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Other drug use does not impact cognitive impairments in chronic ketamine users

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ABSTRACT

Background: Ketamine abuse causes cognitive impairments, which negatively impact on users' abstinence, prognosis, and quality of life.**Results:** of cognitive impairments in chronic ketamine users have been inconsistent across studies, possibly due to the small sample sizes and the confounding effects of concomitant use of other illicit drugs. This study investigated the cognitive impairment and its related factors in chronic ketamine users with a large sample size and explored the impact of another drug use on cognitive functions.**Methods:** Cognitive functions, including working, verbal and visual memory and executive functions were assessed in ketamine users: 286 non-heavy other drug users and 279 heavy other drug users, and 261 healthy controls. Correlations between cognitive impairment and patterns of ketamine use were analysed.**Results:** Verbal and visual memory were impaired, but working memory and executive functions were intact for all ketamine users. No significant cognitive differences were found between the two ketamine groups. Greater number of days of ketamine use in the past month was associated with worse visual memory performance in non-heavy other drug users. Higher dose of ketamine use was associated with worse short-term verbal memory in heavy other drug users.**Conclusion:** Verbal and visual memory are impaired in chronic ketamine users. Other drug use appears to have no impact on ketamine users' cognitive performance.

1. Introduction

Ketamine abuse is a public health problem worldwide (Liao et al., 2017). Fifty-eight countries and territories reported recreational use of ketamine including Australia, Brazil, UK, US, and Hong Kong (United Nations Office on Drug Control, 2016). Recent life time prevalence of ketamine use is 1.5% in 12th grade students in the US, 0.05–1.08% in South American university students, 2.6% in the 16–24 year-old population in the UK and 1.7% in 14 years and older youth in Australia (United Nations Office on Drug Control, 2016). In mainland China, use of synthetic drugs including ketamine has increased from 5.6% to 53.8% in newly reported drug users (Jia et al., 2015). In Hong Kong, ketamine abuse was the second most commonly abused drug in 2014 (Narcotics Division, Security Bureau, 2015).

As an N-methyl D-aspartate receptor (NMDA) antagonist, ketamine affects memory storage and consolidation (Newcomer and Krystal, 2001). Chronic recreational use of ketamine causes neurocognitive

impairments (Kalsi et al., 2011), which may have a negative impact on physical disability, treatment adherence, employment and quality of life similar to cocaine and alcohol use (Aharonovich et al., 2003; Campbell et al., 2016; Curran, 2017; Deloire et al., 2010; McCrady and Smith, 1986). A better understanding of cognitive impairment could help clinicians to improve the prognosis and quality of life for chronic ketamine users.

Except for verbal memory impairment, cognitive deficits, including working and visual memory and executive function deficits, have been inconsistently reported in chronic ketamine users. For example, working memory impairment was reported in frequent ketamine users in some (Morgan et al., 2009), but not other studies (Curran and Monaghan, 2001; Liang et al., 2013; Morgan et al., 2004b). Visual memory was found to be impaired in frequent (Morgan et al., 2004b; Morgan et al., 2009) and poly-ketamine users (Liang et al., 2013), but was not replicated (Chan et al., 2013; Curran and Morgan, 2000). Executive dysfunction in frequent ketamine users has been shown in some

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(Curran and Morgan, 2000; Morgan et al., 2009), but not all studies (Chan et al., 2013; Liang et al., 2013; Morgan et al., 2004b). These inconsistencies may be due to the impact of other drug use in the chronic ketamine users, as the majority of them used other recreational drugs (Liang et al., 2013; Morgan et al., 2010; Morgan et al., 2004c) also causing cognitive impairment (Messinis et al., 2006; Vonmoos et al., 2013).

To better understand chronic ketamine users' cognitive impairment, the impact of other drugs should be taken into account. It is still unknown whether there is a synergistic interaction between ketamine and other illicit drugs on cognitive functions. Non-drug users, poly-drug users (excluding ketamine) and ex-ketamine users have all been controls in studies involving chronic ketamine users. Poly-drug users and ex-ketamine users also showed cognitive impairment, thus non-drug users (healthy persons) are the only appropriate controls. Small sample sizes may have also contributed to the inconsistency of the results regarding cognitive impairment in chronic ketamine use.

This study set out (1) to revisit the issue of cognitive impairment in a large sample of chronic ketamine users, and (2) to explore the possible synergistic effects of ketamine and other psychoactive drugs. We hypothesized that (1) ketamine users would show cognitive impairment in working and verbal/visual memory and executive functions, and (2) additional heavily use of other illicit drugs would be associated with more severe cognitive impairment in chronic ketamine users.

2. Methods

2.1. Subjects and design

The study sample was collected between December 2009 and September 2016 in Hong Kong, China. Ketamine users were recruited from non-government organizations such as residential treatment and counselling centres and district youth outreach teams for psychotropic substance users. Healthy controls were enrolled from community service centres.

Chronic ketamine users were divided into two groups; 'non-heavy other drug users' who used ketamine and low frequency of other drugs and 'heavy other drug users' who used ketamine and high frequency of other drugs. Ketamine users entered the study if they used ketamine at least 24 times over 6 months within the past 2 years. Subjects were assigned to the 'heavy other drug users' group if they used other recreational drugs more than 24 times over 6 months within the past 2 years in addition to ketamine; the less frequent users were assigned to the 'non-heavy other drug users' group. Healthy controls had no history of any illicit drug use. Other inclusion criteria were (1) age between 18 and 40 years, and (2) no history of neurological or any other medical diseases or treatment known to affect the central nervous system (CNS). The exclusion criteria were (1) inability to provide valid consent; (2) pregnancy; (3) any current psychiatric disorder, and (4) for controls, a positive illicit drug urine screen. Healthy controls had a rapid urine drug test. All subjects underwent a semi-structured interview and completed the neurocognitive and mood status assessment detailed below.

The study protocol was approved by the Survey and Behavioural Research Ethics Committee of the Chinese University of Hong Kong. All subjects provided written informed consent.

2.2. Measurement of mood and the severity of drug use

The Chinese version of the Structured Clinical Interview for DSM-IV (So et al., 2003) was used to screen for psychotic symptoms. To establish inter-rater reliability, two qualified psychiatrists performed the psychosis screening on the same 30 subjects, yielding a kappa of 1.0, which indicates a very high level of consistency. Depressive and anxiety symptoms were measured with the Chinese version of the 21-item Beck Depression Inventory (BDI) and the anxiety subscale of the Hospital

Anxiety Depression Scale (HADS), respectively (Leung et al., 1993; Shek, 1990). The Severity of Dependence Scale (SDS) was used to measure the severity of drug dependence (Gossop et al., 1995). Higher scores indicate greater severity on all the above scales.

2.3. Neurocognitive assessments

Working memory was measured with the digit span task of the Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 2005); total scores range from 0 to 30 for forward and backward span, with higher scores indicating better performance. Verbal memory was assessed with the Logical Memory immediate recall, delayed recall and recognition tasks of the WMS-III. Visual memory was measured with the Rey-Osterrieth Complex Figure (ROCF) test, where the accuracy and placement of the elements of a complex figure in copying measure immediate and delayed recall, according to a 36-point scoring system (Taylor, 1959). The subjects were shown 24 geometric items and were asked to recognize which items were in the figure, producing an index score for total correct recognition (Taylor, 1959). Executive function was measured with the Stroop Test and the Wisconsin Card Sorting Test (WCST). In the Stroop Test, subjects named the colours of dots with words with a meaning unrelated to their colour and words with a meaning congruent with the colour (Stroop, 1935). The WCST is widely used to access problem solving. The total number of trials, categories and perseverative errors were chosen as index scores (Heaton et al., 1993).

2.4. Data analysis

Data analyses were performed with the SPSS statistical package, Version 22.0. Continuous variables are presented as the mean \pm standard deviation (SD), and categorical variables as numbers (N) and percentages (%). The data were tested for normality. Non-normally distributed data were log or square root transformed. Demographic data, drug use patterns and the depression and anxiety scores were analysed using the independent *t*-test, Chi-square test, Mann-Whitney *U* test, Kruskal-Wallis H test or ANOVA, as appropriate. Cognitive task scores were analysed with a univariate general linear model with age, sex, education and BDI scores as covariates. Because the HADS and BDI scores were highly correlated ($r = 0.682$, $p < 0.001$), only BDI scores were considered as confounding factors in the model. If a significant main group effect was detected, a post hoc analysis was performed to clarify group differences. The Bonferroni method was used to correct for multiple comparisons. Where clear group effects emerged, correlations were performed separately in the two drug user groups. Pearson's correlations were calculated for normally distributed variables and Spearman's correlations for categorical and non-normally distributed variables, both of which were used to detect the correlations between demographic and clinical data (age, gender, education years and BDI scores) and cognitive impairment scores. Partial correlations were performed between types of cognitive impairment and ketamine use patterns, with age, sex, education, and BDI scores being controlled for only if they were significantly correlated with cognitive impairment. The level of significance was set at 0.05 in all analyses except for the post-hoc tests ($\alpha = 0.016$).

3. Results

3.1. Demographic data, mood status and drug use patterns

The study sample consisted of ketamine users, including 286 non-heavy other drug users and 279 heavy other drug users, and 261 healthy controls. The demographic characteristics and the BDI, HADS and SDS scores are shown in Table 1. Non-heavy other drug users were older than the healthy controls ($p < 0.001$) and heavy other drug users ($p = 0.007$). Both ketamine groups had significantly more males than the healthy control group (both $p < 0.001$) and significantly lower

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