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Stem-completion tasks (indirect, direct inclusion and exclusion) are differently affected by equipotent doses of lorazepam and flunitrazepam

S. Pompéia, O. F. A. Bueno*, J. C. F. Galduróz and S. Tufik

Departamento de Psicobiologia—UNIFESP, Brazil

This study was designed to explore the effects on performance in stem-completion tasks of two benzodiazepines (BZ) in equipotent doses: lorazepam, a drug that atypically disrupts perceptual priming, and flunitrazepam, a compound with standard BZ effects. The study followed a placebo-controlled, double-blind, parallel-group design. Thirty-six young and healthy subjects carried out three completion tasks at theoretical peak-plasma concentrations of drugs: (a) indirect tasks, in which the subjects were instructed to complete stems with the first word that came to mind; (b) direct inclusion tasks/cued recall, in which the participants had to try to use words seen at study as completions; and (c) direct exclusion tasks, in which words seen at study were to be avoided. The PDP was applied to the results in the inclusion and exclusion tasks, to obtain indices of explicit/controlled (*C*) and implicit/automatic (*A*) memory. The *C* index was lowered by both BZs and *A* was equivalent in all treatments, confirming the general amnestic action of BZs. However, lorazepam led to decreases in completions in the indirect and inclusion tasks, while flunitrazepam impaired performance in the exclusion task. The qualitative differences between the drugs in their effects on performance suggest that these BZs may lead to differences in response bias. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — benzodiazepines; memory; stem-completion; lorazepam; flunitrazepam; process-dissociation procedure

INTRODUCTION

Long-term memory comprises an explicit, or 'consciously' retrievable memory system, and an implicit memory, retrievable automatically without 'conscious' control (Graf and Schacter, 1985). Explicit memory is thought to encompass a semantic, or knowledge memory, as well as an episodic memory, or memory of personal experiences (Graf and Schacter, 1985). Implicit memory, on the other hand, includes phenomena such as conditioning, procedural memory and repetition priming (Schacter, 1992).

Episodic memory is the only long-term memory subtype that is affected in amnesic patients (Shimamura and Squire, 1984) and is susceptible to anterograde impairment by all benzodiazepines (BZs) (Buffett-Jerrott and Stewart, 2002; Curran, 1991, 2000). Conversely, implicit memory, such as the phenomenon of repetition priming, is generally unchanged by BZs (Buffett-Jerrott and Stewart, 2002; Curran, 1991, 2000) except for lorazepam, which seems to consistently disrupt it (see Pompéia *et al*., 2000).

Repetition priming in BZs studies is mostly measured through tasks that involve completion or identification of 'incomplete' stimuli (e.g. fragment- or stem-completion, identification of fragmented pictures). The stem-completion task is by far the most commonly used. This test involves showing subjects words (during the 'study' or 'encoding' phase) and then instructing them to complete three-letter word-stems ('test phase'). In general, half the stems can be completed with words that were previously shown (studied words), while the remaining stems complete words that were not seen (non-studied words) and that are used to determine base-rate completion. Memory

* Correspondence to: Dr O. F. A. Bueno, Departamento de Psicobiologia, R. Napoleão de Barros, 925, CEP: 04024-002, São Paulo, Brazil. Tel: 55 11 5539-0155. Fax: 55 11 5572-5092. E-mail: ofabueno@psicobio.epm.br

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is measured by the difference in completions between studied and non-studied words.

The most common instruction in repetition priming tests is 'indirect', in which there is no mention of the relation between study and test (see Johnson and Hasher, 1987). In the case of stem-completion, the classical instruction is that stems be completed with the first word that comes to mind. This, in principle, leads subjects to use mainly implicit mnemonic strategies (repetition priming). This type of task, however, is not considered an ideal measure of priming, for it is widely accepted that subjects may use both priming and explicit memory while carrying it out (Richardson-Klavehn and Bjork, 1988).

Equivalent versions of the stem-completions task can be used to evaluate explicit, episodic memory by changing the instruction from indirect to direct (see Johnson and Hasher, 1987). In this case the task is classically known as 'cued-recall' in which instead of subjects completing stems with the first word that comes to mind, they are required to do so with words seen at study. Here again, though, repetition priming may contaminate results and be responsible for part of the success in completing stems to form previously shown words. Alternative means must therefore be employed in order to determine the contribution of episodic memory and priming to performance in tasks that are not pure measures of specific types of memory.

The 'process-dissociation procedure' (PDP) (Jacoby, 1991; Jacoby *et al*., 1993; Jacoby, 1998) constitutes a paradigm for studying the intra-task contributions of different types of long-term memory and yields alternative measures of explicit, 'conscious' or 'controlled' recollection (C) and implicit, repetition priming or automatic (A) memory. In the case of stem-completion tasks, these indices are considered independent and are calculated on the basis of the proportion of stems completed with words seen at study in two types of direct task:

1. Inclusion task (equivalent to classic direct stem-completion or cued-recall), in which subjects are instructed to use stems to retrieve stimuli seen during a previous learning episode. Performance on this task thus reflects the use of studied words due to explicit/conscious strategies (C) plus that of implicit/automatic memory (A) when C fails $(1-C)$ [Inclusion $= C + A(1-C)$]. For example, performance of a pure amnesic patient, whose explicit/conscious memory is in principle totally impaired, would be solely due to automatic memory $[0 + A(1-0)]$.
2. Exclusion task, in which subjects are instructed to avoid completing stems with stimuli seen before. In this case, responses with studied stimuli are due to the use of automatic memory when conscious (voluntary or involuntary) recollection fails [Exclusion $= A(1-C)$]. In other words, responses with previously shown stimuli are due to implicit or automatic memory, for if subjects have conscious or explicit recollection of these items they do not use them as completions. Thus, an amnesic patient's performance in this task would also be due exclusively to the use of automatic memory $[A(1-0)]$.

The index 'C' can be calculated by subtracting exclusion-test performance—in which completions with studied words are exclusively due to implicit memory—from scores in the inclusion test, in which both explicit and implicit type memories can be employed [$C =$ Inclusion$-$Exclusion]. 'A' can then be calculated with simple arithmetic [$A =$ exclusion/$1-C$]. However, the equations above can be applied only if response criteria are found to be constant, that is, base-rates in the inclusion and exclusion tasks and the proportion of uncompleted stems are equivalent across experimental manipulations.

The PDP was used to investigate BZ memory effects in only one published paper (Vidailhet *et al*., 1996): lorazepam and diazepam were shown to decrease completions in the inclusion task in relation to placebo, and lorazepam was also impaired when compared with diazepam. In the exclusion task, the opposite occurred: diazepam, but not lorazepam, was impaired. This is an interesting result because performance in the exclusion task should reflect the use of unconscious memory for words seen before. This would imply that only diazepam was impaired in this respect. However, when applying the PDP, only lorazepam was found to diminish A; it also led to greater impairment of C than diazepam and placebo. So that the effects of both BZs could be compared in respect to automatic memory, the authors attempted to equate C of both drugs through 'unorthodox' means and concluded that only lorazepam was capable of reducing automatic memory, confirming the purported atypical priming effects of this drug (see Pompéia *et al*., 2000). However, the initial difference between C indices in the lorazepam and diazepam groups made it impossible to determine whether these drugs differed in their impairment of priming or if the dose of diazepam was not high enough to elicit the same effects as lorazepam.

Considering the pharmacological characteristics of lorazepam and diazepam, it is not surprising that

Vidailhet *et al*. (1996) found that lorazepam led to more memory impairment because this drug shows greater affinity than diazepam (K_i; Möhler *et al*., 1978) with the central BZ or ω binding sites on the γ—aminobutyric acid type A receptors ($GABA_A$; see Korpi *et al*., 1997), a pharmacodynamic parameter that seems to account for the extent of BZ memory effects (Vgontzas *et al*., 1995; Pompéia *et al*., 1996b).

The present study aims at comparing the effects of two BZs with similar affinities with their receptors in indirect, inclusion and exclusion tasks, as well as on *A* and *C* memory indices. The drugs employed were flunitrazepam, which has classical BZ effects (Ingum *et al*., 1992, 1993; Pompéia *et al*., 1996a,b, 2000, 2003) and lorazepam, the only BZ consistently shown to impair indirect measures of memory. At the dosages used, both drugs led to similar effects on a large number of cognitive tasks and to double-dissociation, thus lending support to the assertion that they are equivalent in terms of inducing cognitive impairment (Pompéia *et al*., 2003). If lorazepam's unique impairment of implicit memory is attributable to its high potency, it is to be expected that an equipotent dose of a drug such as flunitrazepam should lead to similar effects.

MATERIALS AND METHODS

Subjects

Thirty-six physically healthy, native Portuguese speaking volunteers (18 men), aged 18–36 years (mean $\pm$ SD: 24.8 ± 5.0 years), with an average body mass index (weight/height^2: 22.0 ± 2.1 kg/m^2), more than 12 years of schooling, and trait anxiety scores (STAI: 40.4 ± 6.5) corresponding to normal values for Brazilian university students (Gorenstein *et al*., 1995) were recruited. Participants met the usual exclusion criteria for clinical trials (e.g. pregnancy, allergy, chronic clinical or psychiatric disorders), had no history of drug abuse or heavy alcohol drinking, consumed less than 5 units of alcohol per week, did not smoke or use drugs of abuse such as cannabis and cocaine regularly and were on no medication at the time of the study.

Procedure

This was an independent group-design study using single oral doses of BZs. Subjects were randomly allocated, apart from balancing by sex, to one of three treatments: placebo (P), 1.2 mg of flunitrazepam (F) and 2.0 mg of lorazepam (L). The potency of each BZ was equivalent [K_i: Möhler *et al*. (1978), Arendt *et al*. (1987); IC_{50}: Möhler and Okada (1977), Müller (1987)]. The Ethics Committee of the institution at which the experiment was conducted (UNIFESP) approved the protocol and all subjects signed informed consent forms. Subjects were instructed to abstain from alcohol or other drugs for 24 h before and after the experiment. In the morning of the testing day, subjects ingested a light breakfast (with their usual intake of caffeine) provided at the laboratory. Participants were tested 30 min after the theoretical peak-plasma concentration of drugs, 90 min for flunitrazepam (Mattila and Larni, 1980) and 120 min for lorazepam (Ameer and Greenblatt, 1981). Other cognitive tasks including evaluation of sedation and event-related potentials at peak and one hour after peak were employed and the results are published elsewhere (Pompéia *et al*., 2003). The indirect stem-completion tasks were carried out first, so as to diminish the possibility that explicit strategies be employed in the indirect task (see Buffett-Jerrott *et al*., 1998b), followed by the direct tasks, which had random inclusion and exclusion instructions. Encoding and test lists were counterbalanced within subjects and treatments.

Treatment

Drugs were formulated in identical capsules and administered orally in the following double-blind method: subjects in the F treatments received a placebo capsule at 9:30 a.m. and another containing the drug at 10:00 a.m.; those in the L treatment received the active substance at 9:30 a.m., followed by placebo 30 min later; the P treatment ingested two placebo capsules at the same time. Presentation/encoding of words to be completed in the stem-completion tasks took place at noon (30 min after the theoretical peak of active treatments).

Stem-completion

Materials. A pool of 120 neutral, five-letter Portuguese words (nouns, adjectives, verbs) with unique 3-letter word-stems were used: (a) 108 words were organized into 6 sets of 18 words balanced according to rank among other completions for each stem, number of words with which stems could be completed (3–7), and chance completion (all determined in a pilot study with 69 University students); (b) 12 buffer words to control for primacy and recency effects (not scored). Two study lists were constructed by randomly combining three sets of words plus primacy and recency items. Test lists for indirect stem-completion

consisted of stems of words from two sets, one from each study list, only one of which had been seen by subjects at study (studied words) and was used to determine memory for these items; the completion of stems of the other set was used to determine chance completion. Test lists used in the direct completion tasks comprised four sets of words from the study lists, two that corresponded to stems of studied words, and the other two to words not seen (non-studied) that were used to determine baselines. Subjects completed stems of two sets of studied and non-studied words following inclusion instructions, and the remaining sets of studied and non-studied words following exclusion instructions. Thus, memory could be established by subtracting completions with studied words in the inclusion and exclusion task from completions with non-studied words.

Study/encoding task. Words of one study list were shown on a computer screen at the rate of 1 word every 5 s (font Arial no. 60, uppercase, bold, black over white background). Subjects were instructed to say each word aloud and rate how much each word was liked on a 5-point scale (semantic encoding). Subjects responded aloud and the experimenter recorded their responses.

Tests. Subjects were shown stems from the two test lists. Each stem was presented on the computer screen for a maximum of 25 s, in the same lettering as the one used at study. For the first, shorter list (stems of 36 words), subjects were instructed to complete stems with the first word that came to mind (indirect stem-completion). For the second, longer list (72 stems), volunteers were asked to follow inclusion or exclusion instructions in the following manner: stems accompanied by the word 'old' should be completed with words seen before (inclusion instruction) while stems accompanied by the word 'new' should be completed with words that had not been seen at study (exclusion instruction). 'Old' and 'new' were written in lowercase above each stem. In the latter case, subjects were told that stems should be left blank if no alternative word to the word seen at study came to mind. Inclusion and exclusion instructions were presented randomly. The dependent variables scored were the proportion of stems completed with target words (those that appeared in the word-lists used) and proportion of stems left blank. Indices A and C were determined as outlined in the introduction: inclusion $= C + A(1-C)$; exclusion $= A(1-C)$; $C =$ inclusion$-$exclusion; $A =$ exclusion$/(1-C)$.

RESULTS

Analyses of variance (ANOVAs) followed by Tukey *t*-tests for comparisons of means were used in the statistical analysis and will be detailed below. The significance level of 5% was adopted for all statistical comparisons. Variables and comparisons that are not cited below did not show significant effects. Groups did not differ in age (mean $\pm$ SD $= 22.9 \pm 4.0$) or body mass index (22.2 ± 2.2). Table 1 shows the data for each task, as well as A and C indices.

Data from each stem-completion task were analysed separately using two-way ANOVAs with group (L, F, P) and familiarity (studied, non-studied) as factors. These analyses involved the proportion of stems completed and stems left blank. Chance completion was determined through one-way ANOVAs with group as

Table 1. Proportion (mean $\pm$ SD) of stems completed with studied and non-studied (baseline) target words and stems left blank according to instructions at test (indirect, inclusion and exclusion), and memory indices A and C, per group (L = 2 mg lorazepam; F = 1.2 mg flunitrazepam; P = placebo)

	Measure	L	F	P
Completed	Indirect studied	0.51 ± 0.11	0.68 ± 0.09	0.68 ± 0.16
	Indirect non-studied	0.30 ± 0.09	0.35 ± 0.12	0.36 ± 0.11
	Inclusion studied	0.47 ± 0.16	0.55 ± 0.14	0.61 ± 0.18
	Inclusion non-studied	0.28 ± 0.16	0.37 ± 0.12	0.36 ± 0.16
	Exclusion studied	0.26 ± 0.16	0.32 ± 0.18	0.14 ± 0.14
	Exclusion non-studied	0.26 ± 0.09	0.31 ± 0.11	0.31 ± 0.10
Non completed (blank)	Indirect studied	0.07 ± 0.07	0.10 ± 0.23	0.07 ± 0.12
	Indirect non-studied	0.10 ± 0.06	0.12 ± 0.12	0.12 ± 0.11
	Inclusion studied	0.06 ± 0.07	0.03 ± 0.03	0.07 ± 0.13
	Inclusion non-studied	0.12 ± 0.12	0.07 ± 0.07	0.13 ± 0.11
	Exclusion studied	0.13 ± 0.09	0.06 ± 0.07	0.12 ± 0.10
	Exclusion non-studied	0.12 ± 0.05	0.06 ± 0.09	0.13 ± 0.08
Indices	C	0.21 ± 0.27	0.23 ± 0.15	0.48 ± 0.25
	A	0.30 ± 0.12	0.44 ± 0.15	0.30 ± 0.21

the factor. One subject in the F group did not comply with inclusion/exclusion instructions and another could not be kept awake, so their data were not included in the analysis of the inclusion and exclusion tasks.

Indirect test

For the proportion of completed stems we observed effects of group ($F_{2,33} = 5.08$; $p < 0.02$), familiarity ($F_{1,33} = 155.08$; $p < 0.000001$) and a tendency for group and familiarity to interact ($F_{2,33} = 2.86$; $p = 0.07$). L-treated subjects completed less stems with target words than those who took F and P ($ps < 0.03$), and, overall, stems were more often completed with studied than non-studied words ($ps < 0.0002$). The interaction indicated that in all groups stems were more often completed with studied than non-studied words ($ps < 0.0002$), showing facilitation or memory for previously seen words. Also, the proportion of stems completed with studied words was smaller after L than after the other groups ($ps < 0.0002$), thus confirming previous reports of indirect completion impairment for this drug. All groups showed similar levels of chance completion ($F_{1,33} = 0.74$; $p > 0.49$). Analysis of stems left blank tended to show a familiarity effect only ($F_{1,32} = 3.38$; $p < 0.08$; studied < non-studied, $p < 0.08$), indicating a memory effect because completing stems with words seen at study was facilitated. Covarying these measures from the analysis of completed stems had no effect on the results.

Inclusion test

For completed stems, group ($F_{2,31} = 3.37$; $p < 0.05$) and familiarity ($F_{1,31} = 29.44$; $p < 0.000006$) effects were observed. Only L was impaired in relation to P ($p < 0.05$) and, overall, memory was observed as studied words were completed more often than non-studied ones ($p < 0.0002$). No differences between groups were found for chance completion ($F_{1,31} = 1.28$; $p > 0.29$). Memory of studied words was also apparent in the analyses of stems left blank, in which only a familiarity effect occurred ($F_{1,31} = 10.32$; $p < 0.003$), stems of studied words being completed more often than those of non-studied ones ($p < 0.0002$). Once again, when these results were covaried from analysis with completed stems, the results were unchanged.

Exclusion test

In the analysis of completed stems a group effect was apparent ($F_{2,31} = 3.79$; $p < 0.04$) with opposite results to those observed in the inclusion task: F was impaired in relation to P ($p < 0.04$; other contrasts $p > 0.22$) and this was not due to differences in baseline ($F_{2,31} = 1.20$; $p > 0.31$). Note that in this task lower scores indicate better performance. For the proportion of stems left blank, a group effect was also observed ($F_{2,31} = 4.62$; $p < 0.02$): the F group left stems of non-studied words blank less often than the L ($p < 0.04$) and P ($p < 0.06$) groups (L = P; $p = 0.95$), a fact that suggests poorer memory. Covarying stems left blank from completions with studied words still revealed a tendency of group effect ($F_{2,30} = 3.01$; $p < 0.07$), confirming that F was impaired in relation to P ($p = 0.05$), and that this was not due to this group's small success in stem-completion *per se*.

Process-dissociation procedure (PDP)

Two-way ANOVAs with group and instruction as factors were used to show that response criteria were equated between experimental manipulations (i.e. chance completion and stems left blank did not differ). For baseline completion, no statistical differences were found (treatment $p = 0.11$; instruction $p = 0.14$; interaction $p = 0.87$). For stems left blank, when stems of studied and non-studied words were analysed separately, there were no effects ($ps > 0.41$). However, when group, instruction (inclusion and exclusion) and familiarity (studied and non-studied) were taken into account, effects of treatment ($F_{1,31} = 3.06$; $p < 0.07$), instruction ($F_{1,31} = 3.49$; $p < 0.08$) and familiarity ($F_{1,31} = 3.85$; $p < 0.06$) tended to emerge: stems tended to be left blank more often in the F group than in the others ($ps < 0.12$), in the exclusion condition ($p < 0.08$) and when stems corresponded to non-studied words ($p < 0.05$). There was also a tendency for interaction between instruction and familiarity ($F_{1,31} = 3.97$; $p < 0.06$) (other effects $ps > 0.79$), showing that stems of studied words were completed more often following the inclusion instruction than in all other situations ($ps < 0.05$). This latter effect probably reflects the fact that the exclusion task instruction requested that stems be left blank if subjects cannot generate a completion other than the word seen at study, as well as the fact that memory facilitates completions in the inclusion task, stems of non-studied words being more difficult to complete.

Because of these tendencies, the *A* and *C* memory indices were calculated in an exploratory manner using one-way ANOVAs with treatment as factor. For *C* there was an effect of treatment ($F_{2,31} = 4.44$; $p < 0.02$), L ($p < 0.03$) and F (tendency; $p < 0.07$)

having impaired scores in relation to P. Covarying the proportions of stems left blank in the inclusion and exclusion tasks had no effect on results, except that the difference between the F and P groups reached significance ($p < 0.04$).

Two volunteers from the P group and one from the F group failed to complete any stems with target words in the exclusion task, so there was no *A* index for these subjects (see discussion). For the remaining subjects a group effect tendency was observed ($F_{2,28} = 2.56$; $p < 0.09$), but the Tukey *t*-test did not reveal which contrasts contributed to this effect ($ps > 0.16$). When the proportions of stems left blank were used as a covariate, this tendency disappeared ($F_{2,24} = 1.01$; $p > 0.38$), a fact that implies that possible differences between groups in *A* were due to differences in the difficulty in completing stems with any word, rather than a disruption of automatic memory itself.

DISCUSSION

In the indirect and inclusion stem-completion tasks, all treatments showed memory effects since subjects completed more stems with studied words than by chance. Despite this facilitation in completions, L impaired performance in the indirect task, corroborating findings that have been repeatedly interpreted as impairment of repetition priming (e.g. Curran and Gorenstein, 1993; Legrand *et al*., 1995; Stewart *et al*., 1996; Buffett-Jerrott *et al*., 1998a,b; Martin *et al*., 2002). L also had a deleterious effect in the inclusion task, reflecting general BZ amnestic effects (Curran, 1991, 2000; Buffett-Jerrott and Stewart, 2002), so an alternative explanation for the indirect task impairment would be that L decreased the contribution of explicit memory to performance (see Stewart *et al*., 1996).

Few studies have employed rigorous paradigms to evaluate contamination from explicit memory in indirect tasks. In one such study, Bishop and Curran (1995) applied the retrieval intentionality criterion proposed by Schacter *et al*. (1989) and reported that L impaired indirect stem-completion when no differences between semantic/conceptual and data-driven/perceptual encoding were found, while the direct task benefited from semantic encoding. This lent support to the assertion that L does in fact impair implicit memory. Others (Stewart *et al*., 1996; Buffett-Jerrott *et al*., 1998a,b) who compared performance in a direct and indirect stem-completion task also claimed to have shown implicit memory impairment by oxazepam that was not due to contamination of explicit memory. However, these studies did not follow Schacter *et al*.'s (1989) paradigm in that there was no manipulation that differently effects implicit and explicit memory such as levels of processing nor measures of baseline completions were included in the direct task; both points weaken their claim.

Despite the fact that scores in the indirect and inclusion tasks could not be directly compared in the present study because they differed in more than instruction,[1] the contamination hypothesis could be supported in principle by L not having impaired performance in the exclusion task, which supposedly involves implicit memory only if subjects comply with the instruction. Results for F on this task, however, weaken this hypothesis (see below).

In addition to the retrieval intentionality criterion, the process-dissociation procedure (PDP; Jacoby, 1991) has been used to assess the contribution made by conscious/explicit and automatic/implicit memory to performance in the stem-completion task. In this respect, our data suggest that both L and F exert similar standard BZ amnestic effects (Curran, 1991, 2000; Buffett-Jerrott and Stewart, 2002), for only the measure of explicit memory, *C*, was impaired. However, note that results relative to the application of the PDP were hampered by the fact that baselines tended to differ between treatments ($p = 0.11$) and instructions ($p = 0.14$), despite our best endeavours in selecting appropriate stimuli for use in this paradigm.

The only other study to apply the PDP to investigate anterograde amnestic effects of BZs (Vidailhet *et al*., 1996) did little to clarify the debate as to whether L does in fact impair repetition priming because it did not show equivalent *C* indices for the BZs used (L and diazepam). In order to compare the effects of these drugs on automatic memory, the authors attempted to correct this difference in *C* by removing the data of subjects who completed at most one stem with studied words in the exclusion task. Usually (Jacoby, 1998), however, only data of subjects who did not complete *any* stems in the exclusion task are

[1]Although a direct comparison of performance in the direct and indirect tasks in the present study would have yielded more information concerning this issue, this was not done because these tasks differed not only in instructions, but also in that the indirect task was always carried out first and was evidently easier, subjects not having to switch strategies as occurred when completing stems following either inclusion and exclusion tasks. Also, no direct comparison of exclusion and inclusion tasks was made because scores in the exclusion task are inverted, with higher scores for worse performance. The three types of instructions were not alternated, as in inclusion and exclusion tasks, because this would make it impossible to compare data with those from other studies using the PDP, or with previous reports of results in the indirect task.

removed because *A* cannot be calculated if this happens [$A = 0/(1-C)$]. Another correction was applied by comparing L's effects to those of a subgroup of subjects in the diazepam group that were more affected by the drug. Taking all this into account, Vidailhet *et al*. (1996) concluded that L, but not diazepam, was capable of reducing automatic memory, confirming the widespread assumption that this drug impairs repetition priming. These attempts to equate the *C* effects of both drugs are, however, somewhat artificial. Removing data of subjects who performed well in the exclusion task and of volunteers that were more affected by diazepam could have distorted data and/or decreased statistical power. Thus, the initial difference between *C* indices in the L and diazepam groups makes it impossible to determine whether these drugs differed in their impairment of priming or if the dose of diazepam was not high enough to elicit the same effects as L.

Difficulties in applying the PDP are by no means restricted to studies with BZs. There has been widespread criticism of the theoretical assumption underlying this paradigm, even when drugs are not used (e.g. see Baddeley, 1999; Hirshman, 1998; Jacoby, 1998; Russo *et al*., 1998; Richardson-Klavehn *et al*., 2002). Therefore the issue of L's specific atypical effects on repetition priming remains unresolved.

The comparison of L and F effects in the stem-completion tasks without applying the PDP were more revealing in terms of characterizing L as having atypical effects and less liable to discussions concerning possible methodological flaws. In contrast to L, F did not impair performance in the indirect task, thus showing standard BZ effects (Curran, 1991, 2000). However, F did not impair results in the inclusion task, supposedly a measure of explicit memory that is altered by BZs. Nevertheless, the absence of BZ effects in this type of test has been shown for diazepam (Vidailhet *et al*., 1996), flunitrazepam (Pompéia *et al*., 2000; Pompéia *et al*., 1996b) and nitrazepam (Pompéia *et al*., 1996b) using doses that led to impairment of other measures of episodic memory, as shown here by F's effect on *C*. This probably reflects the limited task demands required in this test (Pompéia *et al*., 1996b).

Contrary to what would be expected, though, F impaired performance in the exclusion task, in which only repetition priming, and not explicit memory, should be involved. This latter result is difficult to accommodate, especially since measures of repetition priming are not consistently affected by BZs other than L, and also because F left the *A* index unchanged. The fact that both drugs had opposite effects on the direct tasks (inclusion and exclusion), however, shows that it would have been impossible to change doses to equate their effects, thus confirming that the doses used were equipotent in terms of cognitive impairment, as shown previously by Pompéia *et al*. (2003) when applying other cognitive tests in the same experiment.

These opposite findings do not seem to be a result of casual variations or methodological artifacts, since impairment by L of the inclusion but not the exclusion task, with the opposite effect for another BZ (diazepam), was reported by Vidailhet *et al*. (1996). Also, zolpidem, a drug that binds selectively to BZ type 1 receptors, seems to impair exclusion and not inclusion scores (Pompéia *et al*., 2001; Pompéia *et al*., submitted). In addition, differences in task sensitivity cannot explain these results without implying that these drugs do in fact have different effects. The absence of impairment by L in the exclusion task also makes it impossible to ascribe L-induced changes in stem-completion to visual alterations, which seem to be specific to this compound (see Pompéia *et al*., 2003), because the three stem-completion tasks were equivalent in terms of visual characteristics. The same applies to the purported effects of BZs on lexical access (Massin-Krauss *et al*., 2002). Also, as both F and L have the same affinity to BZ receptors (Möhler and Okada, 1977; Möhler *et al*., 1978; Arendt *et al*., 1987; Müller, 1987), L's high potency does not explain why it impairs indirect and inclusion stem-completion and not the exclusion version of this task. All in all, our results show that L does indeed seem to have atypical stem-completion effects.

Concerning analysis of stems left blank, it is also unclear how Vidailhet *et al*. (1996), in the other study using the PDP, went about analysing their data. Although stems could be left uncompleted when words that corresponded to them were seen (studied) and not seen (non-studied) at study, these authors only analysed effects of group, condition (exclusion, inclusion) and interaction of these effects; no mention was made of differences between groups or instruction in terms of stems not completed in the studied and non-studied conditions. When we followed their method, there were no significant effects. When considering familiarity as another factor in the analysis, however, stems of studied words were left blank less often than non-studied ones in the indirect and inclusion conditions. This is not surprising since memory facilitates completions. In effect, this did not change the patterns of results in these tasks when the proportion of uncompleted stems was used as a covariate. The only case in which stems left blank differed between groups was in the exclusion task, in which F was

impaired in relation to L and P. Although this did not determine F's results in the exclusion task, because covarying uncompleted stems still left F different from P, differences between drugs in this respect indicated that there seems to be something about performance in the exclusion task, as shown for completed stems, that may indicate why L has atypical effects.

It is difficult to explain the differences between drugs in the indirect and exclusion tasks observed here in terms of distinct effects on different long-term memory subtypes because impairment in both these measures supposedly indicates alterations in the same type of memory. Effects in stem-completion tasks may also, however, be explained without recourse to multiple memory systems. Work on information-processing models proposes that results that may be interpreted as repetition priming in indirect stem-completion can also be attributed to bias effects (Ratcliff and McKoon, 1996). These effects may be understood as temporary modifications to the process of perception, identification and decision that apparently vary across a wide range of experimental paradigms used to evaluate memory (Ratcliff and McKoon, 1996). Alterations in one or more of these processing stages might determine different effects in different tasks. Hence, BZs may alter the way subjects respond to task instructions rather than simply to impair memory itself. Other factors that have also been found to determine performance in inclusion and exclusion tasks and that may explain the different effects of F and L are: alterations in motivation (although this does not seem to influence *A* and *C* indices) (Visser and Merikle, 1999); use of voluntary and involuntary conscious memory (see Richardson-Klavehn *et al*., 1994; Vaterrodt-Plunnecke *et al*., 2002); compliance with instructions (see Richardson-Klavehn *et al*., 2002); feelings of familiarity towards words generated by stems (see Metcalfe, 2000; Toth *et al*., 1994; Toth, 2000); use of strategy to complete stems (i.e. generate, or generate/recognize; Jacoby, 1998); accessibility bias (Jacoby *et al*., 2001), etc. Unfortunately, such effects have seldom been investigated in the BZ literature (for exceptions in studies using L, see Bacon *et al*., 1998; Massin-Krauss *et al*., 2002). Future studies in this area contrasting L-induced effect to those of other BZs in equipotent doses may help to determine the underlying mechanisms that make L unique in terms of cognitive effects.

In sum, lorazepam impaired performance in the indirect and inclusion stem-completion tasks while an equipotent dose of flunitrazepam impaired performance in the exclusion task. The differences between drugs in their effects on performance in the three stem-completion tasks suggest that these BZs may lead to differences in response bias in addition to, or rather than, repetition priming effects, since indirect and exclusion tasks both supposedly measure mainly this type of memory. In the present study lorazepam's effects could not be ascribed to its high affinity to the BZ receptors, task sensitivity, specific changes in visual processing, or access to lexical information. Further research into lorazepam's atypical effects on stem-completion may lead to a better understanding of the mechanisms involved in the way BZs influence results in memory tasks, as well as to a more appropriate clinical application of this BZ.

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