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Report

GABA Shapes the Dynamics of Bistable Perception

Anouk M. van Loon,[1,2,5,*] Tomas Knapen,[1,2,5] H. Steven Scholte,[1,2] Elexa St. John-Saaltink,[1,3] Tobias H. Donner,[1,2,4,6] and Victor A.F. Lamme[1,2,6]

[1]Department of Psychology, University of Amsterdam, 1018 XA Amsterdam, the Netherlands

[2]Cognitive Science Center Amsterdam, University of Amsterdam, 1018 WS Amsterdam, the Netherlands

[3]Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen, 6500 HE Nijmegen, the Netherlands

[4]Bernstein Center for Computational Neuroscience, Charité-Universitätsmedizin Berlin, 10115 Berlin, Germany

Summary

Sometimes, perception fluctuates spontaneously between two distinct interpretations of a constant sensory input. These bistable perceptual phenomena provide a unique window into the neural mechanisms that create the contents of conscious perception [1]. Models of bistable perception posit that mutual inhibition between stimulus-selective neural populations in visual cortex plays a key role in these spontaneous perceptual fluctuations [2, 3]. However, a direct link between neural inhibition and bistable perception has not yet been established experimentally. Here, we link perceptual dynamics in three distinct bistable visual illusions (binocular rivalry, motion-induced blindness, and structure from motion) to measurements of gamma-aminobutyric acid (GABA) concentrations in human visual cortex (as measured with magnetic resonance spectroscopy) and to pharmacological stimulation of the $GABA_A$ receptor by means of lorazepam. As predicted by a model of neural interactions underlying bistability, both higher GABA concentrations in visual cortex and lorazepam administration induced slower perceptual dynamics, as reflected in a reduced number of perceptual switches and a lengthening of percept durations. Thus, we show that GABA, the main inhibitory neurotransmitter, shapes the dynamics of bistable perception. These results pave the way for future studies into the competitive neural interactions across the visual cortical hierarchy that elicit conscious perception.

Results

In bistable perceptual illusions, the contents of conscious perception fluctuate spontaneously in the face of constant sensory input. For instance, in motion-induced blindness, a moving mask causes a salient visual target to frequently disappear from conscious perception, only to reappear moments later. In this experiment, we used three bistable phenomena—binocular rivalry (BR), motion-induced blindness (MIB), and structure from motion (SFM)—to induce fluctuations in visual awareness (see Figures 1A–1C for full descriptions of these illusions).

Several models postulate that these bistable perceptual dynamics result from reciprocal inhibitory interactions between stimulus-selective neural populations in visual cortex [1–5]. If this is true, one may expect a central involvement of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in bistable perception. We used a computational model of these competitive neural interactions in visual cortex (Figure 1D; [3]) to derive specific predictions about the effect of GABAergic inhibition on the perceptual dynamics. Our model simulations show that stronger fast cortical inhibition (likely mediated by $GABA_A$ receptors in the cortex) should slow down perceptual dynamics, that is, induce longer durations of individual percepts and fewer alternations between distinct percepts (Figures 1E and 1F).

As a proxy of cortical inhibition, we measured GABA concentrations in human participants by means of magnetic resonance spectroscopy (MRS). We measured from a region encompassing retinotopic visual cortex (calcarine sulcus), which has been shown to be modulated during perceptual alternations in BR, MIB, and SFM [6–10]. We also measured from a high-level area, the right dorsolateral prefrontal cortex (DLPFC), which is thought to be involved in bistable perception [11, 12] (Figures 2A and 2B).

We observed significant correlations between GABA levels in visual cortex and perception for all three illusions. In line with the model predictions (Figures 1E and 1F), observers with higher GABA concentrations in visual cortex experienced slower perceptual dynamics (Figure 2C). There were no significant correlations for GABA in the DLPFC (see Table S2 available online). This highlights the specificity of the correlations found in visual cortex.

To further assess the specificity of our GABA results, we also measured "Glx": the combined concentration of glutamate and glutamine, a metabolite of glutamate. We found a significant negative correlation between visual Glx and SFM mean duration but no correlation with the other two phenomena (see Table S2).

In order to establish a second, complementary link between GABA and perceptual dynamics, we performed a separate pharmacological manipulation experiment. We stimulated $GABA_A$ receptors by means of systemic administration of lorazepam during MIB and SFM. We focused on MIB and SFM because observers experienced difficulties with binocular fusion under lorazepam, causing difficulties for the BR illusion. Lorazepam, compared to placebo, slowed down the perceptual dynamics of both SFM and MIB, lengthening percept duration and decreasing switch rate. Additionally, cumulative percept durations illustrate a lorazepam-induced increase in the prevalence of relatively long-lasting percepts (see Figures 3, S2, and S3). These pharmacological results are in line with our MRS results and the model predictions (Figures 1E and 1F).

Discussion

Here we show that GABA, the main inhibitory neurotransmitter, shapes the dynamics of conscious perception

[5]Co-first authors
[6]Co-senior authors
*Correspondence: anouk.vanloon@gmail.com

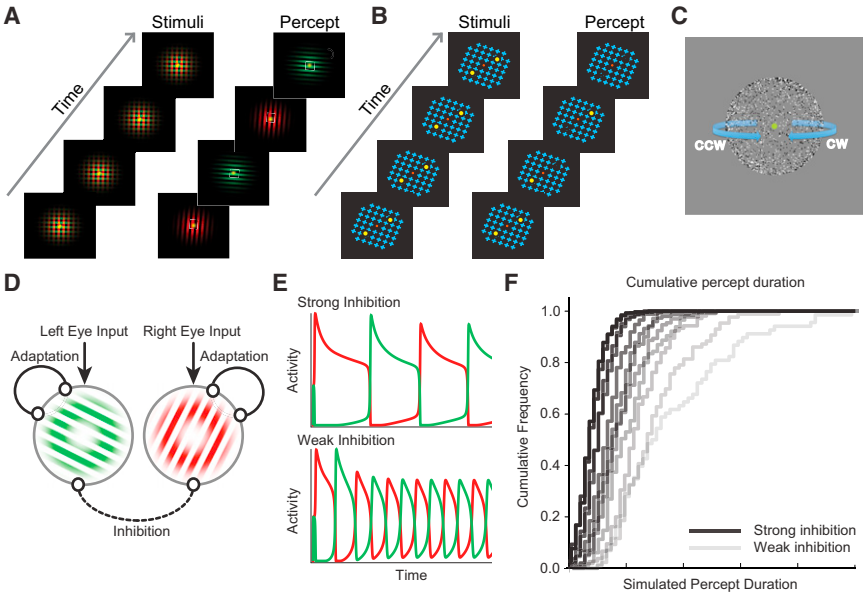

Figure 1. Bistable Visual Illusions and Neural Computational Model

(A) Binocular rivalry (BR): conflicting visual input to each eye cause observers to alternately perceive the left and right eye's images.

(B) Motion-induced blindness (MIB): a moving mask of blue crosses causes the highly salient yellow targets to transiently disappear from awareness.

(C) Structure from motion (SFM): a cloud of moving dots can be perceived as a sphere that rotates clockwise (CW) or counterclockwise (CCW) and causes spontaneous switches in perceived rotation direction.

(D) Neural computational model of bistability as reciprocal inhibition between competing visual cell assemblies [3].

(E) Simulations of the computational model with different levels of inhibition. Percept durations increase and alternation rate decreases with stronger inhibition.

(F) Cumulative percept duration histograms of model simulations for different levels of inhibition strength.

For details regarding the simulations, see Supplemental Experimental Procedures, Figure S1, and Table S1.

during perceptual bistability. As predicted by a computational model of the neural interactions underlying bistable perception, we demonstrate that higher GABA concentrations in visual cortex predict slower dynamics in perceptual bistability. We confirmed this role of GABA by pharmacologically manipulating GABAergic neurotransmission. Stimulation of $GABA_A$ receptors via the selective agonist lorazepam also slowed down the perceptual dynamics. Taken together, our results provide strong and complementary support for the mutual-inhibition account of perceptual bistability [1–5].

GABA-mediated inhibition is a generic property of cortical circuits, and many perceptual phenomena involve interactions between populations of excitatory and inhibitory neurons in the visual cortex [13–15]. Therefore, although a general role of visual cortical GABA concentration in perceptual phenomena would be expected, our present MRS results exhibit anatomical specificity (no effect for frontal cortex), chemical specificity (no or opposite effect for Glx), and task specificity (no effect of visual cortex GABA on a reaction time task; see Figure S2).

The present results are consistent with previous MRS studies and pharmacological manipulation using lorazepam. For example, GABA concentrations have been shown to correlate with visual psychophysical performance [16, 17] and evoked responses in visual cortex [18, 19]. Previous studies administering lorazepam showed reduced perceptual awareness [20] and reduced perceptual integration [21].

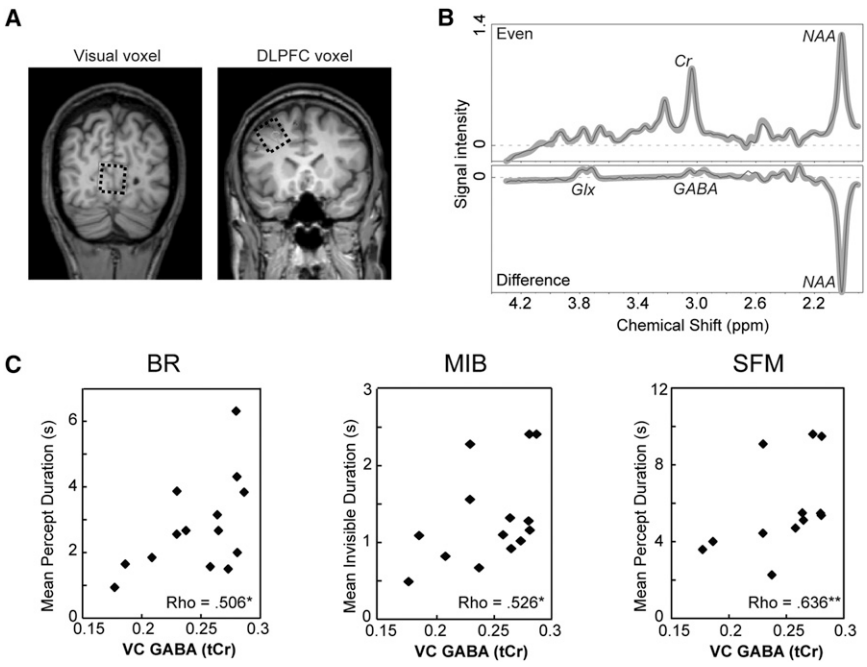

Figure 2. Spectroscopy Details and Correlations between Percept Duration and GABA Concentration in Visual Cortex

(A) MRS voxel locations: visual cortex (VC) voxel and right dorsolateral prefrontal cortex (DLPFC) voxel.

(B) Example spectrograph output for the even and difference acquisitions from the VC voxel.

(C) We calculated Spearman rank correlation coefficients (Rho) and used permutation testing (10,000 iterations) to test for significance: *$p < 0.05$; **$p < 0.01$. Higher GABA concentrations in visual cortex correlated with longer mean percept duration for BR, mean invisible duration for MIB, and mean percept duration for SFM. For detailed results, see Table S2.

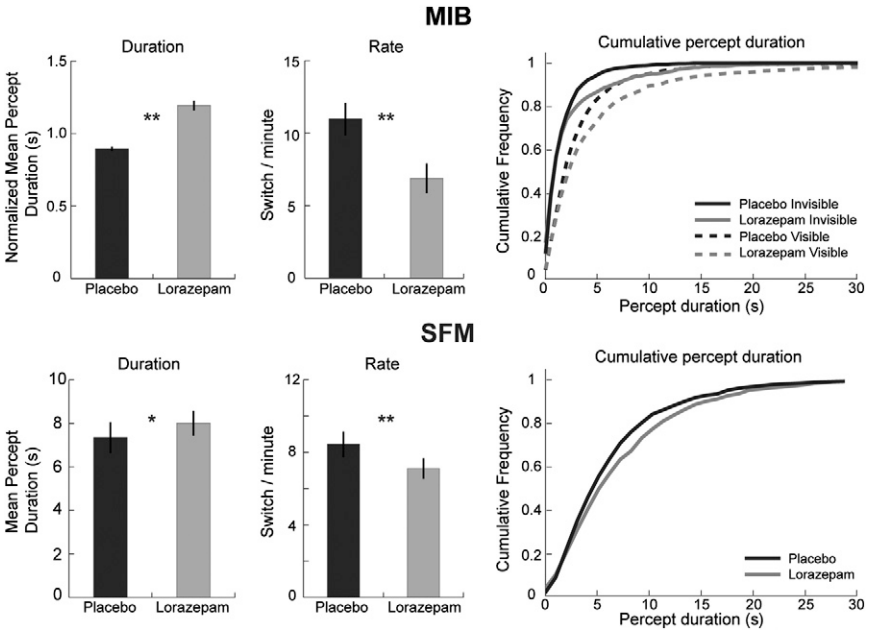

Figure 3. Effects of Lorazepam on Perceptual Dynamics for MIB and SFM

(MIB) During MIB, mean percept durations increase with lorazepam, whereas the switch rate drops compared to placebo. The cumulative percept duration histogram shows that both invisible and visible durations are prolonged relative to placebo.

(SFM) During SFM, we observed fewer switches and longer mean percept duration for lorazepam compared to placebo, as illustrated by the difference in cumulative percept duration histograms. Data are represented as means ± 1 SEM. *p < 0.05; **p < 0.01. For detailed results, see Figure S3.

It is important to note that MRS measurements reflect total GABA concentration and thus do not distinguish between $GABA_A$ and $GABA_B$ receptor functioning. However, in our pharmacological experiment we specifically manipulated the $GABA_A$ receptor with lorazepam, suggesting that this specific receptor is involved in our initial MRS findings. Additionally, inhibition in the computational model is instantaneous, which is more in line with the dynamics of $GABA_A$ receptors than of $GABA_B$ receptors. Further studies using both $GABA_A$ and $GABA_B$ receptor agonists and antagonists, possibly combined with MRS, might distinguish the relative roles of $GABA_A$ and $GABA_B$ receptors in bistable perception.

Different bistable illusions have many similarities in terms of their perceptual dynamics [22–24]. These similarities have prompted the assumption that they depend on common underlying mechanisms [3, 25]. The present results suggest that the dependence on GABAergic inhibition in visual cortex may be this generic mechanism.

Interestingly, MIB is unique in that the rate of perceptual fluctuations depends on both visible and invisible durations. In terms of underlying neural interactions, these different parameters (rate, visible duration, and invisible duration) seem to be governed by neural interactions at different levels of the visual cortical hierarchy (V1–V3 versus V4) [9]. Our visual MRS voxel captured mainly V1 and is unlikely to have sampled V4 GABA concentrations. We observed a correlation only between visual GABA and invisible duration, but not with rate (see Table S2). Furthermore, in our pharmacological intervention, lorazepam affected both the rate and visible duration, and to a lesser extent the invisible duration (see Figures S3A–S3D). This may be caused by the fact that the pharmacological manipulation exerts a systemic influence that encompasses V1 and V4, as well as other areas. Further research could test this directly by combining lorazepam administration and fMRI, or by using smaller MRS voxels to sample different levels in the visual hierarchy.

Evidence suggests that higher-level cortical association areas, such as posterior parietal cortex and frontal areas, also play a role in bistable perception. The nature of the role of these areas in perceptual dynamics is under debate [11, 12]. Frontal cortex could be involved in ways that are not expressed in GABA concentration. For instance, it might send excitatory (glutamatergic) feedback signals during bistable perception, which in turn bias the ongoing competition in visual cortex [26, 27], perhaps in concert with ascending neuromodulatory systems [28]. Regarding the role of parietal areas in bistable perception, continuous theta burst stimulation (cTBS) applied to the posterior intraparietal sulcus leads to longer percept durations in the SFM illusion [29]. Interestingly, independent findings show that cTBS increases GABA concentrations [30].

In summary, our MRS results link individual differences in the dynamics of conscious perception to the neurotransmitter systems that underlie these processes. We have confirmed this link by pharmacological manipulation of the $GABA_A$ receptor with lorazepam. Our results open new lines for further research into the relationship between neurotransmitter systems and the dynamics of conscious perception.

Experimental Procedures

MRS Experiment

Participants

Eighteen subjects (all males) reporting no history of psychiatric or neurological afflictions participated in the MRS visual illusion experiment. Female participants were excluded from our MRS sample, because cortical GABA levels vary during the menstrual cycle [31]. All subjects had normal or corrected-to-normal vision, had normal color perception, and gave written informed consent. Four participants were excluded from the analysis due to low signal-to-noise ratio in the MRS signal. All MRS analyses were based on the remaining fourteen participants (mean 22.71 years of age, SD 1.52 years; twelve participants for the SFM task, mean 22.58 years of age, SD 1.47 years). The experiment was approved by the University of Amsterdam Department of Psychology ethics committee.

Stimuli and Perceptual Tasks

Binocular Rivalry. The BR stimulus consisted of a superimposed orthogonal red-green grating (Figure 1A), modified from a stimulus used previously [11]. The stimulus rotated in a clockwise direction around a small yellow central fixation point at a speed of 1 Hz. Participants wore anaglyph glasses, which filtered the superimposed stimulus so that each eye was presented a monocular grating (i.e., each eye viewed a grating orthogonal in orientation and opposite in color). Participants indicated their percept by pressing and releasing the mouse buttons (left for green; right for red; no button while the grating was a mixture of red and green).

Motion-Induced Blindness. The MIB stimulus consisted of two yellow target dots presented on a moving mask of blue crosses (Figure 1B) on a black background, slightly modified from stimuli used in a previous study [10]. The target dots had a visual angle of 0.5° and subtended

2.5° of visual angle to the left and right of a small red central fixation point. The mask was a square grid measuring 17° of visual angle in width and length. This grid rotated around its center at a speed of 1 Hz. The direction of rotation was reversed after each block. In order to minimize effects of lateral masking and thus ensure pure MIB effects in driving target disappearance, the target was separated from the mask by a "protection zone" subtending about 2° around the target. Participants indicated their perception of each target separately, with the left and right target mapped onto corresponding mouse buttons (pressing a button indicated target disappearance; releasing indicated reappearance). In this way, duration of perceptual states was recorded separately for each target; these durations were subsequently collapsed across to capture MIB dynamics.

Structure from Motion. The SFM stimulus was a rotating sphere (sphere size 4.5°) that consisted of 1,850 black and white dots (dot size 0.011°) presented on an mean-luminance gray background, as used previously [32] (Figure 1C). A green fixation dot was presented in the center of the sphere. The sphere rotated 80°/s, and this rotation could either be perceived as clockwise (CW) or counterclockwise (CCW). Participants indicated spontaneous shifts in their perception by pressing and releasing mouse buttons (left for CW; right for CCW; no button when the direction was unclear). Observers are able to voluntarily control their perception of SFM. Therefore, on even-numbered blocks, participants were instructed to actively try to accelerate the alternations of perception. For this study, we pooled the data from both of these conditions to provide a robust measure of a participant's perceptual dynamics.

Procedure

The experiment consisted of two sessions. At the start of the first session, participants were screened and gave their written informed consent. In this first session, the visual illusions were presented. The BR and MIB illusions were presented in five 90 s blocks and the SFM illusion in ten 90 s blocks with short breaks in between. The stimuli were displayed on a 60 Hz, 32-bit iiyama Vision Master Pro 450 CRT monitor with a resolution of 1024 × 768 pixels, using Presentation (Neurobehavioral Systems), viewed at a distance of 100 cm. The order of presentation of the illusions was counterbalanced across participants. Participants were explicitly instructed to keep their gaze at fixation while attending to the illusions.

During a second session, which was between one and two months after the first session, a 3 T Philips Achieva MRI scanner (Philips Healthcare) with an eight-channel head coil was used to collect MRS measurements for each participant. A 3D turbo field echo acquisition (number of slices = 150; slice thickness = 1 mm; repetition time [TR] = 8.2 ms; echo time [TE] = 3.8 ms; field of view = 256 × 256 × 160 mm; matrix size = 256 × 256; voxel resolution = 1 × 1 × 1 mm) was used to place the spectroscopy voxels according to the individual's anatomical landmarks. The visual cortex (VC) voxel had a volume of 30 × 25 × 20 mm and was centered bilaterally on the calcarine sulcus (Figure 2A). The DLPFC voxel had a volume of 30 × 20 × 25 mm. The center was placed on the middle frontal gyrus, and the posterior border of the voxel was positioned anterior to the precentral sulcus (Figure 2A). Voxels were placed with care to exclude cerebral spinal fluid (CSF) from the ventricles or the cortical surface.

Edited ^{1}H J-difference spectra were acquired for each voxel using a GABA-specific sequence of the MEGA-PRESS method [33]. Scanning each voxel took approximately 12 min, during which time 384 transients were collected from each voxel; TE = 73 ms; TR = 2,000 ms. During the odd transients, a 15.64 ms sinc-center editing pulse (64 Hz full width at half maximum) was applied at 1.9 ppm and 4.6 ppm in an interleaved manner to specifically excite GABA and suppress water, respectively. During the MRS scan, participants viewed the same section of a movie without audio. The total MRS acquisition lasted approximately 1 hr.

Quantification of GABA

The MRS measurements allowed us to quantify the concentration of GABA and Glx (combined signal of glutamate and glutamine) from the VC and DLPFC. The even and the J-difference (odd-even) acquisitions were analyzed with the linear combination (LC)Model [34]. Total creatine (tCr) and N-acetyl aspartate (NAA) were quantified from the even acquisitions, and GABA, Glx, and again NAA were quantified from the difference acquisitions (Figure 2B). GABA and Glx were normalized to the difference-spectra NAA, and the even-spectra NAA was normalized to tCr. This procedure calibrated signal amplitude across even and difference acquisitions within each subject, enabling GABA and Glx concentrations to be expressed in units of tCr [33, 35]. The GABA and Glx concentrations were corrected for the proportion of gray-matter volume within each voxel, using FAST segmentations from the FSL toolbox [36].

Statistical Analysis

Percept durations shorter than 200 ms were removed from analysis. Visual GABA concentrations were correlated with mean and median percept durations for three illusions using nonparametric Spearman rank correlations. Because GABA and Glx concentrations correlated within the DLPFC voxel ($n = 14$, $r_s = 0.697$, $p = 0.006$) and not in the visual cortex voxel, we ran partial correlations to isolate the unique contribution of each neurotransmitter within the DLPFC [37]. Permutation tests were conducted with 10,000 iterations to test these correlations for significance. Our computational model provided specific predictions for the direction of the effects (Figure 1). Therefore, all reported analyses regarding the GABA concentration were tested one-sided.

Pharmacological Experiment

Participants

Fifteen subjects (four males and eleven females, mean 23.04 years of age, SD 2.36 years) participated in the pharmacological experiment. All subjects had normal or corrected-to-normal vision, had normal color perception, and gave written informed consent. Due to problems with the psychophysical setup, SFM results presented are based on 12 subjects. The experiment was approved by the University of Amsterdam Department of Psychology ethics committee.

Stimuli and Perceptual Tasks

Binocular Rivalry. We used the same stimulus as in the MRS experiment, but it was presented here via a stereoscope. However, this experiment revealed that participants experienced difficulties with binocular fusion under lorazepam. Therefore, we did not include these behavioral data.

Motion-Induced Blindness. The MIB stimulus was modified for the pharmacological experiment to induce longer disappearances of the target. The stimulus consisted of a mask made out of 9 × 9 white crosses, a target that was a Gabor patch (six cycles) with a visual angle of 2°, presented on a mean-luminance gray background. Only one target was presented, to simplify the task. The target was always centered on one of the visual field diagonals and was presented at a 5° visual angle from the fixation point, in one of the two lower visual quadrants. The quadrant containing the target was determined individually for each subject, to maximize target-invisible duration. Button presses and releases for target disappearances were counterbalanced.

Structure from Motion. We used the same stimulus as in the MRS experiment.

Procedure

The experiment consisted of two sessions (3.5 hr), with a minimum of one week in between. At the start of the first session, participants were screened for contraindications to the drug and gave their written informed consent. The drug, either a placebo (Plc) or a 1.5 mg lorazepam (Lzp) pill, was administered in a double-blind manner. Lorazepam is a short-acting benzodiazepine that at this dose produces functional potentiation in the $GABA_A$ receptors specifically. The order of the drug conditions was counterbalanced across sessions. Two hours after the drug intake, the tasks started.

The MIB illusion was presented for eight 2 min blocks, and there were four 2 min replay blocks. During the replay blocks, the target was physically removed from the display according to the temporal sequence of subjective disappearance as indicated by the subject during one of the preceding MIB blocks. The BR illusion was presented for five 90 s blocks, and the SFM illusion consisted of ten 90 s blocks. The stimuli were displayed on a 85 Hz, 32-bit LaCie Electron Blue 4 CRT monitor with a resolution of 1024 × 768 pixels, using Presentation (Neurobehavioral Systems), viewed at a distance of 50 cm with the use of a chin rest. During both MIB and SFM, we recorded eye movements with an EyeLink 1000 Desktop Mount eye tracker (SR Research) at 1 kHz to verify that participants maintained fixation. The order of the tasks was counterbalanced across participants.

At four points during the session (start, 2 hr after drug administration, between tasks [2.75 hr], and end [3.5 hr]), participants filled in a set of five visual analog scales to measure the sedative effects of the drug. The mean score of these scales (length 100 mm) assessed complementary aspects of sedation (alert/drowsy, excited/calm, clear-headed/muzzy, energetic/lethargic, and quick/slow), where a high value indicates that participants feel subjectively more sedated [38]. For results, see Figure S3H.

Statistical Analysis

Paired-sampled t tests were performed on the switch rate and percept durations between the lorazepam and placebo condition. Percept durations shorter than 200 ms were removed from analysis. For MIB, the visible and invisible percept durations were normalized (visible and invisible separately) per subject based on the average duration for the two drug conditions

(lorazepam and placebo) combined. These values were separated based on drug conditions and then combined across visible and invisible percept types. Our computational model provided specific predictions for the direction of the effects (Figures 1E, 1F, and S1). Therefore, all reported analyses regarding the pharmacological intervention were tested one-sided.

Neural Model

We implemented a neural model of bistability [3], in which both adaptation and inhibition govern the activity dynamics of two interacting visual cell assemblies (Figure 1D; for a more detailed description, see Supplemental Experimental Procedures, Figure S1, and Table S1). Simulations were run using a fixed-step-size integration procedure implemented in the GNU Scientific Library and were run in Python (see Figures 1E and 1F).

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures, three figures, and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.03.067.

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