

Individual Differences in the Balance of GABA to Glutamate in pFC Predict the Ability to Select among Competing Options

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Abstract

■ Individuals vary greatly in their ability to select one item or response when presented with a multitude of options. Here we investigate the neural underpinnings of these individual differences. Using magnetic resonance spectroscopy, we found that the balance of inhibitory versus excitatory neurotransmitters in pFC predicts the ability to select among task-relevant options in two language production tasks. The greater an individual's concentration of GABA relative to glutamate in the lateral pFC, the more quickly he or she could select a relevant word from among competing options. This outcome is consistent with our computational modeling of this task [Snyder, H. R.,

Hutchison, N., Nyhus, E., Curran, T., Banich, M. T., O'Reilly, R. C., et al. Neural inhibition enables selection during language processing. *Proceedings of the National Academy of Sciences, U.S.A.*, 107, 16483–16488, 2010], which predicts that greater net inhibition in pFC increases the efficiency of resolving competition among task-relevant options. Moreover, the association with the GABA/glutamate ratio was specific to selection and was not observed for executive function ability in general. These findings are the first to link the balance of excitatory and inhibitory neural transmission in pFC to specific aspects of executive function. ■

INTRODUCTION

Left lateral pFC is critical for executive functions, which are the cognitive processes required for goal-oriented and self-directed behavior (e.g., Banich, 2009; Miller & Cohen, 2001). One critical aspect of executive function is the ability to select one particular representation among multiple task-relevant options, such as when we must select a product to purchase (e.g., Iyengar & Lepper, 2000; Tversky & Shafir, 1992) or make a decision when there is no clear best option (e.g., Sethi-Iyengar, Huberman, & Jiang, 2004; Diederich, 2003; Redelmeier & Shafir, 1995). This process is particularly pervasive during language production, in which we constantly choose among competing words to express thoughts. For example, we might choose the words “the building was positioned on a hilltop” or “the house sat at the pinnacle of a ridge,” which both communicate the same thought, but do so using different words. Although we normally can deploy executive function to quickly select among words, this ability is impaired by lateral prefrontal damage (e.g., Novick, Kan, Trueswell, & Thompson-Schill, 2009) and many psychiatric and neurodegenerative disorders (Snyder et al., 2010; e.g., Tippett, Gendall, Farah, & Thompson-Schill, 2004). Even in healthy adults, selecting among responses activates left lateral pFC,

and responding is slowed when there are more competitors (e.g., Snyder, Banich, & Munakata, 2011; Crescentini, Shallice, & Macaluso, 2010; Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997).

Among healthy people, there are large differences in executive function, which are influenced by genetics (Friedman et al., 2008), and have been linked to a variety of real-world outcomes, such as educational attainment (St Clair-Thompson & Gathercole, 2006). However, there has been relatively little research on the extent to which these individual differences in executive abilities and selection in particular are related to specific neural mechanisms in pFC (e.g., Braver, Cole, & Yarkoni, 2010). What aspects of neural function give rise to these important individual differences in selection abilities?

One aspect of neural function that may influence selection abilities is the relative balance of excitatory to inhibitory neural activation. Simulations of a language production task in our neurobiologically plausible computational model suggest that selection is likely influenced by lateral inhibition in the left lateral pFC, which has been shown to be highly involved in selection. The model predicts that the balance of excitation and inhibition in this brain region influences individual differences in selection efficacy (Munakata et al., 2011; Snyder et al., 2010). Specifically, our model demonstrates how competitive,

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inhibitory dynamics among neurons in prefrontal cortical networks could 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 by suppressing competing representations (e.g., for the many other word possibilities; Snyder et al., 2010).

Our model demonstrates how reduced inhibitory (i.e., GABAergic) function could lead to reduced competitive dynamics in prefrontal cortical networks, allowing non-winning competitors (alternative responses that are not selected) to become more active and to compete over a longer period, which impairs selection and increases time for the model to settle, a measure akin to RT in humans. In contrast, greater inhibition allows the most active representation to more quickly suppress less active alternative responses and thus be quickly selected for production (Figure 1A; Snyder et al., 2010). Conversely, our preliminary extensions to these neural network simulations suggest that reduced glutamatergic function, which results in reduced excitation, can improve selection by reducing activation of competing responses. In contrast, increased excitation allows these alternative responses to become more active and to compete over a longer period, which impairs selection (Figure 1B). Thus, our model predicts that the relative balance of inhibition to excitation in pFC will play a significant role in individual differences in selection ability (Figure 1C).

Previous work from our group is consistent with this theoretical model, suggesting increased GABA, the primary inhibitory neurotransmitter, improves the speed of selection. In a double-blind placebo controlled study, administration of a GABA agonist, midazolam, specifically reduced selection cost: the time needed to generate a verb when there were many competing responses (high selection demand, e.g., *ball*, associated with *throw*, *hit*, *bounce*, etc.) versus few competing responses (low selection demand, e.g., *knife*, associated with *cut*; Snyder et al., 2010). Conversely, individuals with high levels of anxiety, who have reduced GABAergic function (e.g., Kalueff & Nutt, 2007), showed increased selection cost and reduced BOLD signal in ventrolateral pFC (Snyder et al., 2010), a cortical area key for selection (e.g., Snyder et al., 2011; Nelson et al., 2009; Thompson-Schill, 2005).

Although this prior work provided support for a role of GABA in selection, it did not provide direct evidence that individual differences in selection depend on inhibition in pFC. First, the effects of midazolam are widespread in cortex and not limited to prefrontal regions. Second, individual differences in GABA concentration were not directly measured: Anxiety and pharmacological manipulations were used as indirect proxies. Thus, more direct measurement of inhibitory and excitatory neurotransmitter function is necessary to investigate if they play an important role in determining individuals' selection abilities.

However, there is converging evidence to suggest that GABAergic inhibition may play an important role in aspects

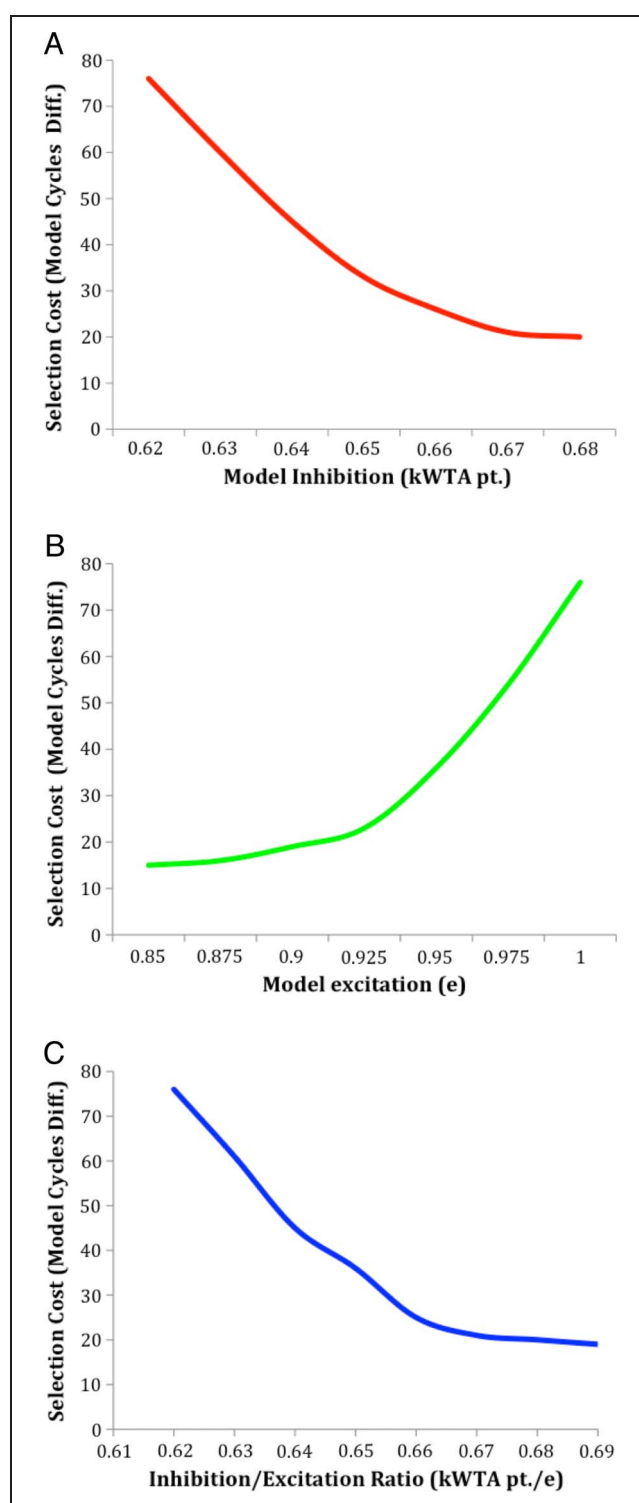


Figure 1. Neural network simulations of the effects of inhibition and excitation in lateral pFC on selection. See Snyder et al. (2010) for details of the model. (A) Effect of inhibition with excitation held constant ($e = 1$). Higher levels of inhibition allow competing responses to be more quickly suppressed and thus allow a response to be more quickly selected. (B) Effect of excitation with inhibition held constant ($\text{kWTA pt.} = 0.62$). Higher levels of excitation lead to greater activation of competing responses and thus slow selection of a response. (A, B) Note that lower levels of excitation can compensate for lower levels of inhibition and vice versa, thus (C) selection costs are predicted by the ratio of inhibition and excitation.

of executive function. For example, GABAergic inhibition has also been found to be important for performance in other tasks that are related to executive function, including motor control in the face of distractors (Boy et al., 2010; Sumner, Edden, Bompas, Evans, & Singh, 2010) and working memory (Durstewitz, Seamans, & Sejnowski, 2000; Rao, Williams, & Goldman-Rakic, 2000). In particular, blockade of GABA_A in monkeys diminishes working memory performance by disrupting the spatial tuning of neurons, suggesting that inhibition plays a general role in selecting representations throughout the brain (Rao et al., 2000). Our model makes the prediction that GABA improves performance in these tasks by allowing efficient selection of the relevant representations through lateral inhibition (e.g., selecting the motor representation for the target response vs. the distractor). However, these improvements could also be attributed to increased efficacy in other common executive processes, such as the maintenance of task-relevant goals. Thus, to disentangle the contribution of GABA to common executive processes and selection specifically, performance in both processes must be measured across individuals in whom we have measures of GABA concentration.

Another limitation of our prior work is that, although our studies implicated the inhibitory neurotransmitter GABA, they did not address the potential that the main excitatory neurotransmitter, glutamate, may have an opposite effect on selection. In our prior studies, we did not pharmacologically attempt to alter glutamate levels, as glutamate agonists increase the potential for the onset of seizures. In addition, fMRI BOLD signal reflects a mixture of inhibitory and excitatory activation, making it impossible to study their relative balance (e.g., Logothetis, 2008). Thus, to test our model's hypothesis that the relative balance of inhibition to excitation is the most powerful predictor of individual difference in selection, both neurotransmitters must be measured across individuals.

To address these issues, in this study we test the hypothesis that the relative balance of inhibitory and excitatory neurotransmitters in left lateral pFC, as measured using magnetic resonance spectroscopy (MRS) predicts individual differences in selection ability. Using MRS, we directly measured concentrations of the major inhibitory and excitatory neurotransmitters in the brain, GABA (GABA⁺) and glutamate/glutamine (Glx) in left lateral pFC in an unselected sample of young adults. We examined individual differences in selection abilities using two well-validated selection tasks. In addition, we assessed common executive function (common EF) abilities to test the hypothesis that the balance of inhibition to excitation specifically improves the ability to select among competing representations and not executive function more generally. Finally, we used a LASSO regression technique to test which of our neurotransmitter measures—GABA⁺ as a measure of inhibitory function, Glx as a measure of excitatory function, or the ratio of inhibition to excitation (GABA⁺/Glx)—is the best predictor of selection abilities.

METHODS

Participants

Participants were 32 University of Colorado Boulder undergraduates (average age = 21 years, 14 men) and gave informed consent. Seven participants were excluded from certain analyses: One participant had missing data for the verb generation task and two had missing data for the sentence completion task because of a computer problem. In addition, four participants' GABA concentration could not be calculated because of excessive motion. To maximize power, all participants who had relevant data for a given analysis were used even if they had missing data relevant to a different analysis.

MRS

Voxel Location and Placement

We measured neurotransmitter concentration in two voxels in left lateral pFC. We centered a ventral voxel on inferior frontal gyrus (pars opercularis) and a dorsal voxel on middle frontal gyrus (Figure 2). The voxels were angled to align with gyri to avoid deviating into other gyri and were placed as close to the cranium as possible without imaging fatty tissue to ensure maximum coverage of gray matter. We used two separate voxels because it would be difficult to use one large rectangular voxel to cover dorsal and ventral pFC without also imaging a large amount of white matter and cerebrospinal fluid. Furthermore, we were interested in possible differences between dorsal and ventral pFC and having two separate measurements allowed for this exploratory aim.

Care was taken to avoid imaging further posterior than the frontal sulcus to avoid motor cortex and further

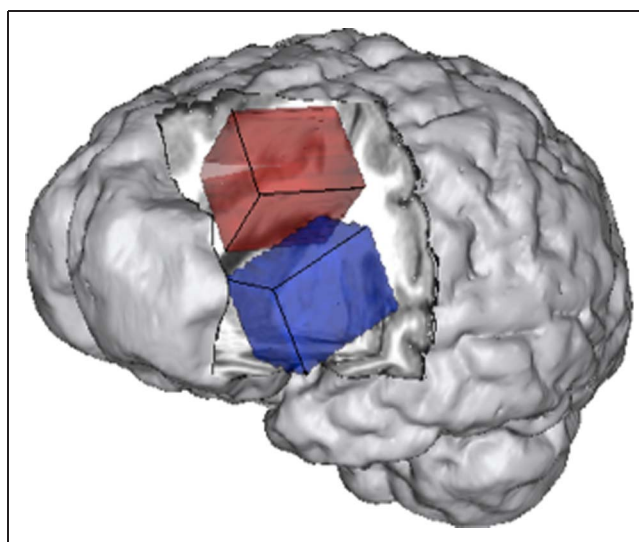


Figure 2. Two lateral prefrontal regions, a dorsal (red) and ventral (blue) voxel, were localized using structural landmarks and magnetic resonance spectra were acquired. Average dimensions and coordinates were used to visualize voxel localization.

anterior than the intermediate frontal sulcus to avoid OFC. However, we also prioritized using the largest volume per voxel possible consistent with the above restrictions to ensure reasonable signal-to-noise ratio; hence, the voxels in participants with smaller brains sometimes exceeded those boundaries by a small amount. To avoid this problem, we did not recruit participants with particularly small heads. Average dimensions for dorsal voxels (RAS coordinates) were 23.6 mm × 34.4 mm × 25.4 mm = 20620.7 mm³ = 20.63 cm³, whereas the average dimensions for the ventral voxels were 24.3 mm × 35.6 mm × 22.7 mm = 19637.9 mm³ = 19.64 cm³. Both a GABA-specific sequence and a standard spectroscopy sequence were run on each voxel.

Acquisition

Data were acquired using an eight-channel phased-array head coil in a GE 3T scanner while participants watched a movie. First, we acquired anatomic information using a T1-weighted sequence (3-D IR-SPGR). Next, to localize spectroscopy voxels, we used a three-plane scout, followed by sagittal and coronal 3-D SPGRs. These localizer scans prescribed two T2 weighted Fast Spin Echo (FSE) acquisitions angled through left ventral and dorsal lateral pFC, respectively, to delineate the ROIs.

We measured glutamate using GE's standard PROBE-P (PRESS) sequence. GABA was measured using a "J-editing" technique (MEGA-PRESS; Mescher, Merkle, Kirsch, Garwood, & Gruetter, 1998) implemented in-house by modification of GE's standard PROBE-P sequence (*presscsi*) with the addition of two spectrally selective 180° Gaussian pulses of 16-msec duration, centered at 1.9 ppm, as previously described (Rojas, Singel, Steinmetz, Hepburn, & Brown, 2014). Using standard spectroscopy, GABA resonances at 3.02 ppm are masked by the creatine peak as they have similar resonance frequencies. J-pulses can "edit out" the GABA signal. Using the J-difference method, we acquired two spectra, one with the J-editing pulses on and one with them off, and obtained the GABA spectrum by subtracting the two acquisitions. We interleaved J-editing on and off acquisitions to minimize misregistration. We also obtained two reference frames (16 averages) without water suppression.

MR-compatible goggles and headphones (Resonance Technology, Inc., Northridge, CA) were used to minimize participant motion. Parameters for 3-D IR-SPGR technique were matrix = 256², field of view = 22 cm, repetition time (TR)/echo time (TE)/IR = 10/3/450 msec, number of excitations (NEX) = 1, no gap, resulting in 138, 1.2 mm thick axial slices with an in-plane resolution of .86 mm². Parameters for T2-weighted FSE acquisitions were field of view = 22 cm, TE/TR = 102/2000 msec, echo train length = 26, slice thickness/gap = 3/0 mm, 1 slice, matrix = 256 × 224, NEX = 1, time = 16 sec. Parameters for PROBE-P (PRESS) spectroscopy sequence were TR/TE = 2500/30, 128 averages, phase cycling NEX = 8, time = 432 sec.

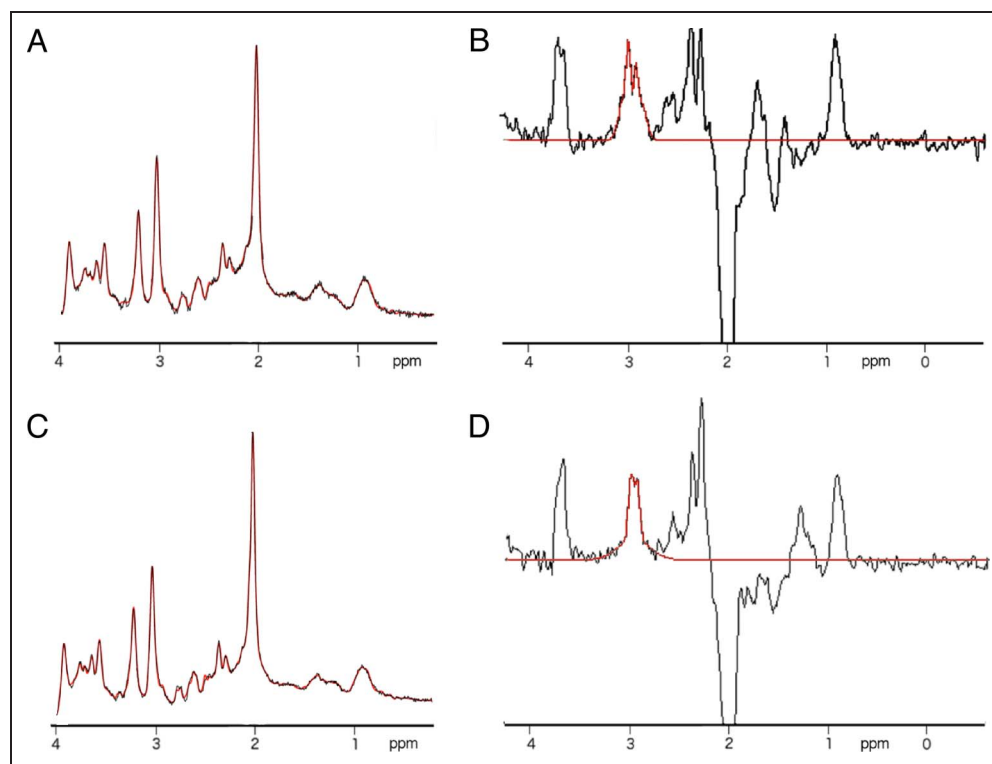
In the MEGA-PRESS sequence, the "edit-off" acquisition were actually done by centering the editing pulses at 7.5 ppm (symmetrically on the other side of the water resonance) to avoid differences in baseline artifacts (Bogner et al., 2010) rather than completely turning the editing pulses off. No eddy current or baseline artifact differences were noted between the edit-on and edit-off data. Acquisition parameters used were TR/TE = 2500/70 msec, 512 total averages (256 edit-on and 256 edit-off, time = 1300 sec).

Preprocessing and Analysis

We analyzed glutamate using LCModel version 6.2-1Q (Provencher, 1993) and used the unsuppressed water signal as a reference to obtain metabolite concentrations given in "institutional units" (nominally millimolar concentrations uncorrected for relaxation) as described in the LCModel software manual. We used the glutamate + glutamine concentration, directly from LCModel, as the Glx metric. LCModel software uses Bayesian analysis starting with solution spectra basis sets to provide estimates of metabolite concentrations without operator bias. LCModel also provides error estimates for each metabolite (given as % SDs but actually Cramer-Rao lower bounds). LCModel estimates with errors higher than 20% are generally not considered reliable. Typical errors for glutamate + glutamine (Glx) were 6–10%. Figure 3 shows the raw spectra and the overlaid fit by LCModel for representative ventral (A) and dorsal (C) volumes.

To produce GABA difference spectra, we used GE's SAGE spectroscopy analysis software version 7.6.2 (GE Healthcare, Waukesha, WI) to separate the J-edit "on" and "off" frames, reconstruct them into the frequency domain, and subtract them from each other. GE's SAGE spectroscopy processing software was used to analyze GABA data because LCModel is not capable of separating the edit-on and edit-off frames of data, and also suitable basis sets for analysis of the subtraction (edited) spectra were not available. First, the edit-on and edit-off frames were separated using the "Remove Frames" function under the "Processing" menu. Then for each set of frames, the following steps were performed: (1) The residual water signal in each frame, referenced to the unsuppressed water frames, was used to correct for phase, frequency, and residual eddy currents (internal water referencing); (2) a high-pass filter (bandwidth = 20 Hz) was applied; (3) a 2.0-Hz Gaussian line broadening filter was applied; (4) zero-filling once; and (5) Fourier transformation into frequency domain edit-on and edit-off spectra. The SAGE "SVQ" recon function was used for these steps. No baseline correction was used, as the offsets for edit-on and edit-off were the same and were removed by the subtraction. No attempts were made to correct for possible coedited macromolecular resonances, and as such, we henceforth refer to the GABA signals as GABA⁺. Although some have argued for using the creatine resonance as a frequency reference

Figure 3. Example of MRS methodology. (A) Ventral short echo PRESS spectrum LCmodel output used for Glx concentration estimation. (B) Ventral J-edited spectrum for GABA estimation with the overlaid fit in red. (C) Dorsal short echo PRESS spectrum LCmodel output used for Glx concentration estimation. (D) Dorsal J-edited spectrum for GABA estimation with the overlaid fit in red.



(Waddell, Avison, Joers, & Gore, 2007), we found the internal water referencing used here worked well for this purpose.

We fit the GABA⁺ peak area using Levenberg–Marquardt least squares (Press, Teulkolsky, Vetterling, & Flannery, 1997). We assumed Gaussian line shapes, with frequency, line width, and amplitude as the fitted parameters. Because the “true” line shape of the edited GABA⁺ has been characterized as a “pseudo doublet” (Waddell et al., 2007) with fine structure from three lines we fit GABA⁺ signals at ~3.02 ppm in the spectrum using three Gaussians. Mullins et al. (2014) recommend using a single Gaussian for these fits; however, we have found that the three Gaussian approach results in lower chi-square values and better fits visually. The initial starting points for these three lines were 3.09, 3.02, and 2.95, with the SAGE “Create Pick Table” function used to refine the initial estimates for the fits. Over parameterization of each fit was checked by using a correlation matrix (obtained by inversion of the covariance matrix generated by the Marquardt–Levinson least squares routine; Brown, 1996) to check that correlations between parameters were less than 0.5. If the correlation matrix revealed that the GABA fit was overparameterized, the number of lines fit was reduced to two (which only occurred for four spectra total). All fits were visually inspected for deviations by generating a FID (assuming Gaussian lines) using the fitted values followed by Fourier transformation to produce a synthesized spectrum. This generated spectrum was then overlaid on the experimental spectrum to check for inaccuracies and errors in the fits. Figure 3 shows the generated spectrum and the overlaid fit in red for representative ventral (B) and dorsal (D) volumes.

The GABA⁺ signals were also quantitated using an integration routine in SAGE, which was used as a further check on the fitted values.

Although the creatine signal in the edit-off spectra is sometimes used to create GABA⁺/creatine ratios, the creatine peak at TE = 70 msec contains contributions from the J-modulated GABA⁺ resonances and separating those contributions using least squares is problematic. In addition, many arguments have been made against using the creatine resonance as an intensity standard. Thus, we divided the sum of the three fitted line areas for the GABA signals by the integrated water peak area at 4.7 ppm from the water reference frames to yield a GABA⁺/H₂O ratio.

Gray Matter Estimation

In all analyses, we included gray matter volume as a covariate to account for individual differences in voxel alignment and baseline gray matter volume. We submitted full brain structural images to FAST (FMRIB’s Automated Segmentation Tool), resulting in estimates for three classes of tissue—gray matter, white matter, and CSF (spatial smoothness = 0.1, bias field smoothing extent = 20 mm, main-loop iterations during bias-field removal = 4). We then calculated the mean percentage of gray matter within each spectroscopy voxel. In the results, when we present a result of a combined measure of metabolites across voxels, we use the average percentage of gray matter volume across the two voxels as the covariate. All results presented are after controlling for gray matter volume except where otherwise noted.

Statistical Analyses

All statistical analyses were performed using R Project for Statistical Computing (www.R-project.org). We performed our analyses using linear models with standardized variables (z -scored) to produce standardized coefficients (betas).

Model Selection Using LASSO

We used LASSO (Tibshirani, 1996), a regression method that penalizes the addition of extra predictors into a linear model. Such penalization discourages the use of excessive predictors in a model and can help in variable selection by shrinking less important variables to zero. This method is akin to stepwise regression but avoids many of its recently derided problems such as multiple comparisons (Mundry & Nunn, 2009; Whittingham, Stephens, Bradbury, & Freckleton, 2006). The parameter lambda determines the extent of the penalization with greater values resulting in very sparse models. To select a lambda parameter, one can choose the lambda parameter that results in the minimal mean square error for the regression. We selected lambda using fivefold cross-validation, a method that trains the model on 4/5 of the data and tests on the remaining 1/5, to avoid overfitting. We used the GLMNET implementation in the R statistical language.

Cognitive Tasks

To test the association between neurotransmitter levels and cognitive function, we assessed performance on two sets of tasks outside of the magnet: (1) those used to specifically assess the ability to select among alternative responses relevant to the current goals and (2) tasks to assess executive function more broadly (Friedman et al., 2008), which served as comparison measures. On average, performance on cognitive tasks was assessed 12.3 days before the MRS session.

Selection Tasks

These tasks measure the ability to select an appropriate word in response to a specific verbal context. For both tasks, selection demand for the stimuli was calculated as in previous work (Snyder et al., 2010, 2011; Snyder & Munakata, 2008) using latent semantic analysis (Landauer, Foltz, & Laham, 1998). Participants responded using a microphone that recorded voice-triggered RTs and advanced the computer to the next trial. Trial order was randomized for each participant.

Sentence completion. Materials were 100 normed sentences with the final word missing (Snyder & Munakata, 2008; Bloom & Fischler, 1980) in two conditions: high selection demand and low selection demand. For the high

selection demand sentences, there was high competition among alternative responses because the sentence could have many possible endings (e.g., There is something grand about the ____). For the low selection demand sentences, there was low competition because there were few possible endings (e.g., He mailed the letter without a ____). Participants were instructed to complete each sentence with the first word that came to mind that could end the sentence. They completed four practice sentences followed by two blocks of 50 trials each. A fixation point appeared on the left side of the screen for 1500 msec (where the first word of the sentence would appear), followed by the sentence. To control reading speed, sentences appeared in four segments of one to three words each (1000 msec/segment, with previous segments remaining visible). The final segment always contained only the last word, followed by a blank.

Verb generation. Materials were 100 normed nouns in two conditions: high selection demand and low selection demand (Snyder et al., 2010, 2011; Snyder & Munakata, 2008). For the high selection demand nouns, there was high competition among alternative responses because the nouns had many verb associates (e.g., *Ball*, associated with *throw*, *hit*, *bounce*, etc.). For the low selection demand nouns, there was low competition because there were few verb associates (e.g., *Scissors*, associated with *cut*). High and low selection demand conditions were matched on retrieval demand (association strength, as determined by latent semantic analysis; Snyder et al., 2010, 2011; Snyder & Munakata, 2008), with half high and half low retrieval nouns. Participants were instructed to say the first verb that came to mind when presented with a noun and were given an example and eight practice trials before completing the task. A fixation-cross appeared for 500 msec, followed by a noun.

Selection task preprocessing. For both selection tasks, microphone errors (e.g., failing to trigger) were excluded, and nonverb errors were removed from the verb generation task. RTs < 200 msec, > 10,000 msec, or greater than three standard deviations above the participant's mean RT were trimmed. RTs were log transformed to remove skew and z -transformed within participants to remove baseline differences in RT. Selection cost was calculated by subtracting the high-demand and low-demand condition z -score averages. For the verb generation task, we used selection cost during the low retrieval condition as previous work has shown this to be a particularly sensitive measure in individual differences analyses (Snyder et al., 2010). We combined selection cost measures from the two tasks ($r = .43$, $p = .02$, two-tailed) to produce a robust measure less sensitive to task-specific variance. To generate our selection composite measure, we averaged z -scored measures of selection cost from each selection task.

General Executive Function Tasks

To assess other aspects of executive function, we used three tasks that have been found in prior research to load highly on a factor common to all executive function tasks (Friedman et al., 2008). This factor is hypothesized to be the ability to maintain a task goal online (Friedman et al., 2008) and is distinct from selection processes. z scores on the three tasks were averaged to create a composite score of common EF.

Antisaccade (Friedman et al., 2008). Participants focus on a central fixation cross (lasting 1–4 sec). When the fixation cross disappears, an initial cue flashes a fixed distance either to the right or left of fixation. Next, the cue disappears, and the target (a digit, 1 through 9) appears for 150 msec a fixed distance from fixation and then is masked with gray cross-hatching. Participants report the target verbally. On prosaccade trials, the cue indicates the location at which the target will appear (e.g., the cue appears on the left of the screen and is followed by the target on the left). On antisaccade trials, the cue appears contralateral to the target location. The task begins with a block of 32 prosaccade trials to establishing an automatic association between the cue and target occurring on the same side of the screen. Next, a block of 130 antisaccade trials is presented to test the ability to override the automaticity of the established response. The dependent measure is the average accuracy for antisaccade trials.

Keep track (Friedman et al., 2008). In each trial, a stream of 15–25 words is presented, one at a time. The words belong to six categories: relatives, countries, colors, animals, metals, and distances, with six words in each category. Participants are asked to keep track of the most recent word presented from each of two to five categories and report their answer verbally at the end of the trial. After two practice trials with two categories to remember, there are 16 trials with two to five categories to remember, randomly ordered. Each trial begins with the list of categories, which remain at the bottom of the screen until the final recall. Each word appears for 2000 msec, followed by the next word. The dependent measure is the percentage of correctly maintained items.

Category switch (Mayr & Kliegl, 2000). In each trial, participants see a word that could be categorized in terms of (a) whether it described a living or nonliving thing or (b) whether it described a thing that is smaller or larger than a soccer ball. A symbol appearing above the word cues which categorization to use. After two blocks of 32 trials categorizing along a single dimension, participants complete two blocks of 64 trials that contain a mixture of trials with judgments along the living and size dimensions. Trials in which participants made an error are excluded from calculation. The dependent measure is switch cost (average

RT for nonswitch trials–switch trials), calculated such that higher scores correspond to better performance for consistency with the other general EF tasks in the study.

RESULTS

Measure Characteristics

Consistent with previous research, participants on average had significant selection costs for the verb generation task, $t(29) = 6.09$, $n = 30$, $p < .001$, and the sentence completion task, $t(27) = 15.72$, $n = 28$, $p < .001$, suggesting our selection tasks appropriately measured selection abilities across participants. Moreover, performance on the two tasks correlated across participants ($r = .42$, $n = 27$, $p < .05$).

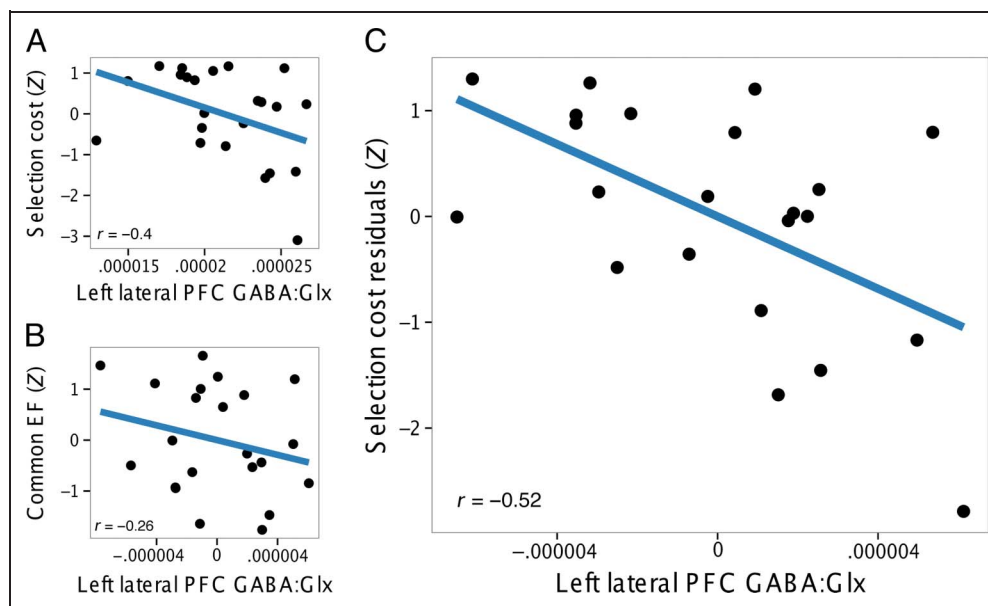
Measures of Glx across ventral and dorsal voxels trended toward being correlated ($r = .31$, $n = 30$, $p = .10$) with Glx concentrations being greater in the ventral than dorsal voxel ($M_{\text{diff}} = 1.02$, $t(29) = 3.54$, $n = 30$, $p = .001$). Levels of GABA⁺ between these two voxels were correlated ($r = .47$, $n = 27$, $p = .01$) but not significantly different in concentration ($M_{\text{diff}} = 4.48e-0.6$, $t(26) = 0.79$, $n = 27$, $p = .43$). The relatively high correlations between the two voxels, especially given the inherent noise in MRS measurement, led us to use measures for Glx and GABA⁺ that were averaged across both voxels for our main analyses.

Effects of GABA⁺ and Glx on Selection

Consistent with a critical role of the balance of inhibition and excitation in selection, we found that a higher GABA⁺ to Glx ratio (GABA⁺/Glx) predicted decreased selection cost ($\beta = -0.49$, $t(21) = -2.48$, $n = 23$, $p = .02$). This relationship was in the same direction, but of marginal significance, without controlling for gray matter volume ($\beta = -0.40$, $t(22) = -2.00$, $n = 23$, $p = .06$; Figure 4A) but remained significant when controlling for voxel size ($\beta = -0.59$, $t(19) = -2.7$, $n = 22$, $p = .01$), which can be viewed as a proxy for brain size. Individually, concentration of GABA⁺ ($\beta = -0.18$, $t(23) = -0.74$, $n = 24$, $p = .47$) and Glx ($\beta = 0.34$, $t(24) = 1.78$, $n = 25$, $p = .09$) did not significantly predict selection cost. However, the direction of each of these effects was consistent with our predictions—increased Glx predicted slower selection RT, whereas increased GABA⁺ predicted faster selection performance. Together these results suggest that it is the balance between inhibition and excitation, rather than either alone, that is most predictive of selection ability.

Next, we performed exploratory analyses to examine potential differences in this effect across ventral and dorsal pFC. Selection cost was significantly predicted by GABA⁺/Glx in the dorsal voxel ($\beta = -0.62$, $t(21) = -3.56$, $n = 23$, $p < .01$) but did not reach statistical significance in the ventral voxel ($\beta = -0.20$, $t(23) = -0.88$, $n = 25$, $p = .39$). However, the difference between the relationship of GABA⁺/Glx and selection cost was not significantly

Figure 4. Relationships between neurotransmitter concentrations in left lateral pFC and behavioral measures of executive function. (A) Selection RT cost (z-score composite) decreases as left lateral GABA/Glx increases. (B) common EF (z-score composite) does not show a significant relationship with GABA/Glx controlling for gray matter volume. (C) After regressing out shared variance with general executive function and gray matter volume, relationship between increased GABA/Glx and decreased selection cost remains, indicating the increases in selection performance are not driven by increases in common EF performance. (B, C) Residuals from a linear model regressing out GM (B, C) and/or common EF (C) are plotted on the *x* axis.



different between the two voxels ($\beta = -0.23$, $t(20) = -1.02$, $n = 23$, $p = .32$). Given the lack of statistical evidence of a difference between voxels, the fact that the two voxel's GABA⁺/Glx measures are correlated, and the inherent noise in spectroscopy measurements, we continue to focus on the more robust measures that average values across voxels.

Specificity of Effects to Selection

To verify the cognitive specificity of our findings, we controlled for common EF, which is not hypothesized to depend on net inhibitory dynamics. Rather, the ability to hold material online has been suggested to rely on recurrent excitatory function in pFC (e.g., O'Reilly & Frank, 2006). We calculated a common EF composite using three tasks found to load on a common factor: an antisaccade task, a working memory task, and a switching task (e.g., Friedman et al., 2008). Higher GABA⁺ marginally predicted lower common EF ($\beta = -0.34$, $t(24) = -1.61$, $n = 26$, $p = .07$), with a trend in the same direction for GABA⁺/Glx ($\beta = -0.34$, $t(24) = -1.61$, $n = 26$, $p = .12$) and with no effect of Glx ($\beta = 0.01$, $t(26) = 0.02$, $n = 28$, $p = .98$)¹ (Figure 4B). Importantly, when controlling for common EF, the relationship between GABA⁺/Glx and selection remains significant ($\beta = -0.56$, $t(20) = -2.77$, $n = 23$, $p = .01$; Figure 4C), demonstrating that the relationship between GABA⁺/Glx and selection is not driven by effects on common EF.

Model Selection Using LASSO

To further verify the specificity of our findings given the number of comparisons performed, we employed LASSO

to perform variable selection. We entered GABA⁺, Glx, GABA⁺/Glx, common EF, and gray matter volume into a LASSO model predicting selection cost. In the sparsest nonempty model produced ($\lambda = 0.37$), GABA⁺/Glx and gray matter volume² were the only two variables selected.³ The results suggest that the ratio of GABA⁺ to Glx is a more powerful predictor of selection than the concentration of either alone and including common EF is not necessary to bolster the model.

DISCUSSION

Our results demonstrate that the ability to select among competing options is linked to individual differences in the balance of inhibitory and excitatory neurotransmitters in left lateral pFC. Importantly, these individual differences in this aspect of executive function are because of differences in neurobiological dynamics at the neurochemical level, are specific to selection abilities, and confirm predictions from our computational modeling of executive functions.

Notably the current findings provide important new support for predictions from our computational modeling and build substantially upon prior empirical research that had less directly suggested a role for GABA in selection (Snyder et al., 2010). In particular, our findings support the idea that the level of inhibitory to excitatory dynamics in left lateral pFC influences selection. In the model, greater levels of inhibitory dynamics result in faster resolution of competition and in turn faster RTs. Both greater inhibition and decreased excitation result in faster selection in the model, leading to the prediction that humans with a greater ratio of GABA to glutamate will exhibit faster

selection abilities. Previous studies, however, did not directly measure neurotransmitter concentrations in individuals and instead relied on spatially unspecific pharmacological manipulations and individual differences in anxiety as proxies for GABA concentration. Moreover, prior studies lacked the ability to measure excitatory neurotransmitters that may have a complimentary role with GABA in determining the balance of inhibition and excitation in cortex and thus the ability to resolve competition to select a response.

In the current study, we eliminated these problems by directly measuring neurotransmitters using noninvasive MRS techniques and demonstrated that the balance of inhibition to excitation, as measured by the ratio of GABA⁺ to Glx, is a critical determinant of individual differences in selection. We also controlled for general executive function abilities to demonstrate the specificity of GABA⁺/Glx as a determinant of individual differences in selection abilities and not executive function more generally. Finally, we used model selection techniques to show that the ratio of GABA⁺ to Glx is a more powerful predictor of selection than either neurotransmitter alone.

Moreover, the differentiation between selection and common EF in our study suggests a reinterpretation of studies showing a role of GABA in executive function tasks. For example, our findings suggest that improved motor control with increased GABA (Sumner et al., 2010) might be better explained by improved selection of the relevant motor representation in that task, rather than improved common EF necessary to maintain the task goals. Similarly, the finding that GABA is important for working memory performance (Rao et al., 2000) may also be explained by a role for GABA in selection of working memory representations. Previous computational models have suggested GABA is important for working memory performance because inhibition reduces spontaneous activity of distracting irrelevant items (Durstewitz et al., 2000; Rao et al., 2000). Our finding is compatible with such models, as the GABAergic sharpening of working memory representations via inhibition of competing irrelevant items is likely analogous to the selection of words during speech, albeit with different underlying representations.

Importantly, the differentiation between selection and other executive functions in our data is consistent with the claim by such models that the sharpening or selection of working memory representations is separate from their maintenance (Durstewitz et al., 2000; Rao et al., 2000). Our findings support these claims as the relationship between GABA⁺/Glx and selection remained significant even after controlling for common EF, which has been hypothesized to reflect the maintenance of task-relevant goals (e.g., Miyake & Friedman, 2012). Moreover, common EF and selection were uncorrelated, further supporting the idea that these processes are relatively independent. Unlike selection of representations, maintenance of representations is not thought to depend on inhibitory mechanisms. Rather, working memory maintenance is hypothesized to

occur via sustained neural firing of neurons in pFC (e.g., Miller & Cohen, 2001) and thus could in fact be negatively impacted by neural inhibition. Indeed, the trend in our data for higher levels of GABA⁺/Glx and GABA⁺ (but not Glx) to predict poorer general executive function suggests that inhibition may interfere with working memory maintenance, and this issue is ripe for further investigation.

Within the broader context of understanding how the brain implements selection, we can speculate on how the inhibitory prefrontal selection mechanism we studied differs from other selection mechanisms, such as those implemented by the BG (e.g., van Schouwenburg, den Ouden, & Cools, 2010; Frank, Loughry, & O'Reilly, 2001). BG gating mechanisms can be thought of as invoking a form of selection, as the BG are proposed to select which posterior brain representations are gated into pFC for maintenance in working memory. Using dopaminergic reward signals, the BG learn over time to gate representations that have led to a positive outcome in similar previous experiences. In contrast, prefrontal inhibitory selection is used to choose among competing representations already present in working memory when task demands (e.g., select a single word) make the response underdetermined. This stage of selection is especially important when prior experience is not sufficient for selecting a response because all of the candidate representations are estimated to be similarly likely to result in a reward. Although lateral inhibition and BG gating mechanisms are thus distinct, there may be points of intersection between them. For example, active maintenance of representations in dorsolateral pFC may play an important role in each—by maintaining representations gated into working memory by the BG (e.g., Frank et al., 2001) and maintaining task goals that can bias the lateral inhibition process in VLPFC toward task-relevant representations (Snyder, Banich, & Munakata, 2011). A promising direction for future work will be to more carefully examine the interaction between selection processes implemented by the VLPFC and those implemented by the BG.

In addition, our study speaks more broadly to a recently voiced idea that, when studying the role of GABA, the tightly intertwined role of glutamate must also be taken into consideration (Stagg, Bachtar, & Johansen-Berg, 2011). Glutamate and GABA are closely related in the brain because of their opposing effects on brain dynamics and because GABA is metabolized from glutamate. However, many studies ignore the role that glutamate may play in modulating the effects of GABA on behavior, and vice versa. Our findings support the idea that looking at the concentration of both of these neurotransmitters is beneficial when investigating neurotransmitter-behavioral relationships.

Despite the important new additional information provided by the current study, there are some limitations and questions for future research. As with all MRS studies, we could not distinguish between pre- and postsynaptic neurotransmitter concentrations (Stagg et al., 2011). Hence, we

are unable to address the specific role that GABA plays in the synaptic cleft to improve selection. To resolve this limitation of MRS, further investigation of the constituents of the MRS signal using *in vitro* samples is needed. Another issue that remains unclear is the degree to which different specific aspects of GABAergic function are responsible for the effects we observe. It would be helpful to try to distinguish the contribution of the fast acting GABA_A and slow acting GABA_B to the MRS signal. GABA_B is thought to be more readily engaged in local circuit activity (Mann, Kohl, & Paulsen, 2009), making it possible that it is more important for resolving competition among options via lateral inhibition. An approach that could further specify the relationship between GABA receptor subtypes and selection would be to use TMS techniques that specifically modulate tonic and phasic inhibitory activity (Stagg et al., 2011; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999). Paired-pulse TMS approaches could be used to measure GABA_A activity in left lateral pFC, and this could be tested as a predictor of selection efficacy. Additionally, comparing the effects of pharmacological agonists specific to GABA_A and GABA_B would help develop a more fine-grained model of the neurobiological processes underlying selection.

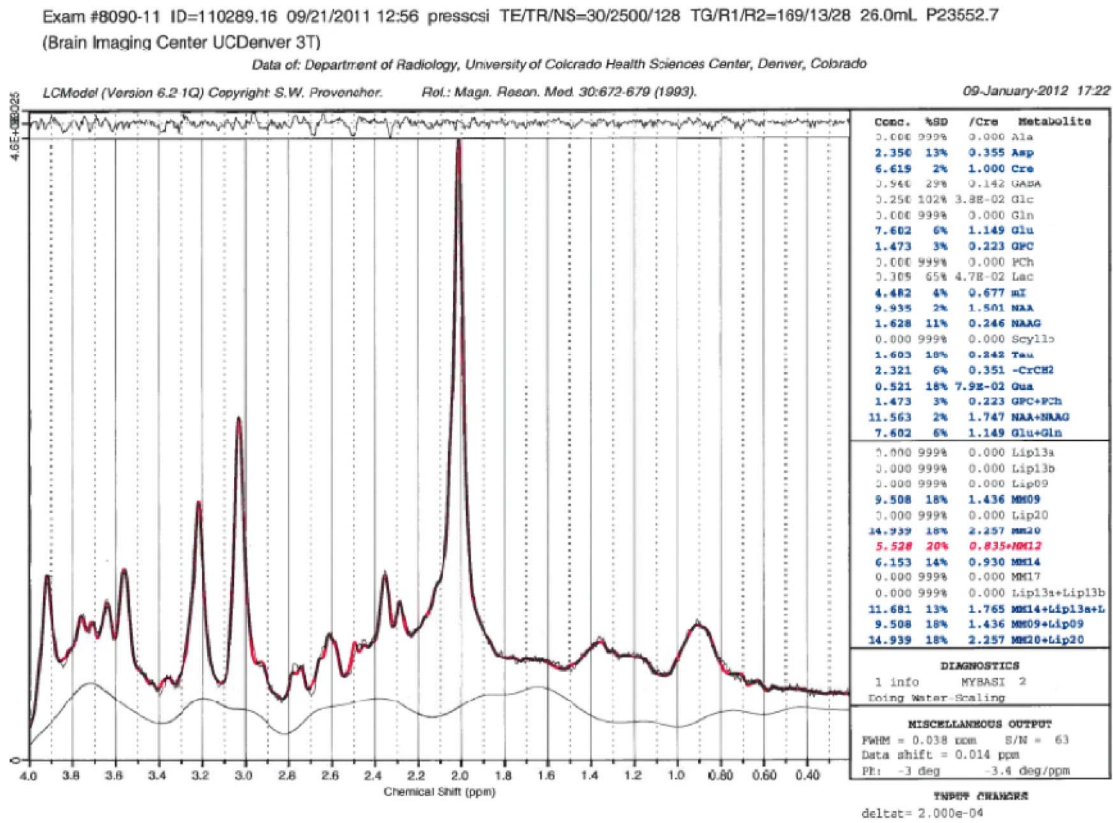
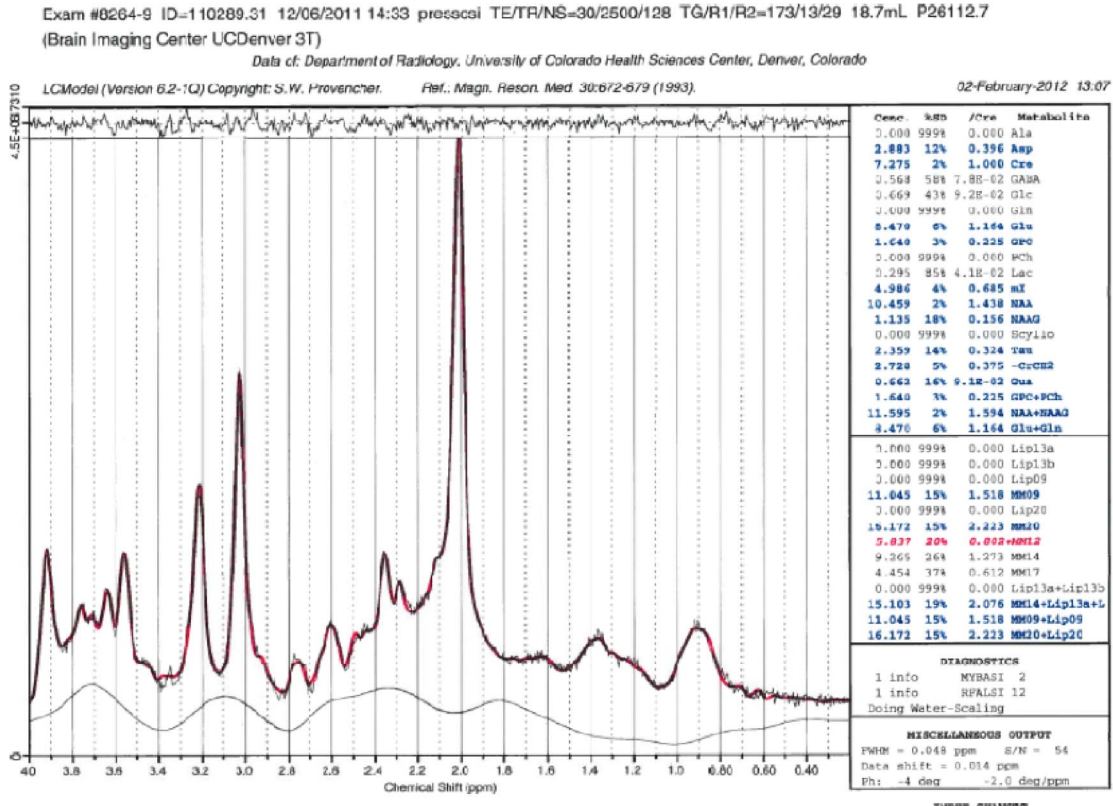
Although the current study addressed the psychological specificity of our effect, showing that it relates to selection and not executive function in general, it would be useful in future studies to examine issues of anatomical specificity

in more detail. Recent evidence suggests that GABA levels in the brain are not uniform; for example, one study found greater GABA concentration in occipital regions compared with medial pFC (van der Veen & Shen, 2013). Hence, although we have good reason to believe that our results are likely to be specific to pFC, it would be helpful in future studies to examine the ratio of inhibitory and excitatory neurotransmitter levels in posterior brain regions, such as visual cortex or temporal cortical areas involved in semantic processing, to serve as comparison regions. Such a contrast would help to determine whether the relationship between selection abilities and GABA⁺/Glx ratio is specific to lateral pFC (as we hypothesize) or to neurotransmitter concentration across the brain more generally.

In summary, our findings highlight the crucial role of the balance of excitation and inhibition in lateral pFC in influencing the ability to select among competing options. Moreover, our study advances our understanding of executive function by showing that individual differences in neurotransmitter levels and net inhibitory dynamics play an important role in the variation in selection abilities within a nonclinical population. Characterizing the neural dynamics underlying individual differences is crucial for fully understanding the nature of highly complex executive function traits; these traits play critical roles in day-to-day activities such as selecting products at the grocery store, making decisions when there is no clear right choice, and fluently expressing our ideas.

APPENDIX A

Original LCModel output for ventral and dorsal volumes. Figure 3 (A and C) was altered for aesthetic purposes. Unaltered output is included here with accompanying LCModel output table.



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Notes

1. Not controlling for gray matter volume yields similar results for GABA+ ($\beta = -0.36, t(25) = -1.85, n = 26, p = .08$), Glx ($\beta = -0.05, t(29) = -0.24, n = 30, p = .81$), and GABA+/Glx ($\beta = -0.33, t(25) = -1.69, n = 26, p = .10$).
2. Gray matter is not a significant predictor of selection alone ($\beta = 0.15, t(24) = 0.80, p = .43$) and is likely selected because it reduces residual error in the model.
3. The next variable added to the model when lambda was decreased was common executive function ($\lambda = 0.34$). LASSO did not add more variables to the model until λ was substantially decreased ($\lambda = 0.1$), at which point the shrinkage is minimal and more akin to a regular linear model, suggesting that extra variables were not necessary to explain selection cost.

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