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Whether grocery shopping or choosing words to express a thought, selecting between options can be challenging, especially for people with anxiety. We investigate the neural mechanisms supporting selection during language processing and its breakdown in anxiety. Our neural network simulations demonstrate a critical role for competitive, inhibitory dynamics supported by GABAergic inter- neurons. As predicted by our model, we nd that anxiety associ- ated with reduced neural inhibition) impairs selection among options and associated prefrontal cortical activity, even in a simple, nonaffective verb-generation task, and the GABA agonist midazo- lam which increases neural inhibition) improves selection, whereas retrieval from semantic memory is unaffected when selection demands are low. Neural inhibition is key to choosing our words.

anxiety choice midazolam ventrolateral prefrontal cortex neural network model

People claim to love the freedom of unlimited choices, but in reality we are often stymied by too many options and dis- concerted by not knowing what the outcomes of our choices will be. Selecting among multiple options is effortful and time con- suming, whether choosing among fruit jams 1), retirement plans 2), or medical treatments 3). This problem is particularly per- vasive during language production, when we must constantly choose words to express a thought 4–6). People with anxiety disorders nd coping with too many options particularly dif cult, and struggle with decision-making problems 7), indecisiveness 8), and intolerance of uncertainty 9). What mechanisms allow us to select among multiple options when speaking, and why does this process break down in people with anxiety? Current psy- chological theories of selection focus on the importance of cog- nitive control 5) and prefrontal cortical regions 4, 6, 10), but do not address questions at the level of speci c neural mechanisms. We address these questions by implementing a uni ed, bi- ologically plausible computational model of selection, and testing its predictions about both brain and behavior in humans making choices in a well-controlled language production task.

Our model demonstrates how competitive, inhibitory dynamics among neurons in prefrontal cortical networks 11) support se- lection between alternatives. Speci cally, these competitive dy- namics serve to sharpen cognitive representations by amplifying activity in the most active, task-relevant, representations e.g., the most appropriate word to complete a sentence) and suppressing competing representations e.g., for the many other word possi- bilities). A tenet of the model is that these critical dynamics occur via inhibitory, GABAergic interneurons 12–14). Here we test the predictions of the model regarding selection processes that are supported by the left ventrolateral prefrontal cortex. We do so for the following reasons: *i*) this region has been implicated in selecting among competing alternatives during language process- ing 6, 15–18); *ii*) this region shows altered activity in individuals who suffer from anxiety particularly anxious apprehension, characterized by worry, and hereafter referred to as "anxiety" 19); and *iii*) GABAergic function is reduced in individuals with anxiety 20–23). Hence, our model provides a uni ed framework that can link these formerly disconnected observations.

Speci cally, our model demonstrates how reduced GABAergic function can lead to reduced competitive dynamics in prefrontal cortical networks, allowing nonwinning competitors alternative responses that are not selected) to become more active and to compete over a longer period, which impairs selection. Con- versely, increased GABAergic function leads to lower and briefer activation of these competitors and to improvements in selection. These basic mechanisms provide a uni ed framework for under- standing how we make choices in language processing and how this process relates to worrying about the future, to a degree of pre- cision that allows us to test and con rm) predictions through neuro- pharmacological manipulation, links to psychopathology, and levels of brain activity. Whereas decision-making de cits in persons with anxiety have previously been shown in complex or affective tasks, our model predicts that selection de cits that lie at the core of these problems should be observed even in a simple language-production task, whereas other cognitive processes should remain intact.

We provide a previously undescribed direct test of this model, and con rm its predictions. We demonstrate that participants high in anxiety, which has been linked to reduced GABAergic function, have more dif culty selecting between competing word options and exhibit reduced VLPFC activation during such se- lection. In addition, we demonstrate that drugs that increase GABAergic function improve selection in a nonclinical pop- ulation. Furthermore, such effects are speci c, as the retrieval of words from semantic memory is unaffected by GABAergic func- tion when selection demands are low, despite the importance of retrieval processes in language processing and the role of VLPFC in retrieval 4).

Results

We investigated selection and retrieval of words from semantic memory with a verb generation task, in which participants are presented with a noun and say the rst associated verb that comes to mind 5, 6). This task allows selection and retrieval demands to be precisely quanti ed and independently manipulated Fig. 1*A* and *Methods*). We present the basic behavioral effects of selection and retrieval demands and their simulation in a neural network model rst, followed by predictions from the model and empirical tests of the effects of increasing and decreasing neural inhibition.

For the basic behavioral data, verb generation data were an- alyzed with a 2 × 2 repeated-measures ANOVA. We replicated previous results showing participants are slowed by *i*) greater selection demand, measured in terms of the competition be- tween alternative responses e.g., cat brings to mind many pos- sible competing verbs such as purr, meow, and lick, and so has
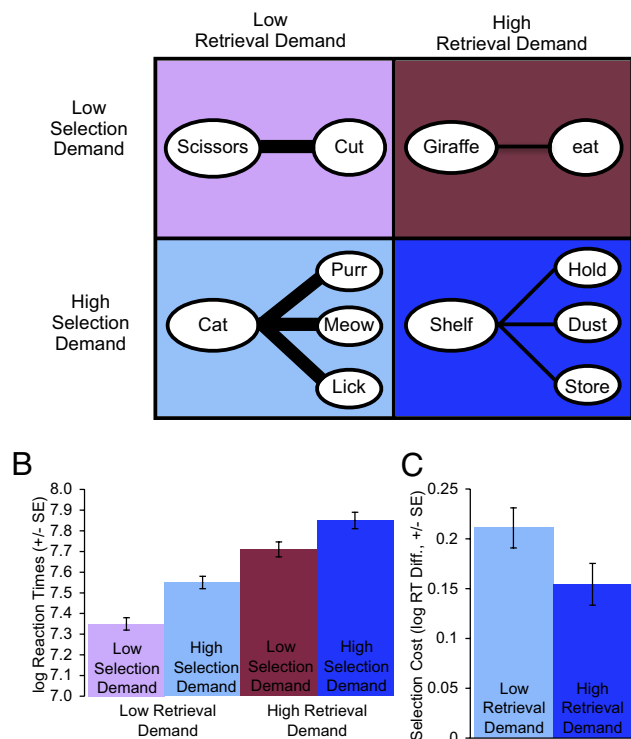
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Fig. 1. Design and basic behavioral findings for the verb generation task. (*A*) Selection demands (high vs. low competition) are crossed with retrieval demands (high vs. low association strength) (*SI Methods 2.1*). (*B*) Participants take longer to generate a response when retrieval demands are high and when selection demands are high. (*C*) Selection costs (RT difference between high and low selection demand conditions) are greater when retrieval demands are low than when they are high. All error bars are SEs.

Fig. 2. Neural network model. (*A*) Network architecture. (*B*) Model simulates human performance, showing independent effects of selection demand (driven by competition between active representations) and retrieval demand (driven by synaptic weight strength). (*C*) Model simulates interaction between selection and retrieval (driven by benefit of spreading activation when retrieval demands are high). All error bars are SEs.

high selection demand, whereas scissors generally brings to mind the single verb cut); and *ii*) greater retrieval demand, measured as the weakness of the association strength between the noun and the appropriate response (e.g., scissors is strongly associated with cut and so has low retrieval demand, whereas giraffe is only weakly associated with any verb). Specifically, reaction times were longer in the high selection demand [log reaction time (RT) mean (M) = 7.70, SE = 0.03; RT 2208 ms, SE = 68] than low selection demand conditions [log RT M = 7.53, SE = 0.03; RT 1,863 ms, SE = 57] [$F(1,82)$ = 215.9, P < 0.001], and longer in the high retrieval demand [log RT M = 7.78, SE = 0.04; RT 2,392 ms, SE = 98) than low retrieval demand (log RT M = 7.45, SE = 0.03; RT 1,720 ms, SE = 52) conditions [$F(1,82)$ = 387.9, P < 0.001] (Fig. 1*B* and Table S1). In addition, we found an interaction between selection and retrieval demands: selection costs were greater under low retrieval demands [log RT difference (diff.) M = 0.20, SE = 0.02; RT diff. 352 ms] than under high retrieval demands (log RT diff. M = 0.13, SE = 0.02; RT diff. 324 ms) [$F(1,82)$ = 12.1, P = 0.001] (Fig. 1*C*).

Our model simulates and provides a framework for understanding these findings. The model uses a powerful framework that simulates the electrophysiological properties of neurons and can use networks of such neurons to simulate human behavior, including language and cognitive control (*SI Methods 2.2, 2.3* and Tables S2 and S3 provides details of the modeling framework, architecture, and simulations). The model contains layers (simulated brain areas) that simulate the following: *i*) presentation of noun stimuli, *ii*) activation of associated verb responses in the posterior cortex, *iii*) selection of responses in the ventrolateral prefrontal cortex (VLPFC), and *iv*) output of a response (Fig. 2*A*). The strength of connections between nouns and associated

verb responses and between alternative verb responses were set according to the known association strengths observed in humans (24); these connections support spreading activation between related semantic representations like that observed in posterior cortex. Simulated neurons in the posterior cortex layer then activate verb representations in the VLPFC layer, which implements competitive lateral inhibition, selecting one response for output.
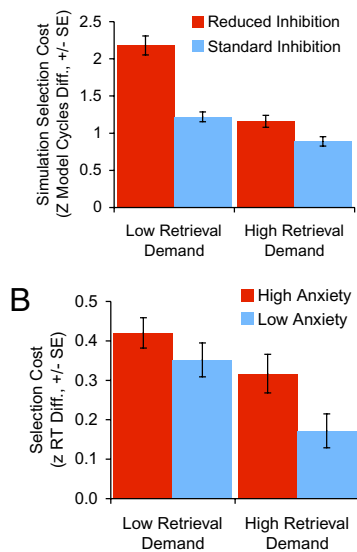
Like people, the model takes longer to respond when retrieval or selection demands are high (*SI Methods 2.3, SI Results 3.1, Table S3*, Fig. 2*B*, and Figs. S1 and S2). The effects of retrieval demand are a direct consequence of the strength of the synaptic weights between a stimulus and its response representation in the posterior cortex layer (25); weaker weights cause a slower buildup of activation, requiring more time to reach the threshold for generating a response. Selection demand increases when multiple alternative responses become simultaneously active and competition must be resolved to select a single response. In the model, this resolution is accomplished through strong lateral inhibition in the VLPFC layer, simulating the effects of GABAergic interneurons.

In addition, the model replicates the interaction between selection and retrieval demands, and provides insight into why such an interaction occurs (Fig. 2*C*). When responses are easily retrieved, activating multiple responses serves only to generate competition, imposing a large selection cost. However, when it is difficult to retrieve any response, activating multiple responses aids retrieval, as spreading activation between these weakly associated alternatives (e.g., between hold and store when generating a response for shelf) boosts their activation levels. Thus, when retrieval demands are high, selection costs are partially offset by the advantage multiple responses confer on retrieval (*SI Results 3.1* and Fig. S2).
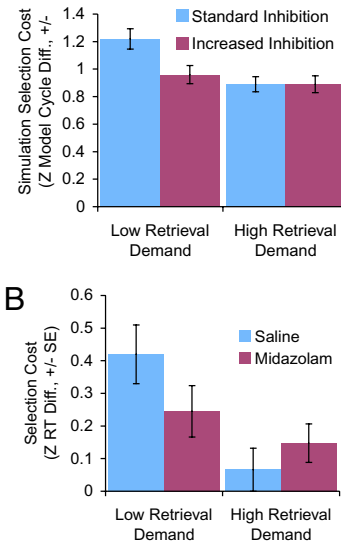
Manipulations of competitive inhibition in the VLPFC layer of the model enabled us to generate novel predictions regarding the effects of reduced GABAergic function associated with anxiety,

and increased GABAergic function under GABA agonists, which we then tested empirically *SI Methods 2.4–2.6* and *SI Results 3.2–3.4*). These simulations showed that competitive inhibition is critical for selection between competing alternatives, and that the effect of competitive inhibition on selection is modulated by retrieval demands. Decreasing competitive inhibition as in anxiety) impairs selection Fig. 3A), whereas increasing competitive inhibition as under GABA agonists) improves selection Fig. 4A). These effects of competitive inhibition on selection are more robust when retrieval demands are low. When retrieval demands are high, increased neural inhibition increases competitive dynamics that support selection, but also reduces spreading activation that aids retrieval, leading to weaker effects Figs. 3A and 4A). In contrast, changes in competitive inhibition do not affect retrieval when selection demands are low i.e., there is one associated response and thus no spreading activation). Thus, the simulations predict that reduced neural inhibition associated with anxiety will impair selection and associated VLPFC activity 26, 27) *SI Discussion 1.2*), whereas increased neural inhibition under the GABA agonist midazolam will improve selection. These effects may be more apparent when retrieval demands are low. In addition, retrieval should not be affected by changes in neural inhibition when selection demands are low. These predictions were supported in three empirical investigations.

The effects of anxiety on selection were investigated in separate behavioral and functional MRI fMRI) studies in nonclinical populations that varied in levels of anxious apprehension, which should in turn influence the level of GABAergic activity. Anxious apprehension was assessed by standard questionnaires in which individuals rated how well statements such as "many situations make me worry" applied to them *Methods*). Behavioral data were analyzed with a 2 × 2 × 2 mixed factorial ANOVA Table S4). As predicted, participants higher in anxiety had larger selection costs z-transformed RT diff. M = 0.37, SE = 0.03; RT diff. 421 ms) than lower-anxiety participants z-transformed RT diff. M = 0.26, SE = 0.03; RT diff. 269 ms) [F 1,57) = 6.32 P = 0.015] Fig. 3B Fig. S3, and Table S5), but the retrieval

Fig. 4. Effect of increased neural inhibition. (*A*) Model predictions. Increased neural inhibition (simulating GABA agonist drugs) improves selection (i.e., reduces selection cost) only when retrieval demands are low. (*B*) Empirical results. Midazolam improves selection only when retrieval demands are low. RTs are z transformed to remove baseline differences between conditions. All error bars are SEs.
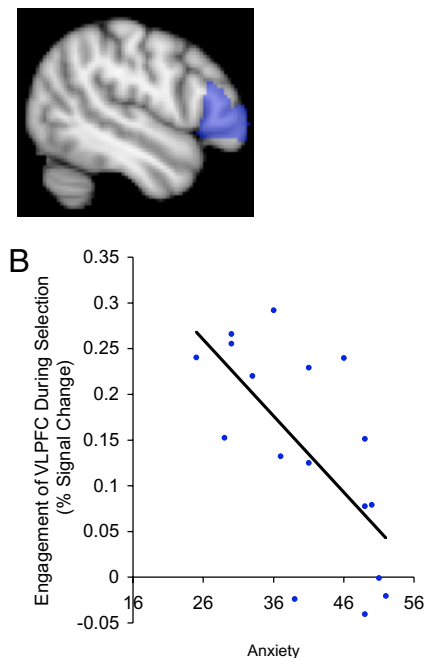
costs were equivalent across the groups [F 1,57) = 0.72, P = 0.4]. Also as predicted, left VLPFC activity correlated with anxiety during selection when retrieval demands were low r = 0.663, P = 0.004, n = 17) Fig. 5 and Fig. S4), but not during retrieval when selection demand was low r = 0.181, P = 0.5, n = 16, Fisher s z = 1.60, P = 0.05, one-tailed). The brain activity thus con rms the model s prediction of larger effect of anxiety on selection when retrieval demands are low, whereas the behavioral data show similar effects of anxiety on selection under high and low retrieval demands, perhaps reflecting a lower sensitivity of RT measures or the role of other brain mechanisms or compensatory strategies.) These ndings suggest that higher anxiety individuals lack suf cient competitive dynamics in VLPFC for ef ciently selecting between competing options *SI Discussion 1.2*).

We tested the predicted effects of increased neural inhibition in a double-blind, placebo-controlled study in which participants completed the verb generation task after injection of the GABA agonist midazolam as compared with a saline control in two counterbalanced sessions *Methods SI Methods 2.6* and *SI Discussion 1.3*). Data were analyzed with a 2 × 2 × 2 repeated-measures ANOVA Table S6). There was an interaction between drug condition, selection demand, and retrieval demand [F 1,19) = 5.67, P = 0.028]. As predicted, when retrieval demands were low, midazolam improved selection with selection costs lower under midazolam, z-transformed RT diff. M = 0.15, SE = 0.06; RT diff. 267 ms, than under saline, z-transformed RT diff. M = 0.37, SE = 0.07; RT diff. 355 ms) [t 19) = 2.95, P = 0.008], whereas midazolam did not improve selection when retrieval demands were high [t 19) = 1.05, P = 0.3] Fig. 4B Fig. S5, and Table S7). Also as predicted, there was no effect of midazolam on retrieval when selection demands were low [t 19) = 0.53, P = 0.6].

Discussion

In daily life, we often face a tyranny of choice 28), and this problem is ubiquitous when we choose words to express a thought. The current studies demonstrate that competitive neural inhibition, via GABAergic interneurons in prefrontal circuits, likely plays an important role in selecting among alternatives during

Fig. 3. Effects of reduced neural inhibition (*A*) Model predictions: Reduced competitive neural inhibition in the VLPFC layer, simulating increasing anxiety, impairs selection (i.e., increases selection cost) under high and low retrieval demands, and suggests that effects of anxiety on selection may be most robust under low retrieval demands. (*B*) Empirical results. Higher anxiety participants show impaired selection under high and low retrieval demands (model fit is further discussed in *Results*). All error bars are SEs.

Fig. 5. Engagement of left VLPFC during selection, as a function of anxiety. (*A*) Anatomically defined region of interest (mid and anterior left VLPFC, shown in blue) was chosen based on prior work establishing its role in selection. Engagement of this region during selection was computed for each participant as the difference in fMRI activation between the high and low selection demand conditions. (*B*) Higher anxiety participants showed reduced engagement of left VLPFC during selection under low retrieval demands, which may reflect reduced activity of GABAergic interneurons (*SI Discussion*).

language processing. As predicted by neural network simulations, selection and associated prefrontal activity in a verb-generation task are impaired by anxiety associated with reduced GABAergic function), whereas selection is improved under the drug midazolam which increases GABAergic function). Of note, retrieval is unaffected by GABAergic function; instead, other mechanisms [e.g., sustained neuronal activation, enabled by recurrent connections in PFC networks *SI Discussion 1.1*)] may support retrieval of weakly active representations. These findings shed light on why choosing among many options can be difficult for anyone, and why it can be paralyzing for people with anxiety.

In complex decision-making tasks, choice-overload is believed to increase when there are many options 1–3), the options are similar 29), or there is conflict between equally good options 30). Similarly, in language production, the difficulty of selecting among words has been described as a function of the number of alternatives 31), or similarity of activation levels across alternatives 5, 32). Each of these factors can be seen as increasing the amount of time necessary to resolve competition among options through neural inhibition, as each increases the degree to which multiple options are represented with equal strength.

Although we are normally able to use cognitive control to overcome these selection difficulties, this process becomes more difficult for persons with anxiety. Our modeling and empirical work suggest that the reduced GABAergic function associated with anxiety leads to impaired competitive neural inhibition and contributes to difficulty in selection. Although GABA agonists are widely used to treat the affective symptoms of anxiety disorders 33), we demonstrate that midazolam improves the cognitive process of selection in a nonclinical population, suggesting that GABA agonists may also be effective in treating the cognitive control and decision-making deficits in anxiety disorders.

Even for individuals without anxiety disorders, the difficulty of selecting between options has important real-world consequences in domains beyond language production. When people are faced with too many options, they may use suboptimal heuristics to reduce the number of alternatives 34), make a decision they regret 1, 28), or delay making a decision altogether 2, 29), often with negative consequences. For example, the more retirement plans that employees must choose among, the less likely they are to join any plan at all 2). Likewise, when physicians are asked to choose between two similar pain medications, they are less likely to prescribe either 3). In these complex domains, and in language production as well, selection is likely to depend on many processes in addition to neural inhibition, such as assigning values to different options 35), which are supported by additional brain areas. A complete model of selection will thus need to incorporate additional processes e.g., generating potential response options and dynamically increasing control when there is response competition) supported by a larger network of brain areas [e.g., anterior cingulate cortex, presupplementary motor area 36, 37)], which may also be affected by anxiety. Therefore, an important goal for future research will be to investigate how these processes interact with competitive inhibition processes in ventrolateral prefrontal cortex to support selection in language processing, and whether these processes generalize across other prefrontal regions to support decision making in other domains 38, 39). Future work should also include imaging methods e.g., SPECT) and modeling frameworks [e.g., detailed neurophysiological models 40)] that provide more direct measures and simulations of GABAergic activity. Whether in the grocery store or speaking a sentence, there is no escaping the necessity of selecting among competing alternatives. In language processing, and perhaps beyond, competitive neural inhibition is critical in helping us to cope with this tyranny of choice.

Methods

All participants were from the University of Colorado and wider Boulder and Denver communities, spoke English as a first language, and did not report any reading disorder. All participants gave informed consent and were treated in accordance with procedures approved by the University of Colorado institutional review board.

Experiment 1: Basic Behavioral Effects and Effects of Anxiety *Participants* Participants were 85 young adults (52 female and 33 male); a subset ($n = 60$) also completed anxiety and depression measures. An additional eight participants were excluded for not following task directions ($n = 4$), self-reported reading disorders ($n = 2$), and equipment failure ($n = 2$). In addition, two outliers with negative selection and/or retrieval effects were excluded from analysis, because the basic effects of the task manipulations are very robust, occurring for the vast majority of subjects, making it difficult to interpret individual differences in cases in which there is a clear manipulation failure. With the inclusion of these subjects, all significant effects remain significant.

Design procedure and analysis. Verb generation stimuli were 100 nouns in a 2×2 design: high and low retrieval demand (association strength between nouns and possible verb responses) crossed with high and low selection demand (degree of competition among alternative responses). Association strength and competition were calculated as in previous work (5), using latent semantic analysis (24). High and low association strength conditions were matched on competition, whereas high and low competition conditions were matched on association strength. The full stimulus set is available upon request.

Participants were instructed to say the first verb that came to mind when presented with a noun (e.g., "meow" or "feed" for "cat"), and were given an example and eight practice trials before completing the task. A fixation-cross appeared for 500 ms, followed by a noun. Participants responded by speaking into a microphone that recorded voice-triggered reaction times (RTs), and advanced the computer to the next trial. Trial order was randomized for each participant. When the microphone was accidentally triggered (e.g., by a cough) or an error made (a nonverb), the trial was eliminated from analysis. The data were trimmed to remove trials with RTs less than 200 ms or greater than three SDs above each participant's mean. For within-subject analyses, RTs were log transformed to normalize the data. For individual differences analyses, RTs were further z transformed to remove baseline differences.

Participants completed four standardized questionnaires to assess anxious apprehension: (*i*) NEO Five Factor Inventory (NEO-FFI) neuroticism subscale (41), (*ii*) Lehrer Woolfolk Anxiety Symptom Questionnaire cognitive factor (LWASQ) (42), (*iii*) Penn State Worry Questionnaire (PSWQ) (43), and (*iv*) Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS) (44) Behavioral Inhibition subscale. These questionnaires were combined into a summary score (*SI Methods*). Participants were classified as characterized by high or low anxious apprehension using a median split (*SI Results* describes converging results from a continuous analysis). In addition, participants completed the Mood and Anxiety Symptom Questionnaire (MASQ) (45) to control for depression and anxious arousal symptoms (*SI Discussion* and *SI Results*).

Experiment 2: Effects of Anxiety on VLPFC Activity during Selection Experiment 2 was part of a larger fMRI study focused on prefrontal organization. Here we focus on the critical test of our theory, the effect of anxiety on VLPFC activity.

Participants. Participants were 18 right-handed young adults (9 female and 9 male). Three additional participants were excluded because of excessive (>25) error rates.

Design procedure and analysis. The verb generation task was identical to experiment 1, except that, to adapt the procedure for fMRI scanning, trail length was fixed to 4,000 ms rather than being self-paced. Verbal responses were recorded with a fiberoptic microphone (Optoacoustics Ltd.). A rapid event-related paradigm and standard blood oxygen level-dependent (BOLD) imaging techniques were used to collect functional data in one run lasting ~9 min (*SI Methods*). Participants completed the PSWQ and MASQ outside of the scanner (refer to experiment 1).

Nonverb errors were removed from analysis, and instead included as a nuisance covariate in the GLMs. (RTs are not available because the scanner environment was too noisy to accurately determine voice-onset RTs.) First, GLMs were conducted estimating signal change for contrasts of high vs. low selection demand and high vs. low retrieval demand conditions (*SI Methods*). Next, an anatomical region of interest (ROI) consisting of left inferior frontal gyrus pars triangularis and pars orbitalis (mid and anterior VLPFC) was defined using the Harvard–Oxford Cortical Structures (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html) and Duvernoy atlases (46), and signal change in each contrast within this ROI was extracted for each participant and correlated with anxiety and depression scores. Outlier analyses were conducted (Cook s D > 3 SD above mean), resulting in the exclusion of no more than two participants from each correlation analysis.

Experiment 3: Effects of Increased Neural Inhibition under Midazolam
Participants. Participants were 24 young adults (10 female and 14 male). One

additional participant was excluded for not completing the second session. In addition, four outliers with negative selection and/or retrieval effects under saline were excluded from analysis, as in experiment 1, because it is difficult to interpret drug effects in cases in which there is a clear manipulation failure. Including these subjects does not change the overall pattern of results; the significant three-way interaction becomes marginally significant ($P = 0.06$), and all other significant effects remain significant.

Design procedure and analysis. A double-blind, placebo-controlled design was used. Participants completed counterbalanced sessions, 1 wk apart, under midazolam (0.03 mg/kg body weight diluted to a total volume of 10 mL) and placebo (10 mL saline solution) (*SI Methods*). The verb generation task was identical to that in experiment 1, except that the stimulus set was divided at random into two lists (with an additional 50 filler items), counterbalanced across sessions and drug conditions. RT data were trimmed and transformed as in experiment 1.

Neural Network Model We used a biologically plausible neural network modeling framework, Leabra (47, 48) (*SI Methods*), implemented in Emergent (http://grey.colorado.edu/emergent/). On each trial, one noun input unit was turned on, activating the relevant verb response units in the posterior cortex layer, which then became active in the VLPFC layer, which implemented strong k-winners-take-all (kWTA) lateral inhibition to select one verb and biased the posterior cortex layer representations toward this response. Multiple simulations were run with differing levels of kWTA lateral inhibition in the VLPFC layer. The level of inhibition was reduced to test the effects of decreased neural inhibition (that is likely associated with anxious apprehension) and increased to test the effect of increased neural inhibition (under midazolam) (*SI Methods* and *SI Results*). Each trial ended when the network settled, producing a response in the output layer. Thus, the VLPFC layer of this model implements mechanisms similar to the leaky, competing accumulator model of perceptual choice (49, 50), in which lateral inhibition between units allows one response to emerge as the winner, whereas decay of unit activations is counteracted by recurrent excitatory connections.

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