Addictive Behaviors 38 (2013) 2661–2666

Contents lists available at ScienceDirect

Addictive Behaviors

Cognitive impairments in poly-drug ketamine users

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HIGHLIGHTS

- Cognitive domains were compared between poly-drug ketamine users and controls.
- Poly-drug ketamine users were further divided into current and ex-users.
- Both current and ex-users had verbal and visual memory impairments.

ARTICLE INFO

Keywords:
Ketamine
Substance abuse
Cognitive function
Memory
Executive function

ABSTRACT

Rationale: Cognitive impairment has been found to be reversible in people with substance abuse, particularly those using ketamine. Ketamine users are often poly-substance users. This study compared the cognitive functions of current and former ketamine users who were also abusing other psychoactive substances with those of non-users of illicit drugs as controls.
Methods: One hundred ketamine poly-drug users and 100 controls were recruited. Drug users were divided into current ($n = 32$) and ex-users ($n = 64$) according to the duration of abstinence from ketamine (>30 days). The Beck Depression Inventory (BDI), the Hospital Anxiety Depression Scale (HADSA) and the Severity of Dependence Scale (SDS) were used to evaluate depression and anxiety symptoms and the severity of drug use, respectively. The cognitive test battery comprised verbal memory (Wechsler Memory Scale III: Logic Memory and Word List), visual memory (Rey–Osterrieth Complex Figure, ROCF), executive function (Stroop, Wisconsin Card Sorting Test, and Modified Verbal Fluency Test), working memory (Digit Span Backward), and general intelligence (Information, Arithmetic and Digit-Symbol Coding) tests.
Results: Current users had higher BDI and HADSA scores than ex-users ($p < 0.001$ for BDI and $p = 0.022$ for HADSA) and controls ($p < 0.001$ for BDI and $p = 0.002$ for HADSA). Ex-users had higher BDI ($p = 0.006$) but equal HADSA scores ($p = 1.000$) compared to controls. Both current and ex-users had lower scores on Logical Memory delayed recall ($p = 0.038$ for current users and $p = 0.032$ for ex-users) and ROCF delayed recall ($p = 0.033$ for current users and $p = 0.014$ for ex-users) than controls. Current users also performed worse on ROCF recognition than controls ($p = 0.002$). No difference was found between the cognitive functions of current and ex-users.
Conclusions: Ketamine poly-drug users displayed predominantly verbal and visual memory impairments, which persisted in ex-users. The interactive effect of ketamine and poly-drug use on memory needs further investigation.

1. Introduction

Ketamine is a frequently abused drug, particularly among youth. In 2009, 1.7% of 12th grade high school students reported the use of ketamine over the past year (Morgan, Muetzelfeldt, & Curran, 2009; National Institute on Durg Abuse, 2010). An investigation in the United Kingdom confirmed the rising trend of ketamine use: in club settings, its life-time prevalence rose from 25.5% in 1999 to 39.8% by 2003 (McCambridge, Winstock, Hunt, & Mitcheson, 2007). Ketamine is currently the most commonly abused drug by young people in Hong Kong; approximately 70% of local ketamine abusers are under the age of 21 (Narcotics Division Security Bureau, 2012).

Pharmacologically, ketamine reacts by non-competitively antagonizing the N-Methyl-D-aspartate (NMDA) receptor, thereby interfering with the transmission of excitatory amino acid glutamate and aspartate, and also with other monoamines such as dopamine and serotonin (Olney, Newcomer, & Farber, 1999). These pharmacological actions mediate the effect of ketamine on cognitive functions and psychiatric symptoms (Wolff & Winstock, 2006). Repeated ketamine consumption induces cognitive impairment, manifested as poor

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http://dx.doi.org/10.1016/j.addbeh.2013.06.017

performances on tasks that tap spatial working memory, planning, visual recognition and semantic memory (Morgan, Muetzelfeldt, & Curran, 2010; Morgan et al., 2009). One study reported intact inhibition in chronic users (Morgan et al., 2009). No previous studies have examined other executive functions like set-shifting, inhibition or perseveration in chronic ketamine users. Inhibition and perseveration are impaired in monkeys treated with phencyclidine, an NMDA receptor blocker (Jentsch, Roth, & Taylor, 2000; Jentsch, Taylor, Elsworth, Redmond, & Roth, 1999; Jentsch et al., 1997).

Cognitive impairment has been observed in frequently ketamine users (e.g. use ketamine more than four times a week), but not in ex-users (abstinent for at least 1 month) and poly-drug users (Curran & Monaghan, 2001; Morgan et al., 2009), suggesting that ketamine-related cognitive impairments are reversible (Morgan et al., 2010).

Ketamine users frequently abuse a wide range of other illicit drugs, such as cannabis, ecstasy, amphetamine, cocaine and hallucinogens (poly-drug ketamine users; Degenhardt & Dunn, 2008). Among Hong Kong poly-drug users, 25% concurrently abuse ketamine (Narcotics Division Security Bureau, 2012). Memory and executive function deficits have been well documented in users of cocaine (Colzato, Huizinga, & Hommel, 2009; Madoz-Gurpide, Blasco-Fontecilla, Baca-Garcia, & Ochoa-Mangado, 2011; Soar, Mason, Potton, & Dawkins, 2012) and methamphetamine (Iudicello et al., 2010). Although previous studies have focused on ketamine users, little is known about poly-drug ketamine users.

This case control study examined cognitive functions in poly-drug ketamine users compared with a control group of non-users of illicit drugs. We predicted that poly-drug users would show impairment in a range of cognitive domains. The study also explored the chronicity of the cognitive impairment following the cessation of ketamine. We hypothesized that cognitive functions would improve after ketamine abstinence.

2. Methods

2.1. Subjects and design

All subjects were recruited from non-governmental organizations (NGOs). Drug users were referred by counseling centers for psychotropic substance abusers (CCPSA) and residential treatment centers or district youth outreach teams (YOT), while controls were enrolled from community service centers. The above NGOs (except residential treatment centers) also provide services for all youth in the community, including leadership training, voluntary work, vocational training, civic and family education, outdoor activities, etc., which emphasize physical, intellectual, moral and social values to facilitate character development.

Subjects were enrolled in the study if they reported using ketamine at least 24 times over 6 months within the past 2 years. Consumption of other drugs in the same period was also recorded. Controls had no history of any substance use except nicotine and alcohol. Other entry criteria for all subjects were (1) aged between 16 and 30; (2) no significant medical condition requiring regular medication; and (3) no history of any neurological disorder or severe head injury.

Between December 2009 and December 2011, 200 ketamine users and 100 controls entered the study. Ketamine users were divided into a poly-drug ketamine group (use of drugs other than ketamine at least 24 times over 6 months within the past 2 years), and a primary ketamine group (use of ketamine only). This study reports on the poly-drug ketamine group ($N = 100$) and controls. The poly-drug ketamine group was further divided into current and former users; former users had stopped taking ketamine for at least 30 days (Morgan et al., 2009).

The study protocol was approved by the Survey and Behavioral Research Ethics Committee of the Chinese University of Hong Kong. All subjects provided written consent. Subjects were given a coupon of HK$150 (approx. US$19) to reimburse their travel expenses.

2.2. Measurements of mood and drug use severity

Depressive symptoms were screened with the Chinese version of the 21-item Beck Depression Inventory (BDI; Shek, 1990). The anxiety subscale of the Hospital Anxiety Depression Scale (HADSA; Leung, Ho, Kan, Hung, & Chen, 1993) was used to screen for anxiety symptoms. The HADSA comprises seven anxiety-related items graded from 0 to 3, with higher scores indicating more severe symptoms. The summed scores for the seven items were entered into the statistical analysis.

The Chinese version of the Structured Clinical Interview for DSM-IV (C-SCID; So et al., 2003) was used to screen for psychotic symptoms. Subjects who scored positively on one or more items were referred to a psychiatrist (AT) for diagnostic clarification. To establish inter-rater reliability, two RAs performed the psychosis screening on the same 20 subjects yielding a kappa of 1.0, indicating a high level of consistency between the two raters.

The Severity of Dependence Scale (SDS; Gossop et al., 1995), a 5-item self-report scale, measured the degree of drug dependence in the past month or the month before abstinence. Each item scores range from 0 to 3, with higher scores indicating more severe dependence.

2.3. Measurements of cognitive functions

The cognitive battery comprised the following tests.

a. The three-subtest Short Form of the Wechsler Adult Intelligence Test—III was used to estimate general intelligence. This test contains Information, Arithmetic and Digit-Symbol Coding subtests and has been validated in the general Hong Kong population (Chan, Chen, & Chan, 2005). Scores on these three sub-tests range between 0 and 22, between 0 and 28 and between 0 and 133, respectively. Scores of these three sub-tests were standardized and combined to generate the estimated intelligence quotient (IQ) as index of general intelligence; higher score indicated better performance, whereas a negative score implied a below average level of intelligence.
b. Executive functioning was evaluated using the Stroop Test (Stroop, 1935), Modified Verbal Fluency Test (MVFT; Chiu et al., 1997) and the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). In the Stroop Test, subjects were required to name the colors of the dots, read the words with a meaning unrelated to the color of the ink, and read the color of the words that their meanings were incongruent with the color of the ink. The additional time spent in the third condition compared to the first was used as the index of interference. In the MVFT, subjects were asked to generate as many animal names as possible in 1 min, as many fruit names as possible in 30 s, and vegetable names in another 30 s. The total number of correct responses was entered into the statistical analysis. This task also taps semantic memory (Henry & Crawford, 2004). The WCST has been widely used to assess shifting. In this study, the number of categories completed, total trials and perseverative errors were selected as index scores (Nyhus & Barcelo, 2009).
c. Working memory was assessed with the Digit Span Backward test (Wechsler, 1997a,b); total scores range from 0 to 14 with higher scores reflecting better performance.
d. Verbal memory was assessed with the two subtests of the Wechsler Memory Scale—Third Edition (WMS III). The Logical Memory subtest assesses immediate recall, delayed recall and recognition of two short stories (Hua et al., 2005; Wechsler, 1997a,b); the Word List subtest measures immediate and delayed recall and recognition of a group of unrelated words (Hua et al., 2005; Wechsler, 1997a,b). The retention rate of these two tests was also counted by dividing the delayed recall score by the immediate recall score. This task taps episodic memory.
e. Visual Memory was evaluated with the Rey–Osterrieth Complex Figure (ROCF; Osterrieth, 1944; Taylor, 1959). The ROCF tests copying,