An fMRI Study of Ketamine Induced Temporal Dissociation

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Background

Dissociation involves a cluster of debilitating symptoms including changes in the perception of self, environment and time. These symptoms occur in up to 80% of psychiatric inpatients (Hunter et al. 2004). However, their prevalence in the general community and in psychiatric populations has been underestimated until recently (Foote et al. 2006). The often intermittent nature of symptoms presents significant difficulties for research. Therefore, a study design utilising ketamine, a NMDA antagonist, which is a strong inducer of dissociative phenomenology was designed to investigate psychophysical and fMRI correlates of dissociation.

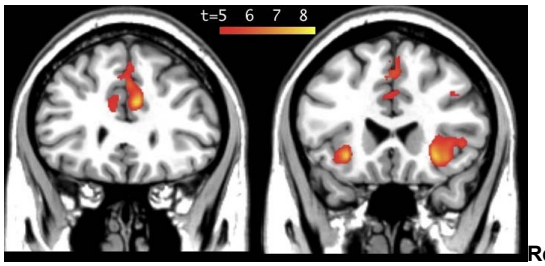
This study focused on a relatively poorly studied area of dissociative phenomenology, temporal dissociation, or changes in the perception of time. The study utilised the Temporal Order Inversion (TOA) task, an unusual paradigm in which flashed stimuli perceived close in time to rapid eye movements result in the ordering of stimuli being perceived as inverted. It was first described by Morrone et al (2005).

Methods

The study utilised a double-blind, placebo controlled, event-related design in which low dose ketamine (100ng/ml) was compared to placebo (saline) infusion. Anatomical and function (EPI) scans were acquired using a 3T scanner .

27 right handed volunteers aged between 18-40 years attended on two visits. The stimuli presented were a 1 degree black fixation square, 7 degrees left of centre on uniform red background, followed after a random fore-period by a target square 7 degrees right of centre. Then two a flashed horizontal green bars, 10 degrees from centre were presented with duration of 20ms and inter-stimulus interval of 60ms. Top and bottom bar presentation order was randomised. Participants responded by button press to indicate which bar they perceived first. 250 trials were collected per session.

Brain imaging data was analysed using SPM8 with a second− level factorial design of ketamine vs placebo and inverted judgements vs non-inverted. Full-brain corrected thresholds were employed (p<0.05 FWE), with supplementary hypothesis driven region of interest analyses with multiple comparisons correction.



Results

Behavioural results revealed a lengthened response latency for ketamine trials: 611ms vs 598ms for placebo (t=2.23, p<0.03). Full brain corrected comparison between inverted and non-inverted trials showed highly significant clusters of increased BOLD signal for inverted trials opposed to non-inverted trails. These regions (see figure) were in the dorsal anterior cingulate cortex (dACC) and bilateral inferior frontal gyri.

Region of interest analysis revealed a significant increased BOLD for ketamine versus placebo in the left tempero-parietal-occipital junction (T=2.40 , p<0.01).

Discussion

A strong effect was found for the Temporal Order Inversion task, demonstrating increased BOLD in the paralimbic network of dACC and inferior frontal gyri. This pattern of activity has been previously described as 'the salience network' (Seeley et al. 2007). However, this network is typically associated with error-monitoring tasks. Since no explicit feedback was given to participants concerning inverted trials, the results indicate that the same network may be implicated in temporal comparator functions without explicit error awareness. Such functions may have an important role in maintaining temporal accuracy of perception.

Ketamine administration increased dissociative symptoms as well as left tempero-parietal-occipital junction activity. This region had been implicated in lesion studies associated with dissociative phenomena.

The study had two major limitations, firstly the nature of the inverted judgement tasks introduces difficulty in differentiating if these judgements represent errors of perception or response, per-trial confidence measures can resolve this issue. Secondly, due to the potential for ketamine to induce nausea, doses were kept to a relatively low 100ng/ml. Theses issues are currently being addressed in follow-up studies.

References

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