



The similarities and differences in impulsivity and cognitive ability among ketamine, methadone, and non-drug users



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ABSTRACT

The study aimed to identify similarities and differences among ketamine, methadone users, and non-drug-using controls, on impulsivity, antisocial personality, and related cognitive abilities. A case-control observational design was used to compare the impulsivity and cognitive function of ketamine users ($n = 51$), methadone users ($n = 59$), and controls ($n = 60$). Antisocial personality traits and emotion states were also measured. One-way ANOVAs and planned *post hoc* pair-wise tests were used to analyze the data. Compared to non-drug-using controls, ketamine and methadone users had elevated scores on BIS and Pd scale of the MMPI, poorer performance on 2-back task, Stop-signal task, and Stroop test. Ketamine users performed the worst in the 2-back accuracy and Stop miss rate compared to methadone users and controls. There were no significant differences between the groups on the Iowa Gambling Task. Ketamine users did not show deficits in decision-making but exhibited strong impulsivity, antisocial personality, and poor response inhibition and working memory at levels similar to methadone users. These deficits may reflect vulnerability to addiction. This suggests that future treatment programs for ketamine users could address drug users' impulsive cognition and psychopathic deviance.

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1. Introduction

Ketamine is attracting increasing research interest around the world, because of three reasons. First, recreational ketamine use has been on the rise worldwide, and more and more adolescents have been involved in it. Second, ketamine can render individuals oblivious to their environment, making users not only at risk of accidental injury to themselves, but also more vulnerable to assault by others (Morgan and Curran, 2012). Third, ketamine also has powerful amnesic effects. Frequent, acute ketamine use is associated with a range of cognitive impairments, including problems in working memory, episodic memory, and executive function (Honey et al., 2004; Morgan and Curran, 2006; Rowland et al., 2005). In addition, chronic ketamine use has been found to impair the learning of new spatial and verbal information in some research (Chan et al., 2013).

Evidence suggests that ketamine users have no impairments in figural fluency, sustained attention, selective attention, visual learning, or verbal/nonverbal memory (Rowland et al., 2005; Chan

et al., 2013; Liang et al., 2013). However, Chan et al.'s functional magnetic resonance imaging (fMRI) research also found that ketamine use causes impairment in frontal and medial temporal functioning, possibly specific to verbal information processing (Chan et al., 2013). In general, researchers believe that chronic ketamine use impairs working memory and episodic memory but not attention and verbal learning (Honey et al., 2004; Rowland et al., 2005; Morgan and Curran, 2006; Morgan et al., 2009), although there have been some conflicting research results (Chan et al., 2013).

However, the information to date is insufficient to explain the phenomenon of repeated ketamine use. In our systematic investigations, we have observed that ketamine users deny being addicted because they do not experience the same type or degree of withdrawal symptoms that they would with other addictive drugs such as opioids or cocaine. Most ketamine users report on questionnaires that they are not dependent on the drug, do not have strong cravings for ketamine, and can extend the time before the next use, but the reality is that they, nevertheless, are not successful when they attempt to stop using ketamine. If ketamine users are not dependent according to established criteria for other drugs, and they experience mild or no withdrawal symptoms of the type experienced by heroin users, why can they not stop using the drug even when they are aware of its negative effects and have to confront aversive results (Morgan et al., 2009)?

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There is conflicting evidence of the existence of a specific “ketamine withdrawal syndrome” following cessation of ketamine use. A study by Morgan et al. reported that 28/30 ketamine users tried to stop taking the drug but failed (Morgan et al., 2009). Some users in the same study reported withdrawal symptoms such as anxiety, shaking, sweating, and palpitations when they stopped using. However, a specific ketamine withdrawal syndrome has not yet been described, there are no large-scale studies of ketamine dependence in the literature (Morgan and Curran, 2011), and the incidence of ketamine dependence is unknown.

Reinforcement of ketamine-using behavior may be part of the reason that ketamine users have difficulty stopping their use of the drug. However, are there other factors that influence the behavior of ketamine users, such as disinhibition or particular personality characteristics? Are ketamine users like opioid users, who show a pattern of strong impulsivity or disinhibition that might influence them to keep using the drug? According to extant research, behavioral impulsivity is a vulnerability characteristic for addiction (Verdejo-García et al., 2008; Zeng et al., 2013) and, therefore, may be a factor in continued ketamine use as well.

Theoretically, impulsivity as a trait is a risk factor for all substance use disorders because impulsive individuals expect and experience greater reinforcement from substance use combined with a lessened ability to limit substance use in the face of negative future consequences (Gullo et al., 2014). Elevated impulsivity has previously been reported in Hong Kong–Chinese club drug users, most of whom were abusing ketamine (Loxton et al., 2008). More precise information is needed about the characteristics of ketamine users, their impulsivity, and their related cognitive abilities in order to determine the reasons for, and treatment of, ketamine use.

In addition to impulsivity, antisocial personality traits might contribute to continued ketamine use. According to Hathaway and McKinley (Hathaway et al., 1940; Butcher, 1989), High scores on the MMPI–Pd scale have been associated with impulsivity, problems with authority, and antisocial acts. In China, ketamine is an illegal drug like heroin. Those who obtain and use it are likely to be more willing than others to engage in other antisocial behavior.

Based on the research to date, this study compared the impulsivity and cognitive abilities, including response inhibition, decision making, and working memory, of ketamine users and opioid users along with a non-drug-using control group. We hypothesized that ketamine users and methadone users would be similar in their levels of impulsivity and cognitive function related to disinhibition. If ketamine users are similar to methadone users on these dimensions, it may explain why they continue using the drug despite the fact that they tend not to experience withdrawal symptoms. In other words, it is likely that impulsivity and inhibition are important factors in explaining why ketamine users continue using in the same way as other drug users do.

2. Methods

2.1. Participants

The study sample ($N = 170$) consisted of 51 (29 male, 22 female) ketamine users, 59 (36 male, 23 female) patients engaged in methadone use, and 60 (30 male and 30 female) healthy non-drug-using controls. Study participants were selected for age (18–45). None had a current or past history of major psychiatric disorders (e.g., schizophrenia or mania) or serious head injury or neurological disorder. None was taking medications known to affect the central nervous system. Based on self-report, ketamine and methadone users were abstinent from drugs at least 24 h prior to the 2-h individual neuropsychological assessment, verified by

urine testing. Participants were excluded if the urine test showed a positive result for heroin or ketamine. In the non-drug-using control group, the participants were required to have no current or lifetime history of substance dependence, including alcohol dependence but excluding nicotine dependence.

2.2. Assessment

2.2.1. Demographic and drug-use information

Demographic data were collected by a questionnaire designed for this study, to assess age, gender, years of education, employment, and use of alcohol/nicotine. Because participants had a difficult time reporting their alcohol consumption in terms of standard drinks, we took the information they reported and converted it to a standard measure based on estimated alcohol content. For example, beer's alcohol content is around 12' and Chinese liquor is 38' or 58'; thus, one glass of Chinese liquor is equal to three glasses or five of beer. Demographic information was used to create categorical or continuous variables for the statistical analyses. For methadone and ketamine users, we characterized the profile of drug use based on the following variables: type of drugs they were using and used before, age of first drug use, duration of drug use and abstinence, and the amount of daily drug use.

2.2.2. Depression

We used the CAS (Chinese Affect Scale) (Hamid and Cheng, 1996) and CES-D (Catchment-Area Epidemiology Survey-Depression) (Rodolff, 1977) to measure participants' affect and depression. Subjects with depression were excluded from the groups.

2.2.3. General intelligence

The Raven's Progressive Matrices (Raven, 2008) test was used as a non-verbal estimate of participants' general intellectual functioning, as a possible confound in group comparisons.

2.2.4. Antisocial personality traits

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2; Butcher et al., 1989) is one of the most widely used, objectively scored self-report tests of personality in the mental health field. The Psychopathic Deviate Scale (Pds) measures a person's need for control or rebellion against being controlled, characterized by conflict, struggle, anger, and lack of respect for society's rules (Butcher et al., 1989; Ben-Porath, 2012). There are altogether 50 items in T/F format. In the current study, a Chinese translated version (Zhang, 1992) was used as a measure of rebelliousness and antisocial acts. The Chinese translated version provided the Chinese MMPI norms and cutoff scores. This measure has been found to be suitable for use in a Chinese population.

2.2.5. Impulsivity and inhibition

Impulsivity was measured using the Chinese translated version of Barratt's Impulsivity Scale Version 11 (BIS-11; Patton et al., 1995). The BIS-11 demonstrates good psychometric properties and is suitable for use in a Chinese population (Yao et al., 2007).

The stop-signal test was used to test response inhibition (Logan, 1994). In the stop-signal test, the more frequent stimulus (75%) constitutes a go signal requiring the participants to respond within a time window, setting up a prepotent response tendency. In the less frequent stop trial (25%), a stop signal appears after the go signal and instructs the participants to refrain from making the response. There are altogether 240 trials, which were divided into three blocks to be shown to the participants. Stop-signal go reaction time, go errors, and reaction time (SSRT) were collected.

The Stroop test is a measure of response inhibition (Ridley, 1935; Milham et al., 2003). We used the color word Stroop task in which participants verbally name the color of “color” words

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