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Running Head: GABA_A inhibition and synchrony coding

Mark A. Elliott¹, Cordula Becker^{1,2}, Muriel Boucart^{2,3} & Hermann J. Müller¹

Unité INSERM U405, Département de Psychiatrie, Hôpitaux Universitaires de Strasbourg,
1, place de l'Hôpital 67091 Strasbourg Cedex, France

¹Institut für Allgemeine Psychologie, Universität Leipzig, Germany

²Unité INSERM U405, Hôpitaux Universitaires de Strasbourg 1, France

³Université Lille 1- SN4 Laboratoire de Neurosciences du Comportement, France

Corresponding author:

Mark A. Elliott,
Institut für Allgemeine Psychologie,
Universität Leipzig,
Seeburgstr. 14/20,
D-04103 Leipzig, Germany

tel.: ++49 (0)341 973 5957.

fax: ++49 (0)341 973 5969.

email: elliott@uni-leipzig.de.

Abstract

The benzodiazepine, lorazepam enhances the efficiency of local, inhibitory GABA_A (γ -aminobutyric acid) synapses in the cortex, which stabilize postsynaptic, excitatory activity by synchronizing their own discharges at around 40 Hz. Treatment with lorazepam has also been shown to adversely influence detection performance in perceptual tasks, suggesting a role for GABA_A-mediated synchronization during visuo-perceptual organization. Consistent with these findings we report that reaction times (RTs) to target stimuli were slower following lorazepam treatment. However, when targets followed presentation of a synchronized prime, presented within a flickering 40-Hz display matrix, the effects of priming were amplified relative baseline and control conditions. We conclude that, while enhanced GABA_A-induced inhibition enhances stimulus-evoked synchronization with differential effects upon mechanisms of perceptual segmentation and grouping.

Key Words

Synchronization, 40 Hz, GABA_A, benzodiazepine, lorazepam, priming, vision, grouping, segmentation.

Introduction

The inhibitory neurotransmitter GABA is ubiquitous in the cortex with receptors at around 40% of all synapses¹. In the visual cortex, interneurons connected by synapses using GABA receptors are considered an important inhibitory mechanism by which the neural-response selectivity to moving stimuli (orientation and direction selectivity) and the coding of line terminations (end stopping) are achieved^{2,3}. In part, these conclusions have been reached through investigation of lorazepam-induced variations in visual performance. Lorazepam is a member of the benzodiazepine family of anxiolytics, which increase fixation of GABA exclusively on the receptor GABA_A. Unlike other benzodiazepines, administration of lorazepam reliably disrupts target detection and object recognition performance^{2,4}, while facilitating visual segmentation². This dissociation of lorazepam-induced effects has led to the suggestion that perceptual grouping and segmentation are qualitatively different outcomes of similar GABA_Aergic inhibitory processes², a proposal supported by the temporal characteristics of GABA_Aergic activity. GABA_Aergic neurons tend to synchronize at between 33 and 50 Hz⁵⁻⁷, a frequency bandwidth of importance for the successful 'binding' of visual feature elements and figure-ground segmentation^{8,9}. Following GABA_Aergic synchronization, postsynaptic, excitatory neurons also synchronize with increased amplitudes but reduced frequencies, which appear to shift from around 40 Hz to between 10 and 30 Hz^{10,11}. The increase in amplitudes and accompanying reductions in frequency have been offered as a mechanism by which low-level groupings produced by GABA_Aergic synchronization compete for access to subsequent perceptual-attentional mechanisms. It seems likely that lorazepam-enhanced GABA_Aergic inhibition attenuates the frequency shift in excitatory neural activity, thereby inhibiting

synchronization at lower frequencies with the result that no single low-level grouping emerges as a clear candidate for subsequent processing.

The present study examined the effects of lorazepam and a second benzodiazepine, diazepam on reaction time (RT) performance in a primed-figure detection task. Observers searched for target Kanizsa-type, illusory squares (formed by the collinear arrangement of 90° corner junctions within a matrix of distracter junctions (Fig. 1a)). Targets were preceded, at the target location, by the synchronized presentation of a figural information within a matrix of premask crosses presented in one of four, temporally asynchronized display frames (Fig 1b). Previous research has indicated that the effects of prime synchrony are confined to target trials and are only revealed when the global frequency of premask presentations is set to 40 Hz¹². At 40 Hz the priming stimuli are non-detectable¹² and have been shown to generate a specific pattern of 40-Hz activity across the prime^{12, 13}, which is specific to the 40-Hz EEG recorded over posterior visual cortex¹⁴. The frequency selectivity of priming suggests GABA_Aergic synchronization as a candidate mechanism for generating prime synchrony, although the non-detectability of the priming stimulus indicates that synchrony maintained at 40 Hz may be of insufficient energy to induce the downward shift in frequency required for access to subsequent visual-coding mechanisms. If this hypothesis were correct, lorazepam-sustained oscillations at 40-Hz should enhance synchrony across the prime and thereby expedite detection of primed relative to unprimed targets.

These expectations differ from those associated with diazepam treatment. Diazepam lowers the firing frequency of individual neurons^{7, 15}, but has little influence on the generation of synchrony¹⁵. Accordingly, it was expected that the mechanisms

responsible for target detection would not be specifically influenced by diazepam, although the accompanying sedative effects of the drug should produce a non-specific slowing of RTs and an attendant loss of sensitivity to prime-stimulus presentation.

Materials and Methods

Following approval of the protocol from the faculty Ethics Committee at the University of Strasbourg, 36 paid volunteers (12 male, mean age 22.4 years, normal or corrected to normal vision), participated in an experimental study comprising a treatment session preceded by a practice session. Observers gave written, informed consent and were paid 1000 FF for their participation. The observers had no medical illness 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 24h prior to the study. All observers were tested under treatment conditions in the morning following the day of the practice session, with an overnight fast in-between. The practice session was conducted under monocular viewing conditions. This produced a mean synchrony enhancement of 47 ms (with an associated $2 * SE$ mean of 6 ms) on target-present trials, which compares well with an enhancement of 41 (8) ms revealed in pilot testing under binocular conditions. Consistent with previous work^{12, 13}, the priming effects were target-specific, that is, confined to target-present trials (target-absent trials: monocular, 6 (7) ms; binocular, 4 (6) ms). Further, the magnitude of the effects was independent of the matrix location of prime/target presentation (central or peripheral relative to fixation at the center of the stimulus matrices).

For the treatment session, the 36 observers were randomly assigned to one of three treatment groups (12 observers per group) and administered with lorazepam (0.038 mg/kg bodyweight), diazepam (0.3 mg/kg) or a placebo. The drug tablet was administered orally using a double blind procedure and experimentation was conducted between 45 minutes and 3 hours following drug administration. The observers' blood pressure and pulse were taken and Stanford tests of sedation applied prior to and at hourly intervals during testing. On each occasion, an additional analog self-rating of sedation¹⁶ was completed by observers, from which mean ratings of pre- and post-drug sedation were calculated.

Figure 1 about here

The treatment sessions were also conducted under monocular viewing conditions to avoid contamination of the results by a benzodiazepine-induced oculomotor imbalance¹⁷. The session consisted of 640 trials (160 trials per experimental condition), divided into ten 64-trial blocks. For each trial, following a brief computer-generated tone, observers were presented with a 5 x 5 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. Observers 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. The flickering premask matrix of 5 x 5 crosses consisted of a repeated sequence of four temporally asynchronous presentation frames (Fig. 1b). The distribution of the 25 premask crosses across four frames permitted definition of a 'synchronous' (prime) condition in which there was one frame comprising four crosses presented at the

same locations as the four collinear corner junctions subsequently defining the Kanizsa-type square (on target-present trials). There was also an asynchronous condition in which the four premask crosses at the subsequent target junction locations were presented in different frames. In synchronous conditions, the synchronous prime and, on target-present trials, the subsequent target elements were presented with equal probability at each of the 16 possible 'square' locations within in the display matrix. The 'non-synchronous' premask frames were presented in pseudo-random order on each trial, with control for the possibility of spurious square groupings in frames comprising more than four elements. Synchronous and asynchronous premask trials, and target-present and absent trials, were presented in random order for each observer.

An IBM-PC compatible computer, running custom software, controlled event timing, data collection and stimulus frame generation, while also controlling oscilloscopic image presentation through an Interactive Electronics point-plotter buffer with 8 MB frame store memory. Stimuli were presented on a Tektronix 608 X-Y plotter with a very fast-decay P15 phosphor, capable of maintaining stimulus image frame presentations at a background rate in excess of 1 kHz per frame. All displays were presented at the center of the plotter screen, and observers viewed the displays at a distance of 57 cm maintained via a chin rest. Experiments were conducted in mesopic lighting conditions (mean surround luminance 0.078 cd/m²), with stimulus luminance maintained at 0.3 cd/m² upon a background field of 0.075 cd/m². The 5 x 5 premask display matrix subtended 11°48' x 11°48' of visual angle, with 1°17' crosses separated from their nearest horizontal and vertical neighbors by 1°59'. The target displays subtended between 11°07' - 11°48' x

11°07' - 11°48', with junction elements of 39', which were separated horizontally and vertically by between and 1°59' - 2°38'.

Results

The observers' mean RTs in the treatment condition were examined by means of a mixed-design analysis of variance (ANOVA), with the between-subject factor treatment (placebo, diazepam and lorazepam) and the within-subject-factors target (present, absent) and prime (synchronous, asynchronous, see Fig. 1(a)). Trials with erroneous responses (2.1% of all trials) and RT outliers (i.e., RTs ≥ 2.5 standard deviations from the means for each condition: 2.5% of all trials) were excluded from the analysis. Examination of the error data revealed no confounding pattern of effects such as speed-accuracy trade offs. The data of three of the 36 observers, one from the diazepam and two from the lorazepam groups, were excluded from the analysis, due to reported problems maintaining visual acuity during the treatment session. For the remaining observers, an a-priori analysis of covariance revealed a measure of self-rated sedation (the mean pre- minus post-treatment ratings) to have no significant influence on the treatment-session RT effects.

Figure 2 about here

Consistent with expectations and as shown in Fig. 2(a), RTs were significantly different for the treatment conditions ($F(2,30) = 6.36, p = .005$) and were slower for lorazepam relative to both placebo (control) and diazepam conditions (the mean differences were 241 (139) ms. (least-significant-difference test, $p = .001$) and 146 (141)

ms. ($p < .05$), for placebo and diazepam respectively). A significant target x prime interaction confirmed the priming effects as specific to trials on which a target was presented ($F(1,30) = 32.055, p < .0001$), although a significant 3-way interaction ($F(2,30) = 3.365, p < .05$) indicated that target-priming also depended upon treatment. The target specificity of the synchrony effects were supported by significant target x prime interactions for the placebo and lorazepam RTs (separate ANOVAs: $F(1,11) = 80.073, p < .0001$ and $F(1,9) = 17.245, p < .005$, respectively), with an increased effect size by a factor of approximately 1.3 for lorazepam relative to placebo. In contrast, priming was not reliable under diazepam conditions ($F(1,10) = .942$, see Figs. 2(a) and 2(b)). The reduced priming under diazepam is likely to be one consequence of the non-specific effects of sedation obscuring the facilitatory effects of prime generation. This differs from the priming effects obtained under lorazepam, which were of sufficient magnitude to be marginally enhanced relative to priming under placebo conditions (planned independent-samples t-test, equal variances not assumed, $t(17.29) = 1.52, p < .075$, see Fig. 2(b)). Despite differences in the magnitude of priming under lorazepam and diazepam, self-rated sedation was elevated by approximately the same measure for both drugs (see Fig. 2(c)). A separate ANOVA of the practice-session RTs revealed no significant effect of treatment upon priming, indicating that the treatment groups were well matched under no-drug conditions (see Fig. 2(b) for priming effect in practice session (all groups combined)).

Discussion

These patterns of results show that lorazepam exerts a specific influence upon the neural mechanisms responsible for low-level perceptual organization, which, in this case,

is likely to involve the pre-segmentation of the synchronous premask elements from the remainder of the premask-display matrix. The priming effects under investigation are also specific to the generation of a 40-Hz process during synchrony coding¹²⁻¹⁴, while the effects of lorazepam specifically influence GABA_A-mediated activity. This confirms the earlier stated hypothesis that, unlike diazepam, the perceptual effects of lorazepam administration are likely to result from adjustment of the frequency characteristics of GABA_A-mediated neuronal activity, in this instance the enhancement of neuronal synchronization at 40-Hz. A further question that arises is why subsequent target detection should be impaired if low-level synchronization is enhanced? One possibility is that the lorazepam-induced enhancement of inhibitory 40-Hz activity suppresses the normal decrease in excitatory firing frequencies, held to be responsible for signaling the output of low-level synchronization to subsequent visual coding mechanisms¹⁰. A second possibility is that the elevation of noise-signal ratios resulting from a general tendency to synchronize at 40 Hz would tend to increase competition between genuine (target-specific) groupings and spurious synchronizations or other possible candidate groupings. These hypotheses are not mutually incompatible and in either case, efficient object coding would become slowed and prone to a greater degree of error during the perception of grouping stimuli as has been shown in other studies^{2, 4, 17}.

Conclusion

One final conclusion offered by this study concerns the precise physiological mechanism by which perceptual grouping by neural synchronization is achieved. Although the temporal consequences of GABA_A-mediated inhibition appear as a clear candidate for

generating synchronization and binding at the network level, it is also clear that the lorazepam influences synchronization in a very specific fashion at the level of molecular action. Accordingly, investigation of the molecular mechanisms, including the subclass of GABA_A receptors by which lorazepam influences GABA_A-mediated synchronization, may offer a promising approach towards an understanding of the physiological mechanisms by which frequency-specific synchronization and perceptual organization are achieved.

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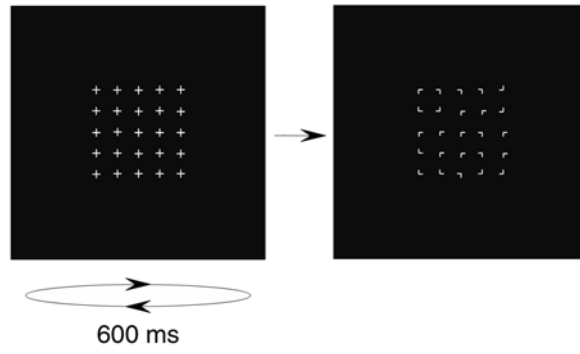
Figure Legends

Figure 1: (a) Example premask and target matrices. Premask matrices flickered for 600 ms and were followed immediately by a target matrix, note that the target appears in the upper left-hand quadrant and consists of 4 grouping corner junctions in collinear arrangement. In (b) are shown examples of the possible arrangement of crosses across the four premask frames. Here, the first frame is a synchronous-premask frame with four crosses in square arrangement at the locations subsequently occupied by the target grouping. By contrast an asynchronous premask frame would not include the four premask crosses in square arrangement. Each frame was repeatedly presented at a rate of 10 frames-per second, with constant frame durations of 25 ms. and with inter-frame intervals of < 1 ms.. These repetitions produced a global 40-Hz presentation frequency across the entire premask matrix, which appeared as stochastic surface flicker on an otherwise static display of 25 crosses (see (a)). Both premask frames and the target display were maintained at a constant 1-kHz background frequency, although unlike the premask matrix, target displays did not oscillate and were presented as static until response keypress.

Figure 2: (a) Mean target-present (TP) and target-absent (TA) RTs rose significantly for lorazepam relative to both diazepam and placebo conditions, while RT variability (see error bars representing standard errors) and the difference between target-present and absent RTs increased for both drug conditions relative to placebo. The increased variability is likely to reflect the non-specific influence of sedation on search performance, over and above any specific drug effects on synchrony coding. (b) Mean self-rated sedation (i.e., the difference between subjective ratings on a scale of 1 - 100 taken prior to and during testing; error bars denote the 95% confidence intervals) increased

following drug administration, with increases approximately equivalent for lorazepam and diazepam relative to placebo. (c) Mean target-specific synchrony priming (i.e., the enhancement of synchronous relative to asynchronous target-present RTs) also showed an increase in variability following drug administration (represented by error bars denoting 95% confidence intervals), likely due to increased sedation. Despite the increased variability, lorazepam was found to enhance the effects of priming by a factor of approximately 1.3 (or 33%) relative to placebo conditions. In contrast priming was evident, but reduced to 67% under diazepam conditions. Given the general increase in RT variability accompanying drug administration, the effects of priming are likely to be obscured by sedation. Despite this sedative influence, priming effects were increased under lorazepam conditions indicating a specific influence upon GABA_A coding of stimulus synchrony.

(a)



(b)

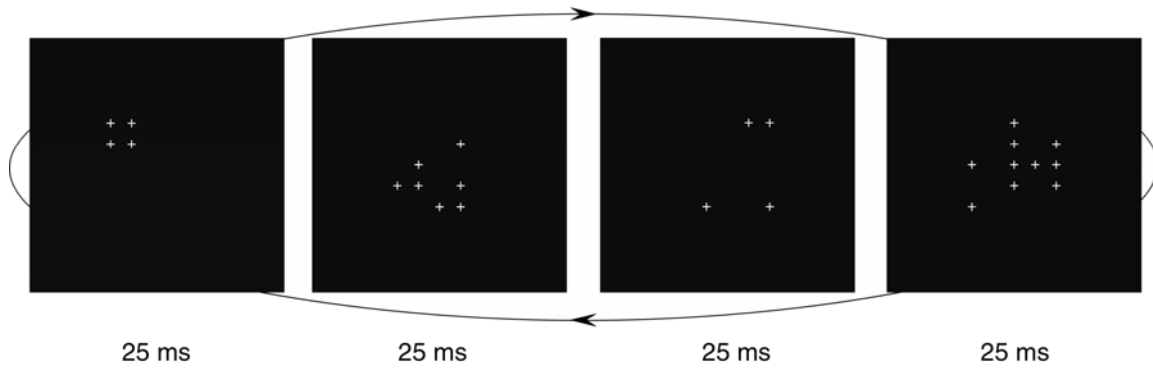


Figure 1

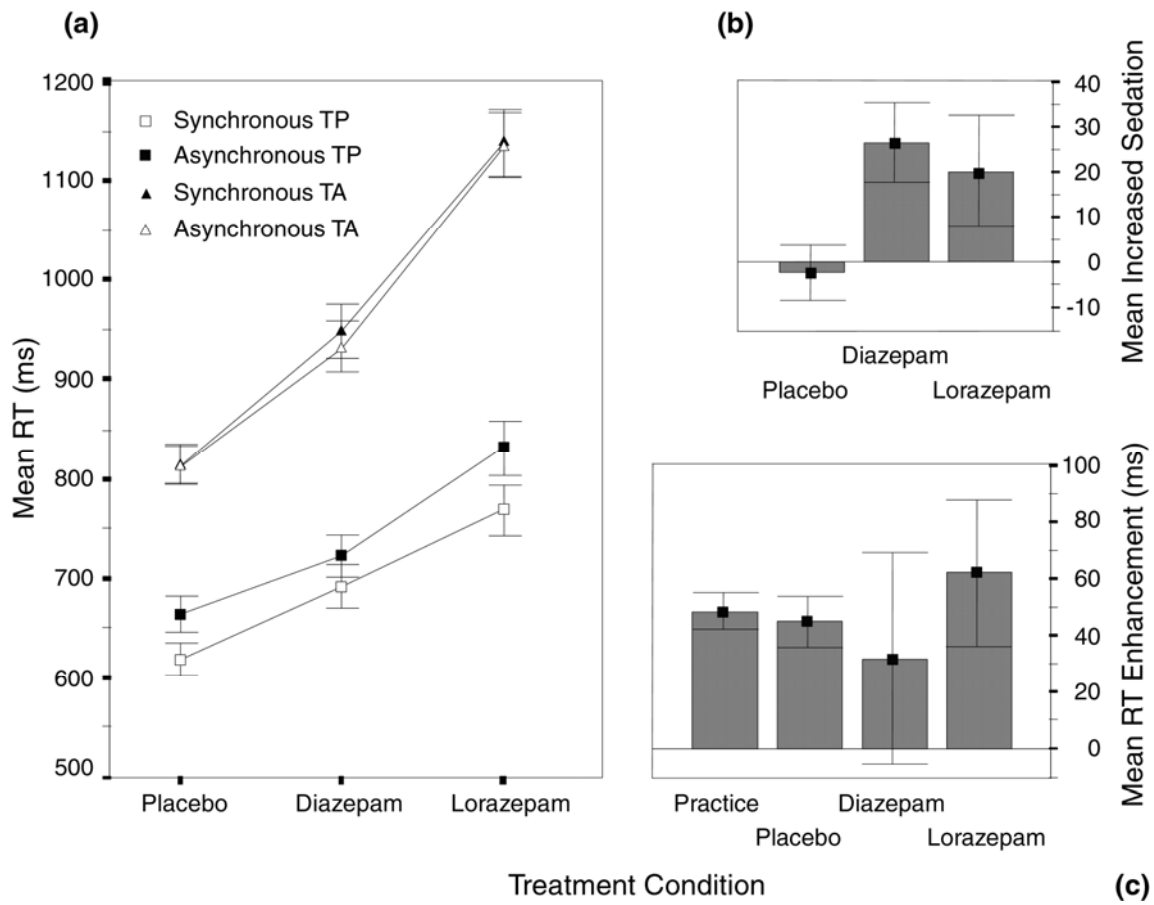


Figure 2