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Temporal Dynamics of Antidepressant Ketamine Effects On Glutamine Cycling Follow Regional Fingerprints of Ampa and Nmda Receptor Densities

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Introduction:
Subanesthetic dose of ketamine was repeatedly shown to improve depressive symptoms with a short latency of 24 hours.
Objective:
We aimed to test if clinical time course of improvement is indeed mirrored by increased glutamine/glutamate ratio and if such effects would show a regional and temporal specificity in two anatomically and functionally distinct subdivisions of ACC.
Method:
We used a glutamine sensitive magnetic resonance spectroscopy protocol at 7 Tesla to compare the longitudinal changes of glutamine/glutamate after 1 hour and 24 hours in pregenual ACC (pgACC, Figure 1A) and anterior mid-cingulate cortex (aMCC, Figure 1B) in 59 healthy controls which underwent a double-blind, placebo-controlled ketamine infusion.
Result:
A significant interaction of time, region, and treatment was found ($F = 3.881$, $p<0.028$). Follow up analysis revealed that, only in pgACC and only after 24 hours, we found significantly increased glutamine/glutamate ratios in ketamine group compared with placebo ($T = 2.331$, $p < 0.042$) (Figure 2). We also found that the changes in pgACC over baseline are significant larger than changes in aMCC ($T = 2.710$, $p<0.022$) at 24 hours after ketamine infusion. Changes of glutamine/glutamate ratios were mainly driven by glutamine but not glutamate levels.
Conclusion:
We found that elevated glutamine/glutamate after a single subanesthetic dose of ketamine infusion was specific to pgACC, a region previously reported glutamategic deficit in MDD. This change of glutamine/glutamate in the pgACC also showed a temporal specificity at 24 hours after infusion.
Figures:

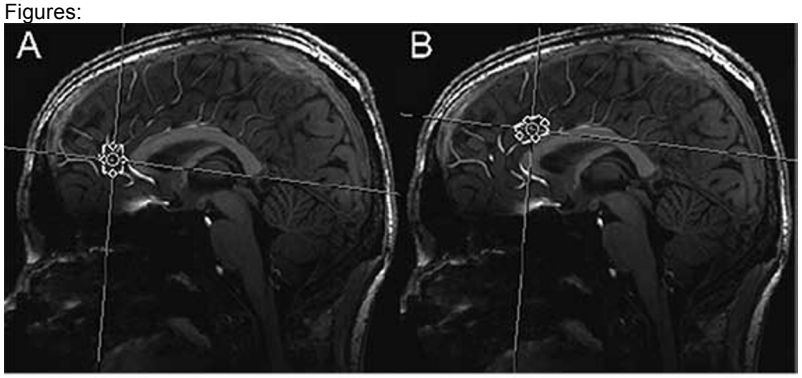

Figure 1. The demonstration of voxel placement for the pregenual anterior cingulate cortex (pgACC, A) and anterior mid-cingulate cortex (aMCC, B).

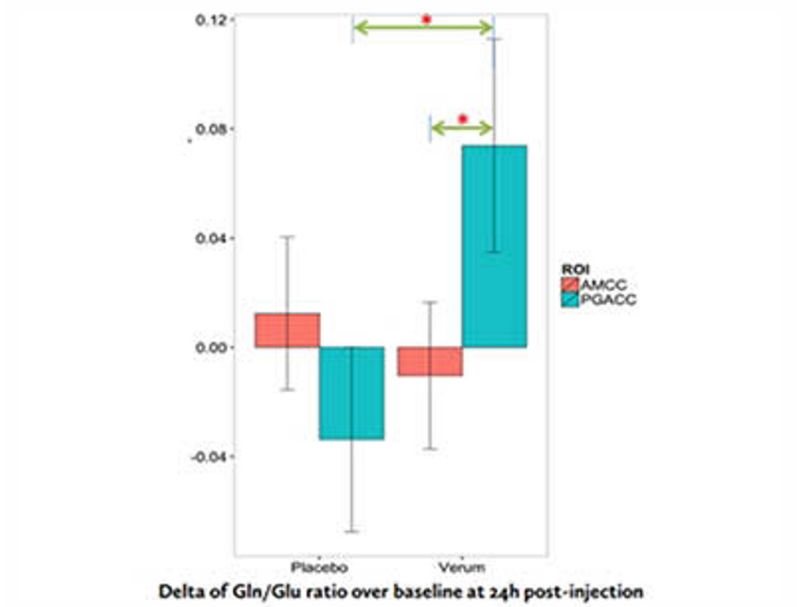

Figure 2. The change for Glutamine/Glutamate ratio at 24 hours after infusion over baseline in two anterior cingulate cortex subregions (aMCC: anterior middle cingulate cortex, in red; pgACC: pregenual anterior cingulate cortex, in dark blue) in groups of health controls with placebo and verum (Ketamine), respectively.

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