# The distinct roles of prefrontal GABA and glutamate/glutamine in two types of cognitive control

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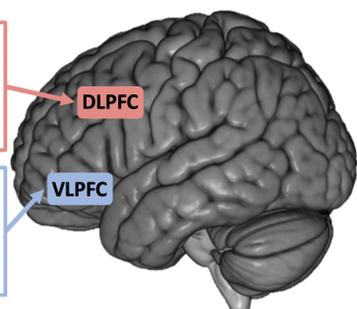UNIVERSITY OF COLORADO BOULDER

## Introduction

The purpose of this study was to examine if individuals differences in resting neurotransmitter levels in lateral prefrontal cortex are associated with hemodynamic activity during two distinct types of cognitive control processes:

**Goal maintenance:** maintaining a goal in the presence of a task-inappropriate information
- Excitatory, glutamatergic processes support recurrent maintenance [1]

DLPFC

**Goal-related selection:** selecting one response from many task-relevant options
- Inhibitory, GABAergic processes support "winner-take-all" goal-related selection [2]

VLPFC

Based on prior work [1-4], we hypothesized that hemodynamic activity during *goal maintenance* would be associated with concentrations of glutamate/glutamine (Glx) in the **dorsolateral prefrontal cortex (DLPFC)**, while activity during *goal-related selection* would be associated with concentrations of GABA in the **ventrolateral prefrontal cortex (VLPFC).**

## Methods

**Sample:** 47 women (age: $48.2 \pm 6.7$ years)

**Verb Generation Task**: Participants were presented with a noun and asked to respond with a related verb. Latent semantic analysis [4] was used to vary the demand (high vs. low) on goal maintenance and goal-related selection for each presented noun.

|  | **Low Demand** | **High Demand** |
|---|---|---|
| **Goal Maintenance** | No associated task-irrelevant noun "Toy" | A strongly associated task-irrelevant noun "Fork" |
| **Goal-Related Selection** | Few task-relevant verb responses "Ladder" | Multiple task-relevant verb responses "Ball" |

**fMRI:** Functional, structural, and spectroscopy data was collected on a SIEMENS MAGNETOM Trio (3-Tesla) MRI system with a 32-channel head coil.

**Spectroscopy:** Resting concentrations of Glx and GABA+ in the left DLPFC and VLPFC were estimated using magnetic resonance spectroscopy.

**Analysis:** A lower level analysis was run for each subject to estimate within-subject effects (high vs. low goal maintenance and goal-related selection). A covariate analysis was run for each spectroscopy voxel (DLPFC, VLPFC) to look at the relationship between neurotransmitter concentration and functional activity during the verb generation task. The reported results are the unique effects of GABA+ or Glx controlling for the other neurotransmitter and age. All reported results have undergone non-parametric permutation testing and family-wise error (FWE) cluster-extent thresholding.

## Main Effects

### High vs. Low Goal Maintenance
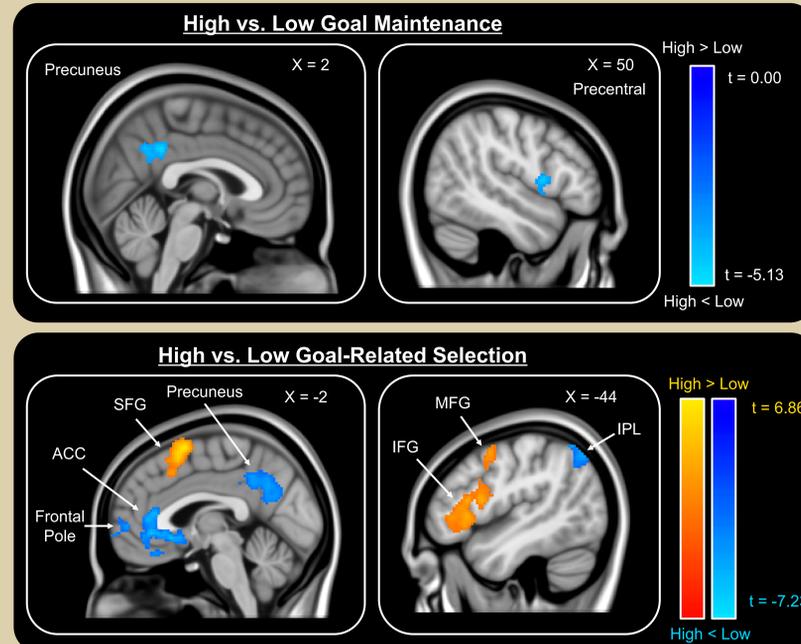


### High vs. Low Goal-Related Selection



**Figure 1.** Group main effects for the contrasts of high vs. low demand conditions. The right precuneus and right precentral gyrus were more active when demands on goal maintenance were low. Prefrontal regions in the left hemisphere (SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus) were more active when demands on goal-related selection were high, while anterior cingulate cortex (ACC), frontal polar, precuneus, and bilateral inferior parietal regions (IPL) were more active when demands on goal-related selection were low.

## Regions of Interest (ROI) Analysis

### Left DLPFC $\beta$-Values for High vs. Low Goal Maintenance



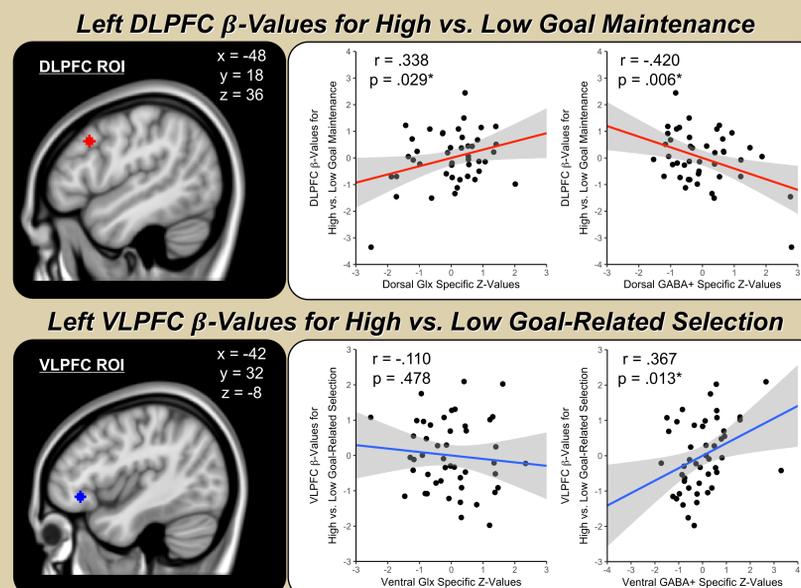### Left VLPFC $\beta$-Values for High vs. Low Goal-Related Selection



**Figure 2.** Beta-values were extracted from 5mm ROIs in the DLPFC and VLPFC [4]. DLPFC beta-values for the goal maintenance contrast were positively associated with dorsal Glx and negatively associated with dorsal GABA. VLPFC beta-values for the goal-related selection contrast were positively associated with ventral GABA. Spectroscopy and beta-values are z-scored. *p<.05

## Whole Brain Analysis: Goal Maintenance & DLPFC Glx, GABA+

### Glx Specific Concentration
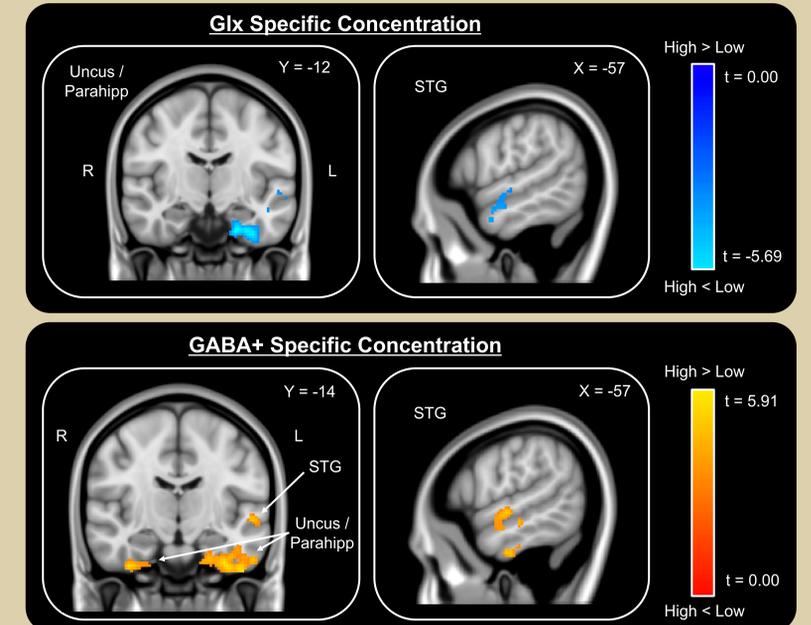


### GABA+ Specific Concentration



**Figure 3.** Regions whose activity for the contrast of high vs. low goal maintenance is negatively associated with Glx specific levels and positively associated GABA+ specific levels in the DLPFC. Parahipp: parahippocampal gyrus; STG: superior temporal gyrus.

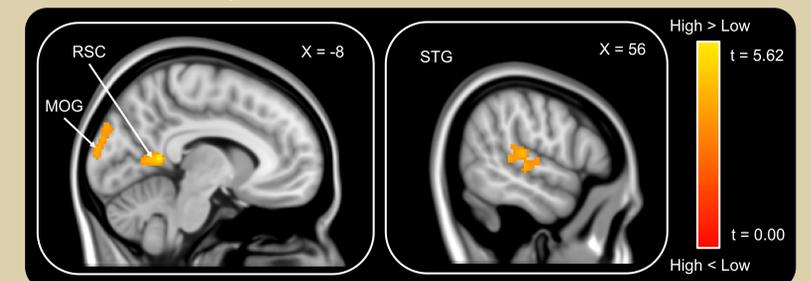## Whole Brain Analysis: Goal-Related Selection & VLPFC GABA+



**Figure 4.** Regions whose activity for the contrast of high vs. low goal-related selection is associated with VLPFC GABA+ specific levels. RSC: retrosplenial cortex; MOG: middle occipital gyrus; STG: superior temporal gyrus.

## Discussion

- Patterns of activity for *goal maintenance* in the **DLPFC** and posterior brain regions were uniquely associated with **DLPFC Glx and GABA+** concentrations in opposite directions.
  - This suggests that the excitatory to inhibitory ratio in **DLPFC** may be important for maintaining a goal in the presence of prepotent, task-inappropriate information.

- Patterns of activity for *goal-related selection* in the **VLPFC** and posterior brain regions are uniquely associated with resting **VLPFC GABA** concentrations.
  - This supports the idea that inhibitory processes in the **VLPFC** are implicated in selecting one response from many task relevant alternatives.

## References and Acknowledgements

[1] Wang et al. (2013). *Neuron*, 77(4): 736-749 [2] Snyder et al. (2010). *PNAS*, 107(38):16483-16488. [3] Snyder et al. (2011). *J Cogn Neurosci*, 23(11):3470-3482. [4] Snyder et al. (2014). *J Cogn Neurosci*, 26(11):2608-2623. [5] Holland et al. (2001). *Neuroimage*, 14: 837-843. **This work was supported by the NIMH grant R01 MH105501.**