Ketamine decreases resting state functional connectivity between networks via the dorsal nexus: implications for major depression

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INTRODUCTION

Increasing preclinical and clinical evidence underscores the strong and rapid antidepressant properties of the glutamate modulating NMDA receptor antagonist ketamine [1, 2]. Targeting the glutamatergic system might thus provide a novel therapeutic strategy for antidepressant drug treatment [3]. Since glutamate is the most abundand and major excitatory neurotransmitter in the human brain, pathophysiological changes in glutamatergic signalling are likely to affect neurobehavioural plasticity, information processing and large-scale changes in functional brain connectivity underlying certain symptoms of major depressive disorder (MDD) [4]. Using resting state functional MRI (rsfMRI), the „dorsal nexus" (DN) was recently identified as a bilateral dorsal medial prefrontal cortex (DMPFC) region showing dramatically increased depression-associated fMRI connectivity with large portions of the cognitive control network (CCN), the default mode network (DMN), and the affective network (AN) [5]. Hence, Sheline and colleagues [5] proposed that reducing increased connectivity of the DN might play a critical role in reducing depressive symptomatology and thus represent a potential therapeutic target for affective disorders. Since little is known about how ketamine affects large-scale neural network dynamics in the human brain, we aimed to test the hypothesis that ketamine as an antidepressant glutamatergic agent decreases resting state connectivties via the DN.

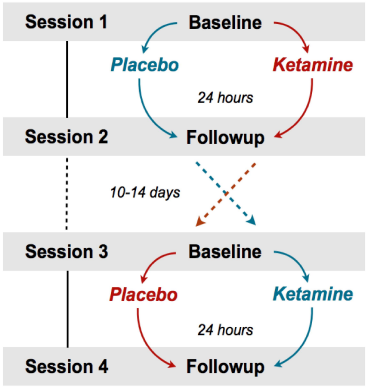

Fig. 1: *Double-blind, randomized, crossover study design (n = 17 subjects)*

METHODS

Study design: 17 healthy subjects (mean age, 40.5 +/- 7.5 [SD]; 9 males) completed four resting state fMRI sessions in a double-blind, randomized, crossover study design (s. Fig 1). The baseline scan was followed by an intravenous infusion (45 mins) of either S-ketamine (0.25 mg/kg) or placebo (saline) outside the scanner. Since the antidepressant effect of ketamine is most prominent after one day [1], the followup scans were scheduled 24 hours after the ketamine or placebo infusion in order to assess the mid-term effects on neuronal network dynamics that might contribute to its antidepressant efficacy. To avoid a possible carry-over effect, the time lag between the two baseline measurements was set to at least 10 days.

rsfMRI data acquisition and analysis: Measurements were performed on a Philips Achieva TX 3-T whole-body MR unit equipped with an 8-channel SENSE head coil. During each session a total of 200 functional images were collected in 10 minute runs (eyes closed) using the following acquisition parameters: TE = 35 ms, TR = 3000 ms (θ = 82°), FOV = 22 cm, acquisition matrix = 80 x 80 interpolated to 128 x 128, voxel size = 2.75 x 2.75 x 4 mm, 32 contiguous axial slices (placed along the anterior-posterior commissure plane), and sensitivity-encoded acceleration factor R = 2.0. A 3-dimensional T1-weighted anatomical scan was obtained for structural reference. Data were analyzed using the SPM8 (Wellcome Trust Center for Neuroimaging, London, England) based data processing assistant for resting state fMRI (DPARSF, by Yan Chao-Gan et al.) which includes a resting state fMRI data analysis toolkit (REST, by Song Xiao-Wei et al.). The postprocessing steps followed the standard protocol described by Yan and Zang (2010) [6].

RESULTS

To test our hypothesis, we created a seed region of interest in the left and right DMPFC (10 mm sphere at ± 6 51 24) representing the DN. 24 h following ketamine administration, functional connectivity was exclusively reduced to the posterior cingulate cortex (PCC), to the subgenual anterior cingulate cortex (sgACC), and to anterior and mediodorsal parts of the thalamus (compared to placebo). The backprojection from a seed in the PCC confirmed these results and revealed an additional significant reduction of functional connectivity to the pregenual ACC (PACC) and medioprefrontal cortex (MPFC). For details, see Fig. 2 A, B and bar diagrams (functional connectivity change, paired t tests).

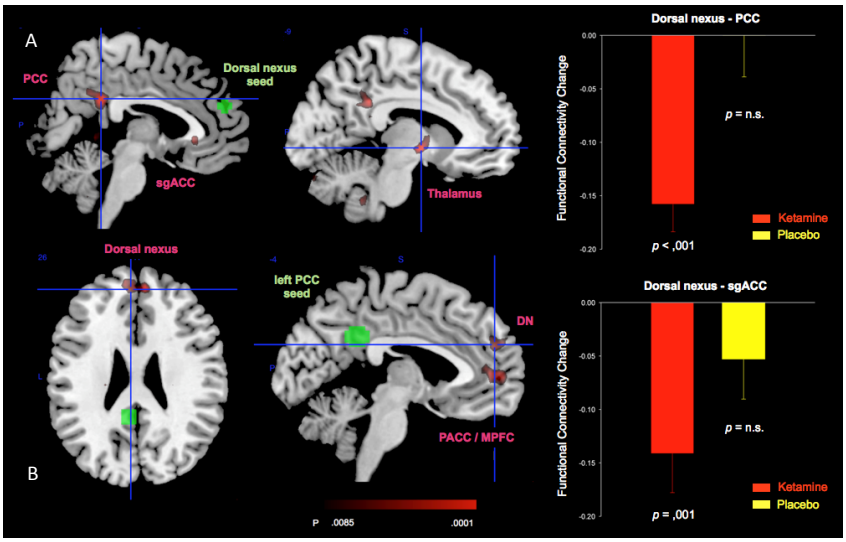

Fig. 2A: *Red voxels in the PCC, sgACC and thalamus showing reduced functional connectivity to the DN seed region (green) after ketamine administration (n=17, paired t-test, s. bar diagrams).*
Fig. 2B: *Red voxels in the DN (backprojection) and PACC/MPFC showing reduced functional connectivity to the left PCC seed region (green) 24 hours after ketamine administration.*

DISCUSSION & CONCLUSION

While pharmacological effects of ketamine on task induced fMRI BOLD signals have been studied extensively, this is the first randomized, placebo-controlled, double-blind, crossover study demonstrating changes in resting state functional connectivity in response to ketamine administration in healthy subjects. Here, we report a significant decrease in functional connectivity of the sgACC (AN) and the PCC (DMN) via the DN 24 hours following ketamine administration, thus reflecting a neuronal pattern of normalization with regard to MDD where increased connectivities of the AN and DMN via the DN have been observed [5]. As critical hub of the AN, the sgACC plays an important role in mood regulation. Subgenual cortical activity was shown to be elevated in MDD and effective antidepressant treatment was associated with a reduction in sgACC activity [for review see ref. 7]. In addition, the observed reduction in functional connectivity between anterior (PACC/MPFC) and posterior parts of the DMN (PCC) may partially reverse the disrupted neurobehavioral homeostasis in MDD where a failure to normally down-regulate activity within the DMN during emotional stimulation was found [8], with increasing levels of DMN dominance being associated with higher levels of maladaptive, depressive rumination and lower levels of adaptive, reflective rumination [9]. Finally, reductions in cortico-thalamic connectivity may reflect functional alterations in thalamocortical loops via the prefrontal cortex. Based on the fact that the antidepressant effect of ketamine peaks one day after a single intravenous administration [1], we conclude that pharmacologically reducing the hyperconnectivity via the DN may play a critical role in reducing depressive symptomatology and in representing a systems level mechanism of treatment response for major depression.

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