Behavioral/Cognitive

GABAergic Inhibition Gates Perceptual Awareness During Binocular Rivalry

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Binocular rivalry is a classic experimental tool to probe the neural machinery of perceptual awareness. During rivalry, perception alternates between the two eyes, and the ebb and flow of perception is modeled to rely on the strength of inhibitory interactions between competitive neuronal populations in visual cortex. As a result, rivalry has been suggested as a noninvasive perceptual marker of inhibitory signaling in visual cortex, and its putative disturbance in psychiatric conditions, including autism. Yet, direct evidence causally implicating inhibitory signaling in the dynamics of binocular rivalry is currently lacking. We previously found that people with higher GABA levels in visual cortex, measured using magnetic resonance spectroscopy, have stronger perceptual suppression during rivalry. Here, we present direct causal tests of the impact of GABAergic inhibition on rivalry dynamics, and the contribution of specific GABA receptors to these dynamics. In a crossover pharmacological design with male and female adult participants, we found that drugs that modulate the two dominant GABA receptor types in the brain, $GABA_A$ (clobazam) and $GABA_B$ (arbaclofen), increase perceptual suppression during rivalry relative to a placebo. Crucially, these results could not be explained by changes in reaction times or response criteria, as determined through rivalry simulation trials, suggesting a direct and specific influence of GABA on perceptual suppression. A full replication study of the $GABA_B$ modulator reinforces these findings. These results provide causal evidence for a link between the strength of inhibition in the brain and perceptual suppression during rivalry and have implications for psychiatric conditions including autism.

Key words: awareness; binocular rivalry; GABA; inhibition; perception; pharma

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Significance Statement

How does the brain accomplish perceptual gating? Here we use a direct and causal pharmacological manipulation to present insight into the neural machinery of a classic illusion of perceptual awareness: binocular rivalry. We show that drugs that increase GABAergic inhibition in the brain, clobazam ($GABA_A$ modulator) and arbaclofen ($GABA_B$ modulator), increase perceptual suppression during rivalry relative to a placebo. These results present the first causal link between GABAergic inhibition and binocular rivalry in humans, complementing classic models of binocular rivalry, and have implications for our understanding of psychiatric conditions, such as autism, where binocular rivalry is posited as a behavioral marker of disruptions in inhibitory signaling in the brain.

Introduction

Perception is often at odds with retinal input. Even highly salient stimuli are sometimes "edited out" of our perceptual experience,

particularly when they are in conflict with probable interpretations of the external environment. How does the brain accomplish such acute and effective perceptual suppression?

Binocular rivalry is a classic test of perceptual suppression. During rivalry, two images, one presented to each eye, vie for perceptual awareness (Leopold and Logothetis, 1996; Tong et al., 2006; Xu et al., 2016). This alternation in perception is modeled to rely on the strength of inhibitory interactions between competitive neuronal populations in visual cortex (Fig. 1A). Specifically, the strength with which an image is suppressed from awareness is thought to be governed by reciprocal inhibition across neuronal populations coding for each eye's percept at multiple stages of visual processing (Blake, 1989; Laing and Chow,

A Binocular Rivalry Reciprocal Inhibition Model
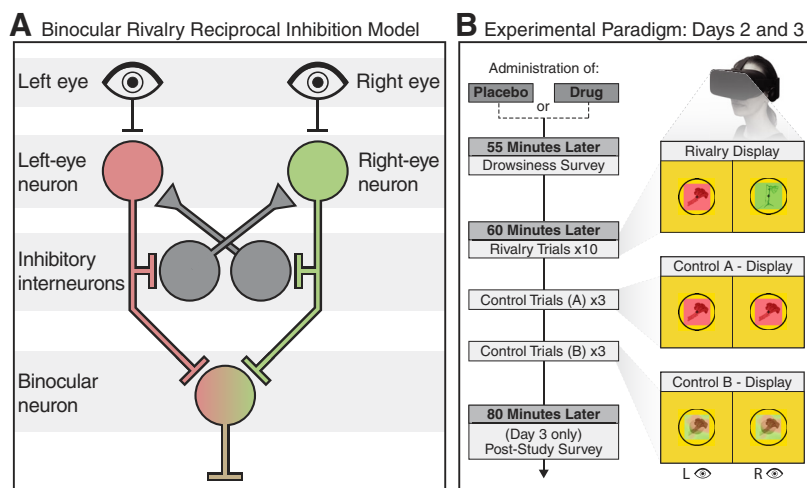

B Experimental Paradigm: Days 2 and 3

Figure 1. Binocular rivalry model and experimental paradigm. *A*, Schematic model of rivalry circuitry. During binocular rivalry, two images, one presented to each eye, alternate back and forth in awareness. This perceptual experience is hypothesized to reflect the activity of competing pools of left-eye and right-eye neurons, which cross-inhibit each other in alternation, presumably via inhibitory interneurons. The strength of cross-inhibition is hypothesized to govern the strength with which an image is suppressed from awareness. *B*, Participants took part in a double-blind crossover design study to test the effect of drugs which increase GABAergic inhibition on perceptual suppression during rivalry. After an initial study visit (Day 1; see Materials and Methods), participants returned for two experimental testing days (Day 2 and Day 3). On each experimental day, participants were first administered either a drug or a placebo pill. Subsequently, participants began experimental testing, completing binocular rivalry and control rivalry simulation trials (see Materials and Methods; Movies 1, 2). Control A trials provided us with an estimate of participants' motor response latencies (how quickly they press and release a button in response to a stimulus change on the screen). Control B trials provided us with an estimate of participants' perceptual decision criteria (the percentage mixture of a stimulus for a participant to report either a mixed or a dominant percept).

2002; Noest et al., 2007; Seely and Chow, 2011; Said and Heeger, 2013; van Loon et al., 2013; Li et al., 2017). Models of rivalry consequently predict that increasing inhibition will increase the strength of perceptual suppression (Klink et al., 2010; Said et al., 2013), decreasing the proportion of rivalry periods where one of the two images is not fully suppressed from awareness (mixed percepts). Magnetic resonance spectroscopy (MRS) data support this prediction: individuals with higher tonic levels of the inhibitory neurotransmitter, GABA, in early visual cortex show increased perceptual suppression during rivalry (Robertson et al., 2016) and shorter dominant percept durations (van Loon et al., 2013; Pitchaimuthu et al., 2017). Further, the dynamics of two other bistable phenomena that are often thought of as computationally related to rivalry (but see Gallagher and Arnold, 2014; Brascamp et al., 2018), motion-induced-blindness and structure-from-motion, have been shown to causally depend on the strength of inhibition in the brain using a pharmacological manipulation (van Loon et al., 2013) and to correlate with GABA levels in visual cortex (but see Sandberg et al., 2016). Despite these results, however, direct causal evidence linking GABAergic inhibition to binocular rivalry dynamics is currently lacking. Further, the specific branches of the GABAergic pathway that might contribute to rivalry dynamics are currently unknown.

Identifying a causal link between inhibition and binocular rivalry holds translational implications for psychiatric research, given recent observations of altered binocular rivalry dynamics in psychiatric conditions, such as autism (Robertson et al., 2013, 2016; Freyberg et al., 2015). Specifically, individuals with autism evidence weaker perceptual suppression during rivalry and slower switch rates (Robertson et al., 2013, 2016; Freyberg et al., 2015). Magnetic resonance spectroscopy evidence suggests that this replicated difference in rivalry dynamics may stem from a

disruption in GABAergic signaling in the autistic brain (Robertson et al., 2016). This hypothesis is consistent with animal-level findings with genetic models of autism, which suggest that disruptions in inhibitory signaling may characterize the autistic brain (Shao et al., 2003; Ma et al., 2005; Fatemi et al., 2009; Gogolla et al., 2009; Sanders et al., 2011; Griswold et al., 2012; Piton et al., 2013; Chen et al., 2014; Orefice et al., 2016; but see Antoine et al., 2019), as well as rivalry model simulation results, which predict that weakening inhibition in the brain would weaken perceptual suppression during rivalry (Klink et al., 2010; Said et al., 2013). Together, this literature suggests that rivalry may index disruptions in inhibitory signaling in visual cortex in autism. But causal evidence linking GABAergic inhibition to rivalry in humans is currently lacking.

Here, we tested whether increasing GABAergic inhibition in the brain strengthens perceptual suppression during rivalry in humans using a randomized, double-blind crossover pharmacological design. We further examined whether specific branches of the GABAergic pathway support rivalry by directly comparing the impact of drugs that target the two dominant GABA receptor types in the brain, GABA$_A$ and GABA$_B$, on rivalry dynamics. In a subsequent replication study, we tested the impact of GABA$_B$ on rivalry in an independent sample of participants.

Materials and Methods

Participants. Healthy adult individuals participated in three studies [Study 1: $N = 21$; Study 2: $N = 22$; Study 3 (replication study): $N = 22$; Table 1]. Written consent was obtained from all participants, and all studies were approved by the Massachusetts Institute of Technology Institutional Review Board. All participants had normal or corrected-to-normal vision, were neither pregnant nor nursing, and were free from: (1) any known history of psychiatric or neurological conditions; (2) any other diagnosed medical conditions, including a history of heart failure; (3) any psychiatric medications; and (4) any known drug allergies (including clobazam or arbaclofen). All studies took place at the MIT Clinical Research Center, under the constant observation of a research nurse/nurse practitioner (C.R.) and nursing team. Because of the experimental nature of the drug used in Studies 2–3, arbaclofen, which is currently classified as an Investigational New Drug by the FDA, this study was monitored by an external drug safety monitor from Tufts Medical Center.

Study drugs: clobazam (GABA$_A$) and arbaclofen (GABA$_B$). Participants participated in three different studies, investigating the effects of: Study 1, a GABA$_A$ modulator (clobazam, 5 mg); Study 2, a GABA$_B$ modulator (arbaclofen, 20 mg); Study 3, a GABA$_B$ modulator (arbaclofen, 20 mg; replication of Study 2) on binocular rivalry dynamics. Clobazam is an FDA-approved GABA modulator, which engages GABA$_A$ receptors at the 1,5-benzodiazepine site (Hanks, 1979). Arbaclofen (also known as R-baclofen or STX209) is an investigational new drug that engages GABA$_B$ receptors as a GABA analog (Hill and Bowery, 1981), and is the (R)-enantiomer of baclofen. Clobazam dosage was chosen to fall within the standard dose prescribed range and arbaclofen dosage was determined based on previous studies in children with fragile X (Berry-Kravis et al., 2012, 2017).

Table 1. Psychometric data from all participants including age, Autism Quotient (AQ) score, KBIT-2 spatial reasoning IQ score, and gender

	Minimum	Maximum	Mean	SD
Study 1 (GABA$_A$) clobazam vs placebo, $N = 21$				
Age	18	34	23.24	4.300
IQ	102	132	124.71	9.804
AQ	7	30	18.19	6.593
Gender	8:M	13:F		
Study 2 (GABA$_B$) arbaclofen vs placebo, $N = 22$				
Age	20	31	23.36	3.317
IQ	55	132	119.27	16.861
AQ	8	30	19.45	5.431
Gender	8:M	14:F		
Study 3 (GABA$_B$) arbaclofen vs placebo replication, $N = 22$				
Age	18	40	25.00	5.912
IQ	70	132	114.59	14.851
AQ	5	26	15.95	6.425
Gender	9:M	13:F		

Experimental design: double-blind placebo-controlled crossover design. Each study took place 3 d: a health assessment/practice session (Day 1) and 2 experimental days (Days 2 and 3). On each of the experimental days, a participant was given either a drug or a placebo and participated in a short binocular rivalry experiment after the drug had come into effect (Fig. 1B). This within-participant crossover design allowed us to compare the effects of each drug, relative to those of a placebo, on rivalry dynamics. In Study 3, we conducted a direct replication of the double-blind crossover design of Study 2 with an independent sample of participants.

On Day 1, participants were briefed on the study and completed an informed consent. Once consented, the nurse practitioner (NP) assessed the participant for drug allergies, reviewed the participant's medical history, and completed a routine physical assessment (including blood pressure, temperature, and a basic metabolic panel to assess kidney function) to ensure that participants were healthy enough to participate in the study. Participants were also assessed for colorblindness. All women of childbearing ages were asked to provide a small urine specimen for a urine pregnancy point of care test to confirm non-pregnancy state. Participants also performed six 45 s rivalry practice trials to become familiarized with the task.

On Days 2 and 3 of testing, each participant received an oral dose of a drug on one day and a matched placebo pill on the other day. Drug day assignment was blinded, randomized, and counterbalanced across participants (i.e., in Study 1, one-half of the participants received a placebo on Day 2 and clobazam on Day 3, whereas the other half received clobazam on Day 2 and a placebo on Day 3). After waiting for a time period to allow for drug absorption and distribution to approximate peak-plasma concentration (60 min; Volz and Kellner, 1980), the participants completed a brief drowsiness scale and performed the binocular rivalry experiment.

Following testing on both Days 2 and 3, the NP performed a physical assessment for adverse events to ensure that each participant was in sufficient health to leave the Clinical Research Center. Additionally, on Day 3, participants answered a series of survey questions regarding their first-person reflections on their rivalry dynamics during the study.

Experimental paradigm. Testing sessions were composed of two blocks of five 45 s experimental runs (binocular rivalry), and six 45 s rivalry stimulation control trials (3 "sudden onset" trials and 3 "gradual onset" trials). During rivalry trials, two different images (red or green) were presented to participants' left and right eyes. During rivalry simulation trials, identical images were continuously presented to both eyes, alternating temporally on the screen (Movies 1, 2). Participants were asked to continuously report whether they perceived a fully dominant percept, the red image (right key) or the green image (left key), or a mixture of the two images (up key). Percept durations as well as switch rates were analyzed during rivalry and simulation trials.

Binocular rivalry experiment: stimuli and analysis. Binocular rivalry stimuli and analysis were identical to those used in our previously pub-
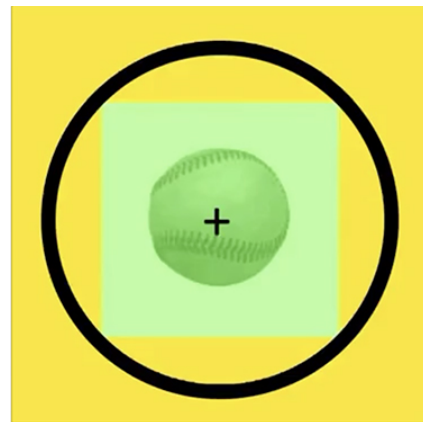
Movie 1. Example of rivalry simulation control trials (sudden transitions, Control A). Participants viewed stepwise, sudden transitions between two stimuli, which allowed us to determine response latencies to clear, obvious transitions. The rate of these transitions followed rivalry transitions from a previous study using the same stimuli (Robertson et al., 2013).
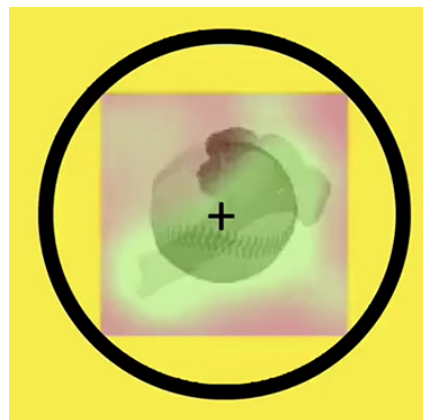
Movie 2. Example of rivalry simulation control trials (gradual transitions, Control B). Gradual transition trials provided us with an estimate of participants' perceptual decision criteria: the extent of image blending each individual required to identify an image as mixed versus dominant. Participants viewed gradual, linear transitions between stimuli created using a series of dynamic Gaussian image filters. Specifically, during a transition, the proportion of either dominant image displayed at any pixel was determined by 15 Gaussian filters, which were distributed randomly within the image. As in Control A, the rate of these transitions followed rivalry transitions from a previous study using the same stimuli (Robertson et al., 2013).

lished studies (Robertson et al., 2013, 2016), except that the stimuli were slightly larger to avoid possible ceiling effects by increasing the expected incidence of mixed percepts (Blake et al., 1992). On each run, two grayscale objects (e.g., a baseball and a piece of broccoli) appeared on the left and right of the screen. Stimuli were drawn from the Bank of Standardized Stimuli (Brodeur et al., 2014) and the subset of stimuli used in our study can be viewed at https://osf.io/bhgyd. Each object was displayed within a tinted square (green or red; width: 5.3°), surrounded by a black circle to support binocular fusion (radius: 3.7°). Participants were instructed to fixate on a cross at the center of each image. Stimuli were viewed through a head-mounted display (Oculus Rift CV1; 1080 × 1200 pixels per eye, 90 Hz refresh rate, FOV = 110°), which displayed the left and right halves of the screen to the participants' left and right eyes such that each eye was presented with only one of the two images (red or green; Fig. 1B). Data, materials, and code are available upon request.

Keypresses were sampled every 4 ms, and a sequence of perceptual events was later computed based on when one continuous key press was terminated and another began. Keypresses lasting <400 ms or periods where no key was pressed were omitted from the analysis. For each participant and trial, the frequency of perceptual transitions as well as the duration of any perceptual event (red, green, or mixed) were calculated. Transitions were subdivided into two classes: "switches" (e.g., red to mixed to green) or "reversions" (e.g., red to mixed to red). Participants were instructed to initiate each trial by pressing and holding down the up key until they first saw a dominant percept (red or green). This initial keypress corresponding to "onset rivalry" (Stanley et al., 2011) was not considered in the analysis. Including short keypresses or onset rivalry periods did not qualitatively affect the results.

Rivalry simulation trials: paradigm and analysis. Binocular rivalry simulation trial stimuli were identical to those used in the main rivalry experiment, and the paradigm was identical to our previously published studies (Robertson et al., 2013; Movies 1 and 2). In brief, participants viewed a simulated series of back-and-forth binocular rivalry alternations as in (Baker and Graf, 2009; Robertson et al., 2013). The stimuli were presented using exactly the same setup and stimulus parameters as in the rivalry trials but, unlike rivalry, identical images were continuously presented to both eyes, presented in temporal back-and-forth alternation on the screen for the duration of the trial. Thus, in these trials, we measured participants' responses to physical changes in the stimuli, rather than perceptual changes associated with binocular rivalry.

These trials allowed us to measure two non-perceptual factors which could, in theory, contribute to any observed drug effects on rivalry: response latencies (Control A) and response criteria (Control B). In sudden-onset trials (Control A), participants viewed stepwise, sudden transitions between two stimuli, which allowed us to determine response latencies to clear, obvious transitions. In gradual-onset trials (Control B), participants viewed gradual, linear transitions between stimuli created using a series of dynamic Gaussian image filters. Specifically, during a transition, the proportion of either dominant image displayed at any pixel was determined by 15 Gaussian filters, which were distributed randomly within the image. This allowed us to determine participants' response criteria: the extent of image blending each individual required to identify an image as mixed versus dominant.

In all control trials, the presentation durations of on-screen events (dominant or mixed on-screen images) were based on data from a previous rivalry study in our laboratory (Robertson et al., 2013). Specifically, we took all percept durations reported in that previous study, created a distribution of percept durations for each percept type, and randomly drew from this distribution to create a simulated series of back-and-forth rivalry alternations. We clipped this duration distribution to eliminate extreme values to ensure that participants had ample time to report each event, and to allow for sufficient back-and-forth alternations. In sudden onset (Control A) trials, the mean presentation duration of on-screen events was 1.96 s, ± 0.69 SD (min: 1 s, max: 3 s). From event onset, 2 s was allocated for the correct response to occur (left or right key). To ensure the response corresponded to the event in question, only correct button presses were logged. If no correct button press occurred within that time frame (<1% of events), no button press was logged. Similarly, in gradual onset (Control B) trials, the mean duration of mixture transitions was 1.85, ± 1.02 SD (min: 0.51 s, max: 4.99 s). To ensure the response corresponded to the transition event in question, only correct button presses that occurred during the on-screen transition were logged. If no correct button press occurred within that time frame (<2% of events), no button press was logged.

Perceptual suppression metric. Perceptual suppression during rivalry is experienced by the viewer as an increased proportion of dominant percepts, compared with mixed percepts. Thus, the primary measure of interest, the proportion of perceptual suppression, was calculated as the proportion of each trial spent viewing a fully dominant percept: (dominant percept durations)/(dominant + mixed percept durations).

Statistical analyses. Data reported in all ANOVAs was normally distributed (Shapiro–Wilk test; all $p > 0.359$). Two-tailed, uncorrected p values are reported for all repeated-measures ANOVAs and spearman's rank correlation coefficients (Rs) are reported for all effects. For each partici-

pant, trials where rivalry was never initiated (one percept was reported for the entire trial) were eliminated. Participants missing >50% of trials or whose rivalry percept durations were determined to fall outside of 2 SD of the group mean were excluded from analyses (Study 1: 4 individuals; Study 2: 4 individuals; Study 3: 3 individuals). One participant in Study 2 was excluded due to drowsiness, and one participant in Study 3 was excluded due to extreme dizziness after drug administration. After removing outliers, Study 2 was no longer counterbalanced for study day. To account for this, we conducted *post hoc* analyses, where we re-ran our main ANOVAs described below, including "study day" as a covariate in our analysis. All reported results remained significant at $p < 0.01$.

Psychometric tests and surveys. Immediately before each rivalry session, participants completed the Karolinska sleepiness scale (KSS) to assess any self-reported changes in drowsiness between drug and placebo testing sessions. The KSS consisted of a single question, "Choose the position on the following scale that best describes your current state", where answers ranged from 1 (extremely alert) to 9 (very sleepy, great effort to keep awake, fighting sleep). Participants also completed the Autism Quotient and a brief spatial reasoning IQ test, the KBIT-2 (Kaufman, 1990; Table 1).

After the final testing session on Day 3, participants completed a post-study survey to assess: (1) "On which day do you think you received the drug and why?", (2) "Did you notice any differences in your experience of binocular rivalry between yesterday and today? If so, please describe.", (3) "How confident were you in determining whether you were seeing a mixture or a dominant state?", and (4) "Describe what mixtures during binocular rivalry look like to you."

Results

We predicted that drugs that increase inhibition in the brain (GABA$_A$ modulator, clobazam, and GABA$_B$ modulator, arbaclofen) would increase perceptual suppression during rivalry. We directly compared these effects to rivalry simulation control trials to assess whether any observed changes were due to non-perceptual effects on response latencies or response criteria (Gallagher and Arnold, 2014; Brascamp et al., 2018). Finally, we conducted a direct replication study to test the repeatability of our main effects using the GABA$_B$ agonist, arbaclofen.

GABA modulators strengthen perceptual suppression

To quantify the effect of each drug on rivalry dynamics, we used a repeated-measures ANOVA, including Drug Condition (Drug vs Placebo) as a within-subjects factor for each study (Study 1: clobazam; Study 2: arbaclofen). As predicted, individuals reported a higher proportion of perceptual suppression on the drug, compared with the placebo day in both studies (Clobazam vs Placebo: $F_{(1,16)} = 5.237$, $\eta_p^2 = 0.247$, $p = 0.036$. Arbaclofen vs Placebo: $F_{(1,16)} = 6.578$, $\eta_p^2 = 0.291$, $p = 0.021$; Figs. 2A, 3A). In Study 1 (clobazam), this effect was driven by reduced time in mixed percepts on the drug compared with the placebo day per trial ($F_{(1,16)} = 6.336$, $\eta_p^2 = 0.284$, $p = 0.023$); no change to dominant percepts was observed ($F_{(1,16)} = 0.593$, $\eta_p^2 = 0.036$, $p = 0.453$). In Study 2 (arbaclofen), this effect was driven by increased time in dominant percepts on the drug compared with the placebo day per trial ($F_{(1,16)} = 7.647$, $\eta_p^2 = 0.323$, $p = 0.014$) and slightly reduced time in mixed percepts ($F_{(1,16)} = 3.181$, $\eta_p^2 = 0.166$, $p = 0.093$). In Study 3 (arbaclofen replication), we again observed a higher proportion of perceptual suppression on the drug compared with the placebo days ($F_{(1,17)} = 5.145$, $\eta_p^2 = 0.232$, $p = 0.037$), which was driven by increased time in dominant percepts on the drug compared with the placebo day (Dominant percepts: $F_{(1,17)} = 5.077$, $\eta_p^2 = 0.230$, $p = 0.038$; Mixed percepts: $F_{(1,17)} = 1.238$, $\eta_p^2 = 0.068$, $p = 0.281$; Fig. 4A).
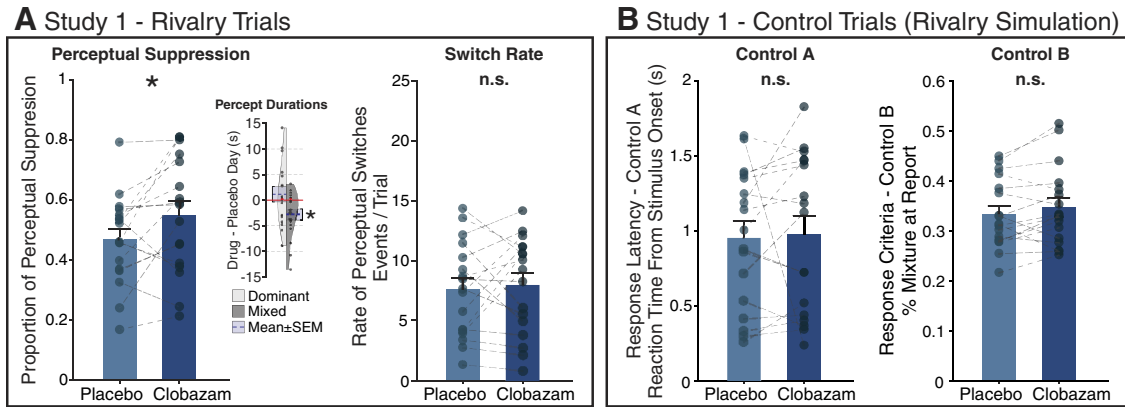
Figure 2. Study 1, $GABA_A$ modulator results. **A**, As predicted, perceptual suppression increased on clobazam compared with placebo days ($F_{(1,16)} = 5.237$, $\eta_p^2 = 0.247$, $p = 0.036$). No effect on switch-rate was observed ($F_{(1,16)} = 0.230$, $\eta_p^2 = 0.014$, $p = 0.638$). **B**, Critically, rivalry simulation trials were unaffected by the drug manipulation: neither response latencies to detect sudden image transitions ($F_{(1,16)} = 0.033$, $\eta_p^2 = 0.002$, $p = 0.858$) nor response criteria to judge a gradually changing image as mixed vs dominant ($F_{(1,16)} = 2.516$, $\eta_p^2 = 0.136$, $p = 0.132$) were changed by clobazam compared with the placebo. In all plots, error bars represent 1 SEM. *$p < 0.05$, n.s. $p > 0.05$ difference between the conditions.
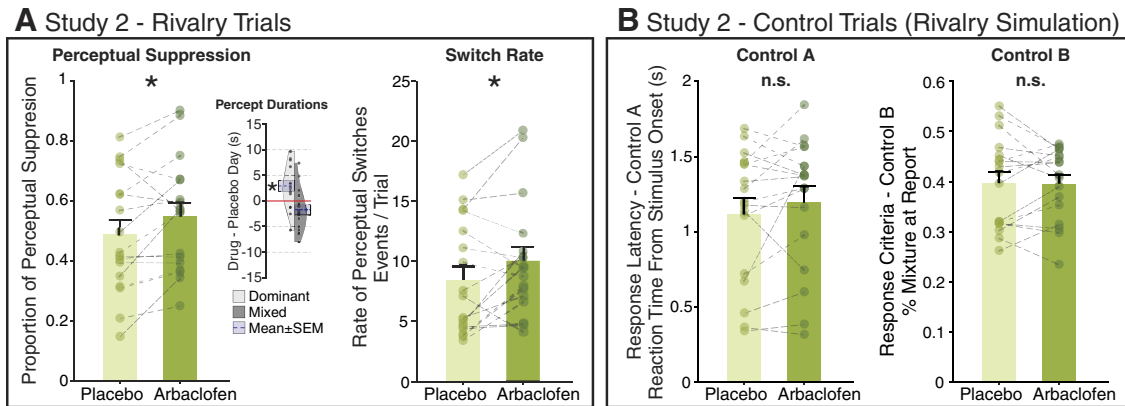

Figure 3. Study 2, $GABA_B$ modulator results. **A**, Again, as predicted, perceptual suppression increased on arbaclofen compared with placebo days ($F_{(1,16)} = 6.578$, $\eta_p^2 = 0.291$, $p = 0.021$). Arbaclofen also modestly increased perceptual switch-rates during rivalry ($F_{(1,16)} = 4.909$, $\eta_p^2 = 0.235$, $p = 0.042$). **B**, Critically, rivalry simulation trials were unaffected by the drug manipulation: neither response latencies to detect sudden image transitions ($F_{(1,16)} = 1.529$, $\eta_p^2 = 0.087$, $p = 0.235$), nor response criteria to judge a gradually changing image as mixed versus dominant ($F_{(1,16)} = 0.002$, $\eta_p^2 = 0.001$, $p = 0.884$) significantly differed between arbaclofen and placebo days. In all plots, error bars represent 1 SEM. *$p < 0.05$, n.s. $p > 0.05$ difference between the conditions.
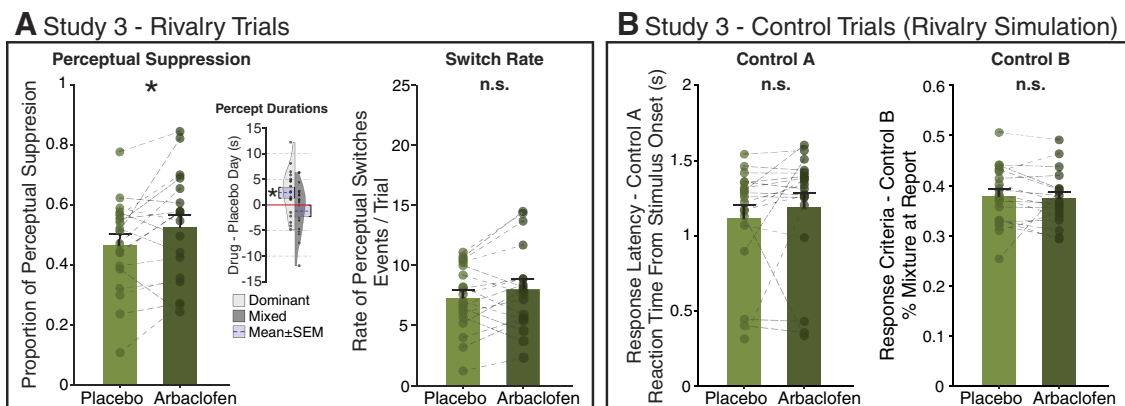

Figure 4. Study 3, $GABA_B$ modulator replication results. **A**, Perceptual suppression increased on arbaclofen compared with placebo days, replicating our predicted and previous effects ($F_{(1,17)} = 5.145$, $\eta_p^2 = 0.232$, $p = 0.037$). However, arbaclofen did not increase perceptual switch-rates during rivalry ($F_{(1,17)} = 4.940$, $\eta_p^2 = 0.122$, $p = 0.142$). **B**, Critically, rivalry simulation trials were unaffected by the drug manipulation: response latencies ($F_{(1,17)} = 0.069$, $\eta_p^2 = 0.004$, $p = 0.796$) and response criteria ($F_{(1,17)} = 0.214$, $\eta_p^2 = 0.012$, $p = 0.649$). In all plots, error bars represent 1 SEM. *$p < 0.05$, n.s. $p > 0.05$ difference between the conditions.

Drug effects on perceptual suppression are stable across experimental time course

To test whether the strength of our effects grew or waned as a function of time, we first split our data to compare the first and second halves of trials in our experiment (Trials 1–5 and Trials 6–10). Next, we calculated the drug effect on the proportion of suppression for each individual (Proportion of Suppression on Drug − Placebo days) in each half of the data and conducted a repeated-measures ANOVA on Drug Effect with Time as a within-subjects measure. No main effect of Time was observed for our arbaclofen studies: Study 1 ($F_{(1,16)} = 0.18$, $p = 0.676$) or Study 3 ($F_{(1,17)} = 1.33$, $p = 0.264$). For Study 2, a trend toward an increase in the drug effect was observed ($F_{(1,15)} = 4.27$, $p = 0.056$), although this effect did not reach significance.

No reliable effects on switch rates

Neither GABA modulator reliably affected switch rates during rivalry. In Study 1, no effect on switch-rate was observed for the $GABA_A$ modulator, clobazam (Clobazam: 8.03 ± 1.01 SE switches; Placebo: 7.62 ± 0.99 SE switches, $F_{(1,16)} = 0.230$, $\eta_p^2 = 0.014$, $p = 0.638$; Fig. 2A). In Study 2, the $GABA_B$ agonist, arbaclofen, modestly increased perceptual switch rates during rivalry (Arbaclofen: 10.07 ± 1.22 SE switches; Placebo: 8.48 ± 1.17 SE switches, $F_{(1,16)} = 4.909$, $\eta_p^2 = 0.235$, $p = 0.042$; Fig. 3A), however this increase did not replicate in Study 3 (Arbaclofen: 8.03 ± 0.867 SE switches; Placebo: 7.29 ± 0.675 SE switches, $F_{(1,17)} = 4.940$, $\eta_p^2 = 0.122$, $p = 0.142$; Fig. 4A). No changes to reversions were observed in any study (all p values > 0.173).

Drug effects are not confounded by shifts in response latency or response criteria

We next analyzed participants' performance on two rivalry replay conditions to assess any drug effects on participants' response latencies and response criteria, and to determine the potential contribution of these non-perceptual factors to our observed changes in rivalry dynamics. Specifically, we analyzed each participant's report of simulated rivalry transitions on both their drug and placebo days. Sudden transition trials (Control A) provided us with an estimate of participants' motor response latencies (how quickly they press and release a button in response to a stimulus change on the screen). Gradual transition trials (Control B) provided us with an estimate of participants' perceptual decision criteria (the percentage mixture of a stimulus for a participant to report either a mixed or a dominant percept). Again, we used a repeated-measures ANOVA as a within-subjects test of the effect of drugs on behavior.

Neither drug was observed to influence response latencies or response criteria in either study. In Study 1 (clobazam), response latencies (Control A) were not significantly slower on the drug compared with the placebo day ($F_{(1,16)} = 0.033$, $\eta_p^2 = 0.002$, $p = 0.858$), and response criteria (Control B) remained unchanged ($F_{(1,16)} = 2.516$, $\eta_p^2 = 0.136$, $p = 0.132$; Fig. 2B). In Study 2 (arbaclofen), again neither response latencies ($F_{(1,16)} = 1.529$, $\eta_p^2 = 0.087$, $p = 0.235$), nor response criteria ($F_{(1,16)} = 0.002$, $\eta_p^2 = 0.001$, $p = 0.884$) significantly differed between drug and placebo days (Fig. 3B). In Study 3 (arbaclofen replication), again neither effects on response latencies ($F_{(1,17)} = 0.069$, $\eta_p^2 = 0.004$, $p = 0.796$) nor response criteria ($F_{(1,17)} = 0.214$, $\eta_p^2 = 0.012$, $p = 0.649$) were observed (Fig. 4B).

Further, the observed drug effects on rivalry were not confounded by changes in response latency or response criteria. To assess this, we re-ran our main analysis, this time including difference scores for each control measure (calculated by subtract-

ing performance on drug vs placebo days) as covariates in our main ANOVA. Observed drug effects on rivalry survived after regressing out any effect of the drug on response latencies (Control 1, Study 1: $F_{(1,15)} = 5.046$, $\eta_p^2 = 0.252$, $p < 0.040$; Study 2: $F_{(1,15)} = 5.573$, $\eta_p^2 = 0.271$, $p < 0.032$; Study 3: $F_{(1,16)} = 4.769$, $\eta_p^2 = 0.230$, $p < 0.046$) or response criteria (Control 2, Study 1: $F_{(1,15)} = 5.697$, $\eta_p^2 = 0.275$, $p < 0.031$; Study 2: $F_{(1,15)} = 6.41$, $\eta_p^2 = 0.3$ $p < 0.023$; Study 3: $F_{(1,16)} = 5.958$, $\eta_p^2 = 0.271$, $p < 0.027$). Overall, these results indicate that our observed drug effects on rivalry dynamics are best attributed to perceptual changes as a result of drug administration, rather than drug effects on non-perceptual measures (response latencies or response criteria).

Baseline rivalry dynamics do not predict magnitude of drug effect

We observed large individual differences in the proportion of suppression at baseline (placebo days). To test the potential impact of individual differences in rivalry at baseline on the magnitude of our drug effects, we asked whether the base rate (placebo day estimate) of perceptual suppression predicted the magnitude of an individual's drug effect on perceptual suppression. For all three studies, base rate perceptual suppression did not predict the magnitude of drug effect on perceptual suppression (Study 1: $\rho = -0.149$, $p = 0.567$; Study 2: $\rho = -0.265$, $p = 0.31$; Study 3: $\rho = -0.102$, $p = 0.686$).

Neither IQ nor BMI predict the magnitude of drug effect

Two other factors might have mediated our drug effect: individual differences in body mass index (BMI), which likely affects the rate of drug metabolism, and IQ, which might affect task understanding. However, neither measure was observed to predict the magnitude of drug effect on perceptual suppression for any study (BMI: all p values > 0.606; IQ: all p values > 0.13). Further, the Drug Effect was not significantly different for men versus women in any study (all p > 0.287).

$GABA_A$, but not $GABA_B$, affects self-reported drowsiness

Participants in Study 1 reported significant drowsiness after the administration of clobazam, as revealed by comparing drowsiness questionnaire scores between drug and placebo days (mean shift: 0.94 questionnaire points $\pm$ 1.69 points, $p = 0.04$). No effect of arbaclofen on self-reported drowsiness was observed in either the main study (mean shift: 0.11 questionnaire points $\pm$ 1.41 points, $p = 0.074$) or arbaclofen replication study (mean shift: -0.33 questionnaire points $\pm$ 1.15 points, $p = 0.259$). Crucially, the observed drug effects on rivalry were not confounded by changes in self-reported drowsiness. Observed drug effects on perceptual suppression survived after regressing out any effect of the drug on self-reported drowsiness (Control 1; Study 1: $F_{(1,15)} = 6.133$, $\eta_p^2 = 0.290$, $p < 0.026$; Study 2: $F_{(1,15)} = 7.236$, $\eta_p^2 = 0.325$, $p < 0.017$; Study 3: $F_{(1,16)} = 5.728$, $\eta_p^2 = 0.264$, $p < 0.029$). These results indicate that drug effects on rivalry cannot be accounted for by non-perceptual effects of the drug on participants' alertness.

Test–retest reliability

To examine the repeatability of our primary measure, perceptual suppression, we calculated test–retest reliability by correlating performance on drug versus placebo days across individuals in each study. As can be seen in Figure 5, participants' rivalry dynamics were stable across testing days (Study 1, clobazam: $Rs = 0.576$, $p = 0.016$; Study 2, arbaclofen: $Rs = 0.887$, $p < 0.001$;
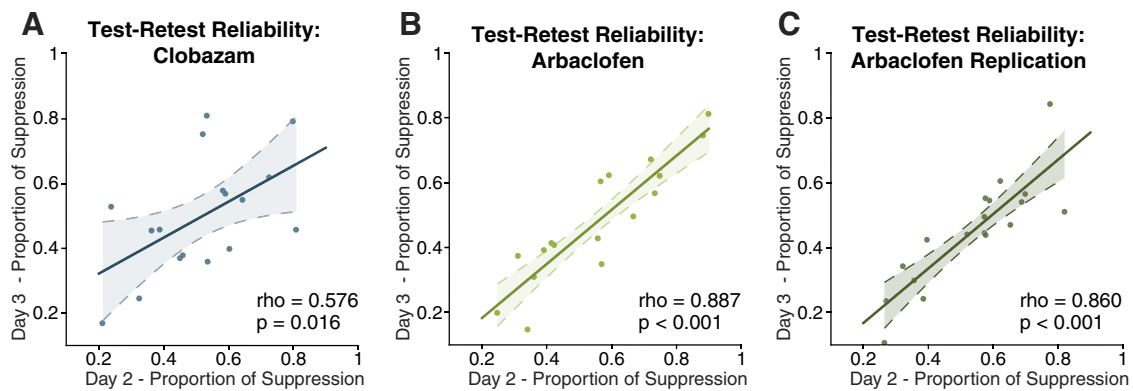
Figure 5. High test–retest reliability of rivalry dynamics. **A**, Participants' rivalry dynamics were stable across clobazam and placebo days ($r = 0.576$, $p = 0.016$), as well as (**B**) arbaclofen and placebo days ($r = 0.887$, $p < 0.001$) and (**C**) replication study; arbaclofen and placebo days ($r = 0.86$, $p < 0.001$). For example, a fast rivaler on Day 2 remained one of the fastest on Day 3, even if the entire group became slower after drug administration. High test–retest reliability is in keeping with prior binocular rivalry studies (Miller et al., 2010; Robertson et al., 2016) and further validates the repeatability of our dependent measure. Dashed lines represent the 95% confidence interval of the regression line.

Study 3, arbaclofen replication: $Rs = 0.86$, $p < 0.001$). For example, a fast rivaler on Day 2 remained one of the fastest on Day 3, even if the entire group became slower after drug administration. This finding is in keeping with prior binocular rivalry studies showing high test–retest in rivalry (Miller et al., 2010; Robertson et al., 2016) and underscores the repeatability of our measure. The test–retest reliability was observed to be slightly higher for arbaclofen compared with clobazam (Study 1 vs Study 2: $p = 0.047$, Study 1 vs Study 3: $p = 0.0873$). One reason for the lower test–retest reliability of our Study 1 results might be that due to the relatively long half-life of clobazam, 18 h, the effect of clobazam may not be fully absent on Day 3 when administered on Day 2 (Brogden et al., 1980). It is therefore also possible that our effects would be stronger if Days 2 and 3 were spaced further apart. Notably, a day effect is also typically observed in rivalry, where switch rates decline and perceptual suppression typically decreases during repeated rivalry presentations (Klink et al., 2010). A day effect on perceptual suppression was also observed in all of our studies, but was the smallest for Study 1 (Study 1: $\eta_p^2 = 0.013$, 5% of the drug effect; Study 2: $\eta_p^2 = 0.450$, 154% of the drug effect; Study 3: $\eta_p^2 = 0.489$, 211% of the drug effect).

Participant's self-reports of perceptual changes
It is interesting to note that participants' self-reports, collected via a post-study survey, somewhat reflected measured effects on rivalry dynamics for the GABA$_B$ agonist arbaclofen. First, when asked "on which day do you think you took the drug?", most participants were correct in their guess: clobazam, 57% ($p = 0.18$); arbaclofen, 74% ($p = 0.051$); arbaclofen replication, 57% ($p = 0.12$). Next, when asked "did you notice any differences in your experience of binocular rivalry between yesterday and to-day", most participants reported a perceptual change in suppression and/or switch rate across both drugs (clobazam, 57%; arbaclofen, 68%; arbaclofen replication, 62%). However, the reported perceptual change was not consistently described precisely enough to be interpretable (clobazam, $N = 4$; arbaclofen, $N = 10$; and arbaclofen replication, $N = 4$). Thus, it was not possible to assess whether participants' descriptions generally aligned with the findings of our study. Notably, however, the drug effect was not significantly different for participants who correctly guessed the day of the intervention compared with those who did not in any study (Study 1: $p = 0.10$, Study 2: $p = 0.95$, Study 3: $p = 0.27$).

Participant's self-reports of mixed percepts
Self-reports of the perceptual quality of mixture states in our study align with the expected perceptual effects of weakened interocular inhibition during rivalry. When asked to freely describe their perceptual experience of mixture states during rivalry, 72% of participants reported a blended percept, a superimposition between the left- and right-eye images, e.g., "Seeing both objects and both colors overlaid at the same time, as if they were slightly transparent" or "It looks like two overlaying pictures and the transparency settings on them keep changing. So while I can always see both of them, one of the pictures is less transparent than the other, but they are both still some amount of transparent." Such superimposition percepts are posited to correspond to periods of weakened interocular inhibition, in contrast to a different type of mixed percept, piecemeal percepts, which are posited to correspond to weakened inhibition between neurons corresponding to local regions of the visual field (Blake et al., 1992). Based on this hypothesis regarding the neural basis of different mixture percepts during rivalry, the effects observed in our study may particularly reflect GABAergic modulation of interocular inhibition. The observation of greater reported occurrences of superimposition percepts, compared with piecemeal percepts, in our study is consistent with previous studies of rivalry that have shown that high-level object stimuli typically produce significantly more superimposition percepts than piecemeal percepts (Alais and Melcher, 2007; Klink et al., 2010).

Discussion
We have shown that both GABA$_A$- and GABA$_B$-mediated inhibition increase perceptual suppression during rivalry. These findings are not driven by drug-induced changes in reaction times or response criteria and are replicated in an independent sample of participants (GABA$_B$). Together, these findings demonstrate a causal link between GABAergic inhibition and binocular rivalry dynamics and identify binocular rivalry as an objective marker of GABAergic drug response in the brain.

Our results provide two main insights into the neural mechanisms of bistable perception. First, these findings validate computational models of binocular rivalry, which predict that perceptual suppression covaries with the strength of cross-inhibition between neuronal pools coding for left eye and right eye percepts (Klink et al., 2010; Seely and Chow, 2011; Said et al., 2013). MRS findings support this model-based prediction: indi-

vidual variation in GABA and glutamate levels in early visual cortex correlates with the strength of perceptual suppression (Robertson et al., 2016) as well as the overall duration of dominant percepts during rivalry (van Loon et al., 2013; Pitchaimuthu et al., 2017). Similarly, studies of brief monocular deprivation show that homeostatic reductions in GABA levels in visual cortex post-deprivation predict an increase in the relative predominance of the deprived eye during rivalry (Lunghi et al., 2015) and a reduction in perceptual suppression (Sheynin et al., 2019). Our results complement these previous findings, presenting the first causal link between GABAergic inhibition and the strength of perceptual suppression during binocular rivalry in humans.

Second, our results implicate specific branches of GABAergic inhibition in rivalry. GABA engages two main receptor subtypes in the human brain, $GABA_A$ and $GABA_B$. In principle, either of these subtypes might have been implicated in binocular rivalry as both receptors are densely expressed in human visual cortex, with particularly high density in layer 4 of visual cortex (V1; D. March and Shaw, 1993; Muñoz et al., 2001), a putative site of interocular inhibition (Sengpiel et al., 1995). However, these receptors operate on different timescales: $GABA_A$, an ionotropic ion-channel mediator, initiates fast IPSCs with brief effects ($\sim$20–50 ms; Connors, 1992), whereas $GABA_B$, a metabotropic receptor, initiates slower IPSCs and has longer lasting effects (250–1000 ms; Connors, 1992; Benardo, 1994). It is not obvious which of these timescales would be most relevant to rivalry, where perceptual suppression typically occurs on the order of seconds (Blake, 2001), sometimes minutes (Carter et al., 2005). Further, the timescale of inhibition in computational models of rivalry is most aligned with that of fast, $GABA_A$-mediated IPSCs ($\sim$50 ms; Li et al., 2017). Our results potentially inform models of rivalry, suggesting that both timescales of inhibition are relevant, and highlighting a novel role for the slower, sustained dynamic of $GABA_B$ inhibition in the phenomenon.

Our findings are consistent with previous findings in the animal literature. For example, antagonism of local inhibitory circuits in cat primary V1 using the $GABA_A$ antagonist bicuculline has been shown to selectively decrease electrophysiological measures of interocular suppression (Sengpiel and Vorobyov, 2005). Further, local administration of the $GABA_A$ agonist diazepam has been shown to increase the width of ocular dominance columns in the developing cat, suggesting that GABA-mediated inhibition influences the development of local competition between right- and left-eye populations in V1 (Hensch and Stryker, 2004), one anatomical substrate of binocular rivalry along the visual hierarchy (Xu et al., 2016). These findings are consistent with our own, suggesting that GABA influences activity and neural development in rivalry-related circuitry in animals.

To date, causal studies of rivalry in humans have focused on implicating different brain regions in rivalry, with little to say about neurotransmission within these regions. For example, repetitive transcranial magnetic stimulation of parietal sites linked to the top-down stabilization of rivalry dynamics (Carmel et al., 2010; Kanai et al., 2010, 2011), implicate posterior and anterior parietal sites in prolonging or shortening dominance durations, respectively. One previous study attempted to test the effects of a $GABA_A$ modulator, lorazepam, on rivalry, but participants failed to achieve binocular fusion and thus could not perform rivalry after drug administration (van Loon et al., 2013). Our study also used a $GABA_A$ modulator, clobazam, but this problem was not observed. We hypothesize that this might be because of the difference in the $GABA_A$ subunits targeted by lorazepam (subunits 1,4) and clobazam (subunits 1,5), where clobazam produces

longer-acting effects and significantly less sedation (Sankar, 2012), although clobazam did significantly increase drowsiness in our study.

Pharmacological studies offer an exciting opportunity to directly manipulate neurotransmission *in vivo*, but there are limitations to this approach. Most notably, drug effects are neuroanatomically global in nature. Thus, it is difficult to attribute our results to inhibitory signaling in a particular visual region of the brain, or specifically to interocular inhibition rather than other visual processes (e.g., sensitivity or adaptation) or even nonvisual processes (e.g., generalized cognitive failures; Sandberg et al., 2014). Further, although we used rivalry simulation trials to control for potential drug effects on participants' response times and perceptual decision criteria and found no drug effects on these two measures, it is possible that our control trials did not fully simulate the degree of decision uncertainty associated with rivalry, which may have been affected if the drugs impacted decision processes in the brain. Acknowledging these limitations, we note that rivalry is a relatively global phenomenon in visual cortex, observed at multiple levels of the visual hierarchy, from V1 (Xu et al., 2016) to IT cortex (Tong et al., 1998). As such, rivalry likely lends itself to a neuroanatomically global manipulation, affording multiple potential sites of reciprocal inhibition for GABAergic modulation to affect. However, future neuroimaging studies are needed to demonstrate that the drugs used in our study specifically affect activity levels in visual areas that are relevant to rivalry, and that these changes predict our observed behavioral effects.

Our results may have important implications for psychiatric research. A major impediment to psychiatric drug development is the lack of robust, objective markers of the neural processes drugs are developed to target (J. S. March and Fegert, 2012; Insel, 2014). Visual tasks may provide particularly promising markers of drug impact in the brain, given that the neural pathways and computational principles underlying many visual processes are well established. Indeed, a number of visual tasks have been shown to be modulated by $GABA_A$ modulators in previous studies (Fisch et al., 1983; MacNab et al., 1985; Giersch and Herzog, 2004; van Loon et al., 2013) and might also be well suited to probe neural inhibition. One practical benefit of the rivalry paradigm is that it is relatively fast to administer ($\sim$15 min), and thus particularly well suited to probe drug effects that wane over time. Additionally, rivalry dynamics are highly test–retest reliable (Fig. 5; Robertson et al., 2016) and show high heritability in twin studies (Miller et al., 2010), suggesting that the large individual differences observed during rivalry likely map onto stable biological phenomena. Thus, given computational (Klink et al., 2010; Seely and Chow, 2011; Said et al., 2013), correlational (Robertson et al., 2016), and now causal demonstrations of the dependence of rivalry dynamics on GABAergic inhibition, we propose that rivalry may serve as a noninvasive marker of inhibitory signaling in the brain. This tool might shed light on the neural mechanisms of psychiatric conditions thought to be affected by disruptions in inhibition, such as autism (Marín, 2012).

Previous work from our laboratory has demonstrated altered binocular rivalry dynamics in individuals with autism, measured using behavioral report (Robertson et al., 2013, 2016; Freyberg et al., 2015), and recent neuroimaging findings have provided a direct neural readout of altered rivalry dynamics in autism using EEG (Spiegel et al., 2019). Specifically, individuals with autism exhibit slower rivalry switch rates and reduced perceptual suppression, both of which predict autism symptom severity. MRS findings link this replicated and robust perceptual difference to a

disruption in GABAergic inhibition in visual cortex (Robertson et al., 2016): GABA levels in early visual areas do not predict rivalry dynamics in autism as they do in control individuals, suggesting that GABA fails to effectively drive inhibition in the autistic visual cortex (Robertson et al., 2016). These behavioral results have been replicated in three independent studies (Robertson et al., 2013, 2016; Freyberg et al., 2015; Spiegel et al., 2019), but one previous experiment did not confirm altered rivalry dynamics in autism with unmatched participant groups, although the reported results in this study were consistent with the direction of other studies when participants were matched for age (Said et al., 2013). Together, these findings suggest that binocular rivalry might be able to serve as a noninvasive perceptual marker of the altered inhibitory signaling implicated in autism.

All in all, these results provide direct evidence for a causal link between GABAergic inhibition and binocular rivalry and implicate specific GABA receptors (GABA$_A$ and GABA$_B$) in perceptual suppression. More broadly, these results identify binocular rivalry as a simple yet powerful perceptual tool to index GABAergic drug response in the brain, which may further research on psychiatric conditions in which neural inhibition is thought to be affected.

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