

Real-time Monitoring of *In Vivo* Human Brain Amino Acid Neurotransmitter Response to a Single Intravenous Dose of Ketamine in Major Depressive Disorder Using the ^1H MRS J-editing Technique

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BACKGROUND. Acute intravenous administration of single sub-anesthetic doses of ketamine has been recently investigated¹ as a potentially fast-acting treatment for major depressive disorder (MDD). The near immediate anti-depressant effects of ketamine, a noncompetitive glutamate (Glu) NMDA receptor antagonist, are postulated to involve the drug's stimulation of a rapid increase in brain Glu that may then enhance transmission at other Glu receptor subtypes. Here, we report the results of a pilot *in vivo* human brain ^1H MRS study that aimed to dynamically monitor Glu and GABA changes following acute intravenous administration of ketamine, which has been shown to be accompanied by a rapid Glu surge in rat brain studies².

METHODS. Seven patients with MDD (4 female and 3 male; age = 38 ± 12.2 ; mean pre-ketamine 24-item Hamilton Depression Rating Scale (HDRS-24) score = 26 ± 5.1) were enrolled into study. For the ^1H MRS studies, 5 of the 7 patients received 0.5 mg/kg of ketamine intravenously over a period of 40 min, while in the MRI scanner. Prior to and approximately every 15 min during and following infusion of the drug, six serial ^1H MR spectra were recorded with the J-editing technique (**Fig. 1**) on a 3T GE MR system, with TE/TR 68/1500ms and 580 interleaved excitations, to measure the levels of glutamate+glutamine (Glx) from their combined resonances in a $25 \times 25 \times 30 \text{ mm}^3$ medial prefrontal cortex voxel. In addition to Glx, the J-editing method achieved simultaneous detection of the major inhibitory neurotransmitter γ -aminobutyric acid (GABA), which has also been implicated in the pathophysiology of MDD. At 230 min following completion of the MRS study, depressive symptoms were assessed in each subject using the Hamilton Depression Rating Scale scoring system.

RESULTS AND DISCUSSION. Clinical Response to Ketamine: At 230 min following ketamine infusion and for up to the next 7 days, all but one of the 7 patients fulfilled the criteria for remission (**Fig. 2A**), as HDRS scores improved on average by 83% (at 230 min HDRS = 4.4 ± 7.9 ; at day 3 HDRS-24 = 5.8 ± 5.3 ; at day 7 HDRS-24 = 5.5 ± 3.4), a powerful and convincing confirmation of the reported antidepressant effect of ketamine.

GABA and Glx Response to Ketamine: Time-course curves describing the dynamic response of Glx and GABA to ketamine are shown in **Fig. 2B** for four of the subjects with successful scans, and illustrate the main features. Both Glx and GABA increased rapidly, reaching values of up to 60% above baseline within 20 min. In all cases, the rise of GABA was more rapid and bimodal, peaking slightly ahead of Glx, with a second lower peak occurring approximately 30 min after the initial maximum. Notably, end GABA and Glx values for the subject with the highest HDRS score prior to ketamine infusion fell below baseline after rising to 60% and 40%, respectively, of their baseline levels. GABA and Glx changes for the subject with the lowest pre-ketamine HDRS were the lowest observed for both neurotransmitters. While it is unclear from these limited data whether the features of the response curves (e.g., relative heights and positions of the maxima, widths or areas of main peaks) correlate with or predict therapeutic response to ketamine, these data provide a compelling rationale for future investigations of Glu and GABA changes in understanding the mechanism of the antidepressant effects of the drug.

CONCLUSION. This pilot study has reported what may be the first observation of **robust *in vivo* human brain** Glx and GABA changes following ketamine administration, in support of the postulated mechanism of action of the drug. These results provide a compelling justification for future studies designed to determine whether the observed changes in GABA and Glu in response to ketamine correlate with therapeutic response and/or predict remission/relapse rates.

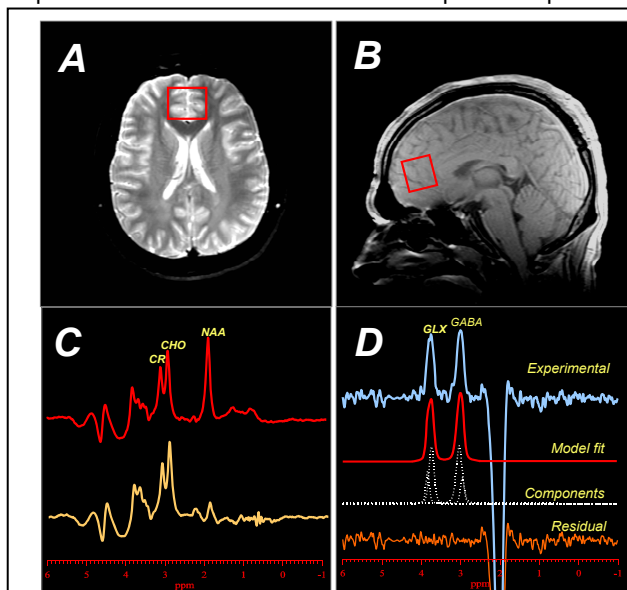


Fig. 1: [A] and [B] Axial images showing the ACC voxel size and location; [C] PRESS ^1H MR spectra with the editing rf pulse (a) off and (b) on. [D] The difference of the spectra in [C] showing (a) the detected GABA and Glx peaks, with (b-d) best-fit model curves and residuals.

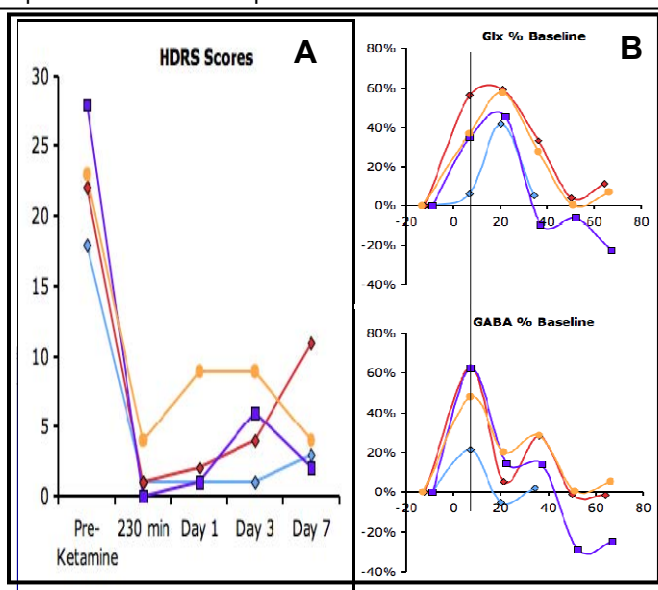


Fig. 2: [A] Depressive symptom scores (HDRS-24) and [B] GABA and Glx time-course (in minutes) in response to IV ketamine infusion (0.5 mg/kg), with matching symbols/colors in the two panels representing the same patients.

REFERENCES. [1] Berman RM et al, *Biol Psychiatry* 2000;47:351. [2] Moghaddam B et al., *J. Neurosci.*, 1997; 17:2921.