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Atypical behavioural effects of lorazepam: Clues to the design of novel therapies?

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ABSTRACT

Aside from their pharmacokinetic properties, e.g. their speed of action and the duration of residual effects, benzodiazepines are still considered as equivalent in terms of their effects on cognition. Here we review evidence suggesting that certain benzodiazepines, especially lorazepam, differ in a number of respects, in particular with respect to their effects on cognition. We focus this review on memory, attention and visual perception, where impairments may be brought about by only a subset of benzodiazepines in spite of their administration at doses inducing similar sedative effects. This precludes an explanation in terms of sedation. Differences in the effects of benzodiazepines have also been found in electrophysiological and animal behavioural studies.

These studies are important for therapeutic approaches for two reasons: first, effects of benzodiazepine prescription on cognitive functions will differ according to the benzodiazepine, contrary to what is usually believed. Less straightforwardly are the possible therapeutic implications of specific effects on cognition following treatment with lorazepam. Indeed, the specific effects this drug has on cognition may reveal not only side-effects but also effects of potential therapeutic value. Current research concentrates on a fine scale analysis of the effects of GABA on different sub-types of GABA_A receptors. We suggest that from looking at what makes lorazepam different in a behavioural sense from other benzodiazepines we may be in a position to design innovative treatments for major aspects of complex disorders, including schizophrenia.

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Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PDP, process dissociation procedure; PET, positron emission tomography; SAI, short-latency afferent inhibition; SICl, short-latency intracortical inhibition; TMS, transcranial magnetic stimulation.

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1. Introduction

Benzodiazepines are widely prescribed for their anxiolytic, hypnotic, myorelaxant and anti-epileptic properties. They facilitate fixation of GABA on GABA_A receptors, and in this way increase the inhibitory effect of GABA (Kaila, 1994). It is widely held that all benzodiazepines affect GABAergic transmission in the same way, but in spite of this a large number of different types of GABA_A/benzodiazepine receptors has now been described (review in Möhler, 2007). This research suggests that different molecules differ in their affinity for sub-types of the GABA_A/benzodiazepine receptor. Moreover, there is now a variety of evidence claiming qualitative differences in the psychological effects of different benzodiazepines. In particular, as reviewed here, there is substantial evidence identifying lorazepam as distinct in its effects on cognitive processes relative to other benzodiazepines (Pompéia et al., 2003b, 2005).

GABA is the main inhibitory neurotransmitter in the brain and benzodiazepine receptors are ubiquitously distributed throughout the central nervous system. It is thus not surprising that benzodiazepines have a number of different effects on cognition beside their desired therapeutic effects. These include effects on memory (Brown et al., 1982; Curran, 1991; Danion et al., 1992; Buffet-Jerrott & Stewart, 2002), visual perception (Giersch et al., 1997; Giersch, 1999; Giersch & Lorenceau, 1999; Giersch, 2001) and attention (Jalava et al., 1995; Johnson et al., 1995; Post et al., 1997; Carter et al., 1998; Boucart et al., 2000, 2007). The effects of individual benzodiazepines have been shown to differ qualitatively in a number of studies, especially those comparing lorazepam with other drugs, usually diazepam. There are few studies in each domain, i.e., cognition, animal behaviour, EEG or TMS, and the methodologies used, as well as the type of drug response differ markedly across studies, making it difficult to realize a meta-analysis. In spite of this the results consistently indicate qualitative differences between benzodiazepines. In our review, we have not selected positive results among papers, but simply extracted the few papers from the literature that directly compared different benzodiazepines with the aim of providing a comparative analysis of the different drug effects. We emphasize only those papers in which effects cannot be explained by a trivial difference in metabolism, with some drugs acting longer than others, or having their peak plasma concentrations at different times relative to the drug intake, or by differences in dosages. Except when otherwise stated, the studies described here compared benzodiazepines at dosages inducing a similar level of sedation and displaying similar effects on anxiety, and the effects of the drugs were compared at their peak of action. The majority of the described studies deal with young healthy volunteers. Detailed information regarding dosages, therapeutic effects and side-effects in such studies can be found in Table 1. There are some aspects we do not develop here, because they seem only poorly supported until now, like the beneficial effects of lorazepam on epilepsy, which might be attributed to the dosages used in the studies, or the effects on mania or catatonia (Table 1). These effects might warrant further exploration, though, and we mention them in the table. With the remaining information, we both review and discuss evidence for a qualitative difference between existing benzodiazepines, with two aims: firstly, it is useful to disseminate this knowledge because it means that different benzodiazepines will differ in terms of their side effects. The studies to date suggest that lorazepam affects visual perception and some aspects of memory ('perceptual priming'). These effects are not shared by all benzodiazepines and they persist at least in part following chronic intake. The effects are not very well known, and we put special emphasis on them and on their possible impact on everyday life. Second, the qualitative difference between benzodiazepines may reveal a property (or properties) of a sub-group of benzodiazepines which might be of interest with respect to novel therapeutics. We will detail the arguments supporting this assertion with the aim of encouraging research at the molecular level to provide

an explanation of qualitative differences between benzodiazepines. This may in turn uncover a target(s) for innovative drug or treatment design especially for complex disorders in which benzodiazepines are frequently prescribed, for example schizophrenia.

2. Dissociating benzodiazepines by their effects on perceptual priming

Following acute dosage, all benzodiazepines provoke anterograde amnesia without retrograde amnesia: they impair explicit memory for information learned after, but not before drug intake. This amnesic effect has been well documented using classic recall and recognition tasks in which subjects are explicitly instructed to recollect past information voluntarily and consciously (Brown et al., 1982, 1989; Curran, 1991; Danion et al., 1992). This amnesic effect is shared by all benzodiazepines, although its magnitude and profile differ quantitatively between drugs depending on a variety of factors including dosage and pharmacokinetic/pharmacodynamic properties (Ghoneim & Mewaldt, 1990). Effects on explicit memory are the best known cognitive effects of benzodiazepine administration. However, these are not effects we intend to focus on here, as to date no qualitative difference has been found between benzodiazepines in explicit memory. There is another form of memory, however, which is differentially affected by benzodiazepines, that is perceptual priming which is an unconscious, non intentional form of memory. Perceptual priming refers to a change in behavioural response to a stimulus following re-exposure. It is explored in tasks such as word-stem or picture completion, in which prior presentation of a stimulus item facilitates its subsequent identification even though no explicit instruction is given to subjects to recollect the item concerned (Tulving & Schacter, 1990). This form of implicit memory can be dissociated from explicit memory in amnesic patients, who are unable to consciously recollect any past information, nonetheless show preserved perceptual priming. Even though these patients are unable to remember whether or not they have experienced an item, they are still facilitated in the identification of that particular item when presented with it on a subsequent occasion. The evidence for this facilitation is the accelerated response or the need for only scant information to identify the item. This form of facilitation is taken as a sign of perceptual priming. To date, most benzodiazepines have been shown to preserve perceptual priming in healthy subjects (Pompéia et al., 2003b) with the notable exception of lorazepam which, in direct contrast to this general trend is reported to impair perceptual priming (Brown et al., 1989; Knopman, 1991; Danion et al., 1992; Sellal et al., 1992; Curran & Gorenstein, 1993; Vidailhet et al., 1994; Bishop & Curran, 1995; Curran et al., 1995; Legrand et al., 1995; Stewart et al., 1996; Buffet-Jerrott et al., 1998a; Vidailhet et al., 1999; Pompéia et al., 2000; Martin et al., 2002; Pompéia et al., 2003a). The impairment by lorazepam of perceptual priming is dose-dependent and maximal at the time of the theoretical peak plasma concentration of the drug (Legrand et al., 1995). It has been observed in different tasks and modalities, i.e. visual or auditory, with words or pictures (Sellal et al., 1992; Vidailhet et al., 1994; Legrand et al., 1995; Vidailhet et al., 1999). This differential effect of lorazepam on perceptual priming is qualitative in nature since it has been reported in studies directly comparing lorazepam to other benzodiazepines, where the deleterious effect on explicit memory and/or on attention and sedation were equivalent (Sellal et al., 1992; Curran & Gorenstein, 1993; Pompéia et al., 2000; Martin et al., 2002; Pompéia et al., 2003a). This suggests it is not related to a difference in potency between drugs: if lorazepam had been more potent than other benzodiazepines, then differences between drugs should have been observed for the different cognitive measures. On the contrary, lorazepam affects some specific aspects of cognition that remain preserved under the effect of other drugs, whereas benzodiazepines are found to be equipotent on other, dissociated aspects of cognition. It is this kind of results that suggests

Table 1
The cited studies take into account possible differences in metabolism, and in particular in action delays (either the compared drugs share the same profile, or their effect is compared at peak of action).

	Dose of lorazepam (except otherwise stated, the intake is oral)	Dose of compared benzodiazepine (except otherwise stated, the intake is oral)	Design	Benzodiazepine effects that are similar	Benzodiazepine effects that differ
<i>Anxiolysis</i> The Ashton Manual, Ashton, 2002	1 mg oral	10 mg diazepam 4.8 mg midazolam 20 mg clobazam 15 mg clorazepate 1 mg flunitrazepam 0.5 mg alprazolam 5.5 mg bromazepam 0.5 mg clonazepam 20 mg oxazepam	Between-subject	Similar effects on anxiety	
<i>Epilepsia</i> Cock & Schapira, 2002, QJM	4 mg IV	10 mg IV diazepam	Between-subject Retrospective N = 72	Similar effect on seizure termination. No difference in reported side effects (sedation, hypotension, respiratory depression)	Fewer seizure recurrence under lorazepam (but see doses)
Qureshi et al., 2002, Seizure	0.13 mg/kg IV	0.32 mg/kg IV diazepam	Between-subject N = 48	Similar effect on seizure termination	
Allredge et al., 2001, New Engl J Med	2–4 mg	5–10 mg diazepam Or placebo	Between-subject N = 205	Similar rate of respiratory or circulatory complications	Better odd ratio for lorazepam than for diazepam (but see doses)
Appleton et al., 1995, Dev Med Child Neurol	0.05–0.1 mg/kg IV or rectal	0.3–0.4 mg/kg diazepam IV or rectal	Between-subject N = 86		Slightly larger efficacy under lorazepam than diazepam, and less respiratory depression.
Leppik et al., 1983, JAMA	4 mg IV	10 mg diazepam IV	Between-subject N = 78	Adverse effects similar (respiratory depression)	Lorazepam slightly more efficient than diazepam (but see doses)
<i>Side-effects (diverse)</i> Mendelson et al., 1996, Sleep	1–2 mg	2.5–10 mg diazepam 0.25 mg alprazolam	N around 1200		Frequency of adverse effects (confusion, mild somnolence, respiratory depression, agitation, sedation, rash) larger in lorazepam-treated (0.05%) than in subjects treated with other benzodiazepines (0.02% or lower, but see doses)
<i>Sympathetic activity</i> Agelink et al., 2002, Crit Care Med	0.06 mg/kg	0.13 mg/kg diazepam 0.07 mg/kg midazolam	Between-subject N = 45	Reduction in the vagal tone Increase in the resting heart rate	
Tulen & Man in't Veld, 1998, J Cardiovasc Pharmacol	2 mg lorazepam	1 mg alprazolam	Within-subject N = 12		Reduction in plasma noradrenaline concentration under alprazolam but not lorazepam, with an increase in the cardiac vagal tone
Van den Berg et al., 1996, Psychopharmacology	2 mg lorazepam	1 mg alprazolam	Within-subject N = 12	Sedation evaluated subjectively	Suppression of adrenomedullary activity under alprazolam but not lorazepam
Roelofse & van der Bijl, 1994, J Oral Maxillofac Surg	0.05 mg/kg IV	0.25 mg/kg diazepam 0.1 mg/kg midazolam	Between-subject N = 60		Dysrhythmia observed in 25% diazepam-treated subjects, 5% midazolam treated subject, and 0% lorazepam-treated subject.
Pomara et al., 2004, Neuropsychopharmacology	0.5–1 mg Acute and chronic	0.25–0.5 mg alprazolam	Between-subjects (N = 68)	Sedation evaluated subjectively	Significant increase of cortisol plasma level under alprazolam but not lorazepam
<i>Catatonia symptoms</i> Schmider et al., 1999, Biol Psychiatry	2 mg	60 mg oxazepam	Within-subject (N = 17)	Similar efficiency on the first day of treatment	Lorazepam was more efficient on the second day of treatment (but the cross-over design makes the interpretation difficult)

Table 1 (continued)

	Dose of lorazepam (except otherwise stated, the intake is oral)	Dose of compared benzodiazepine (except otherwise stated, the intake is oral)	Design	Benzodiazepine effects that are similar	Benzodiazepine effects that differ
<i>Acute Mania</i> Bradwejn et al., 1990, J Clin Psychopharmacol	6–24 mg	6–24 mg Clonazepam	Between-subject (N = 206)		Improvement in the psychopathology score larger under lorazepam than under clonazepam. (but see meta-analysis by Curtin & Schulz, J Affective Disorders, 2004)
<i>Perception</i> Beckers et al., 2001, Vis Res	0.038 mg/kg	0.3 mg/kg diazepam placebo	Between-subject N = 30	Sedation evaluated subjectively (visual analogue scales)	Detection of discontinuities altered in lorazepam but not diazepam
Giersch & Herzog, 2004, Neuropsychopharmacology	0.038 mg/kg	0.3 mg/kg diazepam placebo	Within-subject N = 12	Sedation evaluated subjectively (visual analogue scales) and objectively (pupillography)	Vernier offset discrimination altered in lorazepam but not diazepam
Elliott et al., 2006, Psychopharmacology	0.038 mg/kg	0.3 mg/kg diazepam Placebo	Within-subject N = 12	Sedation evaluated subjectively (visual analogue scales)	Dynamic figural priming increased under lorazepam but not diazepam
Wagemans et al., 1998, Psychopharmacology	0.038 mg/kg	0.3 mg/kg diazepam Placebo	Between-subject N = 36		Impairment in the identification of fragmented pictures under lorazepam, but not under diazepam
<i>Attention</i> Boucarr et al., 2000, Psychopharmacology	0.038 mg/kg	0.3 mg/kg diazepam Placebo	Between-subject (N = 36)		Increase in the magnitude and duration of the attentional blink effect, more pronounced under diazepam than under lorazepam
Jalava et al., 1995, Pharmacol Biochem & Behav	2 mg	15 mg diazepam Ethanol placebo	Between-subject (N = 21)	Effect on focus attention	Effect on divided attention more pronounced under lorazepam than under diazepam
<i>Memory</i> Pompéia et al., 2000, J Psychopharmacol	2 mg	0.6, 0.8, 1 mg flunitrazepam Placebo	Between-subject (N = 60)	Explicit memory	Perceptual priming more severely impaired by lorazepam (only lorazepam < placebo)
Pompéia et al., 2003a, Hum Psychopharmacol	2 mg	1.2 mg flunitrazepam Placebo	Between-subject (N = 36)	Using the PDP, both drugs impaired the estimates of controlled, but not automatic memory processes	Only lorazepam impaired perceptual priming. The profile of impairment of the 2 drugs differed in the exclusion and inclusion test conditions of the PDP
Curran & Gorenstein, 1993, Int Clin Psychopharmacol Stewart et al., 1996, Psychopharmacology Buffet-Jerrott et al., 1998a, Psychopharmacology Martin et al., 2002, Psychopharmacology	2 mg (except for Martin et al.: 2.5 mg)	30 mg oxazepam Placebo	Between subject (N = 30 to N = 36)	Explicit memory	Lorazepam impaired perceptual priming in the 4 studies while oxazepam impaired it in only 2 (for a critical review of these latter studies, see Martin et al., 2002 and Pompéia et al., 2003a)
Curran et al., 1987, Psychopharmacology	1, 2 mg	15, 30 mg oxazepam Placebo	Between-subject (N = 45)	Explicit memory	The magnitude of explicit memory impairment was higher after lorazepam (2 mg) than oxazepam (30 mg)
Block & Berchou, 1984 Pharmacol Biochem Behav Kumar et al., 1987, J Clin Psychiatry Greenblatt et al., 1988, Clin Pharmacol Ther Pomara et al., 1998, Psychopharmacol Bull	2 mg	0.25, 0.5 or 1 mg alprazolam	Between-subject or cross-over (N = 12 to N = 39)	Explicit memory after first or repeated dosage (6 days)	Dissociations in the pattern of tolerance for cognitive effects after 3 weeks of treatment (Pomara et al., 1998)
Brown et al., 1982, Neuropsychologia	3 mg IV	7.5 mg Diazepam IV placebo	Between-subject (N = 27)	Explicit memory	Lorazepam affected recognition more than recall

(continued on next page)

Table 1 (continued)

	Dose of lorazepam (except otherwise stated, the intake is oral)	Dose of compared benzodiazepine (except otherwise stated, the intake is oral)	Design	Benzodiazepine effects that are similar	Benzodiazepine effects that differ
<i>Memory</i>					
Patat et al., 1987, Eur J Clin Pharmacol	2 mg	10 mg diazepam clobazam 20 mg placebo	Cross-over (N = 10)	Explicit memory impaired by diazepam and lorazepam	No deleterious effect of clobazam on memory
Healey et al., 1983, J Clin Psychiatry	1 or 2 mg	5 or 10 mg diazepam 7.5 or 15 mg clorazepate Placebo	Cross-over (N = 10)		Only lorazepam impaired explicit memory
Conner et al., 1978, J Clin Pharmacol	2 or 4 mg IV	Diazepam 10 or 20 mg IV	Between-subject (N = 120)	Explicit memory	
Sellal et al., 1992, Psychopharmacology	1.75 or 2.5 mg	15 or 20 mg diazepam Placebo	Between-subject (N = 60)	Explicit memory	Perceptual priming more severely impaired by lorazepam than diazepam
Vidailhet et al., 1994, Psychopharmacology	0.026 or 0.038 mg/kg	0.2 or 0.3 mg/kg diazepam Placebo	Between-subject (N = 60)	Explicit memory and perceptual priming	
Legrand et al., 1995, Psychopharmacology	0.026 or 0.038 mg/kg	0.2 or 0.3 mg/kg diazepam Placebo	Between-subject (N = 60)	Explicit memory	Perceptual priming impaired by lorazepam but not diazepam
Vidailhet et al., 1996, Psychopharmacology	0.038 mg/kg	0.3 mg/kg diazepam Placebo	Between-subject (N = 60)		In the PDP, only lorazepam altered the estimate of automatic memory processes
Huron et al., 2001, Psychopharmacology	0.038 mg/kg	0.3 mg/kg diazepam Placebo	Between-subject (N = 36)	Conscious recollection for true but not false memories No effect on familiarity	
Curran, 1992, J Psychopharmacol	1.6 mg (mean)	8.6 mg diazepam (mean)	Subjects having bzd dependence (N = 7 for lorazepam and N = 9 for diazepam)	Explicit memory	Only lorazepam altered perceptual priming
<i>Electrophysiology</i>					
Itil et al., 1989, Int Clin Psychopharmacol	1 mg	5 mg diazepam	Within-subject, N = 1		Larger sedation under lorazepam than under diazepam (but see doses), and qualitative differences in EEG signal
Pompeia et al., 2000, 2003a, J Psychopharmacol	2 mg	0.6 to 1.2 mg flunitrazepam	Between-subject N = 30 to 36	DSST, and sedation evaluated subjectively (visual analogue scales)	Larger slowing down under flunitrazepam in the simple reaction time test, but reversed results for shape identification. Longer latencies in evoked potentials under lorazepam than under flunitrazepam
Di Lazzaro et al., 2005a, J Physiol	2.5 mg	20 mg diazepam	Within-subject N = 11	Effects on Short-latency Intra-Cortical Inhibition (SICI)	Short-latency Afferent Inhibition (SAI) affected by lorazepam but not by diazepam

that lorazepam differs qualitatively from other drugs. Moreover, additional methods have been used to distinguish perceptual priming from explicit memory. Indeed, identification of incomplete pictures or completion of word stems that have been presented previously might be based on explicit memory rather than on perceptual priming per se. This 'explicit contamination' usually explains why other benzodiazepines than lorazepam may, in some studies, display a deleterious effect on perceptual priming index, compared to placebo (Vidailhet et al., 1994; Legrand et al., 1995; Stewart et al., 1996; Buffet-Jerrott et al., 1998a,b). With this in mind, some authors have used a 'retrieval intentionality criterion' to eliminate an explanation in terms of a contamination of the priming task by explicit memory (Bishop & Curran, 1995). Finally, using the 'process-dissociation procedure' (PDP) from which non contaminated estimates of controlled and automatic memory processes can be obtained (Jacoby, 1991), our group has shown that lorazepam, and not diazepam, impairs automatic memory processes (Vidailhet et al., 1996; see Pompéia et al., 2003a, for a critical discussion of our results).

As the cognitive mechanisms involved in lorazepam-impaired perceptual priming begin to be understood light may be shed on the mechanisms by which lorazepam differs from other benzodiazepines and in the following we will develop this point. Lorazepam impairs the acquisition of information, whilst leaving intact its storage and retrieval (Vidailhet et al., 1994). Impaired performance is observed when lorazepam is given prior to information acquisition but is not evident when administered immediately after acquisition. Lorazepam impairs both visual and auditory perceptual priming (Vidailhet et al., 1999). According to Roediger and Challis (1992), perceptual priming involves both modality-specific sensory processing alongside modality-independent, more abstract processes (including lexical processes, i.e. the access to the name corresponding to the picture or the word) both of which appear to be impaired by lorazepam in word-stem completion tasks (Vidailhet et al., 1999). This conclusion is further supported by functional brain imaging studies, which permit exploration of the neurobiological foundations of perceptual priming and allow more detailed analysis of the different cognitive processes involved. These

studies typically show a 'suppression repetition effect', that is lower brain activity for primed compared to non-primed stimuli (Schacter et al., 2007) which may correspond to the facilitation of stimulus processing. The suppression repetition effect has been observed in several brain regions, some of which are modality-specific and implicated in perceptual identification while others are more anterior and multimodal and subserve more abstract (phonological, lexical or semantic) processes (Henson, 2003; Bergerbest et al., 2004; Schacter et al., 2007; also see Horner & Henson, 2008 for the implication of some prefrontal regions in increased efficiency in stimulus-decision coupling). Thiel et al. (2001) have used event-related fMRI to explore the effect on the brain of a single dose of lorazepam (2 mg per os) while subjects were performing a visual word-stem completion task. They observed a reduction in the "repetition suppression effect" in several regions, including extrastriatal occipital and left middle and inferior frontal regions. All in all, these results suggest that lorazepam impairs both abstract and more perceptual processes involved in perceptual priming.

3. Dissociating benzodiazepines by their effects on form perception

Several processes involved in visual perception appear to be affected by benzodiazepines and, as found in perceptual priming tasks, lorazepam seems to have effects on visual perception that are not shared by other benzodiazepines. Since our aim is to focus on these differences, we will not describe all visuo-perceptual effects of benzodiazepines. For example we will not describe results suggesting that benzodiazepines affect low-level visual processes such as contrast sensitivity, ocular convergence, and eye movements in general (reviewed in Giersch et al., 2006b; Reilly et al., 2008). Variations in these visual capabilities are important side-effects of benzodiazepine administration and of particular significance to everyday visual cognition which requires good contrast sensitivity and visual acuity. Yet, it is still unclear whether these effects are observed with all benzodiazepines. It should be noted that care has been taken to distinguish between the effects of lorazepam on aspects of cognition, for instance form perception, and its effects on ocular convergence or low level visual functions such as contrast sensitivity (Giersch et al., 1996, 1997, 2006b).

It has frequently been shown that lorazepam affects identification of fragmented pictures. This observation was first made in perceptual priming tasks (Sellal et al., 1992; Vidailhet et al., 1994; Legrand et al., 1995) in which complete pictures were presented during an initial encoding phase and presented again in a test phase where pictures were presented incomplete or fragmented. Each fragmented picture was initially presented with very few contours. Additional contours were added in subsequent steps until identification. Identification performance was then compared between a situation with pictures previously presented and a situation with novel pictures. It was found that administration of lorazepam reduced the advantage provided by the prior presentation of the pictures, indicating a deleterious effect on perceptual priming. However, lorazepam-treated subjects also required more contour information than placebo-treated subjects to identify new pictures. Significantly, this was not the case in diazepam-treated subjects, despite the fact that, as with perceptual priming, diazepam had a similar effect on sedation and explicit memory (Sellal et al., 1992; Vidailhet et al., 1994; Legrand et al., 1995; Wagemans et al., 1998).

Subsequent studies have explored several mechanisms underlying the identification of pictures that are affected by lorazepam but not by diazepam. As was the case for perceptual priming, we will describe these mechanisms because they shed some light on the functional differences between lorazepam and other benzodiazepines. According to classical models of visual perception (Boucart et al., 1994; Boucart, 1996), visual information processing occurs over successive stages,

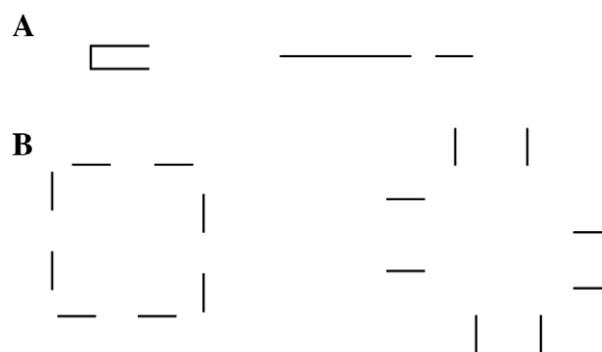


Fig. 1. Illustration of the effects of lorazepam on visual perception. **A:** Treated participants had more difficulties to locate gaps between parallel elements (Fig. 1A on the left) than between co-linear elements (Fig. 1A on the right). **B:** Conversely, participants under the effect of lorazepam integrated elements in a global configuration faster when they were parallel (Fig. 1B on the right) than when they were co-linear (Fig. 1B on the left).

the first corresponding to the extraction of visual primitives, such as orientation, color, and light intensity at stages no later than primary visual cortex. Visual primitives are coded locally, in functionally specific neuronal systems. Later, this contour information must be correctly bound together in order to recover the object's global form. This can be complex, especially if objects are constructed from multiple and different features, and if the object is occluded, i.e., partially hidden behind a foreground object, as they often are in natural scenes. Recovering an object's shape requires the integration of fragmented contour information into a continuous contour, and to correctly separate contours that belong to different objects. The recovered shape must then be compared to representations of objects stored in memory in order to extract the object's identity.

Some results suggest that later processing stages in perception are affected by lorazepam: Wagemans et al. (1998) used fragmented pictures and manipulated the type of gap between contours, i.e. whether gaps were located at the inflexion, the maxima (for convex contours) or minima (for concave contours). Contour integration would permit completion across the gaps but the efficiency of completion differs according to the location of the gap (Lamote & Wagemans, 1999; De Winter & Wagemans, 2008). In fact, it is much easier to complete across two elements that are aligned, because contour alignment is an efficient cue for binding two elements into an integrated whole (Boucart et al., 1994; Kovacs et al., 1999). In contrast, concave contours are natural segmentation cues and elements separated by a gap located at minima are more difficult to bind together (Hoffman & Richards, 1984). Despite this, the difficulty to identify fragmented pictures when treated with lorazepam was equivalent whatever the type of gap. This suggests that the mechanisms influenced by lorazepam involve processes taking place after contour completion and likely involve a comparison of the form with representations stored in memory (see Wagemans et al., 1998, for a complete discussion of these results).

Results differed, however, when stimuli were geometrical shapes (Giersch et al., 1997; Giersch, 1999; Giersch & Lorenceau, 1999; Elliott et al., 2000; Beckers et al., 2001; Giersch, 2001; Lorenceau et al., 2005; Elliott et al., 2006), or when the task did not involve picture identification (Giersch et al., 1995, 1996). In all of these cases, the performance in lorazepam-treated participants differed according to the type of gaps present in the pictures, suggesting that the drug also affects the processes directly responsible for visual integration. Most of the studies published to date concern these visual integration processes with a number comparing the effects of lorazepam and diazepam. While the experimental paradigm was different on each occasion – eliminating arguments appealing to the use of a particular type of test – the results were consistent across studies with a similar difference between lorazepam and diazepam. Whenever the gap is

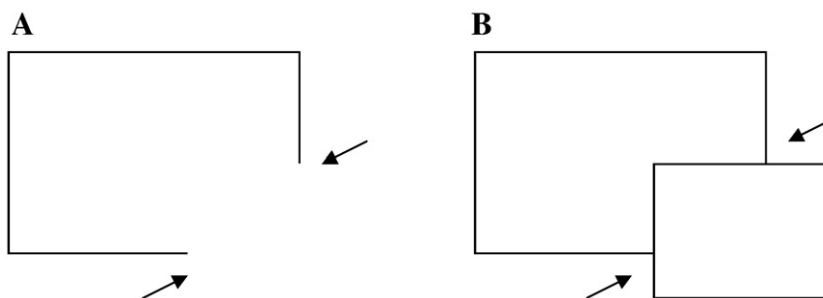


Fig. 2. Illustration of the ambiguity of visual cues like line-ends (or line terminations). In (A) line terminations (indicated by the arrows) represent true line-ends, meaning that they indicate the edge of the shape. In (B), they result of an occlusion, i.e. line terminations are produced only because another object at the forefront hides part of the background rectangle.

located between parallel elements (Fig. 1), lorazepam-treated participants experienced difficulties detecting the gap, whereas this difficulty is not observed and in some cases facilitation is evident when the gap is located between aligned ('co-linear') elements (Giersch, 1999; Beckers et al., 2001; Giersch, 2001; Giersch & Vidailhet, 2006). This leads to difficulty in integrating aligned elements into a global form, this being true for both static and moving forms (Giersch et al., 1995, 1996, 1997; Giersch & Lorenceau, 1999; Elliott et al., 2000; Lorenceau et al., 2005; Elliott et al., 2006). In contrast, the integration of parallel elements appears to be facilitated (Fig. 1).

These effects can be related to the mechanisms underlying the computation of contour at the earliest stages of visual information processing, where forms are not identified and contours are not attributed to forms. The visual system is believed to make use of two types of signals to derive the form of objects and to separate them from the background or from other objects (Boucart et al., 1994): local orientation provides information regarding the contour of objects, whereas line-ends and edges indicate the transition between the object and the background, or between different objects or object parts (von der Heydt & Peterhans, 1989). Such cues are inherently ambiguous, however, since they have to be processed even before an object is identified. Line terminations can represent true line-ends, meaning that they indicate the edge of a shape. Alternatively, they can be the result of an occlusion, i.e. an edge is perceived only because some other object at the forefront hides part of the contour and artificially produces a line-end (Nakayama et al., 1989; Stoner et al., 1990; Grossberg, 1994). In the first case, the line-end signal is

especially important, since it helps to distinguish the object from the background and from nearby objects. In the latter case however, the line-end is not indicating a true edge, and the contour is not ending at the location of the line-end (Fig. 2). On the contrary it should be bound together with the other parts of the hidden object.

This leads to the idea of a competition between integration and separation (or 'segmentation') mechanisms (Lorenceau et al., 2005), and of a possible modulation of the line-end signals in healthy volunteers (Giersch & Fahle, 2002; Giersch & Caparos, 2005). We have proposed that lorazepam affects the balance between integration and segmentation signals (Lorenceau et al., 2005) and the modulation of the processing of line-ends (Giersch, 2001) with the consequence that the resolution of any ambiguity associated with the attribution of a line-end signal to one or other object is slowed. This then increases the time required to identify objects in the environment. This was directly suggested in a masking paradigm using Vernier stimuli (Giersch & Herzog, 2004). Vernier stimuli are composed of two abutting vertical lines that offset in a horizontal direction, and subjects have to decide if the lowest line is offset to either the right or left (Fig. 3A). This offset is very small, i.e. below 200 arc sec (200 arc sec represents 0.5 mm when the stimulus is at a distance of 60 cm from the eyes) and offset discrimination relies on the pooling of information across a large number of neurons that are sensitive to spatial position and orientation (Herzog et al., 2001, 2003). Difficulty to integrate co-linear (aligned) elements was likely to impair this pooling process and indeed, the results showed that five of twelve lorazepam-treated subjects were unable to perform the task and successfully discriminate the offset of the Vernier stimuli. In the seven remaining subjects the Vernier stimulus was masked by a grating of vertical elements (Fig. 3B), allowing the evaluation of the time needed to complete the task before masking. The results showed that for lorazepam-treated subjects, information had to be displayed for a much longer period of time for successful task completion than for placebo-treated subjects (between 3 and 4 times the duration required under placebo). This suggests that visual information processing is prolonged as a consequence of lorazepam administration. In this study and in two others (Beckers et al., 2001; Elliott et al., 2006), the effects of lorazepam administration contrasted markedly with those of treatment with diazepam.

In all the results described until now, lorazepam has additional effects on information processing when compared with other benzodiazepines. This tends to raise a question of the relative potencies of the drugs being compared and in particular the possibility that lorazepam is more potent than diazepam at the dose used. This question has been addressed in several ways: the doses used in studies of visual perception were the same as those used in the memory studies which showed a similar effect of diazepam and lorazepam on explicit memory but a deleterious effect of lorazepam on implicit memory. They were chosen on the basis of earlier studies showing equipotency of the two drugs on sedation levels and explicit memory (Dundee et al., 1979; Kothary et al., 1981). At these doses and

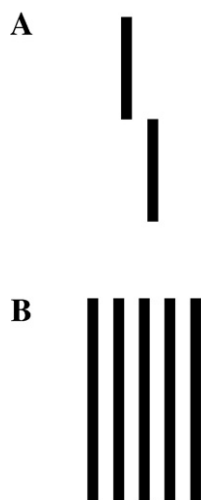


Fig. 3. (A) Example of a Vernier stimulus: subjects are instructed to discriminate the offset direction of the lower line-segment, relative to the upper line-segment (on the example, the lower line-segment is offset to the right). (B) Example of a grating with 5 elements, used to mask the Vernier stimulus.

in our studies, the two drugs also led to similar levels of sedation, confirmed by both subjective evaluations of sedation and pupillography. The latter has the advantage of measuring sedation using an objective method (Schaeffell et al., 1993; Lüdtke et al., 1998). The size of the pupil is measured continuously during 11 min, in order to derive an index corresponding to the pupil's tendency to oscillate. As expected, this index increased systematically following benzodiazepine administration, but there was no quantitative difference between diazepam and lorazepam. A final argument for eliminating hypotheses based upon the different potencies of lorazepam and diazepam can be found in studies showing a somewhat larger effect of diazepam than lorazepam, and therefore showing that lorazepam is not systematically more potent than other benzodiazepines. Double dissociations of this sort have been found in studies measuring event-related potentials or attention (Boucarter et al., 2000; Pompéia et al., 2003a; Boucarter et al., 2007) and are detailed in the following section.

4. Effects of benzodiazepines on attention: is diazepam more potent than lorazepam?

Though it seems reasonable to expect that benzodiazepines will affect vigilance and attention through their sedative, drowsiness and psychomotor slowing properties, relatively few studies have been conducted on the effect of benzodiazepines on attentional processes and even fewer have made a direct comparison between different classes of benzodiazepines.

As with memory, attention is a complex cognitive function that involves several different components. Studies on the effect of benzodiazepines on vigilance and sustained attention (the ability to maintain attention during continuous and repetitive activity) have used simple reaction time to the appearance of a visual signal and a continuous attention task, in which a series of stimuli are flashed on the screen at various intervals with participants asked to respond whenever two consecutive stimuli are the same. In general, both lorazepam and diazepam impair accuracy and slow down response times in these attention tasks (e.g., Duka et al., 1995; see also Buffet-Jerrott & Stewart, 2002 and Stewart, 2005 for reviews) with the results being consistent with the idea that both drugs have similar effects on sedation. Lorazepam and diazepam are suggested to differ, however, in their effects on tasks requiring divided attention, i.e. the ability to focus attention simultaneously on different information levels or locations (Jalava et al., 1995). In one test involving 4 parallel computer screens, a ball appeared to move along a circular obstacle course on each screen at different rates. Participants were instructed to press a key corresponding to the screen (1 to 4) when the ball entered an obstacle on any screen, this task requiring them to simultaneously monitor each screen and thereby divide attention across the 4 screens. It was found that lorazepam impaired divided attention more clearly than diazepam, at least when their doses were matched for their sedative effects.

Results differ across studies when considering the effects on spatial attention which involves the ability to engage attention to or at a particular spatial location, and also to disengage attention from this location in order to move it to another one. In such explorations, a cue typically indicates a location, and is followed by a target which has to be located, detected or identified. The target appears either at the location of the cue or at another location. Some studies suggest that the effect of the cue is facilitated in treated subjects, while others suggest difficulty in disengaging attention from the cue location. It may also be possible that the time course of these effects is slowed. More work is required before one can interpret these effects (Johnson et al., 1995; Post et al., 1997; Carter et al., 1998). Benzodiazepines differ markedly, however, regarding other types of attention mechanisms.

The effects of benzodiazepines on selective attention have been investigated using paradigms involving selective processing of a target and the inhibition of irrelevant distractor information. They

have especially employed negative priming paradigms. Negative priming refers to the increase in response time and the frequency of response error when required to name a stimulus (a word, a letter or an object) that had been suppressed on the immediately preceding trial (e.g., the stimulus to-be-named on T2 "lion" that was preceded by the target to-be-named on T1 "wolf" and the distractor to-be-ignored on T1 "lion"). Mintzer and Griffiths (2003) reported that lorazepam does not affect negative priming whilst, in a previous study using the same paradigm (Mintzer & Griffiths, 1999), they found that another benzodiazepine (triazolam) produced an increase in negative priming, attributed to increased inhibition of the irrelevant distractor.

Research on the effect of benzodiazepines on the temporal dynamics of visual attention has used the attentional blink paradigm (Raymond et al., 1992) in which stimuli are presented in a stream at a rapid rate (e.g., 10–20 items/s) at the same spatial location. Performance is compared in two conditions: in the main condition participants are required (1) to identify a first target specified by a physical characteristic (e.g., the single white letter of the stream) and (2) to detect the presence of a second target (e.g., the letter X) occurring at various intervals following the first target. In the control condition participants are asked to detect the second target and to ignore the first. Participants are able to detect or to identify a single target with high accuracy even at high rates but, when the task involves multiple targets, participants experience difficulties in reporting the second target if it occurs in a temporal window of about 400 ms following the first target, a phenomenon referred to as the "attentional blink" (Raymond et al., 1992; Chun & Potter, 1995). Boucarter et al. (2000) examined the effect of lorazepam and diazepam on the attentional blink using drawings of objects as stimuli. They found that the attentional blink was more pronounced both in magnitude and duration for benzodiazepine-treated participants and especially for diazepam relative to placebo-treated participants. The relatively larger blink effect for diazepam was unlikely to be due to sedation given first, that performance was equivalent for both benzodiazepines in the control condition, and second, that the doses (lorazepam 0.038 mg/kg and the diazepam 0.3 mg/kg) were equally sedative (Dundee et al., 1979). This result was confirmed in a second study (Boucarter et al., 2007) which investigated whether the increased magnitude of the blink effect is dose dependent. Here, it was found that the magnitude and duration of the attentional blink increased with the dose of benzodiazepine: in the main condition performance was 2 times more degraded for the diazepam 0.1 mg/kg, and 4 times more degraded for the diazepam 0.3 mg/kg groups than for the placebo group. Again, performance varied little across the three groups in the control condition and the first target was identified with high accuracy in the three groups suggesting that sedation was not the critical factor for the strong attentional blink observed in the benzodiazepine treated groups. The increased duration and magnitude of the attentional blink under diazepam is likely to reflect impairment in shifting attention from one target to a second target over time.

What is important here is that diazepam appears to exert a more potent effect than lorazepam on selective attention which influences the temporal dynamics of attention. This is all the more remarkable in that the doses used in studies on attention are exactly the same as those used in studies on visual perception and implicit memory suggesting a double dissociation between the effects of lorazepam and diazepam: i.e. lorazepam is more potent than diazepam on visual perception and perceptual priming, whereas the reverse is true for selective attention and temporal dynamics of attention.

5. Physiological arguments for a dissociation between benzodiazepines

If studies on cognition, and especially on memory, have pioneered description of the qualitative differences between benzodiazepines, some evidence can be found in other domains, for example, indirect evidence by means of behavioural studies in animals. Those studies

explore to which extent conditioning with one drug generalizes to another drug. Conditioning consists in training animals to press a specific lever when they are under the effect of the drug with training expected to carry over when the drug is changed but the animal cannot discriminate between the two drugs. In this case the animals continue to respond in the same way irrespective of the drug, indicating that the first drug generalizes to the second. In contrast, in the case where the animals discriminate between the two consecutive drugs, they refrain from pressing on the lever associated with the first drug once treated with the second. This is a strong argument in favour of a qualitative difference between two drugs and there are several such studies that provide evidence that lorazepam differs qualitatively from other benzodiazepines. When rats are trained with pentobarbital or diazepam they generalize their behaviour to all tested compounds with anxiolytic properties, i.e. benzodiazepines and barbiturates, also non-benzodiazepine anxiolytics and even neuroactive steroids (Ator & Kautz, 2000). On the other hand, when rats are trained with lorazepam, their generalization profile appears much more restricted. In fact these rats only generalize to full agonists at the benzodiazepine fixation site on the GABA_A-receptor complex (Ator et al., 1993) and do not generalize to barbiturates or neurosteroids. Results such as these were confirmed in baboons and were dissociated from training doses or route administration (Ator & Griffiths, 1989; Ator, 1990; Ator & Griffiths, 1997). More direct evidence has been revealed by using rats, first trained to discriminate between a low dose of midazolam, a high dose of midazolam and an absence of drug. When tested with benzodiazepines these rats failed to generalize the high dose of midazolam to several benzodiazepines, and especially lorazepam (Sannerud & Ator, 1995). This is the only study of this type which directly suggests a qualitative difference between benzodiazepines.

Another way to discriminate drugs is to examine their impact on the EEG. It is not entirely clear whether or not the effects of lorazepam on EEG differ or not from those of other benzodiazepines, but we will briefly review the existing evidence in studies on the human scalp EEG. Benzodiazepines usually cause a decrease in the α -rhythm (8–12 Hz) and an increase of power in the β -range (13–30 Hz) (Saletu & Grünberger, 1979; Greenblatt et al., 1989; Link et al., 1991; Mandema et al., 1992; Feshchenko et al., 1997). One of the rare studies comparing lorazepam and diazepam during EEG recording found both quantitative and qualitative differences between the two drugs (Itil et al., 1989). Interestingly, they found the classical increase of power in the β -range under the influence of diazepam, whereas power in the alpha range was found to be decreased over time with lorazepam. Consistent with the discrimination studies in animals the authors found that the EEG profile observed under diazepam was closer than lorazepam to the usual profile of anxiolytic compounds. Another qualitative difference between diazepam and lorazepam regarded the location in the brain at which the effects of the drugs are first observed. Whereas the effects of diazepam were mainly confined to the frontal area, the effects of lorazepam originated in occipital areas. An important limitation of this study is that sedation induced by diazepam was lower than with lorazepam, suggesting that the two drugs were not administered at equipotent dosages. Indeed, the ratio of the diazepam vs. lorazepam dosage was 5, whereas dosages can be considered as equipotent for ratios of about 10 (Dundee et al., 1979; Kothary et al., 1981; Vidailhet et al., 1994). This means that it cannot be ruled out that differences between drugs observed in this study could reflect the differences in potencies.

If the study of Itil et al. (1989) requires clarification before firm conclusions can be reached, it should be noted that a specific impact of lorazepam on visual areas in the brain has also been suggested by means of event-related potentials. In elegant studies, Pompéia et al. (2000, 2003a) compared the effects of flunitrazepam with those of lorazepam and observed a double dissociation, with flunitrazepam being more potent than lorazepam on some effects, whereas the

reverse is true for other effects. As with the studies of attention, these results are especially important because they show that the effects observed selectively with lorazepam are not due to a global difference in potency between lorazepam and the other benzodiazepines but are instead due to some specific effect of the drug. Flunitrazepam induced more slowing than lorazepam in simple reaction time, whereas the reverse was true for fragmented shape identification. Furthermore, the latency of event-related potentials was differentially affected by the two drugs. Lorazepam induced a larger increase in the latency of visual relative to auditory evoked ERPs with an increase in the visual modality larger than that observed under flunitrazepam. As with EEG studies, these results suggest a particular effect of lorazepam on visual pathways.

This is further confirmed through MEG and PET studies. Using MEG, Ahveninen et al. (2007) showed a large decrease of alpha activity in the parieto-occipital and calcarine sulci under the effect of lorazepam. These results are consistent with PET studies showing that lorazepam reduces brain metabolic responses mainly in the thalamus and occipital cortex (Wang et al., 1996), even at relatively low doses (Matthew et al., 1995). However, these authors did not compare different benzodiazepines, while high receptor occupancy in posterior brain areas have also been observed with zolpidem (Abadie et al., 1996) or benzodiazepine antagonists such as flumazenil (Frey et al., 1991) or iomazenil (Bremner et al., 1999).

A more recent study using Transcranial Magnetic Stimulation (TMS) found a clear qualitative difference between lorazepam and diazepam-treated subjects (Di Lazzaro et al., 2005b). Stimulation of the motor cortex through TMS usually induces muscle responses and different kinds of inhibition can be observed, namely short-latency afferent inhibition (SAI) and short-latency intracortical inhibition (SICI). In the first case (SAI), the stimulation of the peripheral nerve mediating the motor response suppresses the effect of the TMS stimulation through afferent inhibition within the cerebral cortex (Tokimura et al., 2000). This first kind of inhibition has been shown to be sensitive to the muscarinic antagonist scopolamine and to lorazepam (Di Lazzaro et al., 2000, 2005a). In the second case (SICI) a first sub-threshold TMS stimulation suppresses the following supra-threshold stimulation as long as the interval between the two stimulations is short enough (Kujirai et al., 1993). This phenomenon is supposed to be mediated by GABA_A-ergic inhibitory neuronal circuits (Ziemann et al., 1996; Di Lazzaro et al., 2005b). Di Lazzaro et al. directly compared the effects of both diazepam and lorazepam on the two phenomena and observed that SAI was affected by lorazepam but not by diazepam. Importantly the two drugs did not differ in their effect on the phenomenon putatively mediated by GABA_A-ergic circuits, i.e. SICI. As emphasized above, this kind of dissociation, in which the effects of the two drugs are similar in one condition but differ in another, is an important argument eliminating alternative explanations in terms of quantitative rather than qualitative differences between the two drugs.

6. Effects of chronic intake and significance of the qualitative differences between benzodiazepines in everyday use

Up to this point our review says little about the consequences of chronic intake of benzodiazepines. The effects of chronic intake of a psychotropic substance can differ markedly from that after acute administration (Nordberg & Wahlström, 1992; Follésa et al., 2006) and this is especially true for benzodiazepines which lead to dependence, habituation and tolerance. These effects indicate brain adaptation and can lead to changes in the behavioural consequences of the drug and this also increases the difficulty with which the effects of chronic treatment of the drug can be measured. For example, a dependence-inducing drug cannot be administered for a long period in healthy volunteers and the consequences of an intake of longer than a few weeks must therefore be examined in patients ordinarily

treated with the drug. Such studies, however, entail a number of confounding factors including the lack of knowledge regarding patients' performance prior intake of the drug, the role of the underlying pathology (including factors such as anxiety for example) and the possible intake of other drugs in addition to the one under consideration. For these reasons such studies are rare and when realized rarely distinguish between different benzodiazepines. To the best of our knowledge only two such studies have explored the effects of a chronic intake of lorazepam on visual perception or perceptual priming. Of these, Curran (1992) used an elegant method of testing subjects as they withdrew from chronic treatment with benzodiazepines. This protocol allowed the assessment of cognitive functions under the effect of the drug but also several months after the withdrawal, thus providing data with and without the drug. Curran is also one of the only researchers to have explored perceptual priming as a result of a chronic intake of lorazepam. She found that the deleterious effect of lorazepam on perceptual priming persisted throughout chronic intake as long as perceptual priming was evaluated at the peak plasma concentrations. This contrasts with another study, in which subjects with a chronic intake of lorazepam were tested without taking into account the peak plasma concentration, and where no effect was observed on perceptual priming (Giersch & Vidailhet, 2006). In this latter study however, a deleterious effect was observed on visual integration ability as explored in the same kind of experiment as described above (see chapter 3). These studies require replication, but suggest that effects which are selectively observed under lorazepam persist, at least partially, after chronic treatment. It should be noted here that another pending question regards the effect of lorazepam in aging populations, especially as a degradation of GABA-mediated inhibition has been suggested in aging visual cortex (Leventhal et al., 2003).

These studies raise important questions concerning the impact of these effects on patients in everyday life as compared with the laboratory settings. This question is especially difficult when one considers perceptual priming and visual perception because these processes involve many mechanisms that cannot be accessed directly via introspection. This makes it difficult for patients to report any problems they may experience especially as other impairments, for example sedation, and slowed or impaired memory may obscure other symptoms. It is only through laboratory settings that the consequence of the drug intake can be inferred. Despite these difficulties, we can derive some hypotheses from the studies regarding the effects of lorazepam on perceptual priming or visual integration. Firstly in the case of perceptual priming, lorazepam treated subjects do not benefit as much as controls from the repetition of information. Secondly, disturbance of the process of visual integration is observed mainly when there is some ambiguity regarding contour terminations, i.e. at the junction between objects and ground, or between objects or parts of objects (Fig. 2). In both cases, the processes allow adaptation to environmental information. This suggests that, in addition to the effects observed with all benzodiazepines, it may be harder for lorazepam-treated subjects to adapt to the environment. Lorazepam may especially slow down the resolution of visual information ambiguities occurring when edges and line-ends indicate either a true object border or the location of an occlusion (Giersch et al., 2006a). Patients should thus be especially slowed down in identifying and exploring their environment when many objects are partially hidden. This is actually the case in most environments which compounds the other visual impairments such as impaired contrast sensitivity that also appear to persist with chronic intake (Giersch et al., 2006b). These impairments have to date been largely ignored. However, they may lead to serious consequences especially in everyday tasks that involve control of machinery and more particularly of motor vehicles.

Some studies on driving performance have been conducted but have focused mainly on the impact of reduced attention. O'Hanlon

et al. (1995) compared the effects of benzodiazepines (diazepam, lorazepam) and benzodiazepine-like anxiolytics (alpidem and suriclone) on driving performance in healthy volunteers. The driving tests were carried out 1–2 h following treatment for 8 days and consisted of driving an instrumented vehicle over a 100 km circuit with an instructor (the circuit was a real one). The task was to maintain a constant speed of 95 km/h and a steady lateral position between the delineated boundaries of the slower traffic lane. After a week's treatment, lorazepam (2 mg) and diazepam (5 mg) had similarly marked effects on driving performance while the benzodiazepine-like drugs had a lesser effect. It should be noted however, that the doses used were not equisedative, diazepam at 5 mg being less sedative than lorazepam at 2 mg. Since diazepam should have been less potent than lorazepam, but in fact was not, the results could be equated with the larger impact of diazepam on attention. Hindmarch and Gudgeon (1980), on the other hand observed large effects of lorazepam (1 mg) on car driving abilities (evaluated on the private roads of a driver training centre), indicated by reverse parking between 2 cars and a slalom around fixed bollards, width estimation passage between obstacles and braking reaction. However, their data do not allow for a distinction between effects arising from sedation or to more selective impairments. More work is warranted to define the impact of lorazepam while taking into account its effects on perceptual priming and visual integration abilities. Such studies would be all the more useful that lorazepam, like other benzodiazepines, has been suggested to be at the origin of driving impairments (leading to blood samplings and toxic analysis) even when taken in isolation, i.e. without any additional drug (Clarkson et al., 2004; Augsburger et al., 2005).

7. Possible molecular bases for a qualitative difference between benzodiazepines–metabolites

A question that remains unresolved is the reason why lorazepam exerts qualitatively different effects on visual perception and perceptual priming when compared with other benzodiazepines, particularly diazepam. In fact, all benzodiazepines are full agonists at the GABA_A/benzodiazepine receptor, through which they exert their actions. Consequently, it is generally held that their effects only differ quantitatively, that is to say in terms of time of onset, peak, depth and the duration of their effects. These mainly depend on the method of administration, the dose, the affinity for the receptor, and the pharmacokinetic properties of the drug and its metabolites (Greenblatt, 1992). An explanation in terms of metabolites is unlikely as lorazepam is transformed by conjugation to inactive compounds (Bourin, 1989). Another possible explanation is that lorazepam binds to specific subtypes of GABA_A receptors and has a different brain distribution. Different subtypes of GABA_A receptors, characterized by the nature of their constitutive sub-units do exist within the brain with different regional distributions (McKernan & Whiting, 1996). Indeed the GABA_A receptor is composed of 5 subunits, the most common being the α , β , and γ . Several subtypes have been described for each of these subunits, leading to a large number of combinations and thus to many different types of receptors. These receptors differ in their brain localization and are very probably involved in distinct functions, as indicated by studies in transgenic mice with deletions or mutations on specific subtypes, and by pharmacological studies. These studies have in particular led to a distinction between the different α subunits, with the $\alpha 1$ subunit subserving sedation, $\alpha 2$ anxiolysis, and $\alpha 5$ effects on memory (reviews in Möhler, 2007; Atack, 2008). These receptor subtypes are currently subject to intensive research since they offer the possibility of developing drugs with effects that are more selective, for instance drugs possessing anxiolytic properties without inducing sedation (Whiting, 2006) or displaying pro-cognitive effects without unwanted side-effects (Atack, 2008; Ballard et al., 2009). Consequently, it is conceivable that lorazepam would

bind to some receptor sub-types that play a specific role in perceptual priming and vision and/or are particularly dense in brain regions subserving these cognitive processes. In this way, lorazepam would thus differ from diazepam and other benzodiazepines.

To the best of our knowledge, there is only one study that has compared lorazepam with other benzodiazepines on its receptor profile, as estimated with the IC50 and by taking into account the main different subtypes of GABA_A receptors ($\alpha 1\beta 2\gamma 2$, $\alpha 2\beta 1\gamma 2$, $\alpha 2\beta 1\gamma 3$, $\alpha 3\beta 3\gamma 2$, $\alpha 3\beta 3\gamma 3$, $\alpha 5\beta 3\gamma 2$, $\alpha 5\beta 3\gamma 3$, $\alpha 6\beta 3\gamma 2$). Although lorazepam was not found to differ from other benzodiazepines in its receptor profile (Dämgen & Lüddens, 1999), it remains possible that the EC50, i.e. the concentration required to achieve the half-maximal effect, rather than half-maximal inhibition, differs between lorazepam and other benzodiazepines when looking at individual GABA_A receptor subtypes (Dämgen & Lüddens, 1999). In addition, there are a number of subtypes identified since the work by Dämgen and Lüddens (1999), especially those including a δ unit while there are several subtypes whose existence is probable but not yet established (Reviewed in Olsen & Sieghart, 2009). As stated by Pompéia et al. (2005), very little is known about binding characteristics of benzodiazepines to distinct receptor subtypes in different brain regions. Promoting this type of research is all the more justified if this can lead to new and innovative therapeutics. It would be especially interesting to know to which extent new developed compounds induce the very specific cognitive effects described in the present review.

8. Do the selective effects of lorazepam signify therapeutic properties?

Lorazepam appears to have selective effects that are not shared by all benzodiazepines. It seems reasonable to postulate that such selective effects might also have positive clinical implications. However, regarding main clinical indications, i.e. anxiety, sleep disorders or epilepsy, there is no clear indication that benzodiazepines differ. On the contrary, in the majority of the studies reported here benzodiazepines have been administered at doses that produce equivalent effects on sedation and anxiety, so that selective effects of drugs cannot be explained by a non-specific effect on sedation or a global difference in potency between the drugs. There is only very few studies suggesting a selective effect of lorazepam on clinical symptoms and these have generally not been confirmed (see Table 1). Here we focus on schizophrenia, because the lack of satisfactory curative drugs in this pathology justifies examining alternatives, even though speculative at this time, and because the role of GABA in this pathology has been particularly emphasized

(review in Gonzalez-Burgos & Lewis, 2008). Moreover, our own data suggests an effect of lorazepam that might be beneficial in the case of schizophrenia. Benzodiazepines are frequently prescribed to patients with schizophrenia, usually as an adjunct to antipsychotics (Pecknold, 1993; Pickar et al., 2008). Case reports and controlled studies indicate that lorazepam can be effective in treating some patients with schizophrenia, influencing core symptoms such as delusions, hallucinations, thought disorders as well as negative symptoms, sometimes even as a sole treatment, i.e. without being associated with neuroleptics (Greenberg et al., 1986; Lingjaerde, 1991; Wolkowitz & Pickar, 1991; Jaspert & Ebert, 1994). Lorazepam also seems particularly effective in treating catatonia, a motor condition associated with several neuropsychiatric disorders, including schizophrenia (Seethalakshmi et al., 2008). This has been shown with other benzodiazepines as well (Lingjaerde, 1991; Wolkowitz & Pickar, 1991), but benefits are not that obvious when reviewing controlled studies (Gillies et al., 2005; Volz et al., 2007; Gibson & Walcott, 2008). To our knowledge, no study to date has ever shown that one benzodiazepine is more effective than another in treating schizophrenia. However, in our personal experience (see also Kane, 1996) and in a large cross-sectional survey of patients with schizophrenia occupying psychiatric rehabilitation beds (Paton et al., 2000), lorazepam is the most frequently prescribed benzodiazepine in the mid or long term for this condition. This could reflect the fact that lorazepam is frequently used for rapid tranquilisation and therefore most likely to be continued on a chronic basis (Paton et al., 2000). Another possibility is that it may speculatively reveal specific therapeutic properties. We will now review the arguments in favour of the latter possibility.

Several mental pathologies, and especially schizophrenia, are now believed to be characterized by an absence of proper coordination between cooperating brain areas during cognition and action (Friston & Frith, 1995; Goldberg & Weinberger, 1995; Andreasen, 1999; Tononi & Edelman, 2000; Roach & Mathalon, 2008; Uhlhaas et al., 2008). Interestingly, there is a variety of evidence, both empirical and based upon simulations that support the involvement of GABA in brain systems dynamics, i.e. in synchronization phenomena that allow cooperation between brain areas (reviewed in Whittington et al., 2000). Inhibitory interneurons influence pyramidal cells through the production of rhythmic trains of IPSPs (Whittington et al., 2001) which, in combination with glutamate and acetylcholine systems activation, may permit the pyramidal cells to fire repeatedly and at high frequency for extended periods of time. Neuronal networks would then achieve stability as a consequence of the mutual activity of both inhibitory and excitatory transmission (Whittington et al., 1997). This may also allow spatially separate, but interconnected regions to oscillate in synchrony,

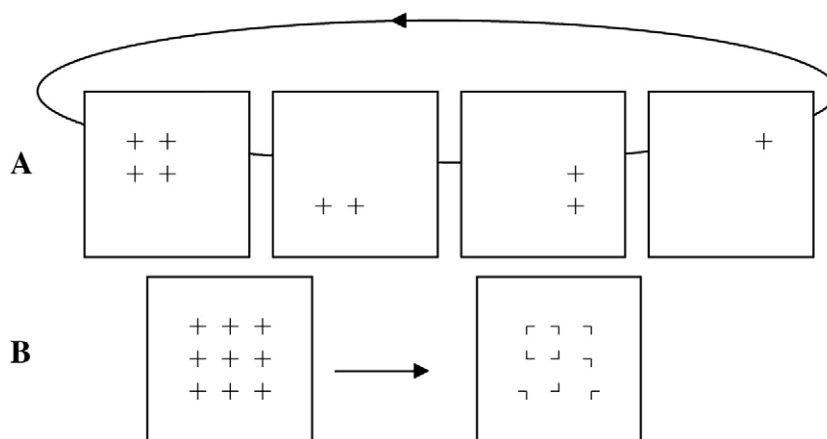


Fig. 4. Illustration of the priming paradigm devised by Elliott and Müller (2000). The four image frames illustrated in (A) are presented one after the other at a frequency of 10 Hz, and form the 3×3 premask matrix illustrated in (B) on the left. This premask matrix represents a prime, and is followed by another 3×3 matrix composed of corners (as illustrated in (B) on the right). Subjects have to tell whether or not this last matrix includes a square made up of four co-linear corners (in the top left part of the matrix in the example).

potentially leading to the common processing of identical stimuli across anatomically and functionally different but physiologically connected regions of the brain (Whittington et al., 1997; Faulkner et al., 1998; Whittington et al., 2001). All in all, this tends to suggest that the type of coordination supposed to break down in disorders like schizophrenia is ordinarily, directly supported by inhibitory interneuron modulation of pyramidal cell activity. That this mechanism is selectively influenced by benzodiazepine administration has been revealed by Faulkner et al. (1999), who have shown that diazepam does not abolish beta oscillations in excitatory neurones, or gamma oscillations in inhibitory neurones. Diazepam did, however, affect the duration of excitatory synaptic events and induced a prolongation of the time taken to stabilize coherent oscillations. They also tested temazepam and found no difference with diazepam, but they never explored, to the best of our knowledge, the effect of lorazepam. Related evidence linking oscillatory synchronization and lorazepam has been shown indirectly in two studies, mediated by an effect on perceptual organization (or visual integration). A relationship with perceptual organization is not surprising, given that initially, synchronization phenomena have been related mainly to visuo-perceptual integration processes (Eckhorn et al., 1988; Gray et al., 1989; see Gray, 1999 or Singer, 1999, for reviews).

The two studies linking oscillatory phenomena to the effects of lorazepam predicate on the priming task devised by Elliott and Müller (1998, 2000, and 2001). Elliott and Müller use a priming stimulus comprising 4 crosses presented in a square arrangement. The prime occupies 1 of 4 separate image frames which, when combined, forms a regular 3×3 element premask matrix (Fig. 3). Image frames (comprising the priming and the other premask matrix crosses) are presented one after the other at a frequency of 10 Hz, with a frame-onset-asynchrony of 25 ms (ms, equivalent to a frame by frame presentation frequency of 40 Hz) and with an inter-frame interval of less than 1 ms. The combination of high-frequency presentation with <1 ms inter-frame interval renders the content structure of a given image frame non determinable (Elliott & Müller, 1998, Experiment 2). Instead, the phenomenological effect of this temporal modulation is of a stochastic surface flicker across an otherwise static 3×3 matrix of premask crosses. This display is followed by another 3×3 matrix composed of disconnected corners, and subjects are instructed to look for a target made up of four co-linear corners (i.e. aligned), arranged to form a square (Fig. 4).

Reaction times are recorded to the presence or absence of a target. Priming effects are measured in terms of the difference between reaction times to targets following the presentation of a prime (i.e. 1 of 4 image frames then contains 4 crosses presented at the same matrix locations as the target elements) relative to reaction times following premask without any prime (i.e. all crosses, including the 4 crosses presented at the target locations are divided pseudo-randomly across two or more frames). Mean priming effects commonly vary across the 25–30 ms range and do not vary substantially with variations in the target reaction times (Elliott & Müller, 1998, 2000, 2001). Elliott and Müller proposed a feedforward-feedback model of priming including 40 Hz phenomena, and confirmed this with an independent-components decomposition of the EEG accompanying premask-matrix presentation (Elliott et al., 2003; Conci et al., 2004). According to this model, neurons in primary visual cortex might become active at ~40 Hz by virtue of this frequency being fed back from later cortical mechanisms (see Conci et al., 2004 for more details).

Testing the effects of benzodiazepines in this paradigm permitted exploration of how the lorazepam, which is known to influence the coding of spatial aspects of a stimulus would interact with the coding of relevant temporal properties. In two different studies, lorazepam significantly enhanced priming, whereas diazepam decreased it (Elliott et al., 2000, 2006). In lorazepam-treated subjects, the priming effect increased threefold in magnitude (to give an RT advantage of around 71 ms for primed targets) when the prime crosses were reinforced by spatial cues that particularly supported the computation

of a cross – cross continuity signal (Elliott et al., 2006). Inasmuch as this effect is mediated through neuronal synchronization, the results show that lorazepam enhanced rather than decreased the magnitude of priming.

Lorazepam can be concluded to positively influence visual organization at a preattentive level of processing and via an influence on the dynamics of the mechanism correlating with perceptual coherence. In this respect, lorazepam is of potential relevance not only to the behaviour of that system under normal circumstances, but is also of interest when that system performs sub-optimally, as it may do in schizophrenia. We may only speculate on the precise mechanism that brings about enhanced priming following lorazepam administration. However, on the basis of Elliott et al.'s (2003) findings, we may tentatively suggest that this involves a facilitation of the long distance synchronization of posterior and frontal neocortex via pyramidal cell activity. This might be all the more interesting that such synchronization is supposed to be impaired in mental disorders like schizophrenia. It might also imply that the specific effects of lorazepam, as compared to the effects of other benzodiazepines, might be related with those receptors that are involved in phenomena of long distance synchronization. It would be of special interest to know if some subtypes of the GABA_A receptor are involved in a special way in these phenomena.

9. Conclusion

In summary, some results suggest that lorazepam may have a positive effect on synchronization phenomena that are known to be impaired in disorders like schizophrenia. Inasmuch as disordered connectivity is a key target for new therapeutics in mental diseases, and given the involvement of GABA in these phenomena (review in Gonzalez-Burgos & Lewis, 2008), the special effect of lorazepam on synchronization phenomena represents an interesting possibility to remediate synchronization impairments in schizophrenia, which warrants exploration. The possibility that lorazepam has selective effects on neuronal synchronization may explain why lorazepam seems more efficient than other benzodiazepines in treating some aspects of mental diseases, and why lorazepam seems to differ from other benzodiazepines in all the tests we have described in this paper. Moreover, isolating the mechanisms of this effect of lorazepam may promote the discovery of new drugs that act selectively on synchronization phenomena, independently of the other effects that are shared by all benzodiazepines. Such new drugs might be of special interest for mental diseases.

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Glossary

Explicit and implicit memory: are defined by the type of instructions given to the subjects. In explicit memory tasks, subjects are explicitly asked to remember previously presented information. Usual tasks are free recall tasks, in which items are first presented to subjects during a study phase. During the recall phase, subjects are instructed to cite as many items as they remember, but without any cue to help them. In recognition tasks in contrast, new and old items are presented to the subjects during the recall phase, and they are instructed to tell whether they saw these items or not in the study phase. In implicit memory tasks, no reference is usually made to the previous study phase, and typical tasks are to identify fragmented pictures or to complete word stems. Priming effects are revealed by the improvement of performance observed when the item to identify has already been presented during the study phase, as compared to new items.

Priming task: The main task in a priming task concerns a target, which most often has to be identified. This target is preceded by a 'prime', i.e. a stimulus which is not relevant to the task at hand but which influences performance during the main task, either in a facilitatory way (perceptual priming) or in an inhibitory way (negative priming). In some cases, the prime is presented long before the target, like in implicit memory tasks (chapter 2). It can also precede immediately the target, defining short-term priming effects (chapter 8).

Acquisition, storage and retrieval: define different stages of processing during memory tasks. Acquisition occurs during the study phase, when items to be memorized are presented to the subjects. Storage defines the maintenance of information in memory, whereas retrieval defines the processes occurring when subjects restitute information.

The retrieved intentionality criteria: is a method used in the domain of memory to explore the possibility that subjects make use of explicit strategies in a task designed to measure implicit memory. The main idea is to manipulate a variable that affects implicit and explicit memory in a different way. For example, during the study phase, subjects are asked either to process the meaning of words or to count syllables. The effect of this variable on memory performance is then compared when instructions are referring to the study phase (explicit instructions) or not (implicit instructions). In our example, the manipulation during study phase is supposed to have a larger effect on explicit than on implicit memory. A large effect of this manipulation in a task designed to measure implicit memory would then indicate the use of explicit strategies.

Controlled and automatic processes in memory: represent a distinction of memory processes that overlap partly with the implicit and explicit distinction, but refers to a conceptualization of the processes involved in memorization rather than to the instructions given to the subjects. More specifically, it refers to the idea that memory involves mechanisms that are unconscious and automatic, or conscious and controlled. This distinction is supported by the process-dissociation procedure (see below).

The process-dissociation procedure (PDP): is used to distinguish between controlled and automatic processes involved in memorization. The procedure includes a classical recognition task in which subjects are first presented with two series of items. During recognition, two conditions are used. In the first condition, subjects are asked to select all items they recognize in a list including new and old items. In the second condition, subjects are instructed to avoid items of one of the two series. This avoidance is supposed to be based exclusively on controlled processes, whereas the items selection in the first condition includes both automatic and controlled processes. A quantitative estimation of automatic processes is derived through subtraction of performance observed in the two conditions. The same procedure can be applied to word-stem completion.

Visual integration and binding: refer to processes allowing to derive the form of objects in the visual environment. Since visual information is first processed in the primary visual cortex by specialized neurons coding for some specific aspect of visual information (orientation, color), information needs to be bound together correctly in order to identify objects and not only local contours. It is the binding mechanisms that bring about visual integration and ultimately complex object perception.