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## Dual Diagnosis

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### Developing dual-diagnosis models in laboratory animals to capture self-medication strategies for remediation of cognitive deficits

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Cognitive deficits represent one of the core disabling symptoms within this disorder, accountable for the majority of disruption to everyday life. Over 80% of patients with schizophrenia smoke compared to just 30% of the general population, which has been postulated as a form of self-medication to remediate the cognitive symptoms. Our laboratory has shown that a sub-chronic, sub-anesthetic dosing regimen of the NMDA antagonist ketamine can induce cognitive deficits on a variety of cognitive domains such as memory capacity of working memory and executive decision-making in the attentional set-shifting task. The objective was to examine the effects of treating rats with ketamine (daily injection of 30mg/kg IP for 5 days) on acquisition to self-administer intravenous nicotine (0.015 & 0.03mg/kg/inj) using two-lever operant conditioning chambers. Following 5 days of a 'washout' period from the sub-chronic treatment, groups of rats (n=12) were given access to intravenous nicotine in 1 hr sessions under a fixed-ratio schedule of reinforcement. Both ketamine- and vehicle-treated subjects showed steady rates of acquisition with no significant difference between the treated groups. Differences were however apparent when rats were presented a choice between nicotine and sucrose (0.2ml of 5mg/ml solution) under a concurrent choice procedure (VR4). Over 3 three concurrent sessions, vehicle-treated rats migrated their responses exclusively to the sucrose lever, whilst ketamine-treated rats were resistant and made fewer responses on the sucrose lever but more importantly maintained their intake of nicotine. The results from this experiment suggest that the sub-chronic ketamine regimen used to model cognitive deficits associated with schizophrenia does not modify the primary reinforcing effects of nicotine. However, within value-based decision making in nicotine addiction, ketamine exposure made rats resistant to non-drug alternative reinforcers such as sucrose. These findings suggest that the high prevalence of tobacco smoking amongst people diagnosed with schizophrenia may represent self-medication in order to restore cognitive deficits, rather than an increase in their subjective feeling of satisfaction from the nicotine. (Research supported by Newcastle University UK)

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