GABA-ergic control of visual perception in healthy volunteers: effects of midazolam, a benzodiazepine, on spatio-temporal contrast sensitivity

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- 1 We studied the effects of midazolam (MDZ), a benzodiazepine, on spatio-temporal contrast sensitivity, choice reaction time, and mood visual analogue scales in healthy volunteers.
- 2 Eight extensively trained, healthy volunteers were included in a placebo-controlled cross-over double-blind trial of MDZ (0.15 mg kg⁻¹). Treatments were injected intramuscularly and evaluations were performed before and 0.5, 1, 2, 3 and 4 h after drug administration. Spatio-temporal contrast sensitivity was measured using a micro-computer with appropriate software. Stimuli were vertical gratings with adjustable contrast, with spatial frequencies of 0.25, 1 and 4 cpd. Four conditions of temporal modulation were used: the grating was either static or drifting laterally with temporal frequencies of 1, 3 and 9 Hz.
- 3 An analysis of variance was performed on the data. As compared with placebo, MDZ induced an increase in choice reaction time and sedation (as assessed on visual analogue scales). From 0.5–4 h after the injection, MDZ produced an overall decrease in visual sensitivity, as compared with placebo. More specifically, MDZ preferentially affected medium to high spatial frequencies and low temporal frequencies. Several non-exclusive hypotheses may account for the results: 1) an increase in the size of the receptive fields, 2) a preferential effect on the visual parvocellular pathways which mediate the sensitivity to high spatial and low temporal frequencies.

Keywords GABA spatio-temporal contrast sensitivity midazolam benzodiazepine motion perception

Introduction

There is now abundant evidence suggesting that γ -amino butyric acid (GABA) is a functional transmitter along the entire length of visual pathways in mammals.

The role of GABA as a neurotransmitter in the mammalian retina is well established. Studies on the uptake of tritiated GABA or muscimol [1, 2] and immunocytochemistry with antibodies against glutamic acid decarboxylase (the GABA-synthesizing enzyme GAD) or against GABA [3, 4] showed that, next to glycine, GABA is the predominant transmitter of amacrine cells in the mammalian retina. Amacrine cells

of rat, cat and most animal species contain GAD. GABA is present in detectable amounts, and these cells have an energy and sodium-dependent uptake system which has a high affinity for GABA [for a review see 5, 6]. A subtype of horizontal cells also use GABA as a neurotransmitter [7], and GADlike-immunoreactivity (GAD-LIR) is present in the horizontal cells of humans. GABAlike immunoreactivity is present in all sites where GAD-LIR occurs, as well as in the outer plexiform layers and interplexiform cells of the human retina [8].

GABA-ergic neurons and synapses have been identi-

fied in the lateral geniculate nucleus (LGN), and these neurons are thought to be interneurons receiving retinal input. Their dendrites provide presynaptic inhibitory input to the dendrites of geniculocortical relay neurons. They might also have axons providing further GABA-ergic inhibition [9, 10].

The presence of a strong GABA-ergic neurotransmission has been demonstrated for the superficial grey layer of the colliculus which contains both GABA A and GABA B receptor subtypes [11]. GABA seems to play an important role in retino- and cortico-collicular neurotransmission [12].

Finally, the existence of GABA and GAD-containing neurons has been demonstrated in the visual cortex of mammals [13, 14], and there is abundant evidence suggesting that GABA may be an inhibitory transmitter in the visual cortex [15, 16].

The effects of benzodiazepines are thought to be mediated by the facilitation of central GABA-ergic transmission via specific benzodiazepine receptors [17]. These receptors are functionally coupled with GABA A receptors and form 'GABA A receptors/Benzodiazepine receptors/Chloride channel' complexes [18]. In central nervous structures, benzodiazepines potentiate the action of GABA [19]. The presence of benzodiazepine binding sites has been demonstrated in various structures of the visual pathways [20], including the retina [21], and the superficial grey layer of the colliculus [22]. Thus, benzodiazepines may serve for studying central GABA-ergic mechanisms in man.

In humans, only a few studies have been performed on the effects of benzodiazepines on visual perception. Bartel *et al.* [23] did not find overall significant effects of a single oral dose of oxazepam (15 mg) on pattern electroretinogram and visual evoked potentials. Only a decrease of the b wave latency of the ERG and an increase in the OP4 latency of the VEP were observed. To the contrary, Harris & Phillipson [24] claimed, in a preliminary report, that lorazepam induced a dose-related loss in contrast thresholds for the perception of movement in sinusoidal gratings. The assessment method used was contrast sensitivity evaluation.

In fact, the contrast sensitivity (CS) function has become a powerful tool in evaluating spatial vision (visual perception of the environment). CS is usually defined as the reciprocal of the contrast level required for the detection of gratings whose luminance is modulated sinusoidally with various spatial frequencies (in cycles per degree, cpd, resulting in gratings of various 'widths') and/or temporal frequencies (in hertz, resulting in flickering or drifting patterns). Hence, spatio-temporal contrast sensitivity (STCS) assesses both spatial vision and motion perception. It is a better predictor of the visual system's performance than is pure visual acuity, and it gives a more complete description of the functional range of the visual system [25]. STCS modifications have been demonstrated across the life span [26], in pathological conditions such as Parkinson's disease [26, 27] and under the influence of pharmacological treatments [28].

Here we studied, in a controlled trial on healthy volunteers, the effects on visual perception of a single dose of midazolam, a water-soluble benzodiazepine with a rapid onset of action and a very short half-life,

which has a useful role as a premedication, or a sedative for minor surgical procedures. We sought generalized vs differential effects of MDZ on STCS, using various spatial and temporal frequencies. We also investigated the time-course of the effects of midazolam as compared with placebo on both STCS and psychomotor functions.

Methods

Healthy volunteers

Eight healthy male volunteers with normal vision were selected for the study. Their ages ranged from 22 to 34 years (mean 25.4), their weight from 68 to 88 kg (mean 75.4) and their height from 175 to 185 cm (mean 180.6). All were physically healthy according to general, neurologic and ophthalmologic examinations. Subjects were asked not to drink alcohol for 24 h prior to each treatment and up to the end of each session, and to abstain from all central nervous system (CNS) drugs. Subjects were advised not to drive on treatment days. Approval was obtained from the Ethics Committee of the Timone Hospital and each subject gave written informed consent before the study.

Experimental design

Each subject was given each of the two treatments, which were assigned to the eight subjects according to a cross-over design under double-blind conditions. At least 7 days were allowed between the treatments to ensure wash-out of the study medication.

Treatments

Midazolam (0.15 mg kg^{-1}) or saline was administered intramuscularly at 08.00 h by a nurse who was independent from the study.

Assessment

During each experimental session, an evaluation battery was performed before (t_0) and 0.5, 1, 2, 3 and 4 h after drug administration ($t_{0.5}$, t_1 , t_2 , t_3 , t_4 , respectively).

Contrast sensitivity to static and moving gratings (spatio-temporal contrast sensitivity—STCS) was measured using a micro-computer (Hewlett Packard QS 20) and a graphics software developed by ourselves (STCS software ©). Stimuli were projected on the screen of a Hewlett Packard graphics display (HP D1192) with a medium-short P22 phosphor (10% decay times: $R = 1 \text{ ms}$, $G = 0.004 \text{ ms}$, $B = 0.003 \text{ ms}$) and a 0.28 mm pitch matrix. Refresh rate was equal to 60 Hz. The actual display resolution was 320 pixels in the horizontal direction $\times$ 200 pixels in the vertical direction. Extensive description of the device has been given elsewhere [26]. Briefly, static vertical sinusoidal gratings with adjustable contrast, with spatial frequencies of 0.25, 1 or 4 cycles/degree (cpd) were used to measure static contrast sensitivity. Motion sensitivity was tested using the same grat-

ings drifting laterally with temporal frequencies of 1, 3 or 9 Hz. The subjects were instructed to look at a display subtending a visual angle of 10×7 degrees at a viewing distance of 1.7 metres. Testing was binocular. Mean luminance of the display was held constant at 1 cd/m^2 .

In the static condition, the subjects had to detect the vertical gratings. In the moving condition, they had to detect the direction of motion of the gratings. Contrast threshold measurement was based on a modified version of the Von Beke's tracking procedure. At the beginning of the test, the grating's contrast was increased from 0 (uniform field). The subject depressed a button whenever the pattern or direction of movement became visible on the screen, signalling the computer to decrease contrast. The subject then depressed the button when the pattern or movement became invisible, signalling the computer to increase contrast, and then depressed the button when the pattern or movement became visible again. Three successive contrast-reversal values were averaged, and this value was taken as the subject's threshold for each experimental trial. Contrast sensitivity was defined as the reciprocal of the contrast threshold. Randomization of trial presentation and response recording were performed by the computer. Subjects were extensively trained (four sessions) with this method during the week preceding the study and 15 min of adaptation to the ambient illumination level was allowed before testing. All tests were performed at the same time of the day since circadian variations of contrast sensitivity have been reported at least in Parkinson patients [29].

Sedation and mood were assessed using visual analogue scales (VAS) translated from Hindmarch & Gudgeon [30] and previously validated [31].

Choice reaction time (CRT) was measured using a Sodelec Electronic (France) display [32]. The subject was asked to scan two light bulbs of different colours which were randomly turned on. As soon as a bulb lit up, the subject had to press one of two buttons to turn it off. The response time was automatically recorded with a precision of 10^{-2} s. For each test, 50 attempts were recorded.

Side effects were assessed throughout the session by the experimenter. Safety was assessed by the monitoring of blood pressure, heart rate and pulse oxymetry. Treatment was administered under the care of an anaesthesiologist who decided when the subject could be released from the ward.

Statistical analyses

The effects of the studied drugs were evaluated using an analysis of variance which computed Snedecor *F*-values [33]. For CRT and VAS, analyses of variance were conducted on the subjects' result values, with treatment (midazolam vs placebo), and repetition (successive measurements at t_0 , $t_{0.5}$ –0.5 h after injection, t_1 –1 h, t_2 , t_3 and t_4) as experimental factors. For contrast sensitivity, analyses of variance were conducted on the subjects' contrast sensitivity values, with treatment (midazolam vs placebo), repetition (successive measurements at t_0 , $t_{0.5}$ –0.5 h after injection, t_1 –1 h, t_2 , t_3 and t_4), spatial frequencies (0.25, 1 and 4 cpd) and temporal frequencies (1, 3 and 9 Hz) as experimental factors.

Results

Tolerance

All subjects felt drowsy during midazolam treatment and fell asleep about 15 min after injection. Subjects were woken up to perform the first evaluation. No serious side-effects occurred.

Constant sensitivity

1) Overall treatment effects Spatio-temporal contrast sensitivity (STCS) was significantly depressed during the session when MDZ was administered, as compared with the placebo session ($F[1, 7] = 77.34$; $P < 0.001$). Overall STCS (averaged across subjects, successive measurements from t_0 to t_4 and spatio-temporal frequencies) was equal to 25.37 during the MDZ session and to 34.11 during the placebo session. STCS was also significantly affected by repetition of the task, from t_0 to t_4 ($F[5, 35] = 25.94$; $P < 0.001$). Moreover, there was a significant interaction effect between treatment (MDZ vs placebo) and repetition of the task ($F[5, 35] = 25.03$; $P < 0.001$), suggesting a different evolution of STCS depending on the treatment received.

With placebo, repetition of the task resulting in a significant increase in STCS ($F[5, 35] = 9.27$; $P < 0.001$), which, however, accounted for less than 2% of the total variance. This indicated that, with the placebo, overall STCS tended to increase slightly with repetition of the task, from t_0 to t_4 . With midazolam, repetition of the task resulted in significant changes in STCS ($F[5, 35] = 45.71$; $P < 0.001$), which accounted for 9% of the total variance. *Post-hoc* analyses revealed that STCS decreased significantly between t_0 and $t_{0.5}$ ($F[1, 7] = 73.57$; $P < 0.001$) and increased again between $t_{0.5}$ and t_4 ($F[1, 7] = 57.59$; $P < 0.001$). Mean values of STCS (averaged across subjects and spatio-temporal frequencies) are plotted in Figure 1 as a function of the successive measurements times (t_0 to t_4), for midazolam and placebo.

2) Time-course of the treatment effects At t_0 (before treatment), STCS was equivalent for placebo and midazolam conditions ($F[1, 7] = 0.5$; $P < 0.001$). Mean values of STCS (averaged across subjects and spatio-temporal frequencies) were equal to 28.50 for midazolam and to 27.28 with placebo (Figure 1). We thus observed comparable pre-treatment evaluations of STCS for all subjects on the day when they received placebo and on the day when they received midazolam (Figure 2a). This was expected, since subjects were extensively trained on the task before the experiment itself.

At $t_{0.5}$ (0.5 h after the treatment), STCS was overall significantly depressed following midazolam injection, as compared with placebo ($F[1, 7] = 166.25$; $P < 0.001$). Mean values of STCS were equal to 13.30 for midazolam and to 34.12 with placebo (Figure 1). *Post-hoc* analyses, using Student's *t*-test, revealed that this depression existed at all spatio-temporal frequencies tested (with $P < 0.01$ or better), except for the spatial frequency of 4 cpd modulated at 9 Hz (Figure 2b).

At t_1 (1 h after the injection), there was also a large significant effect of the treatment ($F[1, 7] = 91.45$; $P <$

Figure 1 Overall values of spatio-temporal contrast sensitivity (averaged across the eight subjects), spatial and temporal frequencies, from t_0 (pre-treatment) to t_4 (4 h after treatment) for midazolam (○) and placebo (●).

0.001). Mean values of STCS were equal to 16.94 for midazolam and to 34.71 with placebo (Figure 1). *Post-hoc* analyses revealed that visual sensitivity induced by midazolam was significantly inferior to that induced by placebo for every combination of spatial and temporal frequency, except for the case of a static stimulation with the spatial frequency of 0.25 cpd and for the spatial frequency of 4 cpd drifting at a temporal frequency of 9 Hz.

At t_2 (2 h after the injection), the pattern of results was quite comparable with that observed at t_1 . Mean values of STCS differed significantly and were equal to 22.81 for midazolam and to 35.32 with placebo ($F[1, 7] = 90.29$; $P < 0.001$). Here again, the visual sensitivity induced by midazolam was significantly inferior to that induced by placebo for every combination of spatial and temporal frequency, except for the case of a static stimulation with the spatial frequency of 0.25 cpd and for the spatial frequency of 4 cpd drifting at temporal frequencies of 1 or 9 Hz.

At t_3 (3 h after the injection), there was still a significant effect of the treatment ($F[1, 7] = 5.97$; $P < 0.05$). Mean values of STCS were equal to 28.54 for midazolam and to 35.08 with placebo (Figure 1). *Post-hoc*

analyses revealed that, for static stimulations, the sensitivity induced by midazolam was significantly inferior to that induced by placebo only for the spatial frequency of 4 cpd (mean values of STCS were equal to 8.66 for midazolam and to 15.46 with placebo). With temporally modulated stimulations, the only significant differences were found for the spatial frequency of 1 cpd drifting at 3 Hz (mean values of STCS were equal to 39.8 for midazolam and to 52.2 with placebo) and 9 Hz (mean values of STCS were equal to 9.64 for midazolam and to 11.39 with placebo), and for the spatial frequency of 0.25 cpd drifting at 9 Hz (mean values of STCS were equal to 13.19 for midazolam and to 19.4 with placebo).

At t_4 (4 h after the injection), there remained an overall significant effect of the treatment ($F[1, 7] = 12.24$; $P < 0.025$). Mean values of STCS were equal to 31.30 for midazolam and to 38.12 with placebo (Figure 1). *Post-hoc* analyses revealed a significant effect of the treatment for spatial frequencies of 1 and 4 cpd associated to temporal frequencies of 0 (static), 1 and 3 Hz ($F[1, 7] = 10.82$; $P < 0.025$) (see Figure 2c). However, a more detailed analysis revealed that STCS was decreased by midazolam only for the spatial frequency of 1 cpd when either static (mean values of STCS were equal to 56.87 for midazolam and to 76.97 with placebo) or modulated at 3 Hz (mean values of STCS were equal to 45.70 for midazolam and to 58.04 with placebo). The temporal frequency of 9 Hz and the spatial frequency of 0.25 cpd were overall unaffected by the treatment.

Visual analogue scales

Overall, subjects felt more drowsy, more tired, more clumsy and less energetic during midazolam sessions than during placebo sessions. Analyses of variance conducted on visual analogue scales (VAS) values revealed that all differences were significant (with $P < 0.025$ or better). For placebo, the values were relatively stable across sessions (Table 1), indicating that subjects felt 'as usual' on the average. For midazolam, subjects experienced an important subjective change between t_0 and $t_{0.5}$ (they felt more drowsy, more tired, more clumsy and less energetic at $t_{0.5}$, as compared with t_0). This was followed by a progressive return to 'normality' from $t_{0.5}$ to t_4 . A significant difference between midazolam and placebo was observed at $t_{0.5}$, t_1 , t_2 . No difference was significant at t_3 and t_4 (Table 1).

Table 1 Mean visual analogue scale values (averaged across subjects) for the items 'drowsy' 'tired' 'clumsy' and 'energetic', for midazolam and placebo, at the 5 test times (t_0 , $t_{0.5}$, t_1 , t_2 , t_3 , t_4). Values are expressed on a scale from 0 to 100. 50 means that the subject feels 'as usual'. A value above (below) 50 means that the subject feels supranormal (subnormal) concerning a given item. *F* values are also noted.

Time (h)	Drowsy			Tired			Clumsy			Energetic		
	MDZ	Placebo	<i>F</i> value	MDZ	Placebo	<i>F</i> value	MDZ	Placebo	<i>F</i> value	MDZ	Placebo	<i>F</i> value
0	50	50	0.012	47	52	1	51	50	1	51	50	0.26
0.5	75	51	52.65***	73.5	49	17.72***	62	49	11.56*	33	49	20.41**
1	75	49	17.06**	68	50	13.14**	65	49	8.09*	36	50	6.56*
2	80	51	15.72**	72.5	52	14.82**	66	49	15.39**	34	52	7.95*
3	61	51	3.93	57	51.5	8.2	54.5	49	2.08	44	48	3.52
4	44	49	0.59	45	51	0.09	50	49	1.76	52	53	0.06

* $P < 0.05$ ** $P < 0.01$, *** $P < 0.001$.

Figure 2 Effects of placebo (on the left column of the figure) and midazolam (on the right) on spatio-temporal contrast sensitivity in healthy volunteers before (Figure 2a), 0.5 h after (Figure 2b) and 4 h after (Figure 2c) intramuscular injection. Contrast sensitivity is plotted as a function of spatial frequency (in cycles per degree) and temporal frequency (in Hz). Half an hour after the injection, midazolam resulted in an overall depression of the sensitivity surface. Four hours after the injection, the sensitivity surface remains significantly depressed, as compared with placebo, for spatial frequencies of 1 and 4 cpd associated to temporal frequencies of 0, 1 and 3 Hz.

Figure 3 Mean values of choice reaction time (expressed in milliseconds) from t_0 (pre-treatment) to t_4 (4 h after treatment) for midazolam (○) and placebo (●).

Choice reaction time

Midazolam increased overall choice reaction time (CRT), as compared with placebo ($F[1, 7] = 131$; $P < 0.001$). Average CRT across sessions was equal to 542 ms (s.d. = 225.5) for midazolam and to 357 ms (s.d. = 10.9) for placebo. For placebo, CRT was relatively stable across sessions (Figure 3). For midazolam, CRT increased maximally between t_0 and $t_{0.5}$ (from 328 to 912 ms, see Figure 3) and returned progressively to a 'normal' value from $t_{0.5}$ to t_4 (Figure 3). CRT was significantly increased at $t_{0.5}$, t_1 , and t_2 ($F[1, 7] = 175.26, 61.71, 30.26$, respectively; $P < 0.001$). At t_3 and t_4 , the difference in CRT between midazolam and placebo conditions was not significant.

Discussion

In this study on healthy volunteers, we evidenced that midazolam, which acts through the GABA A macromolecular complex, induced an overall loss in visual sensitivity lasting for more than 4 h. We also found that this effect evolved in time: the sensitivity deficit was maximal at $t_{0.5}$ (which corresponds to what is known about the kinetics of MDZ), and was followed by a progressive recovery of normal sensitivity from t_1 to t_4 (see Figure 1).

Concerning static sensitivity, we found that the contrast sensitivity to low spatial frequencies (0.25 cpd) was affected by midazolam for only 0.5 h after the injection ($t_{0.5}$). From t_1 to t_4 , visual sensitivity at 0.25 cpd was comparable with that induced by placebo. Spatial frequencies of 1 and 4 cpd led to decreased sensitivity, and 4 cpd tended to be more than 1 cpd. This result suggests that midazolam induced a decrease in contrast sensitivity to static stimulation, which was more pronounced in the domain of intermediate to high spatial frequencies.

Concerning motion sensitivity, midazolam affected

all tested temporal frequencies. However, we found that temporal frequency of 9 Hz with the spatial frequency of 4 cpd was relatively unaffected by midazolam. Moreover, 4 h after the injection, the temporal frequency of 9 Hz and the spatial frequency of 0.25 cpd were overall unaffected by the treatment, whereas temporal frequencies of 1 and 3 Hz associated with spatial frequencies of 1 and 4 cpd still resulted in decreased sensitivity. These results suggest that midazolam preferentially affected low temporal frequencies and intermediate to high spatial frequencies.

Half an hour after MDZ administration, we observed an overall decrease in visual sensitivity (except for the spatial frequency of 4 cpd modulated at 9 Hz), which might be principally related to non-sensory-specific effects. In fact, midazolam-induced sedation led to an increase in reaction time and was easily quantified by VAS, as previously demonstrated [34, 35]. It would be interesting to test other non-benzodiazepine sedatives on STCS in order to determine the effects of general CNS depression on STCS.

At subsequent testing times, the effects of midazolam on STCS depended on the spatial and temporal frequencies tested. Thus, the results cannot be simply related to sedation and were probably a specific set of effects. In fact, we observed fundamental differences between the effects of MDZ and those related to normal ageing [26] or apomorphine administration [28]. Normal ageing led to a deficit in static high spatial frequencies and drifting low spatial and temporal frequencies, and apomorphine administration (a reference dopaminergic agonist) led only to a decrease in sensitivity to moving low spatial frequencies, whereas MDZ led to a decrease in static high spatial frequencies and drifting high spatial and low temporal frequencies.

Moreover, pure sensitive effects have already been described with midazolam. Threshold amplitude for the perception of flickering light increases after oral midazolam. Median maximal changes from baseline were 360% (7.5 mg midazolam, 5 Hz) and 380% (7.5 mg midazolam, 30 Hz) [36]. These effects on visual perception are related to the effects of midazolam on benzodiazepine receptor- GABA A-chloride channel complexes, since midazolam-induced critical fusion frequency threshold alterations are reversed by flumazenil, a benzodiazepine receptor antagonist [37].

Our results can be compared with those obtained by Harris & Phillipson [24], who showed, using gratings with spatial frequencies from 0.5 to 8 cpd and temporal modulation of 8 Hz, that lorazepam induced a dose-related increase in the slope of the low-spatial frequency roll-off of the CS function. At 0.5 cpd, they demonstrated a dose-related sensitivity loss. However, these authors did not test low temporal frequencies, which were principally modified in our experiment.

Theoretically, midazolam may act on visual perception at different levels: sensitivity to light, sensitivity to spatial frequencies, sensitivity to temporal frequencies, and/or sensitivity to the combination of spatial and temporal frequencies (spatio-temporal contrast sensitivity).

The decrease in visual sensitivity corresponds to a decrease in the sensitivity to light. From the evaluation of electroretinograms in rats, it was concluded that

GABA decreased the sensitivity of the retina to light [38]. This is consistent with the results of our experiment which demonstrated a decrease in contrast sensitivity with midazolam.

Moreover, the effects of midazolam occurred for static and high spatial frequencies which might be related to an increase in the size of the receptive field in the visual system. In fact, the spatial arrangement of ON and OFF areas in receptive fields changes when GABA-mediated inhibition is removed [39]. Rose & Blakemore [40] showed that topical application of bicuculline, a GABA antagonist, reduced the sensitivity of visual cortex neurons and increased the size of their receptive fields.

Motion sensitivity was markedly affected by midazolam. This might be related to what is known about the involvement of GABAergic systems in the orientation and direction of motion selectivity in the visual system. This selectivity may occur in the retina [41], the lateral geniculate nucleus [42], and/or the visual cortex [39, 43]. Several lines of evidence suggest that the orientation and direction of motion sensitivity may be partially due to GABA inhibitory mechanisms in the retina [44] or the cortex [45]. These data suggest that GABAergic systems are involved in motion perception and direction selectivity all along the visual pathways rather than at a specific anatomical site.

Finally, midazolam principally reduced sensitivity to low temporal frequencies and intermediate to high static spatial frequencies. This suggests that midazolam might be principally active on a parvocellular retino-geniculo-cortical pathway, in which cells are pre-

dominantly sensitive to colour and shape, with high spatial and comparatively low temporal resolution [46, 47, 48]. Moreover, colour vision in vertebrates mediated by the parvocellular pathway, is also assumed to be related to GABA A receptors [49]. By contrast, we previously demonstrated that apomorphine preferentially reduced sensitivity to moving patterns at low spatial frequencies [28]. This result might be interpreted as a preferential involvement of the dopaminergic system in magnocellular pathways, which have broad band characteristics, with high sensitivity to contrast and temporal modulation, and mediate motion perception and stereopsis [48].

In conclusion, the pertinence of STCS has been demonstrated for a clinical pharmacological use. The sensitivity of the evaluation method to different drug doses [28], and its capacity to follow the action of a drug over time (this experiment) allows us to recommend STCS in the evaluation of a compound's action on the central nervous system. Furthermore, STCS reveals pharmacologically-induced perception alterations that standard evaluations (CRT, VAS) are not able to detect. Finally, these pharmacologically induced alterations are clinically significant, given the role of visual acuity and motion perception in the control of everyday visuo-spatial behaviours (e.g. catching and avoidance behaviours, locomotion, car driving).

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