Sub-anesthetic ketamine modulates intrinsic BOLD connectivity in the hippocampal-prefrontal system in the rat: dose-dependence and PK/PD relationships

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Purpose: Resting state fMRI (rsfMRI) is well-established in humans [1] and has been shown to be sensitive to pharmacological modulation [2]. More recently, consistent intrinsic connectivity networks have been demonstrated in the rat [3], but drug effects on rsfMRI are only beginning to be characterized in the rodent. The utility of rsfMRI as a translational biomarker depends on (1) its sensitivity to pharmacological modulation in preclinical species and (2) the degree of convergence with effects using the same compound in humans. Ketamine, a potent n-methyl-d-aspartate (NMDA) receptor antagonist, is of substantial current interest both (a) as a pharmacological model of glutamatergic dysfunction in psychiatric disease [4], and (b) as a rapidly acting antidepressant, effective in treatment-resistant depressive patients [5]. The aim of this work was to systematically characterize the effects of ketamine on rsfMRI in the rat.

Methods: Male Sprague-Dawley rats (368-447g) in 4 parallel groups (N=10/group) received either vehicle (saline) or one of three sub-anesthetic doses of S-ketamine (5, 10 and 25 mg/kg; s.c.). Rats were scanned at 9.4T scanner under 0.14 mg/kg/h medetomidine infusion. Three 8.5-min rsfMRI datasets (TR/TE 1700/17.5 ms) were acquired from each rat: pre-injection and 15 and 30 min post-injection. Blood samples were taken from each rat after scanning to determine exposure to ketamine. Seed-based connectivity mapping was used to test the hypothesis that ketamine modulates functional connectivity within the hippocampal-prefrontal system [6]. An ROI-ROI correlation analysis, based on a parcellation of the brain into 44 atlas-derived regions, was also performed to profile the ketamine effects throughout the brain.

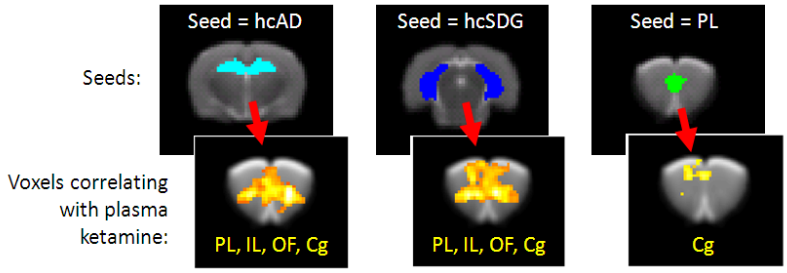

Fig.1: Seed-connectivity maps showing changes in correlation significantly correlating with plasma drug levels (z>3.87). Ketamine preferentially increased connectivity between both posterior and anterior hippocampus and the prefrontal cortex, and also within prefrontal structures. [hcAD, anterodorsal hippocampus; hcSDG, subiculum and dentate gyrus; PL, prelimbic cortex; OF, orbitofrontal cortex; IL, infralimbic cortex; Cg, cingulate cortex].

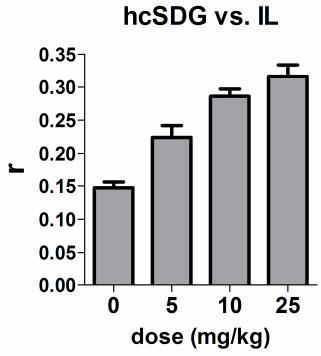

Fig.2: Ketamine dose-dependently increases correlation between posterior hippocampus (subiculum) and medial prefrontal (infralimbic) cortex.

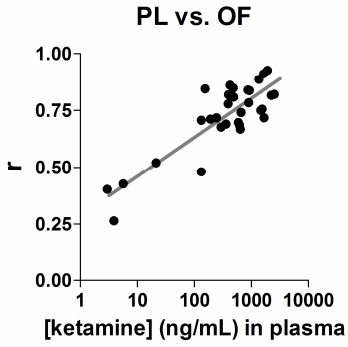

Fig. 3: PK/PD (exposure-response) relationship for connectivity within the prefrontal cortex.

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Results: Pharmacokinetic/pharmacodynamic (PK/PD) image and ROI analyses revealed increased functional connectivity between the hippocampus and regions in the prefrontal cortex (PFC), and within the prefrontal cortex, that positively correlated with ketamine plasma levels (Figs). The effects were strongest 30 min post-injection. Whole-brain ROI-ROI correlation analysis revealed additional dose-dependent increases in connectivity between the PFC and cortical structures, in particular the temporal and parietal association cortices.

Discussion: The observed increases in functional connectivity reveal possible neural mechanisms underlying established behavioral effects of ketamine, including increased wakefulness and locomotor activity, and are consistent with ketamine-induced increases in cortical EEG gamma band coherence [7].

Conclusion: This study provides further evidence that rsfMRI is a sensitive probe of central pharmacological effects in preclinical species, and characterizes, for the first time, the effects of ketamine – a tool compound of considerable current interest in psychiatry research – on rsfMRI in the rat. These results provide an important comparator to (a) other preclinical modalities and (b) analogous rsfMRI experiments emerging in humans.

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