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Title: Imbalance between the amygdala and the hippocampus in down-modulating dopamine system responsivity in animal models of depression

Abstract
Dysregulation of the mesolimbic dopamine (DA) system has garnered increasing attention as a key component of major depressive disorder (MDD). It is thought to be particularly relevant to anhedonia, the reduced interest in pleasurable stimuli, which is considered to be a core symptom of MDD. We have shown that rats exposed to either Chronic Mild Stress (CMS) or Learned Helplessness, two stress-induced animal models of depression, resulted in stress-exposed animals showing a reduction in ventral tegmental area (VTA) DA neuron population activity, i.e. the number of DA neurons active and available to respond to environmentally salient rewarding stimuli. This suggests that in MDD, there is a reduced ability of the DA system to respond to rewarding stimuli, which could therefore represent the neural substrate of clinical anhedonia. Drawing from human neuroimaging research, we identified two candidate regions that were reproduced ketamine’s effect nor blocked it.2 Because of this, we hypothesized that another way to mimic the antidepressant-like effect of ketamine would be to block or reduce GABAergic transmission in the hippocampus. L-655,708 is a negative allosteric modulator of GABA_A receptors and as such, would be expected to block GABAergic activity. In addition, it exhibits selectivity for the α5 subunit of the GABA_A receptor with this subunit being localized primarily in the hippocampus.3 Systemic administration of this drug produced a sustained (7 days) antidepressant-like effect in the FST. To examine possible rewarding effects of ketamine that could contribute to its abuse potential, self-administration experiments were carried out. Ketamine was self-administered by rats. However, L-655,708 was not. It should be possible, then, to develop novel antidepressants that recapitulate the beneficial effects of ketamine without having abuse-liability.