

# Ketamine Associated Anterior Cingulate GABA Increase & Depression Remission: Preliminary Data with Dynamic Sliding-Window Functional MR Spectroscopy

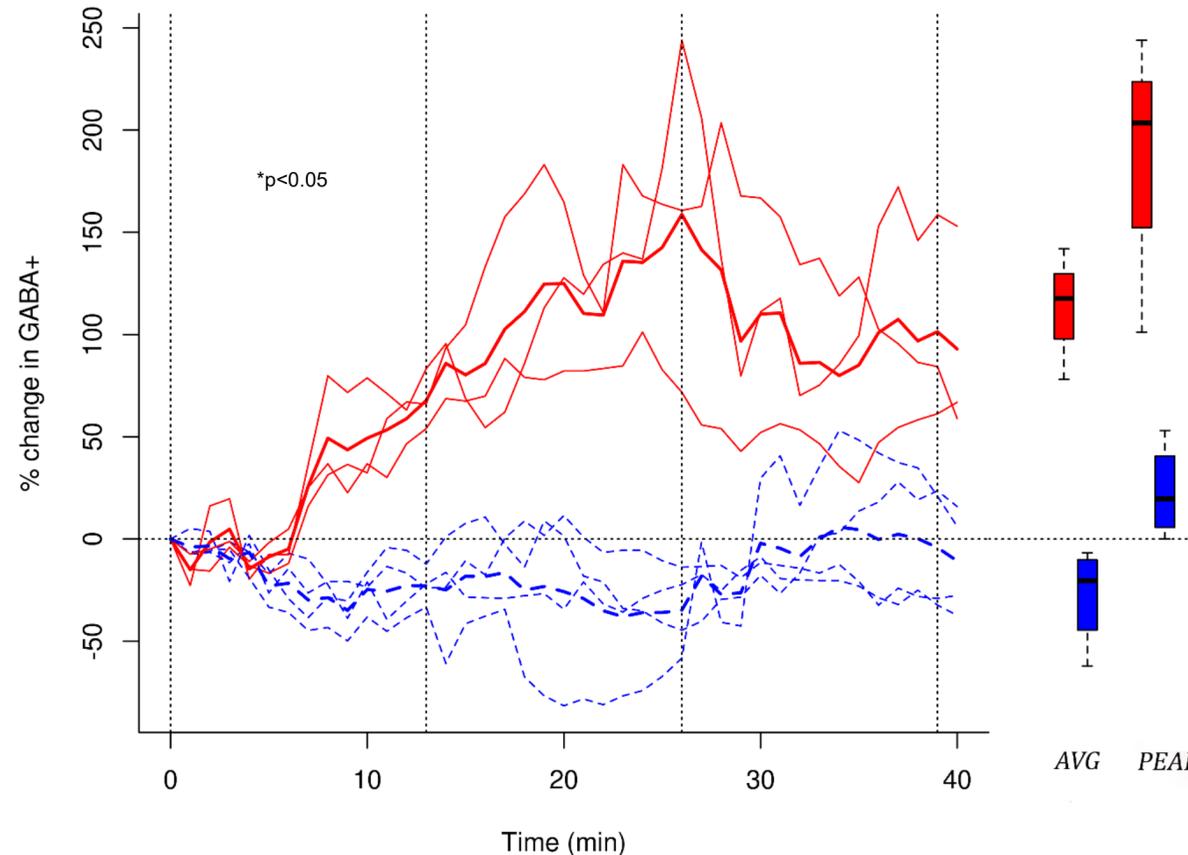
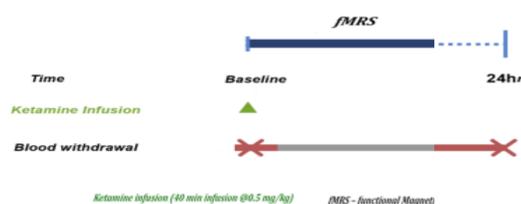
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## Background

- Gamma-aminobutyric acid (GABA) and glutamate (Glu) neurotransmission implicated in pathophysiology of treatment-resistant depression (TRD).
- Anterior cingulate cortex (ACC) - associated with antidepressant treatment response - a central target for engagement.
- Peripheral—not central—targets/potential biomarkers may have greater generalizability for clinical development.
- We investigated relationship between GABA and Glu levels measured centrally and peripherally, respectively, with change in depression symptoms after a single infusion of IV ketamine in TRD patients.

## Methods

- Open-label feasibility trial.
- Innovative comparative study utilizing functional magnetic resonance spectroscopy (fMRS) and liquid chromatography-mass spectrometry (LCMS).
- Received single IV ketamine infusion (0.5 mg/kg, infused over 40 minutes) while in an MRI scanner.
- Novel dynamic sliding-window fMRS method at 3T using the MEGA-PRESS sequence to generate continuous measurements of central Glu, glutamate+glutamine (Glx), and GABA in the ACC during the 40-min infusion.
- Corresponding peripheral metabolites measured at baseline and 24 hours post-infusion.
- Treatment response measured with change in MADRS scores from baseline to 24 hours post-infusion.
- Spearman correlation analysis tested for a relationship between percent change in central (from baseline to peak) and log2 change in peripheral biomarkers (from baseline to 24 hours) with change in MADRS.



**Figure 1.** ACC fMRS GABA Levels in Ketamine-Associated Remission vs Non-Remission. Red solid lines/red boxes: Remitters; Blue dashed lines/blue boxes: Non-remitters; BOLD Red and BOLD Blue lines: Remitters and non-remitters mean percent change in GABA+ at each time point vs baseline 0 min (in min)



**Figure 2.** MRS Voxel (3x3x2.5 cm) Placement in the Midline Anterior Cingulate Cortex

## Results

- 12 subjects completed the study, 5 excluded from analysis (3 excessive patient motion, scanner/IV pump failure)
- Remaining 7 subjects: 4 females/3 males, average age 45 ± 11.7 yrs
- Mean MADRS at baseline 23.1 ± 3.6; at 24 hours post-infusion 14.0 ± 8.6; 3 remitted at 24 hours
- No significant correlations observed between central and peripheral metabolite changes

## Conclusions

- Increase in peak ACC GABA levels with ketamine is associated with remission in treatment-resistant depression.
- These novel findings provide insights into the neurobiological mechanisms of ketamine.

**Table 1.** Comparison of Metabolite Change with Remission Status and Change in Depression

Central Metabolite % change	Mean Peak Time Point	Mean Peak Metabolite by Remission Status*			Change in MADRS (baseline to 24 hr)	
		Remitters (n=3)	Non-Remitters (n=4)	p	Spearman rho	p
<b>GABA</b>	24.3 min	182.9 (73.5)	23.2 (23.0)	<b>0.034</b>	-0.837	<b>0.019</b>
Glutamate	16.9 min	241.8 (218.8)	72.8 (28.6)	0.077	-0.691	0.086
Glx	14.3 min	129.8 (75.2)	42.9 (33.2)	0.077	-0.091	0.846
Peripheral metabolite**						
Δ Log2 GABA	24 hr	0.96 (1.85)	0.17 (0.52)	0.724	-0.032	0.926
Δ Log2 Glutamate	24 hr	-0.10 (1.07)	0.12 (1.14)	1.000	-0.158	0.623
Δ Log2 Glutamine	24 hr	0.25 (0.07)	0.05 (0.10)	<b>0.034</b>	-0.267	0.401

\*Remission = MADRS ≤ 9 at 24-hr

\*\*blood log2 change from baseline to 24 hr

GABA = Gamma aminobutyric acid; Glx=Glu+Gln; SD = standard deviation

## Reference

Singh B, Port JD, Vande Voort JL, et al. Psychiatry Res 2021; 301:113953. DOI: 10.1016/j.psychres.2021.113953