Dynamics of Ketamine-Related Resting State Connectivity Changes in Healthy Controls


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Introduction

Ketamine functions as a model for psychosis (1) and as an effective antidepressant (2). Numerous studies have shown that ketamine influences resting-state functional connectivity (rsFC). Results from previous studies vary in regards to the networks shown to be ketamine-sensitive as well as the mode of ketamine’s influence. Seed-based and static rsFC estimation methods may distort assessments of ketamine’s influence on the brain (3) and may oversimplify FC (4). These limitations can be addressed through use of dynamic resting-state functional connectivity estimation methods and whole-brain approaches.

Aims

We believe this is the first study to investigate the influence of esketamine on fMRI rsFC with whole-brain, dynamic rsFC quantification methods.

We aimed to elucidate only highly robust effects of esketamine on dynamic rsFC. We used 8 combinations of methodological measures gleaned from two dynamic rsFC estimation methods (exponentially weighted sliding-window (4) and multiplication of temporal derivatives (5)), two functionally defined atlases (6,7) and two statistical measures.

Methods

DESIGN: 27 healthy subjects were measured twice with 3T resting state fMRI, data published in previous study by our group (1). One MRI was performed under esketamine challenge and one under placebo (randomized, controlled, cross-over).

STUDY DRUG: Esketamine was administered i.v. with a MR-compatible perfusor pump in a bolus plus infusion model (0.11 mg/kg over one min followed by 0.12 mg/kg over 19 min). Placebo = 0.9 % NaCl i.v.

PLASMA LEVELS: Esketamine plasma levels were derived from a pilot study performed without MRI (n=5) and drawn at standardized time points (1).

rsFC QUANTIFICATION: Dynamic resting state functional connectivity was assessed with two complementary methods (exponentially weighted sliding-window (4) and multiplication of temporal derivatives (5)) and two functionally defined atlases (Power-atlas (6) and Craddock-atlas (7)).

STATISTICS: 1) For each computational method, ordinary least-squares regression was used to ascertain the relationship between dynamic rsFC and plasma levels. Matrix of regression coefficients were entered into repeated measures model and significant networks were elucidated with network based statistics (NBS) (8). NBS provides intensity- (strength of connections) and extent- (number of connections) statistics. 2) Connections shown by NBS to be significant were superimposed onto networks described by Yeo et al. (9) and three additional regions based on the Harvard-Oxford atlas, all split by hemisphere (right and left for each network/region). See Figure.

Results

1) NBS revealed one significant network per methodological combination, except for three combinations (two networks were revealed for the combination of the exponentially weighted sliding-window method, intensity statistics and the Power-atlas, as well as for MTD, using both statistics (extent and intensity), and the Craddock-atlas). Each network was found for the comparison esketamine < placebo, suggesting a negative effect of esketamine on dynamic rsFC.

2) After compartmentalization of NBS results into networks based on Yeo et al., all methodological combinations revealed a negative influence of esketamine on dynamic rsFC within the left visual network and between the left and right visual networks (p < 0.05, corrected, correction intrinsic to NBS). Numerically, after organization into Yeo et al.’s networks (9), MTD elucidated more significant connections than the exponentially weighted sliding-window method, as did the Craddock atlas in comparison to the Power atlas.

Conclusions

The negative influence of esketamine on dynamic rsFC within and between visual processing networks may be reflective of the high density of NMDA-receptors in visual processing regions (10). Our results are in accordance with ketamine’s role as a model for psychosis, a state which is associated with changes to visual processing on the neurobiological and behavioural level.

Some authors have suggested that depression can conceptually and neurobiologically be modeled as a perceptive disorder, as it is associated with changes to processing of visual stimuli (11). Considering that ketamine is a potent antidepressant, the negative influence of esketamine on dynamic rsFC in visual processing networks may be reflective of this concept.

References


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Figure 2: Connections for which esketamine had a negative influence on dynamic resting-state functional connectivity

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References