Project Details	
Project Code	MRCNMH26Ex Morgan
Title	Ketamine Use Disorder: Exploring Psychological and Neurological Mechanisms
Research Theme	NMH
Project Type	Dry lab
Summary	Ketamine use disorder is the fastest growing addiction in the UK, with ~ 300% increase in people seeking treatment over the past year. This project explores the psychological and neurobiological determinants of ketamine use disorder. Working closely with local drug services, the PhD student will use a variety of techniques including acute drug challenge, neuroimaging, cognitive testing and interviews to develop a rich understanding of the causes and consequences of ketamine use disorder. Through this we hope to inform treatment of this sometimes life threatening, and frequently misunderstood, health condition.
Description	Ketamine is a dissociative anaesthetic that has been established as a rapid acting antidepressant in treatment resistant depression (e.g. Morgan et al., 2014). The past two decades have simultaneously seen a surge in recreational ketamine consumption, such that ketamine has become the fourth most commonly used drug in clubbing environments in the United Kingdom (UK) (ONS, 2024), with a threefold increase among individuals under 25 years old (ONS, 2024). Concurrently, the number of adults requiring treatment for ketamine use disorder (KUD) has risen fivefold since 2015 (Home Office UK, 2024). Despite the growing prevalence and associated burden on healthcare services still relatively little is known about KUD, which often has serious physical health complications including ketamine-induced ulcerative cystits. Our group has recently published the largest study of ketamine users (Harding et al. 2025) which has identified significant gaps in knowledge concerning KUD, particularly in the extent of its addictive potential and effective treatment strategies. Studies in animals (Jiang et al.2024) and humans (Williams et al. 2019) have demonstrated that ketamine's antidepressant and anti-suicidal effects are at least partly dependent on the opioid system. Recent work has proposed that bifunctional, synergistic interactions between n-methyl d aspartate (NMDAR) and mu opioid receptor (MOR) underlie its mechanism of action in depression (Levinstein et al. 2025). Additional findings further support an opioid component in ketamine's mechanism: its analgesic effects are MOR-dependent (Panckeo et al. 2014), and even at subanaesthetic doses, ketamine achieves sufficient MOR occupancy to trigger downstream signalling (Bonaventura et al. 2021). Elevation of β-endorphin levels following ketamine administration (Jiang et al. 2024), along with the attenuation of ketamine's effects by opioid antagonists, further supports the involvement of opioid system activation in its pharmacological action. Collectively, these findings provide a compelling rationale for exploring the role of the mu opioid receptor action in ketamine addiction. The key research question of this thesis will examine the impact modulating mu opioid receptor activity on the rewarding effects of ketamine and addictive properties of ketamine in ketamine users (Harding et al. 2025).

	Objectives the student will address: Proposed Study 1) Understanding the lived experience of ketamine addiction. The student will co-create with our lived experience representatives an interview and survey of ketamine addiction to capture the key withdrawal symptoms and explore predictors of relapse and maintenance of addiction in ketamine users and then gather this data using links with local drug services in Bristol, Bath, Cardiff and Exeter. This will serve two functions: a) will inform understanding of ketamine use disorder b) this information will then be used to develop into experimental stimuli Proposed Study 2) Explore the impact of mu opioid modulation on acute response to ketamine in ketamine users. The student will conduct an acute challenge study with ketamine and naltrexone in ketamine users exploring whether the modulation of mu opioid activity reduces rewarding effects of ketamine. Proposed Study 3) Chronic Effects of mu opioid modulation in ketamine users. This study will explore the impact of chronic dosing with naltrexone over 14 days on the experience of daily craving and reward sensitivity in people with ketamine use disorder. The end goal of this study would be to inform the development of treatment for ketamine use disorder.
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