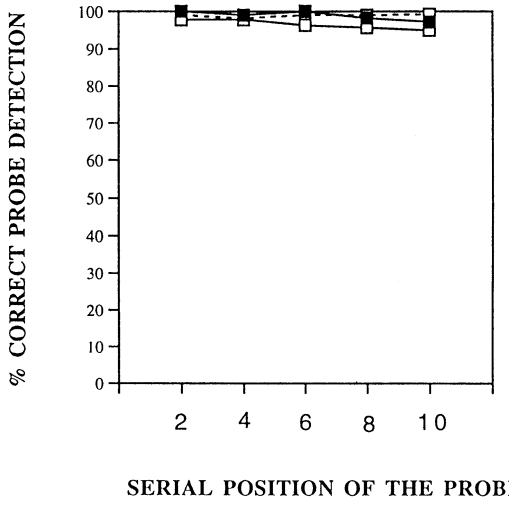


Fig. 2 Percentage of correct probe detections (averaged over participants) as a function of treatment and serial position of the probe for the dual-task condition (*left*) and the single-task condition (*right*). The *vertical bars* represent SE

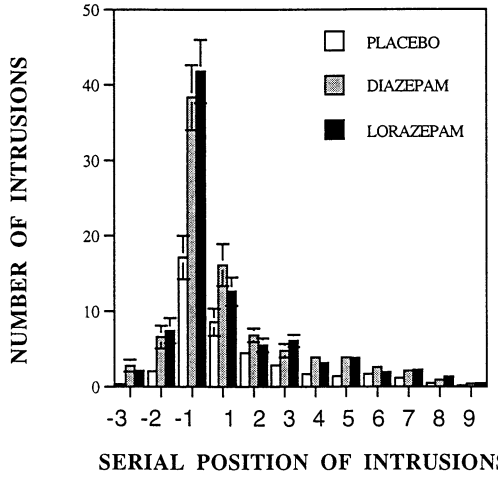


Fig. 3 Distribution of intrusions as a function of treatment and serial position of the target (*T1*) in the sequence: (negative=pre-target intrusions, positive=post-target intrusions). The *vertical bars* represent SE

cant [$F(4,200)=158$, $P<0.001$]: accuracy increased as the target-probe lag increased. A significant interaction was observed between task condition and probe serial position [$F(4,200)=66.4$, $P<0.001$]. Performance was stable across probe serial position in the single-task condition whilst a strong impairment in probe detection was observed in the dual-task condition: the attentional blink effect. Task condition also interacted significantly with group [$F(2,50)=4.4$, $P<0.017$]. This interaction resulted from a larger impairment in probe detection in the benzodiazepine groups than in the placebo group in the dual-task condition [$F(2,50)=4.72$, $P<0.013$] whilst performance was not significantly affected by drug in the single-task condition [$F(2,50)=2.16$, NS]. As can be seen from Fig. 2, the magnitude of the attentional blink effect was larger for benzodiazepine-treated subjects than for the placebo group. A significant difference was found between placebo and diazepam [$F(1,33)=11.73$, $P<0.002$] and between placebo and lorazepam [$F(1,33)=4.2$, $P<0.049$] in the dual-task condition. However, while accuracy in probe detection was significantly lower in the diazepam than in the placebo group for all target-probe lags [position 2: $F(1,33)=12$, $P<0.001$, position 4: $F(1,33)=6.9$, $P<0.013$, position 6: $F(1,33)=9.14$, $P<0.001$, position 8: $F(1,33)=8.9$, $P<0.005$, position 10: $F(1,33)=6.8$, $P<0.014$], the difference between placebo and lorazepam was significant only for serial position 2 [$F(1,33)=5.33$, $P<0.027$]. The interaction between group and serial probe position did not reach statistical significance.

Identification errors

The percentage of correct identification of the target was higher in the placebo group (77%) than in the diazepam (56%) and the lorazepam (59%) groups [$F(2,50)=13.1$, $P<0.001$]. The response “nothing” was given in about 8% of the sequences. Intrusions were numerous, averaging about 98% of errors. Less than 1% of the errors were perseverations (i.e., the name of an item from the previous sequence) and about 1% were misidentifications (i.e., the name of objects not present in the experimental set).

The distribution of intrusions is displayed in Fig. 3 as a function of the treatment group. Given that the target was randomly displayed at positions 2, 3 or 4 in sequences of 15 items, there were three possible positions for pre-target intrusions and 13 possible positions for post-target intrusions. In fact, no intrusions were observed beyond position 9 following the target. As can be seen from Fig. 3, there was a predominance of pre-target intrusions, especially involving the item immediately preceding the target (the –1 item). The number of intrusions was higher in the benzodiazepine groups than in the placebo group. The main effect of group was significant both for pre-target intrusions [$F(2,50)=11.85$,

$P<0.001$] and for post-target intrusions [$F(2,50)=5.2$, $P<0.009$]. Group and serial position of intrusions interacted significantly [$F(2, 50)=6.1$, $P<0.004$]. Figure 3 shows that the number of pre-target intrusions (the item immediately preceding the target) was two times larger than the number of post-target intrusions (the +1 item) for placebo- and diazepam-treated subjects. It was four times larger for lorazepam-treated subjects.

Discussion

The results show that benzodiazepines, especially diazepam, increased both magnitude and duration of the attentional blink effect. The impairment in probe detection was less pronounced with lorazepam. A differential effect of these two benzodiazepines on cognitive processes has often been reported before, although both diazepam and lorazepam interact with the $GABA_A$ receptors. For instance, lorazepam has been found to impair both explicit and implicit memory whilst diazepam affects only explicit memory (Legrand et al. 1992; Vidailhet et al. 1994) and lorazepam is more detrimental than diazepam on perceptual integration (Giersch et al. 1995 1996; Wagemans et al. 1998; Beckers et al., submitted). The second main result of our experiment was the disproportionate increase in the number of pre-target intrusions (the name of the item preceding the target) in the two benzodiazepine-treated groups, and particularly for lorazepam-treated subjects.

The larger blink effect for benzodiazepine-treated subjects is very unlikely the result of a non-specific sedation given that performance was unaffected in the single-task control condition (see Fig. 2).

Might the larger blink effect be due to a higher sensitivity to masking by benzodiazepines? Fish et al. (1983) found that diazepam enhances visual masking. In their study, sequences of letters composing a word were displayed successively. Each letter was displayed for 70 ms and the temporal interval between letters was manipulated (10, 100 or 200 ms). Subjects were asked to report the word at the end of each sequence. The decline in performance with decreasing interval was more pronounced for diazepam-treated subjects than for placebo and methylphenidate-treated subjects. From this result the authors suggested that the GABA agonist diazepam enhances type A masking characterized by intrachannel inhibition. However, other experimental results suggest that the attentional blink effect is unlikely to be explained by masking by integration (type A masking): a probe immediately following the target (as +1 item) is classically detected with high accuracy (see Shapiro and Raymond 1994; Shapiro et al. 1997 for reviews). Performance then drops up to 500 ms of target-probe lag, thus giving rise to the typical U-shape function (see Vogel et al. 1998) that characterizes type B masking by interruption (Turvey 1973; Breitmeyer 1984).

Let us consider the data in the framework of the theoretical accounts of the attentional blink effect. In the attentional account (Ward et al. 1996, 1997), the blink reflects the time for focal attention, having already been allocated to an initial target, to be re-allocated to a subsequent target. As mentioned above, a benzodiazepine (triazolam) has been found to increase the time to disengage attention from the location of the cue to that of the target in the spatial domain (Johnson et al. 1995). If spatial and temporal attention share common mechanisms, then benzodiazepines should increase the duration of the attentional blink effect. That was the case in the present study but this account does not predict intrusions.

In the memory account, the attentional blink effect is thought to reflect the time to consolidate the target into short-term memory (Chun and Potter 1995) or to transfer the selected target into working memory (Vogel et al. 1998). The effect of benzodiazepines on memory processes has been investigated with paradigms involving long intervals between the phase of encoding and the time of retrieval. The paradigms classically used to assess the effect of benzodiazepines on memory are either free recall tasks of a list of words or priming tasks based on a study phase and a test phase occurring several minutes later (Sellal et al. 1992; Curran and Gorenstein 1993; Schifano and Curran 1994; Vidailhet et al. 1994; Legrand et al. 1995; Stewart et al. 1996; Buffet-Jerrott et al. 1998). From these studies, it is difficult to formulate hypotheses about the effect of benzodiazepines on the short-term memory systems operating in RSVP paradigms (i.e., consolidation in short-term visual memory or transfer of selected information into working memory). Indeed, to our knowledge, no pharmacological study on benzodiazepines involving a priming paradigm with the target immediately following the prime has been reported. Therefore, we do not know whether short-term memory systems are impaired by benzodiazepines. Impairment in transferring or consolidating the target in short-term memory should result in misidentifications, a failure to report the target, or random guesses. A large number of errors were observed in the benzodiazepine groups but they were almost exclusively due to a tendency to report an item that was present in the sequence (i.e., intrusions). This result is difficult to reconcile with a hypothesis in terms of impaired short-term memory.

A predominance of pre-target intrusions has been reported before with pictures as stimuli. Intraub (1985, 1989) reported a predominance of pre-target intrusions when subjects were asked to report the identity of a picture surrounded by a frame in a RSVP paradigm. She argued that the frame and the picture dissociate because they are not conceptually related. She proposed that whether the frame migrates to the preceding or to the following picture depends on whether subjects attend to the frame first or to the picture first. If they attend to the frame first then the frame is more likely to be linked to the previous picture which identification is not achieved. The speed of processing account can also hold for our results. If color (the blue background) is detected quickly whilst the identity of the previous item is still being processed, then the blue background will be integrated to

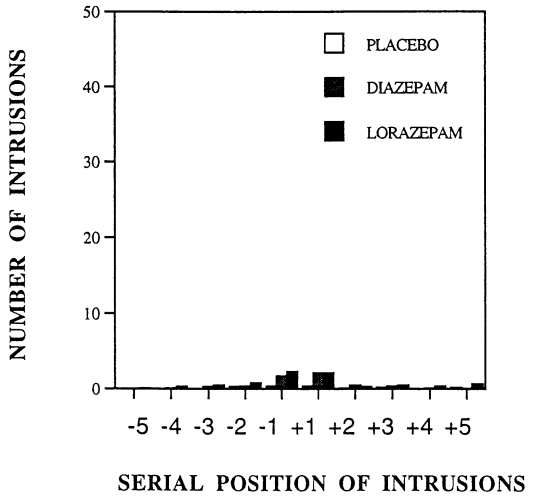


Fig. 4 Percentage of correct target identification (averaged over participants) as a function of the serial position of the target in the sequence for each treatment group

the previous picture thus resulting in a high number of pre-target (T1–1) intrusions. A high number of pre-target intrusions can reflect either impaired temporal integration (i.e., a longer temporal interval would be required in benzodiazepine-treated subjects to dissociate temporally adjacent pictures), or it can reflect a slower decay of the representations activated by pictures preceding the target. There is evidence that temporal integration is affected by benzodiazepines. For instance, the flicker-fusion threshold is lowered by benzodiazepines. A longer interstimulus interval is required for subjects to perceive two independent stimuli (Kleinknecht and Donaldson 1975; Danjou et al. 1992).

To dissociate the impaired temporal binding account from the slow decay account, we introduced a 100-ms interval between the target and the previous picture (the pre-target item). The same subjects were tested on 80 new trials. The duration of short-term semantic memory lasts about 300 ms (Irwin and Yeomans 1986; Tiberghien 1997). A 100-ms interval between the target and the pre-target item added to three possible pre-target pictures was still within the range (three pictures×51 ms each+2×17 ms ISI between pictures+100 interval between the pre-target item and the target=287 ms) of short-term semantic activation. If benzodiazepines slow down the decline of activated representations then pre-target intrusions should outlast a 100-ms interval. In contrast, if pre-target intrusions occurred because the key feature (the feature defining the target: the blue background) and the identity of the previous item are temporally integrated, then a 100-ms delay between the two items might reduce the number of intrusions (we assumed that the deficit in temporal integration would not exceed 100 ms). The results displayed in Fig. 4 show that pre-target intrusions were almost completely eliminated by the 100-ms interval, in line with the notion that benzodiazepine impairs visual integration in the temporal domain. This extends previous findings that benzodiazepine impairs visual integration in the spatial domain (Giersch et al. 1995, 1996; Wagemans et al. 1998; Beckers et al., submitted).

This result is consistent with previous studies showing increased threshold for flicker-fusion under benzodiazepines (McNab et al. 1985; Lucki et al. 1986; Danjou et al. 1992; King and Henry 1992).

The results of the present study suggest that it is the time to dissociate different visual signals that seems to be increased by lorazepam and diazepam. Of course, we cannot exclude that time to disengage attention from a stimulus to another stimulus is also increased by benzodiazepines but this account, by itself, cannot explain the presence of intrusions found in this study.

Acknowledgements This study was supported by a EEC Biomed grant (N°PL962775) to the first author and a twin grant INSERM/MGV to the first and the third authors. The authors are grateful to Dr. Welsch and Dr. Giersch for selecting participants, to Isabelle Meyer and Tom Beckers for running subjects and to Felix Wichmann for improving the language of the final version of this paper.

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