Some facilitatory effects of lorazepam on dynamic visual binding

[1,3]Mark A. Elliott, [2]Anne Giersch & [3]Doerthe Seifert.

[1]Department of Psychology, National University of Ireland Galway, Galway, Ireland.
[2]Unité INSERM U666 Hôpitaux Universitaires de Strasbourg 1 Place de l'Hôpital F-67091 Strasbourg Cedex, France
[3]Department Psychologie Ludwig-Maximilians Universität Leopoldstr 13 D-80802 Munich/München, Germany

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Corresponding author:

Mark A. Elliott
Department of Psychology,
National University of Ireland, Galway,
Ireland
Tel: +353 (0)91 495345
Fax: +353 (0)91 521355
email: mark.elliott@nuigalway.ie

Abstract

Rationale: The benzodiazepine, lorazepam enhances the potential for inhibitory $GABA_A$ (γ-aminobutyric acid) synapses in the cortex to stabilize postsynaptic, excitatory activity by synchronizing discharge rates at frequencies of around 40 Hz. Treatment with lorazepam also affects contour integration processes, suggesting $GABA_A$-mediated synchronization plays a role in visuo-spatial organization. This conclusion is supported by other physiological studies that link visual feature integration with neuronal synchronization.

Objectives: One experiment was conducted to assess variations in dynamic figural priming as a result of lorazepam administration.

Methods: Observers were presented a modified version of a figural priming paradigm designed to investigate the effects of dynamic synchronization upon visual feature integration. The priming paradigm consisted of premask crosses presented in square arrangement within the same phase of a multiphase premask matrix oscillating at 40 Hz. Observers responded to a subsequently presented target square. The modification consisted of line elements presented at various distances relative to the unspecified extension of the lines making up the premask crosses. It was expected that priming effects would be enhanced for lines terminating close to the unspecified extension but only following administration of lorazepam.

Results: As anticipated priming was enhanced substantially when the premask crosses flickered around static lines that terminated adjacent to the unspecified extension between the premask crosses. This effect was maximal following treatment with lorazepam.

Conclusions: This finding supports the idea that $GABA_A$-enhanced inhibitory synchronization mediates continuity coding during early visual processing.

Keywords: lorazepam, diazepam, benzodiazepine, visual binding, synchronization, temporal factors

Introduction

Following previous studies in which the benzodiazepine lorazepam was found to influence visuo-spatial integration and visually-mediated temporal segmentation (Elliott et al., 2001; Giersch et al., 1995, 1996, 1997; Giersch & Lorenceau, 1999), we sought to investigate further the idea that the effects of lorazepam upon temporal segmentation occur because the drug has a direct effect on the processes responsible for the 'binding' of visual-features. Lorazepam is a member of the benzodiazepine family of anxiolytics which increase fixation of GABA exclusively on the receptor $GABA_A$. The inhibitory neurotransmitter GABA is widespread in the cortex occupying receptors at around 40% of all synapses (Leonard, 1992). In visual cortex interneurons connected by synapses using GABA receptors are considered an important inhibitory mechanism by which neural-response selectivity to motion (i.e. orientation and direction selectivity) is achieved. Additionally, and in contrast to the effects of other benzodiazepines, lorazepam has been shown to influence perceptual organization affecting both perceptual integration and segmentation processes (Giersch et al., 1995, 1996, 1997; Giersch & Lorenceau, 1999). In particular it has been shown that lorazepam brings about disruption in target detection and object recognition performance (Wagemans et al., 1998) while facilitating spatial segmentation (see Giersch, 1999 for a general overview and Beckers et al., 2001, for details).

A functional relation between Lorazepam and the dynamics of perceptual organization is suggested by evidence that $GABA_A$ergic neurons encourage rhythmic patterns of discharge in postsynaptic neurons: This evidence has been gathered in studies of hippocampal neurons on slice preparation and consists of two relevant findings. Firstly, $GABA_A$ergic neurons tend to synchronize their own activity at rates of between 33 and 50 Hz (Whittington et al., 1995; Traub et al., 1996; Faulkner et al., 1998): A pattern of neural activity and frequency range associated with the binding of simple visual features such as line elements (see e.g. Gray et al., 1989; Eckhorn et al., 1988). Secondly and following $GABA_A$ergic synchronization, postsynaptic excitatory neurons also synchronize their rate of discharge with increased amplitudes but reduced frequencies, which appear to shift from around 40 Hz to between 10 and 30 Hz (Whittington et al., 1997; Traub et al., 1999).

- Figure 1 here -

More direct evidence to link $GABA_A$ergic synchronization with the dynamics of perceptual organization has been reported by Elliott et al., (2001) who combined lorazepam administration with a paradigm consisting of the repeated presentation of a priming stimulus known to encourage the formation of an oscillatory prime (Elliott & Müller, 1998, 2000). Elliott and Müller's priming paradigm consisted of a 3 x 3 element premask matrix, the elements of which were 9 crosses distributed across four asynchronously presented image frames. Each image frame consisted of between one and four premask crosses and each cross was both specific to a given image frame and a particular matrix location (illustrated in Figure 1(b)). The four images frames were repeatedly presented one after another in a regular sequence and with a frame-by-frame exposure duration of 25 milliseconds (ms i.e. a local frame rate of 10 Hz and considering all four frames together a global frame rate of 40 Hz). Premask-matrix presentation as a whole generally lasted between 300 -1200 ms.

On 50% of trials the premask matrix included a priming stimulus made up of 4 premask crosses presented in square arrangement. The priming stimulus was defined by virtue of its spatio-temporal distribution and relative to the other premask crosses: specifically, the crosses making up the priming stimulus were confined to a single image frame and were thus specific (and unique) to 1 of the 4 phases of premask-matrix presentation. The premask crosses were also presented as a general rule at the precise matrix locations subsequently occupied by a square target grouping: a target matrix was presented immediately upon termination of the flickering premask matrix. Unlike the premask matrix this display did not flicker but like that matrix comprised 9 corner junctions in a 3x3 arrangement. On 50% of trials four of these junctions were arranged to define a square target by virtue of collinearity grouping (see Figure 1a, right panel). Observers were asked to make a speeded but accurate response to the presence or absence of the target grouping.

Observers were faster to detect targets when the target grouping was preceded by presentation of the intraphasic priming stimulus. This RT advantage was not evident in consideration of target-absent trials (in which no collinearity grouping was presented) and was thus defined in terms of the four-cross premask frame 'priming' presentation of the target grouping. Priming effects are relative in that they measure the difference between RTs to targets following priming-stimulus presentation relative to target RTs following the 'interphasic' presentation of 4 premask crosses (i.e. crosses presented at the target junction locations that were divided pseudo-randomly across two or more image frames). Mean priming effects commonly vary across the 25 – 30 ms range and do not vary substantively with variations in the target RTs

(Elliott & Müller, 1998, 2000, 2001). In addition, given that the premask matrix image frames were repeated at high frequency (in this instance at 40 Hz) and with close to 0 ms inter-frame interval the contents of a given image frame were indeterminable within what appeared to be stochastic surface flicker across an otherwise static 3 x 3 matrix of premask crosses. In other words, observers were unable to reliably detect the presence or absence of a priming stimulus during premask-matrix presentation (see Elliott & Müller, 1998, Experiment 2). Elliott and Müller examined but found no evidence to suggest that the target was explicitly cued by priming-stimulus presentation (see Elliott & Müller, 1998, Experiment 3). In addition there was no evidence that priming effects varied substantially as a result of varying the specification, or potential goodness of the priming stimulus. These findings tended to support a suggestion made by Elliott and Müller (2000) that priming came about as a result of the coincident response of neurons coding the simultaneous presentation of the four intraphasic priming crosses and was not sensitive to variations in the spatial configuration of the prime.

In spite of slowed target detection and independent of the effects of sedation Elliott et al., (2001) found priming effects to be significantly larger following treatment with lorazepam relative to both control and diazepam conditions [Footnote 1]. Slowed target detection is consistent with previous findings associating a visual integration deficit with lorazepam administration; while enhanced priming is consistent with the idea that lorazepam enhances spatial segmentation by means of temporal segmentation. As regards spatial segmentation, the influence of lorazepam has been suggested to be indirect and associated with low-level and preattentive processes responsible for organizing simple features such as line terminations. Indeed Giersch (1999, 2001) has provided evidence to support the idea that lorazepam suppresses collinearity coding for the sake of coding line terminations. She identifies two stimulus properties of central impotance in visual integration and segmentation. These properties being visual collinearity and the presence of line terminations in the visual scene (Boucart et al, 1994; Lorenceau et al., 2005). Element – element collinearity promotes integration and allows the recovery of visual continuities even when contours are disconnected. Grouping by collinearity is believed to be based on the long-range connections between V1 neurons coding lines of similar orientation (Gilbert & Wiesel, 1989; Kovacs et al., 1999; Séries et al., 2004). Line terminations, on the other hand, indicate singularities in the contour, and help to separate different parts of objects or objects from one another. End-stopped cells are believed to underlie the coding of line terminations. These two spatial properties, collinearity and line terminations, have been suggested to compete in contour processing, and

several studies have suggested that line terminations can be ignored in order to integrate contour elements, or reinforced in order to scrutinize a detail (Shimojo, Lorenceau et al., 2005; Giersch & Caparos, 2005). In this context, lorazepam has been suggested to induce an imbalance in the competition between integration and segmentation processes, by enhancing the coding of line terminations (but leaving integration processes per se intact).

These effects should account for impairment in target detection and also an impairment in the binding of the priming crosses that flicker in Elliott and Müller's paradigm because the line elements of the priming crosses may link with one another by virtue of collinearity grouping. Unlike the performance of healthy control subjects this type of grouping should be impaired following treatment with lorazepam. Thus, the spatial effects of lorazepam cannot account for an enhanced priming effect (Elliott et al, 2000) and reinforces Elliott and colleagues' argument that visual features are coded together solely due to their synchronous presentation. Quite in contradiction to Giersch's account this entails that variations in the spatial relations between the priming-stimulus elements and variations in the grouping potential possessed by those elements may be relatively unimportant and would be expected to bring about little if any variation in the efficiency of priming.

However the question remains as to whether this temporal account for priming-stimulus segmentation should also take into account the coding of spatial relations between the priming stimulus crosses. We sought to establish whether or not lorazepam can be shown to influence temporal segmentation in fashion that clearly links to the type of spatial segmentation effects described by Giersch. This question effectively asks whether or not oscillatory priming becomes active at the level of simple feature organization. It also raises the question of whether priming-stimulus presentation has an effect on the same or similar neuronal mechanisms as those observed to synchronize discharges in the presence of simple line elements that group according to one or another Gestalt principle. To that aim, we used a property of line terminations that has been shown to be effective in lorazepam treated subjects: Aligned line terminations tend to induce the perception of an orthogonal illusory contour (see e.g., Gove et al., 1995; Kennedy, 1988; Lesher & Mingolla, 1993; von der Heydt & Peterhans, 1989; Westheimer & Li, 1996). When line terminations are not numerous enough, the orthogonal contour is not visible anymore, but is produced (what does this mean?). To this end, lorazepam has been shown to effectively promote the production of lines that are orthogonal to line terminations and this consequence of lorazepam administration can be used to facilitate grouping between priming crosses. As already noted, the

premask crosses may come to be bound together by virtue of the coding of spatial properties such as the cross – cross continuation afforded by the collinear arrangement of premask-cross line segments (see Figure 1(c)). Whereas lorazepam should impair this type of binding, this might be compensated through an additional line element, spatially arranged so that its termination is orthogonal and adjacent to the amodal continuance linking the priming crosses. Lorazepam is expected to reinforce this continuance through its effect on the coding of the additional element termination, and thus to help binding the crosses.

The general aim of this study was to examine whether or not priming performance is influenced by simple line elements presented orthogonally to and at varying distances from the unspecified continuation linking the lines that comprise the priming crosses.. Our hypotheses were as follows: On Elliott et al's. (2001) account and if priming arose as a function of temporal segmentation processes alone we should expect priming to be enhanced following lorazepam administration (relative to control and diazepam performance) but unaffected by the positioning of orthogonal lines. However, if priming arose as a function of grouping (arising by virtue of the arrangement of the crosses) lines presented close to the cross-cross extensions might be expected to enhance any continuity signal and thus reinforce the binding of the premask crosses. On the strength of the studies reviewed earlier, lorazepam should enhance the effect of these additional elements by reinforcing the line that is orthogonal to the elements and that links the crosses. As a consequence, reinforcement of this nature should be amplified, with priming effects of greater magnitude, for observers treated with lorazepam, but only when the additional orthogonal elements are close to the cross-cross extensions, and not when they are randomly dispersed.

Materials and methods

Subjects

Following approval of the protocol from the 'Comité Consultatif de Protection des Personnes dans le Recherche Biomédicale d'Alsace I – Strasbourg' and in accordance with the code of ethics of the World Medical Association (the Declaration of Helsinki, 1996), 12 paid volunteers (7 female, mean age [male, female] 21.4, 23.14 years, mean weight 61.6, 55.29 kg, all subjects with normal or corrected-to-normal vision), participated in an experimental study comprising three treatment sessions preceded by a practice session. Subjects gave written,

informed consent, were insured and paid €304.90 (Euro) for their participation. The subjects had no medical illness (cardio-vascular pathologies, renal hypertension, hepatitis, gastro-intestinal disorder or neurological diseases) and did not abuse drugs or consume tobacco in excess of 10 cigarettes/day. They were not chronic users of benzodiazepines and had not taken any medication for at least 15 days. They were instructed to abstain from beverages containing alcohol or caffeine for the 24 hours prior to the study. Following each session, subjects were informed that they should not work and not drive cars or other vehicles for 24 hours following, and that they abstain of taking alcohol on the day of treatment. Subjects were also informed that it was possible for them to contact the hospital within the 24 hours following the experiment at any time they wished.

Experimental design

The stimulus display (illustrated in Figures 1 and 2) consisted of a premask matrix of crosses distributed across four repeatedly, but asynchronously (interphasically) presented image frames. The premask matrix was presented for 600 ms after which the premask crosses reduced to a semi-static display of 90° corner junctions. On 50% of trials, the premask matrix included a figurally relevant frame of priming crosses which were presented synchronously or intraphasically, in square arrangement and at the precise matrix location which could (on 50% of trials) be subsequently occupied by the 4 corner junctions that defined a Kanizsa-type target square. The remaining 5 premask crosses were presented interphasically in pseudorandom organization.

Presentation of the priming crosses was controlled for by distributing all of the crosses in the premask matrix pseudo randomly across one or more phases of premask-matrix presentation rhythm. Given appropriate control against the possibility for 4 crosses to appear in the same phase and in the same locations as the target junctions, this ensured the pseudorandom distribution of the premask crosses presented at target locations across two or more phases of premask-matrix presentation rhythm. As with priming-stimulus presentation, following the complete interphase randomization of cross presentations, the matrix of corner junctions presented immediately after premask matrix presentation could, on 50% of trials, include presentation of a target square. The target comprised four corner junctions presented in collinear arrangement, alternatively, the matrix of corner junctions could, on 50% of trials not include any combination of elements that grouped to form an illusory square (i.e. target-absent matrices).

- Figure 2 here -

On three among four experimental conditions, the 4 premask-matrix frames were presented concurrent with a matrix of 12 lines, each line presented at some common distance, but orthogonal to the unspecified continuance between the premask matrix crosses. Using a within-subjects repeated-measures design, all subjects experienced each combination of the premask, target and line condition on 40 occasions per experimental session. In order to control for order effects the presentation order of the different conditions was fully randomized across all trials and separately for each subject in each experimental session.

Apparatus

Stimulus image frame generation, event timing, and data collection were controlled by an IBM compatible PC, which also controlled oscilloscopic image presentation through an Interactive Electronics Systems point plotter buffer with 8 Mb frame store memory (Finley, 1985). Image frames were presented on a 6" Tektronix 608-oscilloscope monitor equipped with a very fast-decay P15 phosphor. The use of a P15 phosphor ensured that on-screen image persistence reduced to 10% of normal image intensity within 2.8 μs of image termination (Bell, 1970). The Interactive Electronic Systems point plotter buffer allowed pixels to be plotted at a rate of one pixel every microsecond.

Stimuli

The 4 elements comprising the priming- and corresponding random-premask frames were presented within premask/target matrices comprising 9 matrix elements (i.e. 4 possible priming/target location quadrants), with the additional premask-matrix elements divided across 3 other premask frames. The 4 possible presentation locations of the synchronous-premask frame and, subsequently, of the target square were covaried and presented in equal proportions across the overall sequence of trials in each experimental session but with location randomized on a trial-by-trial basis for each session. Presentation of the premask matrix was kept constant at 600 ms. Premask-matrix frame presentation frequency was fixed at 40 Hz, while subsets of the premask matrix (i.e. the 4 separate premask frames) recycled at a rate of 10 repeats per second. Frames had a constant exposure duration of 25 ms and an inter-frame interval of less than 1 ms. The continual recycling of the premask-frame sequence produced the phenomenal experience of a flickering matrix of 3 x 3 crosses, within which, previous research had established that normal

subjects were unable to discern the structure of a given frame (Elliott & Müller, 1998, Experiment 2).

The matrix of 12 orthogonal lines did not flicker but was presented with each premask-matrix frame such that the orthogonal lines remained 'in place' while the contents of the premask-matrix frames flickered around them (see Figure 2, Panels 2[b-c] – 4[b-c]). The orthogonal lines were presented in three conditions, in Condition 1 (Figure 2, Panel 2) the orthogonal lines were presented overlapping the cross-cross continua, in Condition 2 (Figure 2, Panel 3) the orthogonal lines were positioned such that they terminated adjacent to the cross-cross continua while in Condition 3 (Figure 2, Panel 3), orthogonal lines were positioned such that they terminated some distance from the these continua. In a fourth condition (Condition 0) no orthogonal lines were presented (Figure 2, Panel 1). The orthogonal lines were pseudo-randomly but deliberately misaligned relative to one another such as not to induce their own, spurious collinearity groupings. In an additional procedure designed to preclude the crosses of themselves defining an internal figural region in Conditions 2-4 the lines were also presented either within or outside of any given premask matrix quadrant with the precise location decided pseudo-randomly and with a 50% probability for either location for each line. The precise presentation locations were also calibrated to avoid any overlap between lines that might co-occur within a given premask-matrix quadrant. These procedures for line location and alignment were identical for both synchronous and random premask-presentation conditions and thus ensured that, in the unlikely event that a particular pattern of line alignment came to influence the coding of the premask matrix, these effects would be, on average, identical and independent of the spatio-temporal organization of the premask matrix.

At a viewing distance of 57 cm the 3 x 3 premask matrix subtended 8°42' x 8°42'of visual angle, with 1°42' crosses separated from their nearest horizontal and vertical neighbors by 1°48'. Orthogonal lines were of size 1°42' and the matrix of orthogonal lines subtended 8°42' x 8°42' (Condition 1), between 7°51'-9°33' x 7°51'-9°33' (Condition 2) or between 7°-10°24' x 7°-10°24' (Condition 3) of visual angle. The orthogonal elements were minimally displaced along horizontal or vertical axes by 26' of visual angle with maximum displacements of 51'. The target displays subtended between 6°59'-8°42' x 6°59'-8°42', with junction elements of 51', which were separated horizontally and vertically by between and 1°48'-3°30'. The matrix of orthogonal lines accounted for a total of 132 pixels that were presented alongside each premask frame.

Premask frames could consist of 1, 2, 3, or 4 crosses presented simultaneously, so the amount of pixels presented in a given frame were 132 with an additional 21, 42, 63, or 84, for 1-, 2-, 3- or 4-cross frames, respectively. This would also have resulted in the luminance of premask stimuli varying across frames, with frames comprising fewer elements appearing brighter than those with more elements. Thus, an additional 847, 826, 805, and 784 pixels were plotted for 1, 2, 3, and 4 element frames, respectively, to an invisible corner of the display with X, Y coordinates 0,0.

The individual premask frames, the matrix of orthogonal lines and the target-matrix frame were presented semi-static at a fixed 1-kHz refresh frequency to keep the image point luminance constant. Subjects viewed the stimuli arranged around the center of the monitor screen at a distance of 57 cm (maintained via a chin rest). The experiments were conducted under controlled lighting conditions (mean screen surround luminance 7.8 cd/m^{-2}), with stimulus luminance maintained at 30 cd/m^{-2} upon a background field of 7.5 cd/m^{-2}. The level of stimulus-background contrast (4:1) was kept consistent with previous studies with stimulus luminance calibrated to avoid luminous distortion.

Experimental procedure and drugs

Each observer conducted a practice session under binocular viewing conditions on a separate day to the treatment sessions, which were conducted within the 4 days following practice. Using a within-subjects treatment design, each observer was assigned to one of three different treatment groups in one of three experimental sessions such that all subjects experienced each treatment condition. Depending upon the session wise assignment, subjects were administered lorazepam (0.038 mg/kg bodyweight), diazepam (0.3 mg/kg) or a placebo (lactose, 190 mg), orally using a double blind procedure. At the chosen doses both drugs could be considered to be equally potent as evidenced by the equivalence of their effects upon sedation and explicit memory performance (see e.g. Dundee et al., 1979; Kothary et al., 1981; Sellal et al., 1992; Vidailhet et al., 1994). The time of administration was designed so that action peak of both drugs was achieved at the same time (1 hour after the intake of diazepam vs. 2 hours after the intake of lorazepam). A first tablet was administered at 7.30 am, and a second one at 8.30 am. On placebo days, both tablets were placebos. On lorazepam days, the first tablet was lorazepam and the second one placebo. On diazepam days, the first tablet was placebo and the second one was diazepam. Thus, peak action was reached between 9.30 and 11.00 am for both drugs. The order of administration of the placebo, the lorazepam, and the diazepam tablet was counterbalanced across subjects. During

each session the subjects completed an additional analog self-rating of sedation (Bond & Lader, 1974) immediately prior to, during and after the experiment (i.e. at 7:20 am, 8:05 am, 10:00 am and 12:00 noon) from which mean ratings of pre- and post-drug sedation were calculated.

The treatment sessions were conducted under monocular viewing conditions to avoid contamination of the results by a benzodiazepine-induced oculomotor imbalance (Giersch et al., 1996). Each experimental session consisted of 640 trials (40 trials per experimental condition), divided into sixteen 40-trial blocks separated by at least a 5-second break: the experimenter, who remained with the subjects during the entire experiment, manually initiated each new block once it had been established that the observer was ready to restart testing. Each session had a duration time of approximately one hour. For each trial, following a brief computer-generated tone, subjects were presented with the 3 x 3 matrix of premask crosses, which flickered at 40 Hz for 600 ms. Upon termination, the premask matrix reduced to a target matrix of simple 90° corner junctions. Subjects had then to discern the presence or absence of a Kanizsa-type square within the target matrix and produce a target-present/absent RT response as rapidly as possible.

Analysis

RTs on trials on which a response error was made and trials that timed out without response (after 5 seconds), which might occur as a consequence of some non-specific sedative effect were removed from the RT data set prior to analysis. The RT data were then examined by means of an a-priori analysis of covariance which aimed to examine the extent to which differential patterns of sedation (i.e. the average of the pre- minus that of the post-treatment self-rated sedation scores) may have influenced the treatment-session RTs. Subsequent analysis was carried out by means of repeated measures analysis of variance (ANOVA) with main terms for treatment (placebo, diazepam and lorazepam), target (present, absent), prime (the intra- vs. interphase presentation of crosses at the target-element locations) and the positioning of the orthogonal lines (conditions 0, 1, 2, 3, for explanation see introduction). In order to correct for a pronounced positive skew all analysis of variance or covariance calculations were made on the exponents of the means of the log-transformed RT distributions (a procedure employed to standardize non-normal distributions; see Box & Cox, 1964, 1982). Violations of the homogeneity of variance assumption were corrected by applying either Greenhouse-Geisser or Huynh-Feldt epsilon adjustments (as recommended by Huynh & Feldt, 1976). The arcsine-transformed error data were analyzed by means of identical repeated-measures ANOVA to that applied to the RT

data with the object of evaluating any patterning in the production of response errors against trends revealed from analysis of the RTs.

Results

RT Analysis

Response errors accounted for 3.8% of all trials (or 874 of 23,040 trials) while trials that were allowed to time out without response accounted for .003% of all trials (74 of 23,040 trials). The error RTs tended to be overall slower than correct RTs and analysis of the probability correct by RT revealed no significant correlation, arguing against the correct data being contaminated by fast guess responses. Self-rated sedation scores were found to exhibit no significant influence on the treatment-session RT effects (overall mean self rated sedation [and standard errors] were 10.33 [2.76], 28.83 [5.4] and 22.9 [5.08] on a scale 1:100 for placebo, lorazepam and diazepam, respectively). The a-priori analysis of covariance showed no significant differences attributable to the differential effects of lorazepam- and diazepam-induced sedation.

The omnibus ANOVA conducted on the mean correct RTs revealed a significant main effect of treatment ($F(2,22) = 21.95$, $MS_e = 132988.66$, $p < .001$) was examined using Bonferroni-adjusted simple main effects analyses. These analyses revealed significant differences between placebo relative to diazepam ($p < .001$; mean difference [and standard error of the difference] was 177 [31] ms) and placebo relative to lorazepam treatment RTs (($p < .001$; 237 [38] ms.). No significant differences were found between the diazepam and lorazepam treatment conditions ($p > .17$; 60 [42] ms) suggesting the elevated RTs for both drug treatment conditions relative to placebo treatment were a function of sedation. A significant main effect of target ($F(1,11) = 35.78$, $MS_e = 58120.03$, $p < .001$) was due to significantly faster RTs on target-present relative to the target-absent trials indicating the task to include some matrix search on target-absent trials (mean RTs [and associated standard error of the means] in ms were 693 [27] vs. 813 [39] ms). A main effect of prime was also revealed ($F(1,11) = 12.35$, $MS_e = 1493.641$, $p < .005$) based upon faster RTs following the intraphase presentation of priming crosses relative to those following interphase cross presentation (747 [32] vs. 758 [32] ms).

- Figure 3 here -

A significant treatment x target interaction ($F(2,22) = 10.05$, $MS_e = 20308.04$, $p < 0{,}001$) was examined by means of Bonferroni-adjusted simple main effects analyses, which revealed

substantially increased differences between target-present and absent RTs as a result of both diazepam and lorazepam administration relative to the placebo condition. The non-specific nature of these increases tend to suggest that target detection became more difficult but as a function of sedation rather than due to any particular drug related effect upon target coding or search performance.

Consistent with previous research (e.g. Elliott & Müller, 1998, 2000, 2001; Elliott et al., 2000) a significant target x prime interaction was due to the priming of target but not non-target RTs ($F(1,11) = 40.08$, MSe = 861.68, $p < .001$, the mean differences random-prime RTs [and SE mean] were: 27 [4] ms and 4 [4] ms for the target and non-target trials, respectively). Of primary importance was the significant four-way interaction (i.e. treatment x target x prime x line position: $F(3.32, 54.12) = 3.00$, MSe = 2723.54, $p < .05$) which emerged as a function of a very substantial (73 ms), target-specific priming when the orthogonal lines terminated adjacent to the cross-cross continua - but only following lorazepam administration (see Figure 2 Panel 3, The mean RTs [and 95% confidence intervals lower - upper bounds] were 732 [668 – 797] ms and 805 [734 – 877] ms for the priming and interphase cross RTs respectively).

An alternative and less conservative analysis of the 4-way interaction employed Bonferroni-adjusted simple main effects analyses. This revealed priming effects for no-line conditions following placebo and diazepam treatment ($p < .025$ and $p=.001$; the mean difference random-prime RTs [and SE mean] were 20 [7] ms and 41 [9] ms for placebo and diazepam respectively), for orthogonal lines that overlapped the cross-cross continua following placebo and lorazepam treatment ($p < .05$ and $p < .005$, 13 [6] and 45 [12] ms, respectively). Similarly, for orthogonal lines that terminated adjacent to the cross-cross continua, significant priming effects were particular to the placebo and lorazepam treatment conditions (respectively, $p < .025$ and $p < .005$, 22 [7] and 73 [20] ms). In spite of numerically large differences (illustrated in Figure 3), the prospective priming effects under diazepam treatment failed to achieve statistical significance. These patterns of effects can be taken to indicate that, while ordinary priming effects are substantially enhanced following the precise termination of the orthogonal line adjacent to the cross-cross continua, lorazepam-enhanced priming can also arise when the orthogonal line terminates in close proximity to these continua (i.e. when it overlaps them). This effect seems likely to arise given that lorazepam tends to impair slightly the precise spatial precision with which line terminations are coded (see Giersch, 2001).

Error Analysis

Error RTs tended to be overall slower than the correct RTs, and analysis of the probability correct by RT revealed no significant correlation, both factors argue against the correct data being contaminated by accuracy-speed trade offs. Consistent with the pattern of effects in the RT data the ANOVA performed on the arcsine-transformed error data revealed a significant treatment main effect ($F(2,22) = 0.70$, $MS_e = 0.10$, $p < .005$). Bonferroni adjusted simple main effects analysis revealed that the rate of error production was greater for both diazepam and lorazepam relative to placebo conditions ($p < 0.01$ and $p < 0.01$, respectively). The mean rates of error production were 1.16%, 3.92% and 5.39% for placebo, diazepam and lorazepam, respectively, but there were no significant differences in the rate of error production for diazepam compared with lorazepam treatment. The target main effect was significant ($F(1,11) = 22.48$, $Ms_e = 0.01$, $p < .001$) indicating that misses were more likely to occur than false alarms (the mean rate of error production on target-present trials was 4.42 % and on target-absent trials was 2.56 %). No other significant main effects or interactions were obtained.

Discussion

There were two findings of significance to the issue under investigation: Firstly and on the basis of post-hoc analyses, priming was revealed following placebo administration and thus the results presented here can be considered consistent with (albeit slightly weaker than) previously reported oscillatory-priming effects in healthy, unmedicated volunteers (see e.g. Elliott & Müller, 1998, 2000, 2001, Elliott et al., 2001). Secondly, and of greatest theoretical interest was the finding that priming effects were substantially increased following lorazepam administration when orthogonal lines were positioned such that they terminated adjacent to the unspecified portion of the continuation between premask crosses. Priming effects were not revealed to be of a comparable magnitude under any other combination of orthogonal line with treatment conditions although they were also revealed through post-hoc analysis to be significant when subjects had been treated with lorazepam and when lines overlapped the unspecified portion of the continuation between the premask crosses. This result offers the strongest evidence to support the idea that prime formation relates quite specifically to the coding of spatial relations between the priming crosses. It suggests that temporal segmentation is not the only mechanism whereby the target is primed; spatial binding is also involved, as revealed by the effect of lorazepam.

These results are in complete accord with the idea that lorazepam enhances the response to line terminations (Giersch et al., 1997). Lorazepam thus enhances production of a 'virtual line' that is orthogonal to the additional elements and that links the priming crosses. Given that line terminations are supposed to be coded by end-stopped cells (Sillito, 1977), these results offer further support for the idea that lorazepam has an indirect influence upon visual grouping by means of a direct enhancement of end-stopped, simple cell responses. These results go further to suggest that lorazepam influences end stopping by modulating the oscillatory response of the neurons concerned. It cannot be claimed that the type of spatial relations coded during prime formation are entirely synonymous with the Gestalt principle of good continuation given that the latter represents a perceptual unit forming factor while the oscillatory prime takes shape in the absence of conscious perception of the priming stimulus. However, this does seem to add strength to Giersch's claim that lorazepam operates on the outcome of low-level processes responsible for organizing simple features such as line terminations, while extending upon this claim by suggesting that the types of processes susceptible to lorazepam administration are essentially dynamic in character.

One further, albeit puzzling pattern of effects requires description: Lorazepam and diazepam yield the same sedation but they have been shown in a number of occasions to differ in their effects on temporal and spatial contour integration [Footnote 1]. The present results show that while priming is increased in all condition except when additional lines are presented some distance from continuance, these effects are non significant following treatment with diazepam. This provides no argument for an effect of diazepam upon spatial grouping but might suggest an effect of diazepam upon temporal segmentation. This might in fact suggest that diazepam and lorazepam share a common effect on neuronal dynamics but differ in respect to which these dynamics concern spatial grouping. This dissociation of the effects of diazepam and lorazepam is consistent with previous studies, in spite of which both drugs serve to enhance fixation of GABA on the $GABA_A$ receptor and may be thus considered to be equivalent. The reason why both drugs differ on these effects is still unknown but would suggest the temporal dynamics associated with lorazepam induced neural synchronization to be a special case for investigation related to the question of the neural correlates with low-level perceptual organization.

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Figure Legends

Figure 1: The stimulus presentation paradigm used by Elliott and Müller: In (a) premask-matrix presentation was followed by a target matrix of 90°-corner junctions to which observers had to make a speeded target (i.e. Kanizsa square) present or absent response. In (b) are shown example sequences of the four premask frames in both the synchronous or intraphase (upper panels) and random or interphase (lower panels) conditions: In the former condition, one premask frame consists of four elements in square arrangement; see the upper far left panel. Panel (c) illustrates the notion of unspecified continua (denoted by the dashed lines) between the collinear line elements of two or more separate but spatially aligned crosses. Panel (d) illustrates a subset of the stimuli employed by Giersch (1999). Stimulus (1) is collinear and discontinuous and under these conditions lorazepam enhances the coding of line terminations. Stimulus (2) is parallel and discontinuous. Giersch argues that the alignment of line terminations across parallel lines tends to induce perception of an orthogonal illusory contour which in turn leads to the two parallel lines being perceived as the edges of a rectangle and not as separate features. Under these conditions lorazepam does not enhance the coding of line terminations.

Figure 2: Numbered 1 – 4 from left-to-right, the descending panels show sample premask-matrices with (0) no additional orthogonal lines or with orthogonal lines presented (1) overlapping, (2) adjacent to, and (3) at some distance from the unspecified cross-cross continua. Orthogonal lines (shown separately in the top row of panels [a]) were presented continuously (i.e. they did not flicker with the premask matrix) and were presented for as long as the premask matrix flickered around them. The panels in row (b) show the 4 priming crosses (in panels 2 – 4 combined with the orthogonal lines). The panels in row (c) show the 4 priming crosses (presented in one image frame) in combination with the remaining 5 premask-matrix crosses which were distributed across 3 remaining image frames. The panels in the bottom row (d) show a target matrix which was not presented with accompanying orthogonal lines.

Figure 3: The upper panels give the mean synchronous and random premask, target-present and target-absent RTs and the lower panels give the mean priming effect (in ms) as a function of the orthogonal line conditions illustrated under the abscissa (i.e. from left to right no orthogonal lines, orthogonal lines presented overlapping to the unspecified cross-cross continua, orthogonal lines presented adjacent to the unspecified cross-cross continua and orthogonal lines presented at some distance from to the unspecified cross-cross continua. Separate graphs are shown for (a) placebo, (b) diazepam and (c) lorazepam treatment conditions. In the upper panels

the square symbols represent target-present conditions and the triangle symbols target-absent conditions. The unfilled and filled symbols represent synchronous and random premask presentation conditions respectively. In the lower panels the error bars represent the standard error of the mean priming effects (in ms). Irrespective to orthogonal line position, RTs were elevated for both diazepam and lorazepam relative to placebo administration, while RT variability and the difference between target-present and absent RTs increased for both drug conditions relative to placebo. Increased variability is likely to reflect the non-specific influence of sedation on search performance, over and above any specific drug effects on premask, feature or phase-related coding. In spite of increased variability, lorazepam was found to substantially enhance the effects of priming when the premask matrix was presented with orthogonal lines that terminated adjacent to the unspecified continuance between the premask matrix crosses (see (c) lower panel).

Footnotes

Footnote 1: Diazepam was chosen as a control for lorazepam in this experiment because although both drugs have equi-sedative effects, as measured subjectively and objectively, and equivalent effects on explicit memory (see e.g. Legrand et al., 1995; Sellal et al., 1992; Vidailhet et al., 1994) they have been shown to differ in their effects on visual perception. In particular, lorazepam, but not diazepam, has been shown to specifically facilitate the detection of a discontinuity between collinear contours (Beckers et al., 2001; Giersch, 1999, 2001) resulting in the impaired integration of local visual information into global configurations (Giersch et al., 1997; Giersch & Lorenceau, 1999). Diazepam and lorazepam have also been shown to differ with respects to the identification of fragmented pictures (Legrand et al., 1995; Vidailhet et al., 1994; Wagemans et al., 1998), perceptual priming effects (Legrand et al., 1995; Vidailhet et al., 1994; Sellal et al., 1992), the detection of discontinuities in lines (Beckers et al., 2001), and in their effects on masking and vernier offset detection (Giersch & Herzog, 2004). The reason why both drugs differ in these effects has still to be determined. On the one hand there is evidence to suggest that diazepam and lorazepam may affect different sub-types of $GABA_A$ receptors (Mohler et al., 2002), but other more parsimonious explanations should also be considered, in particular the different influence of the two drugs on the dynamics of neural activity: While diazepam lowers the firing frequency of individual neurons in a similar fashion to lorazepam unlike lorazepam it appears to have little influence on the generation of synchrony (Faulkner et al., 1998; Whittington et al., 1996). This characteristic tends to suggest that perceptual performance may be affected by lorazepam as a direct result of its effects upon the patterns of neural synchronization that have been found to emerge between neurons in the dynamic binding of visual features (i.e. Gray et al., 1989; Eckhorn et al., 1988; for review see Singer, 1999).

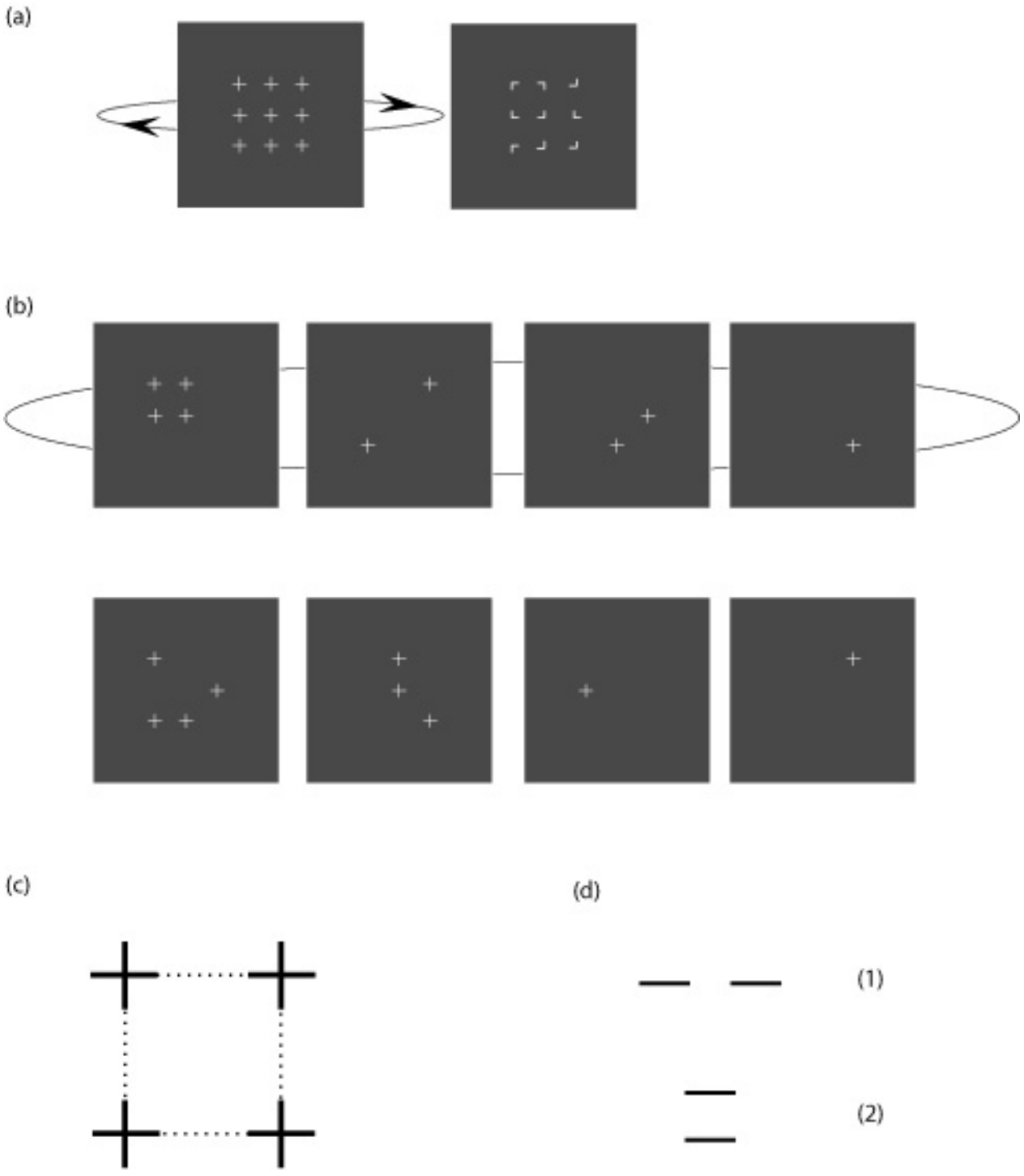

Figure 1

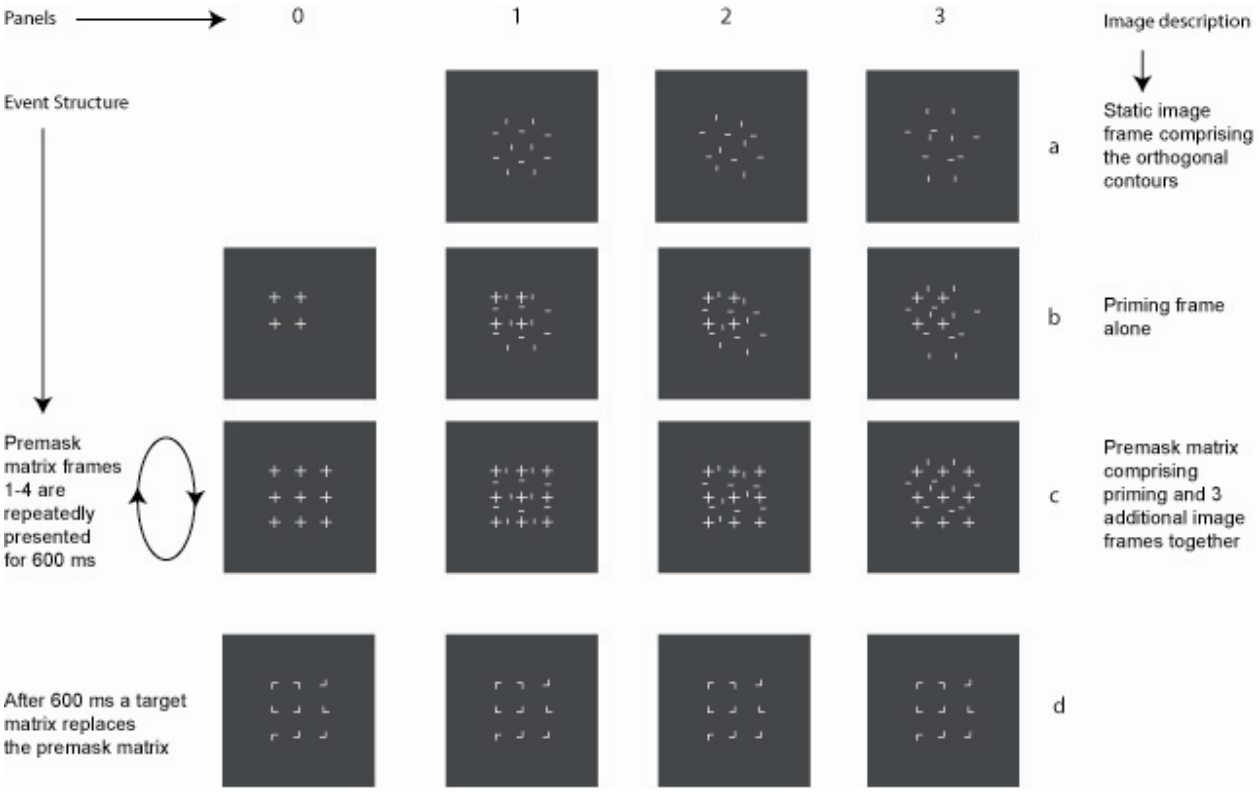
Panels
0
1
2
3
Image description
Event Structure
Static image frame comprising the orthogonal contours
a
b
Priming frame alone
Premask matrix frames 1-4 are repeatedly presented for 600 ms
c
Premask matrix comprising priming and 3 additional image frames together
After 600 ms a target matrix replaces the premask matrix
d

Figure 2

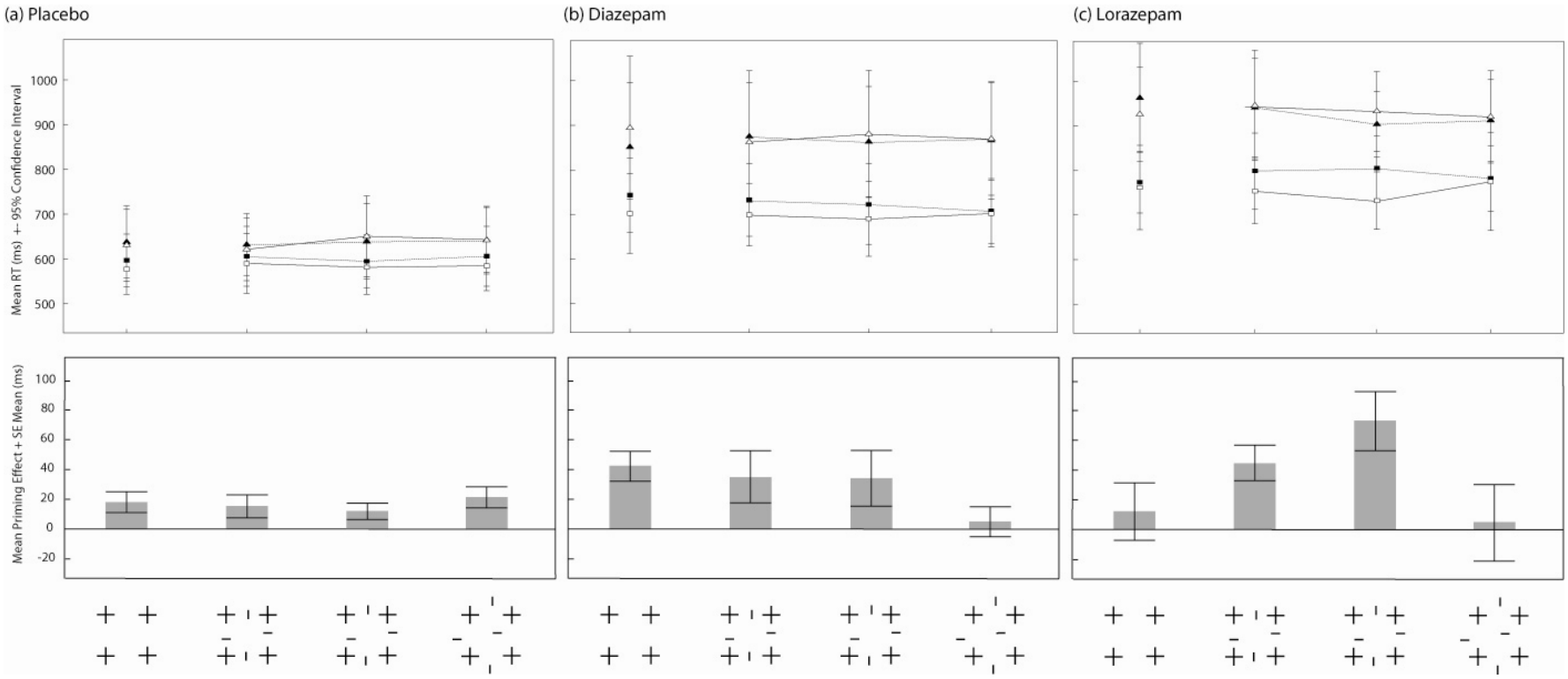
(a) Placebo
(b) Diazepam
(c) Lorazepam
Mean RT (ms) +- 95% Confidence Interval
1000
900
800
700
600
500
Mean Priming Effect + SE Mean (ms)
100
80
60
40
20
0
-20

Figure 3