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Imaging the pharmacological effect of acute ketamine challenge using resting-state fMRI co-activation patterns and gene expression data

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Background:

Ketamine occupies a unique position in antidepressant treatment. Preliminary evidence suggests that antagonism of GluN2B-containing N-methyl-D-aspartate receptors (NMDARs) underlies ketamine´s antidepressant effect, however human in vivo studies are missing [1]. Extraction of co-activation patterns (CAPs) from the resting-state functional magnetic resonance imaging (fMRI) signal allows for the identification of ketamine induced changes in functional networks [2]. Association of CAPs and predicted mRNA expression of NMDAR subunits as determined by a recently introduced whole-brain transcriptomic map will add knowledge on subunit dependent changes in functional connectivity [3].

Methods:

We assessed fMRI data from 25 healthy volunteers (11 male, mean age ± SD = 24.68 ± 4.61) who underwent two 55-minute resting-state scans, once under subanesthetic, intravenous esketamine and once under placebo, in a randomized, placebo-controlled, cross-over design. Clustering was performed using the k-means algorithm. The number of clusters was determined based on the baysian information criterion. Explorative spatial correlation between CAPs and expression maps of NMDAR subunits was performed.

Results:

In total, fifty-two CAPs were extracted. While one CAP can be attributed to the placebo condition, 19 CAPs were characterized during ketamine administration. Correlation analyses revealed a low association between CAPs and mRNA expression. While the highest positive correlation was determined between CAP10 and GluN2A (r = 0.28), the highest negative correlation was revealed between CAP3 and GluN2A (r = -0.25).

Conclusions:

So far, human PET data on NMDAR subunit distribution is missing, thus, our approach provides a valuable tool in the investigation of its impact on brain activation. However, correlation between mRNA transcripts and expression is unknown and needs to be validated using in vivo PET data. The distribution of the NMDA receptor subtype GluN2B has been measured and modelled in Vienna using the radioligand [11C]Me-NB1 during the last months, therefore we will be able to provide NMDA distribution data soon. Low correlation between CAPs and NMDAR subtypes may highlight the role of NMDAR independent mechanisms in ketamine´s acute dissociative effect.

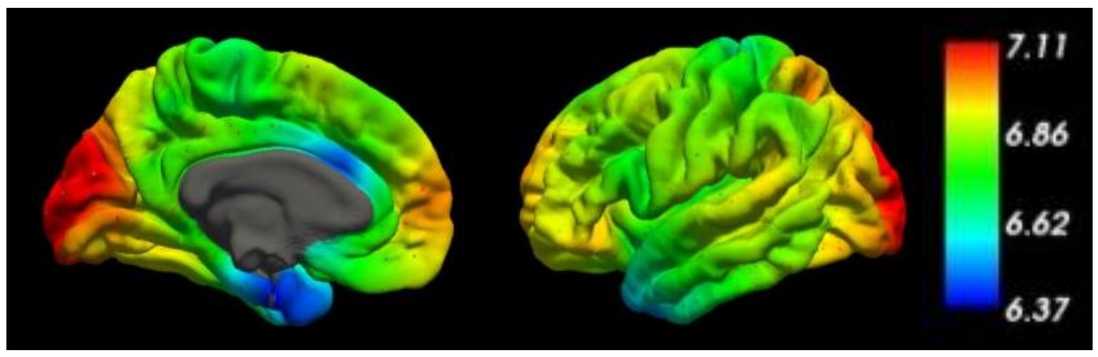

Fig. 1: Predicted cortical mRNA expression of the GRIN2A gene (Entrez ID: 2903) that codes for the GluN2A subunit of the NMDA receptor. Color scales represent log2 mRNA expression intensity.

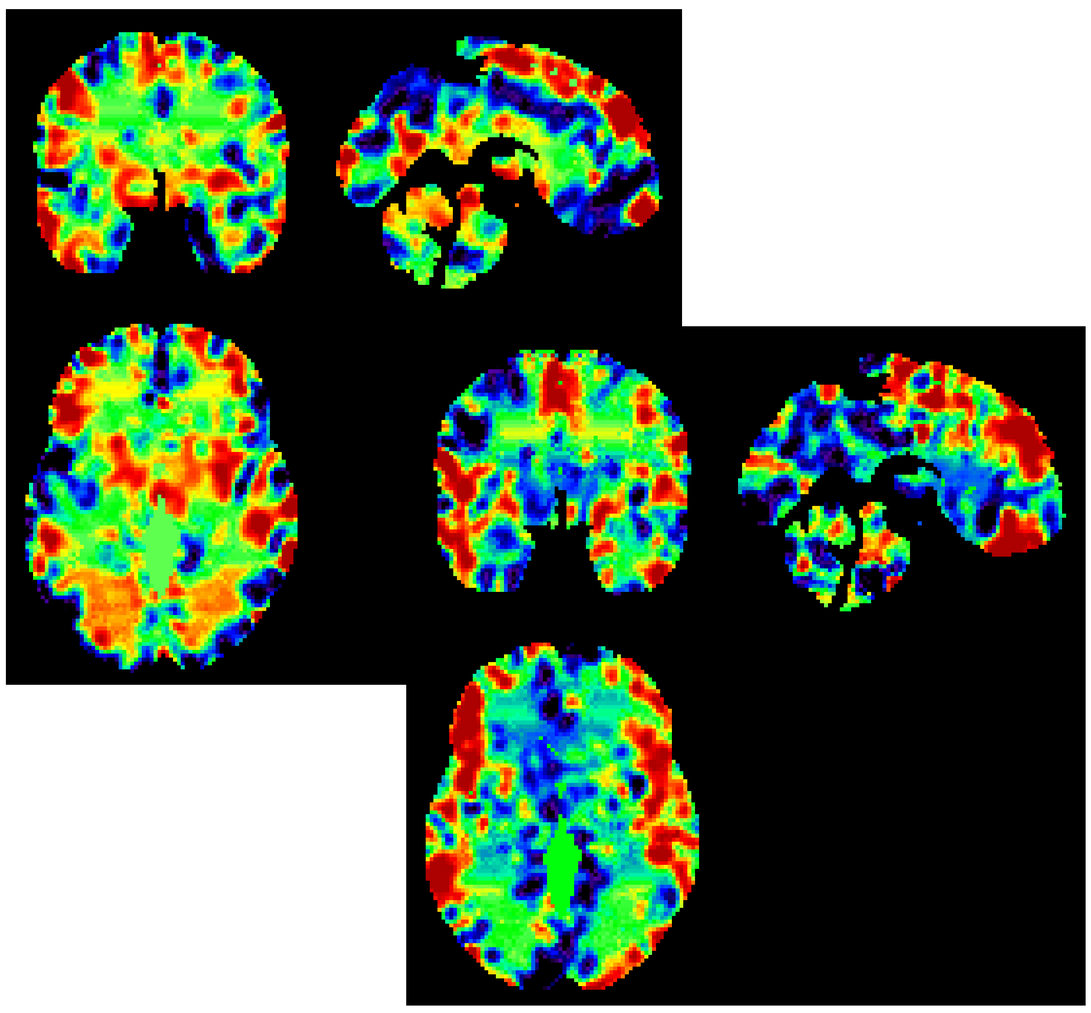

Fig. 2: Co-activation patterns with the highest correlation with GluN2A mRNA expression are shown in coronal, saggital and axial view (CAP3 left, CAP10 right).

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References:

[1] Miller OH. et al., Elife 2014. 3: p. e03581
[2] Liu X. et al., Neuroimage 2018. 180: p. 485-494
[3] Gryglewski G. et al., Neuroimage 2018. 176: p. 259-267