Acute ketamine infusion alters functional connectivity between dorsal attention and default mode networks

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BACKGROUND

Ketamine challenge has been used as a model for schizophrenia since it mimics psychotic symptoms as well as alterations in consciousness, perception, self-awareness and mood [1, 2]. These effects seem to emerge from blockade of N-methyl-D-aspartate (NMDA) receptors on γ-aminobutyric acid (GABA) interneurons, which in turn increases glutamate signalling [1]. Although regional effects and associations with clinical symptoms have been thoroughly described [2], investigations on a network level are still missing.

OBJECTIVE

Here we investigated the effects of acute ketamine infusion on the dorsal attention network (DAN) due to its involvement in the regulation of attention control and assessment of stimulus novelty [3].

METHODS

SUBJECTS & TREATMENT: 10 healthy subjects (23.2±3.4 years, 6 females) underwent functional MRI during intravenous infusion of esketamine hydrochloride (15.12±2.76mg) given as 1min bolus (0.11mg/kg) plus 19min constant infusion (0.37mg/kg/h).

RESTING-STATE FUNCTIONAL MRI (rsfMRI): Resting-state fMRI data were obtained on a 3T scanner (Siemens Trio) using single-shot gradient-recalled echo planar imaging (TE/TR = 38/1800ms, 128x128 voxels, 23 slices each 4.8mm thickness). First, 5min baseline were recorded, followed by 5min of saline injection (to enable adaption to intravenous drug administration) and 35min during and after ketamine infusion.

DATA PREPROCESSING was carried out in SPM8 and comprised motion correction, spatial normalization to MNI-space and smoothing with a 9mm Gaussian kernel. Data were then split into 5min blocks and corrected for potential confounders using linear regression against motion parameters as well as ventricular, white matter and global signal and band-pass filtering with 0.007<f<0.08 Hz [4]. Two seeds in the bilateral inferior parietal cortices (cubic regions of 27 voxels centered at x/y/z = ±36/−54/42mm) were used for functional connectivity analysis. For each 5min block the average signal course of the seeds was cross-correlated with the entire brain, followed by z-transformation to enable group evaluation.

STATISTICAL ANALYSIS: To investigate the effects of ketamine on functional connectivity of the DAN a repeated measures ANOVA was carried out in SPM8. Here, each functional connectivity map obtained from 5min blocks after start of infusion was compared with the baseline network (Fig. 1).

RESULTS

The bilateral dorsal attention network (DAN) covered the inferior parietal, inferior temporal, middle frontal and middle cingulate cortices [5] and an expected anticorrelation with the medial prefrontal cortex (mPFC, Fig. 1). Compared to baseline, increases in functional connectivity with the DAN within the mPFC (t=5.38, p<0.05 FWE-corrected) and the posterior cingulate cortex (PCC, t=4.08, p<0.001 uncorrected, Fig. 2) were observed immediately after ketamine infusion (0-5min). Hence, the mPFC showed almost no connectivity with the DAN at this time point (Fig. 2). On the other hand, functional connectivity with the DAN decreased for almost the entire scanning period reaching its peak 15-20min after ketamine injection (t=-5.39, p<0.05 FWE-corrected, Fig. 3). At this time point further reduced connectivity was observed in the midbrain (t=-4.42), thalamus (t=-4.07 and -4.02 for left and right hemisphere, respectively) and the supragenual anterior cingulate cortex (t=-3.81, p<0.001 uncorrected).

CONCLUSIONS

Acute ketamine infusion induced altered functional connectivity across networks rather than within the DAN. Specifically, decoupling was observed between DAN and midline core hubs (mPFC, PCC) of the default mode network (DMN) [6]. The interaction of DAN and DMN has been suggested to be responsible to switch attention between external and internal stimuli [3]. This disruption of the two networks complements an overall brain hyper-connectivity with the anterior DMN in schizophrenia [7]. In contrast, the stronger negative connectivity with the amygdala may relate to changes of emotional processing in schizophrenia patients. Taken together, our findings suggest ketamine-induced alterations across brain networks indicating shifts between external attention, introspection and emotion, which may explain the corresponding deficits of schizophrenia.

DISCLOSURE

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REFERENCES