Research report on
Psychiatric comorbidity and cognitive dysfunction in primarily ketamine users: A closer look

Submitted to

Beat Drug Fund Association

Submitted by

Prof. Wai Kwong Tang, MD, Department of Psychiatry, Shatin Hospital

Huajun Liang, MPhil, Department of Psychiatry, the Chinese University of Hong Kong

Chieh Grace Lau, MA, Department of Psychiatry, the Chinese University of Hong Kong

Dr. Alan Tang, MRCPsy, Department of Psychiatry, Shatin Hospital

Hezon, Tang Kwok Hei, BA (Hons), MSc, Center-in-Charge of the Hong Kong Lutheran Social Service – Lutheran Cheer Centre.

Leung Yuk Kin, BSW, the Center-in-Charge of the Hong Kong Sheng Kung Hui Welfare Council Neo-Horizon.

Ng Suet Kam, Carol (RSW), Center-in-Charge of the Hong Kong Lutheran Social Service Evergreen Lutheran Centre.

Contents

Acknowledgements

The research team is grateful to the following agencies for their support in the recruitment of participants for this study:

Caritas HUGS Centre;
Caritas Lok Heep Club;
Cheer Lutheran Centre, Hong Kong Lutheran Social Services;
Christian New Life Association;
Evergreen Lutheran Centre, Hong Kong Lutheran Social Services;
Hong Kong Christian Services PS33- Shanshuipo Centre;
Hong Kong Christian Services PS33- Tsinshatsui Centre;
Hong Kong North District Hospital UROK Clinic;
Hong Kong Sheng Kung Hui Welfare Council Neo-Horizon;
Jockey Club Ma On Shan (South) Children and Youth Integrated Services Centre, Hong Kong Sheng Kung Hui Welfare Council;
Jockey Club Wah Ming Lutheran Integrated Service Centre, Hong Kong Lutheran Social Services;
Jockey Club Yung Shing Lutheran Integrated Service Centre, Hong Kong Lutheran Social Services;
Operation Dawn;
Rainbow Lutheran Centre, Hong Kong Lutheran Social Services;
Sha Tin Youth Outreaching Social Work Team, Chinese Young Men's Christian Association of Hong Kong;
The Society for the Aid and Rehabilitation of Drug Abusers;
and Yuen Long District Youth Outreaching Social Work Team, Hong Kong Christian Services.

Abbreviations

ASI: Addiction Severity Index
BDI: Beck Depression Inventory
BPRS: Brief Psychiatric Rating Scale
CCPSA: Counseling Centres for Psychotropic Substance Abusers
CHC: Cattell-Horn-Carroll
CK: Current primarily ketamine user
CPK: Current poly-ketamine user
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EK: Ex-primarily ketamine user
EPK: Ex-poly-ketamine user
HADSA: Hospital Anxiety Depression Scale
HC: health control group
IQ: intelligence quotient
K: Primarily ketamine group
KAIT: Kaufman Adolescent and Adult Intelligence Test
NMDA: N-Methyl-D-aspartate
Poly K: Poly-ketamine group
RAs: research assistants
RIAS: Reynolds Intellectual Assessment Scales
ROCF: Rey-Osterrieth Complex Figure
SB5: Stanford-Binet Intelligence Scales, Fifth Edition
SDS: Severity of Dependence Scale
WAIS-III: Wechsler Adult Intelligence Scale, Third Edition
WAIS: Wechsler Adult Intelligence Test
WCST: Wisconsin Card Sorting Test
WISC: Wechsler Intelligence Scale for Children
WJ-III: Woodcock-Johnson III Test of Cognitive Abilities
WMS-III: Wechsler Memory Scale, Third Edition
WPPSI: Wechsler Preschool and Primary Scale of Intelligence

Executive summary

The objective of this study was to evaluate the long-term effects of ketamine on both the cognition and psychological well-being of youths in Hong Kong.

A total of 300 participants were recruited for this study from December 2009 to December 2011. Participants were divided into three groups, each comprising 100 participants: primarily ketamine users, poly-ketamine users, and health controls. Psychiatric assessments included screening with self-rating questionnaires and face-to-face interviews. All of the participants completed a detailed cognitive battery that covered general intelligence, verbal memory, visual memory, executive function, motor speed, and language.

Participants in the primarily ketamine group predominantly used ketamine, whereas participants in the poly-ketamine group also frequently used cocaine and ice. The most common psychiatric disorder in both ketamine groups was depressive disorder. Participants in the ketamine groups scored poorly on most of the cognitive tests administered compared to the health control group in univariate analyses. After adjustments for age, sex, education, and BDI scores, the verbal and visual memory of participants remained impaired in both ketamine groups compared to the health control group. Recent use of ketamine in the previous month was independently related to memory impairment in the primarily ketamine group. The subgroup analyses of primarily ketamine users revealed significant impairment of verbal memory, visual memory, motor speed, and some executive function indexes in current users, but not in ex-ketamine users. This suggests a reversibility of the cognitive influence of ketamine. Moreover, current ketamine users had a higher BDI score than the other two groups. However, both ex- and current poly-ketamine users showed similar memory impairments compared to the health control group.

In conclusion, ketamine use alone and its use in combination with other psychotropic drugs are associated with deficits in memory and executive function. The observed memory impairment of ketamine users is mainly relevant in relation to recent ketamine use, with current primarily ketamine users presenting with more severe memory problems than poly-ketamine users. However, cognitive impairment improved in primarily ketamine users after abstinence from ketamine use, which was not the case with poly-ketamine users. In addition to cognitive function deficits, more than half of ketamine users suffer from depressive disorder. This study's findings are helpful in treating ketamine abuse because they reinforce the benefits of abstinence from drug use. An additional investigation that includes a longitudinal study is required to determine the reversibility of the effects of ketamine because the mechanism of this reversibility remains unclear.

行政撮要

本研究的目的是評估長期服用氯胺酮對青少年認知功能和精神健康狀況的影響。自 2009 年 12 月至 2011 年 12 月，共 300 名受試者入組。受試者分爲 3 組：氯胺酮組，氯胺酮及多種藥物組和健康對照組，每組有 100 名受試者入組。精神狀況評估包括問卷篩查和面談。所有受試者均完成一套詳細的認知測試。該測試涵蓋一般智慧、詞語記憶、視覺記憶、執行功能、動作速度和語言。

氯胺酮組受試者主要濫用氯胺酮，而氯胺酮及多種藥物組受試者除氯胺酮外主要濫用可卡因和冰毒。兩組氯胺酮濫用者最常見的共患精神障礙是抑鬱障礙。在單因素分析中，兩組氯胺酮濫用者幾乎在所有的測試中得分低於健康對照。多因素分析控制混雜因素如年齡、性別、教育程度和 Beck 抑鬱量表總分後，兩組氯胺酮濫用組與健康對照組在詞語記憶和視覺記憶仍存在顯著差異。本研究進一步將氯胺酮組及氯胺酮多種藥物組分別分爲現用藥者和戒斷者。在氯胺酮組中現用藥者在詞語記憶、視覺記憶、動作速度和部分執行功能測試上得分低於戒斷者和健康對照，而且現用者 Beck 抑鬱量表總分高於戒斷者和健康對照，而戒斷者和健康對照在認知測試和 Beck 抑鬱量表總分沒有顯著差別。但在氯胺酮及多種藥物組，現用藥者和戒斷者均在多數測試中得分低於及 Beck 抑鬱量表總分高於健康對照。

本研究認爲氯胺酮或氯胺酮及多種藥物均能導致記憶和執行功能的損害。這種損害主要與近期濫用氯胺酮有關，並且氯胺酮組現用藥者詞語記憶損害較氯胺酮及多種藥物現用者嚴重。單純氯胺酮導致的記憶和執行功能損害在戒斷 1 月後明顯好轉，但氯胺酮及多種藥物者戒斷一月後未能見到記憶功能好轉。超過半數的氯胺酮濫用者共患抑鬱

障礙。本研究的結果爲治療氯胺酮濫用有用資訊，亦有助於戒毒者鞏固其戒斷行爲。但氯胺酮所致認知損害的可逆性還需要前瞻性或縱向研究進一步證實，並且這種可逆性損害的機制還不明確。

Background

Introduction of ketamine and ketamine abuse

Ketamine [2-(2-chlorophenyl)-2-(methylamine)-cyclohexanone] was developed in 1962 by Parke-Davis Laboratories in the United States as an anesthetic to replace its precursor, phencyclidine. The effects of ketamine are less potent and have a shorter duration than phencyclidine. It also has a "dissociative effect" that is relatively rare, unlike leading side effects such as hypotension. Ketamine is legally used in human analgesia cases varying from pediatric to trauma and cancer patients [Wolff et al. 2006]. Ketamine is also commonly used in veterinary practices [Wolff et al. 2006].

Ketamine reacts pharmacologically through non-competitively antagonizing NMDA (N-Methyl-D-aspartate) receptors [Wolff et al. 2006]. NMDA receptor antagonists may prompt the interference transmission of excitatory amino acid glutamate and aspartate, which may underlie ketamine's prevention of the perception of auditory, visual, or painful stimuli; responses to the environment; and memory effects. Ketamine enhances the neurotransmission of noradrenaline, serotonin, and dopamine systems in a dose-dependent fashion that leads to its psychotomimetic and sympathomimetic effects [Wolff et al. 2006] and addiction potential [Ross et al. 2009]. Ketamine can be effectively administered through intranasal, intravenous, subcutaneous, intramuscular, and intrathecal routes. In recreational ketamine users, intranasal use is the most common route due to the rapid initiation and long lasting effect (about 2-3 hours). Ketamine's dissociative effects can be achieved with a low dose of 50-100mg, whereas a dose of 5-10mg/kg is required to achieve anesthesia. However, the perception and mood changes indicative of non-medical use are highly diverse based on age, dosage, route of administration, and previous experience [Curran et al. 2000]. Lower doses of ketamine typically generate a stimulant effect while higher doses produce psychedelic effects and environmental disassociation [Oye et al. 1992].

Ketamine has been misused in North America since the 1970s [Wolff et al. 2006] with recreational use reaching its peak around 2000 in the United States and thereafter gradually decreasing within the drug abuse population. However, in 2002, 2.6% of 12th graders in US high schools reported witnessing the use of ketamine in the previous year – a number that dropped to 1.7% in 2009 [National Institute on Durg Abuse 2010]. Trends in Hong Kong differ considerably from those in the United States. According to the Narcotics Division's Central Registry of Drug Abuse (CRDA), ketamine was recognized as an abused drug in Hong Kong after 2000. Its use increased rapidly and reached its peak in 2008 with a slight decrease in subsequent years. Ketamine is currently the most commonly abused drug in Hong Kong, especially among youths. About 70% of ketamine abusers are under the age of twenty-one,

with binge and withdrawal symptoms reported in most recreational ketamine users [Critchlow 2006; Leshner 2001; Wolff et al. 2006].

Introduction of cognition and intelligence and their assessments

Cognition describes the information acquisition, storage, transformation, and use of knowledge. It includes a wide range of mental processes such as perception, memory, and problem solving [Matlin 2005]. The definition of intelligence is less consistent and can be interpreted from different angles using variant theories [Cianciolo et al. 2004]. This section introduces the main components of cognitive processing, intelligence, and their related measurements in relation to this study.

Memory and memory assessments

"Memory refers to the persistence of learning in a state that can be revealed at a later time" [Squire 1987] (p.3). Widely accepted theory considers memory as consisting of short-term memory (later called working memory) and long-term memory. Short-term memory stores information temporarily while long-term memory offers more stable and permanent storage. Long-term memory can be further divided into procedural and declarative memory. Procedural memories contain information about how to perform automatic functions such as riding a bicycle, whereas declarative memory is the ability to store and retrieve facts or knowledge [Schwartz 2011]. Declarative memory can be divided into semantic and episodic memories with the former storing general facts and concepts while the latter stores situation- and context-specific information [The Psychological Corporation 2002]. Knowledge and awareness of one's memory regulation is known as meta-memory [Schwartz 2011]. Encoding, retrieving, and autobiographical memories are the essential elements of long-term memory. Encoding is the initial acquisition of information and retrieval is the location and access of stored information. Autobiographical memories store information about events related to oneself and one's daily life [Matlin 2005].

Extant memory tests focus largely on testing episodic memory [The Psychological Corporation 2002] and memory encoding/retrieval. Recall and recognition are the most common tasks for testing memory [Matlin 2005] and source judgments determine where and from whom we learned something, which is also a direct test of episodic memory [Schwartz 2011]. Memory can also be divided into implicit and explicit categories. Implicit memory occurs on an unconscious level, whereas explicit memory is conscious. In conditions developed to test implicit memory, participants do not realize that they are being tested. In contrast, participants whose explicit memory is being tested are conscious of what they should remember know that they will be asked to recall the information. In summary, recall, recognition, implicit memory testing, source judgments, and metamemory judgments constitute the majority of the memory testing battery [Schwartz 2011].

The Wechsler Memory Scale, developed in 1945 by Wechsler, is an individually administered clinical instrument that assesses the components of memory and learning in older adolescents and adults. The Wechsler Memory Scale-Third Edition (WMS-III) includes 6 primary subtests (logical memory, letter-number sequencing, verbal paired associates, faces, family pictures, and spatial span) and 5 optional subtests (word-list, mental control, digit span, visual reproduction, and information and orientation). Primary index scores reflecting 3 global composite indexes (immediate, general, and working memory indexes) and 5 additional index scores (auditory immediate, visual immediate, auditory delayed, visual delayed, and auditory recognition delayed) are calculated from core subtests [The Psychological Corporation 2002]. This construction of composites and indexes is based on theoretic principle and the factor structure analysis of the predecessor version. Research on the previous version consistently verified a three-factor model containing working, immediate, and delay memories [The Psychological Corporation 2002] in which the latter two theoretically corresponded to the encoding and retention of memory [Tulsky 2004]. However, a factor analysis of WMS-III otherwise supports another three-factor model containing working, auditory, and visual memories. There have also been comments encouraging the continued use of immediate and delay indexes in clinical studies based on clinical and theoretic considerations [The Psychological Corporation 2002; Tulsky et al. 2004].

Working memory, which is the brief and immediate memory of material that is currently being processed, is an active form of short-term memory in which calculation and manipulation occur. Compared to long-term memory, working memory is limited in both information and capacity [Matlin 2005]. The basic design of experiments intended to gauge working memory is to present a large amount information and require participants to retain the end product. The level of difficulty for a working memory task can be increased in two dimensions: by expanding the amount of material included in a single task and by limiting the availability of the participants' attention capacity by requiring that they perform two tasks simultaneously. However, these dimensions are highly related and have no practical differences. Digit span is widely used in working memory and its forward mode measures the storage component of working memory while the backward mode increased the complexity by deemphasizing the manipulation of material and reordering the presented digits [The Psychological Corporation 2002].

Executive function and assessments of executive function

Baddeley and Hitch [1974] first described the "central executive" in their working memory model as a supervisory system that controls and adjusts two subsystems: a phonological loop and a visuospatial sketchpad. The single unit property of executive function has since been refined by Lezak, who also defines executive function as the integration of initiation, planning, purposive action, self-monitoring, self-regulation, and volition [Lezak 1995]. Components such as inhibition and shifting are also well defined in executive function

[Stuss 2011]. Later theories have presented executive function as a collaboration of several abilities that allows us to shift our minds to adapt to new situations and inhibit inappropriate responses by initiating a goal, creating a plan, and executing that plan [Jurado et al. 2007]. The Stroop test, the Wisconsin Card Sorting test (WCST), and verbal fluency are the most widely used methods designed to measure executive function [Alvarez et al. 2006].

Stroop test

The Stroop test (1935) consists of 300 items and is divided into 3 types of stimuli: neutral color naming, neutral word reading, and color-word incongruent naming. The raw score, presented as reaction speed, is calculated using the number of correct responses in 45 seconds for each stimuli type. In color-word incongruent naming, participants respond relatively slower, producing fewer total responses and making more errors than in the other two conditions because of the contradiction between color naming and word reading [Golden 1976; Stroop 1935]. Despite modifications to this test, the 3 different types of stimuli have remained (color dot naming (part D), neuter colored words (part W), and incongruently colored words (part C)) [Lezak 1995; Perret 1974; Regard 1981] and it has been translated into Chinese [Lee et al. 2000]. Each condition consists of 24 items and participants are required to read the given color of the dots in part D, the color of the unrelated words in part W, and the printed color of the incongruently colored words in part C. The number of errors and reaction times are then recorded for each condition. Participants tend to take a longer time and make more errors in part C due to the activation of the inhibitory process or interference effect. The additional time spent in part C is considered time spent on inhibiting word reading or solving interference [Ludwig et al. 2010], whereas the increased error rates are seen as an index of temporally maintaining the task goal [Kane et al. 2003].

Wisconsin Card Sorting test (WCST)

The WCST was first developed by Esther Berg [Eling et al. 2008] in 1948 to test "shifting", which involves learning a rule and then switching to another rule. Milner (1963) first reported the WCST's specific relation with frontal lobe injury. Subsequently, popular use of the WCST has focused on the evaluation of frontal lobe and executive function in different populations [Nyhus et al. 2009]. The main purpose of the WCST is to test abstract reasoning, concept formation, and response strategies in changing conditions [Eling et al. 2008]. The original, full version of the WCST comprises 4 stimulus cards and 128 response cards. Participants are asked to match each response card with a stimulus card in each attempt according to the examiner's feedback of "right" or "wrong". More details will be provided in the method section. Sixteen index scores are available in this test, but a participant's performance in the WCST can only be reflected by 2 or 3 index scores with integrity and a strong correlation with the outcome measurements [Nyhus et al. 2009].

Verbal fluency

Verbal fluency (VF) is another test frequently used to assess executive function [Henry et al. 2004]. The VF test has two common forms: semantic (category) and phonemic (letter). Both are widely used in various populations for the assessment of executive function. Semantic VF uses semantic memory to produce as many words as possible within a given category [Henry et al. 2004]. Lexical representations, the organization of verbal retrieval and recall, self-monitoring, and response inhibition are all essential cognitive components of phonemic VF, which requires participants to produce words that begin with a given letter. In clinical and fMRI studies, phonemic VF was more likely to stimulate the frontal lobe while semantic VF more commonly stimulated the temporal lobe. A number of studies have provided evidence documenting the associations between phonemic VF and neurological factors, yet this could be confounded by verbal intelligence [Henry et al. 2004]. Furthermore, due to the distinctive linguistic properties of Chinese language [Chan et al. 2003; Chiu et al. 1997], most studies in conducted within Chinese populations adopt the use of semantic VF. Consequently, this study uses the modified Chinese semantic VF test because it has been validated in local populations [Chan 2004].

Intelligence and intelligence tests

Intelligence

The definition of intelligence has been debated since the time of the ancient Greeks. The psychological conception of intelligence was first introduced by Spearman in 1927. He believed that the individual differences in intelligence are primarily the result of a general factor "*g*" and specific factors "*s*" that play important roles in relation to "*g*". Thurstone (1938) and Guilford (1956) argued against the idea of "*g*", even after Thomson (1939) extended its nature. Research has supported the multiple-factor structure of intelligence and its models, which were proposed sequentially. Horn-Cattell's fluid-crystallized theory (1990s) and Carroll's (1993) three-stratum theory [Kamphaus et al. 2005] have been the most influential.

Cattell developed fluid-crystallized theory in 1941, which stated that there are two distinct general factors of intelligence: fluid and crystal, as based on a factor analysis of existing intelligence tests. This idea was further expanded in the 1990s by Horn to include 9 general ability factors [Wasserman et al. 2005] and this revision is known as Horn-Cattell's fluid-crystallized theory. Simultaneously, Carroll published a three-stratum theory after reviewing and reanalyzing 460 data sets that included all of the important factor-analytic studies of human intelligence available at the time [Carroll 2005]. In this hierarchical theory, stratum III ability or "g" is the highest ability level, stratum II ability contains eight

broad-abilities, and stratum I ability refers to numerous narrow-abilities. Compared to Horn-Cattell's fluid-crystallized theory, Carroll's theory expands the general abilities (stratum II) to include a lower, narrow-ability level (stratum I) and a higher level (stratum III or "g") [Carroll 2005]. The classifications of the broad-abilities did not change [McGrew 2005] and these two theories were ultimately integrated into the Cattell-Horn-Carroll (CHC) theory in 1998 by McGrew and Flanagan.

The nature of intelligence cannot be fully explained by the aforementioned structured models. Complex models of intelligence that consider other aspects have also been constructed. For instance, Naglieri described a model that used the brain's function and structure. He conceptualized cognitive function within the framework of three brain units: the project, associated, and overlapping areas. These units provide four basic cognitive processes related to performance, in contrast to the verbal-nonverbal model [Naglieri et al. 2005]. Gardner (1983/1993) identified 7 distinct domains of intelligence in the original Multiple-Intelligence theory. He also emphasized the interaction between the components that contributed to the domain and the participants' biological predispositions and environmental and cultural contexts. These domains of intelligence can be interpreted in both conventional and unconventional ways. A conventional interpretation includes linguistic, logical-mathematical, and spatial elements while an unconventional interpretation involves musical, body-kinesthetic, interpersonal, and intrapersonal elements. Consequently, Gardner developed the Project Spectrum Preschool Assessment Activities to measure performance in 7 areas: movement, language, mathematics, social, music, visual arts, and science with the goal of portraying participants' intellectual profiles [Chen et al. 2005a]. Sternberg's Triarchic theory identified three notions of intelligence: componential, experiential, and contextual. Participants succeed intellectually by recognizing their strengths and weaknesses when dealing with environmental changes to find a balance among these three abilities [Sternberg 2005]. These theories mainly focus on guidance in education [Chen et al. 2005a; Naglieri et al. 2005; Sternberg 2005]. Sternberg eventually proposed the conception of "successful intelligence", which identified intelligence as the balance of analytical, creative, and practical abilities [Sternberg 2005].

Despite the progress that has been achieved through various explorations into the nature of intelligence, its definition is far from consistent [Wasserman et al. 2005]. Wechsler (1939) defined intelligence as "the aggregate or global capacity to act purposefully, to think rationally, and to deal effectively with his environment" [Wechsler 1939] (p. 3). He believed intelligence to be a global function composed of elements and abilities that are qualitatively different, which is representative among structured theories of intelligence. Furthermore, in his later career, Wechsler realized that non-intellective factors such as personality traits, motivations, and attitudes also contribute to intelligence performance, along with one's effectiveness in daily living and meeting challenges [The Psychological Corporation 2002].

Intelligence tests

The measurement of intelligence is accompanied by and based on the development of intelligence theories such as the Kaufman Adolescent and Adult Intelligence Test (KAIT) [Kaufman et al. 1993], the Woodcock-Johnson III Test of Cognitive Abilities (WJ-III) [McGrew et al. 2001], and the Wechsler Intelligence and Stanford-Binet intelligence scales - Fifth Edition (SB5) [Roid 2003]. The following section introduces several of the intelligence batteries applied to adults.

Intelligence was first assessed by Sir Francis Galton in the late nineteenth century and expanded by James McKeen Cattell later in the United States. The original test focuses on simple psychological processes, such as speed of movement and sensory capabilities. It was a milestone, but it is not flawless. It showed poor internal correlation and concurrent validity when applied to more complex levels of intellectual performance such as those required in college [Cianciolo et al. 2004]. Binet's work is considered the beginning of modern intelligence testing [Wasserman et al. 2005]. In 1916, Binet and Simon proposed a set of tests for a higher level of cognitive function and well-developed judgment skills such as verbal skills and social comprehension. They arranged the tasks in increasing difficulty to represent the intelligence levels of different ages. Consequently, the concept of mental age – the age level at which a child can successfully perform in an intellectual way – was introduced. The Binet-Simon scale, once revised, had better practical utility. Lewis Terman renamed the test the "Stanford-Binet intelligence scales" in 1916 and launched the concept of intelligence quotient (IQ) [Cianciolo et al. 2004]. The Stanford-Binet intelligence scales, fifth edition (SB5) was launched in 2003 and contains 5 verbal subtests and 5 non-verbal subtests. The SB5 provides a global IQ score and 5 factor index scores: fluid reasoning, quantitative reasoning, general knowledge, visual-spatial abilities, and working memory. Both the Rasch analysis used in the scales' design and development and the modification of the sensitivity score to track cognitive change across time strengthened the SB5 [Roid et al. 2005] to the extent that it was the most widely used intelligence test in the first half of the twentieth century, supplanted only by the Wechsler intelligence scale [Wasserman et al. 2005].

The Wechsler-Bellevue intelligence scale, developed by David Wechsler in 1939, is another major contemporary test that incorporates both verbal and performance index scores into the overall score. In subsequent decades, Wechsler intelligence scales sustained several modifications to its norms, items, and scoring rules [The Psychological Corporation 2002]. Wechsler developed a series of scales, including the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) for preschool and primary students, the Wechsler Intelligence Scale for Children (WISC) for children between the ages of 6 and 16, and the Wechsler Adult Intelligence Scale (WAIS) for adults and older adolescents. The Wechsler scales are notable because they combine verbal and performance tests into a single battery aligned with psychological assessment, clinical practice, and the introduction of deviation IQ, which measures how one's intelligence performance deviates from that of other individuals from the same age group [Wasserman et al. 2005]. Three primary index scores: the full scale index (FSIQ), the verbal intelligence index (VIQ), and the performance intelligence index (PIQ) are provided in the WAIS-III. In addition to these scores there are another four, more discrete,

cognitive index scores that support using factor analysis: verbal comprehension (VCI), perceptual organization (POI), working memory (WMI), and processing speed (PSI). Table 1 shows the subtests that contribute to these four composite scores. The WAIS-III has been revised to include short forms due to the administrative demand for the full WAIS-III [Axelrod 2001], particularly in clinical samples. The short forms vary in the number of subtests. For instance, there is a 3-subtest model [Chan et al. 2005]; the Wechsler Abbreviated Scale of Intelligence (WASI), which contains 4 subtests extracted from the first 2 index factors [The Psychological Corporation 1999]; a 4-subtest model extracted from each of the WAIS-III's 4 index factors [Blyler et al. 2000]; a 7-subtest model [Axelrod et al. 2001]; and an 8-subtest model that generates a General Ability Index [Tulsky et al. 2001]. However, there has been limited evidence of a link between participants' profile variability and the accuracy of the composite score.

Table 1 Subtests grouped according to WAIS-III factor structure

Verbal comprehension	Perceptual organization	Working memory	Processing speed
Vocabulary	Block Design	Digit Span	Digit Symbol-Coding
Similarity	Matrix Reasoning	Arithmetic	Symbol Searching
Information	Object Assembly	Letter-Number Sequencing	
	Picture Completion		

The KAIT and the WJ-III are derived from the C-H-C theory. The KAIT produces two composite scores: a crystallized scale score and a fluid scale score. The KAIT also has a 6-subtest core battery and a 10-subtest expanded battery. Among these 10 subtests, 6 are from the core battery [Kaufman et al. 2005]. The WJ-III consists of 31 subtests that are organized according to the WJ III Test of Cognitive Ability (WJ III COG) (20 subtests) and the WJ-III Diagnostic Supplement to the Test of Cognitive Ability (11 subtests). The performance of the WJ-III can be interpreted on 4 levels. The first level is narrow abilities such as single subtest-related abilities. The second level measures broad abilities, which contain 7 clusters. The third level identifies cognitive category clusters and contains 3 clusters. The top level represents general intellectual ability. The most notable properties of the WJ-III are its rich, concrete subtests and the proficiency statement portion of the result report, which is also based on the Rasch analysis [Schrank 2005].

The Reynolds Intellectual Assessment scales (RIAS) and the Reynolds Intellectual Screening test (RIST) are also based on C-H-C theory. The RIAS includes a two-subtest verbal intelligence index, a two-subtest nonverbal intelligence index, a globe intelligence indicator, and a composite intelligence index. The RIAS also includes 2 subtests for memory testing and thus produces a composite memory index. The RIST, which contains two subtests and can be completed in 10 minutes, screens the need for a full-scale RIAS. In addition, the RIAS has also been widely used in childhood psychopathology and a series of neurological diseases (e.g., dementia and brain injury) that might contribute to efficacy advantages without decreasing participants' intelligence information [Reynolds et al. 2005]. Although the aforementioned

tests are well known and widely used, the WAIS-III remains the gold standard [Umphress 2008] as the most frequently used [Rabin et al. 2005] intelligence test for adults.

Ketamine and cognition

The substantial effects of ketamine lie in the antagonistic action of NMDA receptors, which is important in inducing long-term potentiation (LTP). LTP is a long-lasting increase in synaptic efficacy induced by brief, high frequency afferent stimulation and research has identified it as the underlying mechanism of learning and memory at the neuron level [Rowland et al. 2005]. NMDA receptor antagonists disrupt LTP in the hippocampus and has been shown to impair information acquisition in animals [Rowland et al. 2005]. In human studies, researchers have proven that one-off doses of ketamine lead to temporary memory impairment in health volunteers, including working memory (N-back test) [Krystal et al. 2005; Morgan et al. 2004a] and episodic memory [Morgan et al. 2004a, b; Parwani et al. 2005; Rowland et al. 2005]. Ketamine has been found to consistently impair the process of encoding information [Hetem et al. 2000; Rowland et al. 2005], prose recall [Morgan et al. 2004b], and the Hopkins verbal learning test [Krystal et al. 2005], but not the retrieval of information [Rowland et al. 2005]. Studies have also noted impairment to the early consolidation of information [Parwani et al. 2005]. For executive functioning, performance remained intact in the Stroop color-word test [Parwani et al. 2005], Trailmaking A/B [Morgan et al. 2004a], and the fluency test [Morgan et al. 2004b; Rowland et al. 2005] while response inhibition was impaired in the Hayling test [Morgan et al. 2004b] and rule learning and shifting in the WCST [Krystal et al. 2000; Krystal et al. 1999]. Moreover, acute use of ketamine caused no residual effects in health volunteers [Morgan et al. 2004b] and infrequent ketamine users [Curran et al. 2001], but the same was not true in frequent ketamine users [Curran et al. 2001].

Most extant studies have explored the acute effects of ketamine, although investigations into the chronic effects of ketamine in humans have been limited for ethical reasons. These studies have focused on recreational ketamine users in which semantic and episodic memory remained impaired three days after dosage [Curran et al. 2001; Morgan et al. 2004d]. However, the same was not true in health volunteers who were given a dose of ketamine [Morgan et al. 2004b]. In another study, 18 recreational ketamine users were retested 3-4 years after recruitment and their semantic memory had improved with decreases in ketamine use, whereas deficits in episodic memory and attention remained [Morgan et al. 2004c]. Recent evidence has suggested that frequent ketamine users (more than four times a week) sustain impairments in spatial working memory, pattern recognition, Stockings of Cambridge tasks (planning), and category fluency compared to infrequent users, ex-users (abstinent for at least one month), normal controls, and poly-drug users (except in the use of ketamine) [Morgan et al. 2009]. Retrieval from source memory, prose recall (episodic memory), VF, and the Hayling test (response initiation and inhibition) were preserved in the frequent ketamine group, with no difference found between ex- and infrequent ketamine users compared to no-drug users

[Morgan et al. 2009]. In addition, a correlation has been found between the amount of ketamine used and the user's performance in pattern recognition and working memory in frequent ketamine users [Morgan et al. 2010]. The chronic effects of ketamine have also been thought to be reversible, given the similarities between the performances of ex-ketamine users and non-drug users in this study. A local study [Chen et al. 2005c] was unable to detect cognitive dysfunction among ketamine users, but there are flaws in the aforementioned studies. First, they feature small sample sizes. Moreover, in Morgan's studies, the ketamine users all co-abused other drugs such as cocaine or cannabis, which may confound ketamine's effect profile.

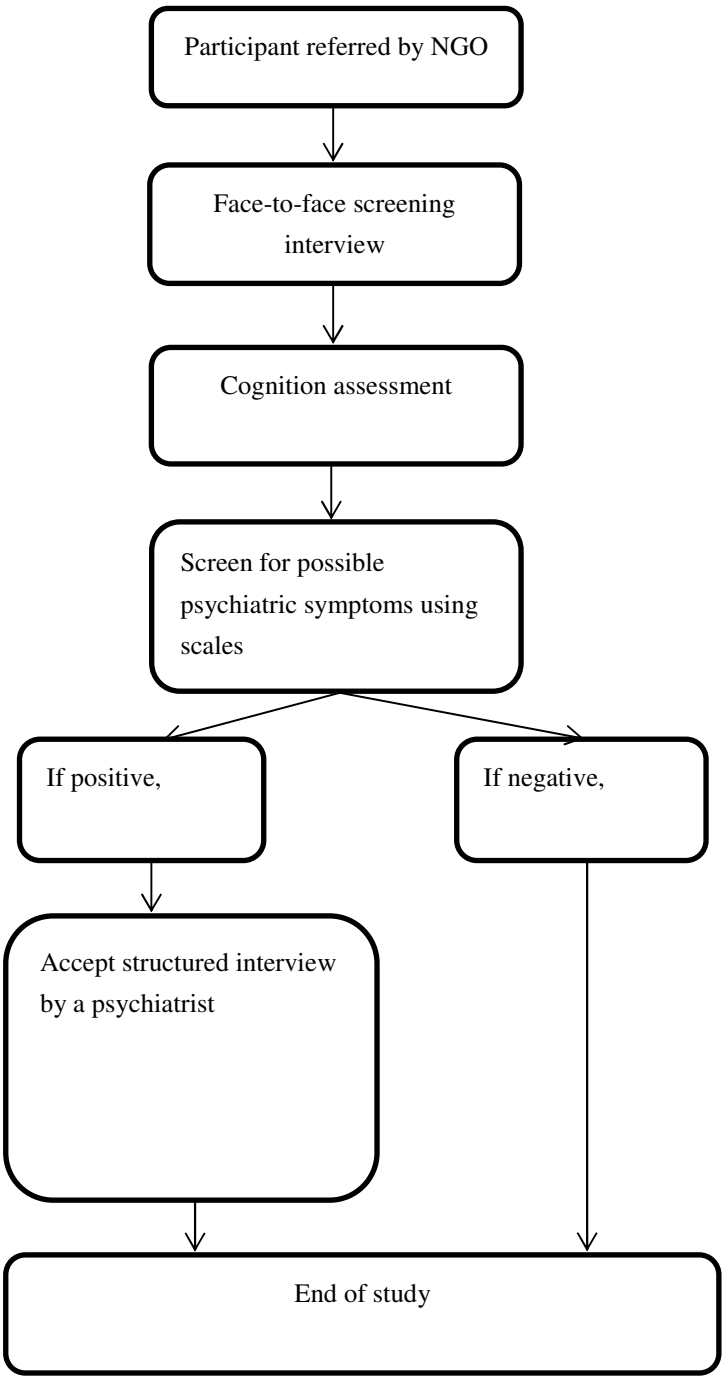
In summary, additional effort is required in preclinical and clinical research on ketamine. Substantial evidence has proven the acute effects of ketamine on human memory in ketamine naïve volunteers. However, the long-term outcome profile of ketamine's effects remains unclear. Therefore, this study evaluates the long-term effects of ketamine on both cognitive function and psychological well-being in Hong Kong youths. The hypotheses are as follows: (a) memory will be significantly impaired in primarily ketamine and poly-ketamine drug users; (b) drug use severity will be a risk factor in cognition impairment; (c) psychiatric problems will be notable in ketamine users; and (d) poly-ketamine drug users display inferior cognitive and psychological functioning compared to primarily ketamine users.

Methods

Design

This is a cross-sectional study, the participants in which were recruited according to their drug abuse patterns: a primarily ketamine abuse group, a ketamine and other psychotropic drug abuse group, and a healthy control group. Cognitive function is compared between groups in relation to common confounding factors such as education level, psychiatric comorbidities, and drug use severity. The procedure for this study is illustrated in Figure 1 and each of the participants were given a $150 coupon as compensation for attending the basic assessment and another $250 coupon for attending the psychiatric interview. This study is approved by the Survey and Behavioural Research Ethic Committee of the Chinese University of Hong Kong.

Figure 1 Study procedure



Participants

Participant recruitment sites

The participants were recruited from non-governmental organizations (NGOs) in Hong Kong. Drug abusers were referred by the Counseling Centres for Psychotropic Substance Abusers (CCPSA), residential treatment centers, and district youth outreach teams (YOTs) while the normal controls were recruited from community service centers based on the inclusion and exclusion criteria. The NGOs were as follows:

a. Jockey Club Ma On Shan (South) Children and Youth Integrated Services Centre, Hong Kong Sheng Kung Hui Welfare Council;
b. Yuen Long District Youth Outreaching Social Work Team, Hong Kong Christian Services;
c. Sha Tin Youth Outreaching Social Work Team, Chinese Young Men's Christian Association of Hong Kong;
d. Hong Kong North District Hospital UROK Clinic;
e. Evergreen Lutheran Centre, Hong Kong Lutheran Social Services;
f. Rainbow Lutheran Centre, Hong Kong Lutheran Social Services;
g. Cheer Lutheran Centre, Hong Kong Lutheran Social Services;
h. Hong Kong Christian Services PS33- Tsinshatsui Centre;
i. Hong Kong Christian Services PS33- Shanshuipo Centre;
j. Hong Kong Sheng Kung Hui Welfare Council Neo-Horizon;
k. Caritas HUGS Centre;
l. Caritas Lok Heep Club;
m. Jockey Club Wah Ming Lutheran Integrated Service Centre, Hong Kong Lutheran Social Services;
n. Jockey Club Yung Shing Lutheran Integrated Service Centre, Hong Kong Lutheran Social Services;
o. Christian New Life Association;
p. Operation Dawn;
q. The Society for the Aid and Rehabilitation of Drug Abusers.

Inclusion criteria

a. aged between 16 and 30;
b. capable of giving valid consent;

c. receiving service at an NGO;
d. for the primarily ketamine group, used ketamine at least 24 times over 6 months within the previous 2 years and used other illicit psychotropic drugs less than 24 times over 6 months within the previous 2 years;
e. for the ketamine poly-drug group, used ketamine together with other illicit psychotropic drugs such as ecstasy, marijuana, or methamphetamine with a frequency of at least 24 times over 6 months within the previous 2 years;
f. for the healthy youth group, no history of substance abuse [Chen et al. 2005b];
g. no history of any neurological disorders, significant medical diseases that require regular medication, or severe head injury.

Data collection

Demographic information

Two research assistants (RAs) approached the participants in the NGOs and performed all of the data collection and cognition function assessments. Geographic information included:

a. age;
b. sex;
c. level of education;
d. marital status;
e. employment status;
f. monthly income;
g. district of residence;
h. housing property.

Drug use patterns and severity

The Severity of Dependence scale (SDS) [Gossop et al. 1995] – a 5-item, self-report scale – was administered to measure the degree of drug dependence in the previous month or the month before abstinence. Each item was scored from 0 to 3 with a higher score indicating increased severity of dependence.

The Addiction Severity Index-Lite Version (ASI-Lite) [Cacciola et al. 2007], measures a multi-dimensional index of participants' substance use, health, and social problems [McLellan et al. 2006]. It is a semi-structured scale that covers aspects of medical, employment/support, drug and alcohol, legal, family/social, and psychiatric use. The ASI-Lite collects information on these areas across the participants' life span. In this study, a composite score was calculated for each area with higher scores indicating greater severity of the problems in these areas. Each composite score ranged from 0 to 1.

A psychiatrist also made a diagnosis of lift time or current drug dependence for each participant according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition's (DSM-IV) [American Psychiatric Association 2000] criteria for substance dependence, based on the information recorded by the RAs.

Psychiatric comorbidities

This study used a 21-item version of the Beck Depression Inventory (BDI) [Shek 1990] to screen for depressive disorder. The BDI had been previously applied in a group of ecstasy users in Hong Kong [Chen et al. 2005b] with total BDI scores ranging from 0 to 63. A lower cutoff of 8/9 was chosen for this study because it was better for screening out participants with potential depressive symptoms. The sensitivity and specificity are 100% and 82%, respectively [Lee et al. 2001].

An anxiety subscale of the Hospital Anxiety Depression scale (HADSA) [Leung et al. 1993] was used in this study to screen for anxiety disorders. The HADSA has 7 items, each graded from 0 to 3. The total score was count and higher score, which indicates a heavier severity of symptoms. The sensitivity of a cut-off at 4/5 was 96% [Bunevicius et al. 2007].

Psychosis screening questions derived from the Chinese version of the Structured Clinical Interview for DSM-IV (C-SCID) [So et al. 2003a] were administered to screen for possible psychosis disorders. Participants who scored positive on one or more of these items were referred to a psychiatrist for further diagnosis. Two RAs performed psychosis screening on the same 20 participants with a kappa of 1.0, which meant that the two RAs were highly consistent regarding whether a participant displayed possible psychotic symptoms.

The Brief Psychiatric Rating scale's (BPRS) [Lukoff et al. 1986] subscales of suspiciousness, unusual thought content, and hallucinations were used to assess the severity (ranging from 1 to 7) of each of the symptom domains at their worst point during the previous year. A cut-off of 4 or greater on each subscale was used to define a clinically significant symptom.

Participants who screened out positive on any of the above BDI, HADSA, psychosis symptoms screen of C-SCID, or BPRS were referred to a psychiatrist (Alan Tang) for a structured psychiatric interview based on the C-SCID [So et al. 2003a; So et al. 2003b]. The interview was conducted in a meeting room within the Department of Psychiatry at Shatin Hospital or via phone, by the same psychiatrist.

Cognition function evaluation

The cognitive battery was composed of the following domains and tests:

a. general intelligence: the 3-subtest short form of the WAIS – III [Chan et al. 2005];

b. executive function: the Stroop test [Stroop 1935], modified VF test [Chiu et al. 1997], and the WCST [Heaton et al. 1993];
c. attention and working memory: Digit Span Forward and Digit Span Backward [Wechsler 1997a];
d. verbal memory: story recall/immediate, delayed recall, and recognition [Hua et al. 2005; Wechsler 1997b] and wordlist recall/immediate, delayed recall, and recognition [Hua et al. 2005; Wechsler 1997b];
e. visual memory: the Rey-Osterrieth Complex Figure [Osterrieth 1944; Taylor 1959];
f. language: modified Boston Naming [Wechsler 1997a].

General intelligence was examined using the 3-subtest short form of the Wechsler Adult Intelligence Test – III. The full WAIS-III scale involves 13 subscales and has been used worldwide for the evaluation of intelligence. However, its application is time-consuming. Therefore, a short form of the WAIS-III was successively developed [Axelrod et al. 2001; Blyler et al. 2000]. The 3-subtest short form of the WAIS-III contains information, arithmetic, and digit-symbol coding subtests and has been tested in local normal populations [Chan et al. 2005]. The score ranges for these 3 subtests are 0-22, 0-28, and 0-133, with higher scores indicating better performance.

A simple version of the Stroop test [Lee et al. 2000] was adopted in this study, the details for which are introduced elsewhere in this report. After standardizing the scores, the number of errors index in part C and the differences in the reaction time indexes in parts C and D provide the Stroop score for executive function.

In the modified VF test, participants were asked to generate as many animal names as they could in one minute, as many fruit names as they could in 30 seconds, and as many vegetable names as they could in 30 seconds. The number of words, preservative errors, and intrusive errors in each category were then counted. A preservative error was counted when a word was produced repeatedly and an intrusive error was counted when a word did not belong to the current category. The total number of correct responses and the total number of preservative and intrusive errors were used as the index for the modified VF test.

The WCST is composed of 4 stimulus cards and a set of 64 response cards. The response cards differ in three dimensions: color (red, green, yellow, or blue), pattern (triangle, star, cross, or circle), and number (one, two, three, or four). Participants were asked to work out a sorting principle to match each response card to the four stimulus cards (one red triangle, two green stars, three yellow crosses, or four blue circles) according to the feedback of the examiner (wrong or correct). Once the participant had made 10 consecutive correct matches to the sorting principle, the sorting principle was changed without warning and participant had to develop a new sorting principle. The test was terminated under two circumstances: (1) when the participant had successfully maintained 6 correct sorting principles (color, pattern, number, color, pattern, and number) or (2) when 128 attempts had been made by the participant. To evaluate the participants' abstract reasoning ability and their ability to shift cognitive strategies, each response made by each participant was accurately recorded for subsequent scoring. Subsequent scores such as correct responses, perseverate responses, perseverate errors, and

non-perseverate errors were recorded. The number of categories completed, the total number of attempts, and the preservative errors were selected as the index score in this study.

Digit Span, a standardized measure that assesses attention and working memory, consists of two modes – digit forward and digit backward – that are administered separately. In the forward mode, participants were instructed to repeat a digit string composed of 2 to 9 digits in the same order that it was presented by the examiner. In the backward mode, the digit strings contained up to 8 digits and the participant was instructed to repeat each string in the reverse order. Each session started with a 2-digit item and the test terminated when the participant failed to repeat the digit string correctly after two attempts, or once all of the items had been successfully completed. Subscores and a total score were generated for this test. The backward mode requires more working memory effort than the digit forward mode, thus it is more potent in discriminating deficiencies [Davis et al. 2003]. The subscores of the digit backward mode were selected as the index of working memory and ranged from 0 to 14 with a higher score reflecting superior performance.

Verbal memory capacity is measured using word lists and logical memory subtests in the WAIS-III. Both subtests include 3 elements: immediate recall, delayed recall, and recognition. In the word list subtest, the participant is presented with 2 separate word lists (Lists A and B), each of which contains 12 unrelated words. The examiner read List A aloud four times and each time the participant was asked to perform a free recall of the words. Participants were given 4 consecutive attempts to recall List A, then the total number of words recalled correctly across all 4 attempts was calculated. The examiner then read List B aloud once and the participant was asked to recall the words comprising it in any order. Finally, the examiner asked the participant to recall the words from List A again without rereading List A aloud. A total of 3 subscores were then generated: the learning slope (the difference between the participants' first and fourth attempts to recall List A), the difference between the first attempts for both Lists A and B, and the difference between the fourth attempt at and delayed recall of List A. After a 30-minute interval, the participant was asked to recall List A by recognizing a list of 24 words and responding "Yes" if it had been on List A or "No" if it had not been on List A. The number of correct recognitions was recorded and all of the measurements were transformed into standard scores.

In the logical memory subtests, the participant was asked to listen to and then immediately retell two stories (Stories A and B), one after the other, after a 30-minute interval of listening. Story B was recalled twice during the immediate recall and the elements within the retelling were divided into story and thematic units. The story unit included each story's content while the thematic unit identified its theme. Finally, the examiner posed 15 questions about the content of each story. The outcome scores included the total number of story units in the immediate recall of Stories A and B, the total number of story unit recall in the delayed recall of Stories A and B, and the total instances of correct recognition. Furthermore, the story unit retention score was calculated using the following formula: (immediate recall for story 1±

second immediate recall of story 2) / (delay recall of story 1±delay recall of story 2). Again, all measurements were transformed into standard scores.

Visual construction and visual memory were tested using the Rey-Osterrieth Complex Figure (ROCF), which contains the conditions of copy, immediate recall, delayed recall, and recognition. Participants were instructed to copy a complex figure that had been presented to them and the figure was removed from their sight once the copy had been completed. A total of 3 minutes (immediate recall) and then 30 minutes (delayed recall) later, the participant was asked to redraw the figure without any visual confirmation. The accuracy and placement of the elements in the figure were counted to produce the score for this test, according to the 36-point scoring system [Taylor 1959]. After the completion of delayed recall, 24 geometric items were shown to the participants, who were asked to recognize which item had been in the complex figure that they had been asked to copy earlier. The recognition of the total correct attempts (sum of true positive and false negative items) was marked as the index score.

Language ability was evaluated using the Modified Boston Naming test in which participants name 15 pictures portraying common objects. The total number of correct name is then taken as the index for this test.

A summary of cognition tests and maximum scores are listed in Table 2.

Table 2 Cognitive battery

	Tests	Maximum score
General intelligence	Wechsler Adult Intelligence Test – III	
	Digit Symbol-Coding	133
	Arithmetic	22
	Information	28
Executive function	Stroop	
	Reaction Time (seconds)	
	Color Dots	---
	Chinese Characters	---
	Color Words	---
	Number of Errors	
	Color Dots	0
	Chinese Characters	0
	Color Words	0
	Modified Verbal Fluency Test	
	Animals	---
	Fruits	---
	Vegetables	---
	Wisconsin Card Sorting Test	
	Number of Attempts Administered	---
Working memory	Digit Span	

	Forward	16
	Backward	14
	Total	20
Verbal memory	Logical Memory/ Storytelling	
	Logical Memory I	
	Total Immediate Recall	50
	Logical Memory II	
	Delayed Recall	50
	Recognition	30
	Percent Retention	---
	Word List	
	Word List I	
	First Recall	12
	Total Recall	48
	Learning slope	-/+12
	Word List II	
	Total Recall	12
	Total Recognition	24
	Percent Retention	---
Visual memory	Rey-Osterrieth Complex Figure	
	Copy	36
	Immediate Recall	36
	Delayed Recall	36
	Recognition Total Correct	24
Language	Modified Boston Naming Test	15

Statistical method

Data analyses were performed using SPSS 17.0. Continuous variables were described as mean ± SD and categorical variables were described as N (%). ANOVA was used to compare continuous variables among groups and a chi-square test was used to analyze categorical variables. The significance level was set at 0.05. Multiple comparisons were used in post hoc analyses and the significance level was adjusted to 0.017. Correlations between two continuous variables were measured using Pearson correlation. When the combining the scores of several subtests, standard transformation was performed before combination. Logistic regression (LR) was used to explore the independent risk that ketamine use represented regarding the pattern of memory impairment it caused.

Results

Demographics and basic information

Two hundred ketamine users and 100 healthy controls (HCs) participated in this study. The primarily ketamine users (primarily K) were significantly older than the HCs and the ketamine poly-drug users (poly K) (22.4±4.2 vs. 20.6±3.6, P=0.003; 22.4±4.2 vs. 20.4±3.9, P=0.001, respectively).

The primarily K and poly K groups had lower levels of education and a lower proportion of participants with stable jobs and monthly incomes compared to the HC group. No difference was found between the primarily K and poly K groups in these areas. More of the participants in the primarily K group reported religious preferences compared to those in the HC group (p=0.014). Sex and marital status were distributed relatively across all of the groups. Approximately 83% of all of the participants were recruited from non-residential community service centers. The demographic characteristics of this study's population are summarized in Table 3.

Table 3 Descriptive statistics of demographic characteristics

	HC N=100	Primarily K N=100	Poly K N=100	p
Age	20.6±3.6	22.4±4.2 (p=0.003)*	20.4±3.9 (p=0.001)**	<0.001 [a]
Sex (female), n (%)	42 (42.0)	47 (37.0)	44 (44.0)	0.774 [b]
Education (year)	11.7 ± 2.4	9.6 ± 1.8 (p=0.000)*	9.2±1.9 (p=0.000)*	<0.001 [a]
Marital status (single)	96(96.0)	95(95.0)	92(92.0)	0.445 [b]
Monthly income	$5,467 ± $6,022	$2,971 ± $4,713 (p=0.002)*	$2,342 ± $4,244 (p=0.000)*	<0.001 [a]
Occupation				
Employed/homemaker /student	96(96.0)	47 (47.0) (p=0.000)*	52(52.0) (p=0.000)*	<0.001 [b]
Unemployed	4(4.0)	53 (53.0)	48(48.0)	
Resource of referral				
Non-residential	100(100.0)	71(71.0)	78(78.0)	---
Residential	0(0)	29(29.0)	22(22.0)	
Religious (yes)	23 (23)	39 (39) (P=0.014)*	27 (27)	0.036 [b]

*Compared to the HC group ; ** compared to the primarily K group. The adjusted significance level is 0.017 for post hoc comparisons.

[a] ANOVA; [b] Chi-square test.

HC: health control group; poly K: poly-ketamine group; primarily K: primarily ketamine group.

Drug use patterns

The drug use patterns of the participants in this study are depicted in Table 4. The participants in the poly K group showed a significantly higher frequency in the use of psychotropic drugs other than ketamine. The three most commonly misused drugs in the previous 2 years among the poly K group were ketamine, followed by cocaine and ice. According to the self-report from the poly K group, lifetime use of cocaine was counted as 68%, cannabis was 56%, ice was 50%, ecstasy was 48%, and hypnotics were 46%. Only one participant reported opioid use in the previous 2 years. In contrast, fewer participants in the primarily K group reported lifetime use of other drugs, with 38% reporting the use of cocaine, 28% the use of cannabis, 27% the use of ice, 31% the use of ecstasy, and 26% the use of hypnotics. The primarily K group experienced earlier exposure to drug use (15.4 ± 2.9 vs. 17.1 ± 3.5, P=0.006), used ketamine more frequently in the previous month (8.9 ± 11.7 vs. 4.3 ± 9.1, P=0.003), and was less likely to abstain from ketamine (49% vs. 66%, P=0.015) compared to the poly K group. The HC group reported no drug use history.

The primarily K and poly K groups scored similarly on the Severity of Dependence Scale (SDS) and the Addiction Severity Index (ASI) – Lite Version (Table 4). No difference was found regarding the level of alcohol use across all three groups.

Table 4 Descriptive statistics of drug use patterns among groups

Variables	HC N=100	Primarily K N=100	Poly K N=100	P
Total days of drug use in previous two years				
Ketamine	-	364.3 ± 237.2	429.3 ± 209.9	0.031[c]
Cocaine	-	8.7 ± 28.8	110.8 ± 168.8	<0.001[c]
Ice	-	1.9 ± 7.6	58.2 ± 130.1	<0.001[c]
Hypnotics	-	0.9 ± 3.5	47.8 ± 127.8	<0.001[c]
Cannabis	-	1.6 ± 5.4	30.0 ± 94.8	0.011[c]
Ecstasy	-	0.8 ± 3.7	19.1 ± 55.4	<0.001[c]
Opioids	-	0	3.6 ± 36.5	0.317[c]
Total days of drug use	-	441.7 ± 212.5	532.1 ± 238.5	0.005[d]
Total days of drug use in previous month	-	9.9 ± 12.1	7.8 ± 15.5	0.287[d]
Alcohol in previous month (days)	2.3± 5.9	4.2 ± 7.7	4.3 ± 7.0	0.272[c]
Ketamine used in previous month (days)	-	8.9 ± 11.7	4.3 ± 9.1	0.003[c]
Duration of ketamine use (month)	-	60.28 ± 34.63	56.09 ± 37.35	0.411[d]
Age of first drug use	-	15.4 ± 2.9	17.1 ± 3.5	0.006[d]
General duration (month)	-	64.0 ± 35.2	68.9 ± 36.7	0.361[d]
Abstinent more than 1 month	-	49 (49)	66 (66)	0.015[b]

SDS	-	7.8 ± 3.5	7.2 ± 4.0	0.154[d]
ASI Composite Score - Medical	0.18 ± 0.25	0.28 ± 0.34	0.28 ± 0.32	0.065[c]
ASI Composite Score - Employment	0.35 ± 0.72	0.120 ± 0.97	0.25 ± 0.87	0.551[c]
ASI Composite Score - Alcohol	0.11 ± 0.0	0.12 ± 0.11	0.12 ± 0.07	0.195[c]
ASI Composite Score - Drugs	-	0.10 ± 0.08	0.07 ± 0.07	<0.001[c]
ASI Composite Score - Legal	0	0.06 ± 0.29	0.05 ± 0.28	0.137[c]
ASI Composite Score - Family	0.46 ± 0.15	0.45 ± 0.17	0.48 ± 0.17	0.080[c]
ASI Composite Score - Psychiatry	0.09 ± 0.14	0.23 ± 0.18	0.28 ± 0.25	<0.001[c]

[b] Chi-Square test; [c] Mann-Whitney U test; [d] T test.

ASI: The Addiction Severity Index – Lite Version; HC: health control group; poly K: poly-ketamine group; primarily K: primarily ketamine group.

The majority of the participants started using psychotropic drugs by age 18, with the exception of cocaine, and took drugs with peers at home or in peers' homes. The most popular route of ketamine administration was via nasal inhalation and the most popular administrative route for cocaine was inhalation in cigarette form (Table 5).

Table 5 Patterns of drugs use

	Ketamine n = 200	Cocaine n = 105	Ecstasy n = 78	Ice n = 73	Cannabis n = 73	Hypnotics n = 70
Days of use in previous 2 years	396.8 ± 225.7	112.8 ± 163.0	25.1 ± 61.2	78.0 ± 142.9	32.8 ± 102.3	67.2 ± 145.9
Days/months in previous 2 years (median)	16 / month	4 / month	4 / month	4 / month	1 / month	2 / month
Age of first use	16.0 ± 3.0	18.0 ± 3.3	15.8 ± 2.2	16.7 ± 3.0	15.2 ± 2.2	16.3 ± 2.9
Duration (month)	58.2 ± 36.0	32.3 ±32.6	35.4 ± 32.5	27.0 ± 27.4	42.0± 40.4	36.6 ± 36.7
Place The most, n (%)	Home or peer's home 116 (58.0)	Home or peer's home 52 (49.5)	Disco 47 (60.3)	Home or peer's home 61 (83.6)	Home or peer's home 28 (38.4)	Disco 34 (48.6)
With whom The most, n (%)	With peers 143 (71.5)	With peers 89 (84.8)	With peers 66 (84.6)	With peers 57 (78.1)	With peers 51 (69.9)	With peers 52 (74.3)
Route of administration The most, n (%)	Nasal inhalation 198 (99.0)	Cigarette inhalation 89 (84.8)	Oral 68 (93.2)	Smoking 48 (65.8)	Cigarette inhalation 62 (84.9)	Oral 62 (88.6)

Comorbid psychiatric problems

As Table 6 reveals, the participants in the primarily K and poly K groups had higher BDI and HADSA scores compared to the participants in the HC group ($p<0.001$ and $p=0.005$, respectively). One trend was that the participants in the primarily K and poly K groups were more likely to present with psychotic symptoms ($p=0.076$). In addition, the participants in both ketamine groups were more likely to have a history of psychiatric outpatient treatment ($P=0.028$). According to the designed criteria in this study, the percentage of participants required to submit to a psychiatric diagnostic interview varied from 77% to 87% across groups. However, less than 60% of the participants referred for a psychiatric interview actually attended, with similar attendance rates across groups. Among the participants referred for an interview, those who attended scored higher in BDI and HADSA than those who did not attend (17.1± 10.3 vs. 15.4 ± 10.5 of BDI; 7.5 ± 4.0 vs. 6.5 ± 3.9 of HADSA), but the differences did not reach a significant level ($P = 0.230$ of BDI and $P = 0.074$ of HADSA).

Of the 168 participants who attended psychiatric interviews, 77 received a diagnosis of either previous (n =17) or current (n = 62) psychiatric disorders. Mood disorders were the most common psychiatric diagnoses, with 16 depressive disorders and 1 general anxiety disorder in previous psychiatric histories. Likewise, 51 out of 62 diagnoses of current psychiatric disorders were depressive disorders, 25 were anxiety disorders, 6 were psychotic disorders, and 4 were mixed mood disorder. However, no significant difference was found across groups regarding the types of diagnoses, although there was a notable trend of more psychiatric problems in ketamine users.

Table 6 Psychiatric problems among the three groups

Variables	HC N=100	Primarily K N=100	Poly K N=100	p
BDI score	9.14 ± 8.129	16.29 ± 10.56 (p<0.001)*	17.12 ± 11.59 (p<0.001)*	<0.001[a]
BDI >=15, n (%)	49 (49.0)	78 (78.0)	78 (78.0)	<0.001[b]
HADSA score	5.73 ± 3.68	5.57 ± 3.76	7.30 ± 4.79 (p=0.020)* (p=0.009)**	0.005[a]
HADSA>=8, n (%)	29 (29.0)	33 (33.0)	40 (40.0)	0.251[b]
Psychotic symptoms, n (%)	10 (10.0)	13 (13.0)	23 (23.0)	0.076[b]
Previous visit in a psychiatric outpatient setting	0.01 ± 0.10	0.16 ± 0.53	0.48 ± 2.12 (p=0.024)*	0.028[c]
Psychiatric interview required, n (%)	77(76.0)	83(83.0)	87(85.0)	0.175[b]
Psychiatric interview completed, n (%)	54 (54.0)	56 (56.0)	58 (58.0)	0.445[b]
Previous diagnosis, n (%)	4 (4.0)	2 (2.0)	11 (11.0)	0.057[b]
Current diagnosis, n (%)	14 (14.0)	25 (25.0)	23 (23.0)	0.256[b]
Mood disorder, n (%)	11 (11.0)	21 (21.0)	21 (21.0)	0.242[b]

Substance induced depressive disorders, n (%)	-	17 (17.0)	19 (19.0)	0.772[b]
Substance induced mixed disorders, n (%)	-	2 (2.0)	0 (0.0)	0.460[e]
Substance induced dysthymia disorders, n (%)	-	1 (1.0)	0 (0.0)	0.986[e]
Non-substance induced depressive disorders, n (%)	11 (11.0)	1 (1.0)	2 (2.0)	-
Anxiety disorders, n (%)	9 (9.0)	5 (5.0)	11 (11.0)	0.496[b]
Substance induced anxiety disorders, n (%)	-	1 (1.0)	3 (3.0)	0.496[e]
Psychotic disorders, n (%)	0 (0.0)	2 (2.0)	4 (4.0)	0.299[b]
Substance induced psychotic disorders, n (%)	-	1 (1.0)	3 (3.0)	0.789[e]
Non-substance induced psychotic disorders, n (%)	0 (0.0)	1 (1.0)	1 (1.0)	-

[a] ANOVA; [b] Chi-Square test; [c] Mann-Whitney U test; [d] T test; [e] Fisher's Exact test.

*compared to the HC group and ** compared to the primarily K group. The adjusted significance level is 0.017 for post hoc comparisons.

BDI: Beck Depression Inventory; HADSA: The anxiety subscale of the Hospital Anxiety Depression scale; HC: health control group; primarily K: primarily ketamine group; poly K: poly-ketamine group.

Cognitive functions

Cognitive functions among primarily K, poly K, and HC groups

A univariate analysis reveals differences across the groups in general intelligence (Digit Symbol-Coding, arithmetic, and information), verbal memory (WAIS logical memory and word list), visual memory (ROCF), executive function (WCST, Stroop, and VF), language, and motor speed (Stroop total reaction time) (Table 7). After adjusting for age, sex, education, and BDI score, significant differences remained among the groups in the WAIS Logical Memory immediate and delayed recall and the ROCF immediate, delayed recall, and saving (Table 7). In post hoc comparisons, the performances of both the primarily K and poly K groups were inferior to that of the HC group in general intelligence, verbal memory, visual memory, executive function, language, and motor speed. The primarily K group had a lower score on immediate recall in the logical memory test compared to the poly K group (17.7 ± 8.7 vs. 20.5 ± 7.7, P=0.017, respectively). The primarily K group also scored lower on delayed recall (P=0.017) and recognition (P=0.017) in the word list test than the HC group, although no difference was found between the poly K and HC groups (Table 7).

Table 7 Performance on cognitive tests for the three groups

	HC N=100	Primarily K N=100	Poly K N=100	P [a]	P [b]	R square
WAIS III Digit Symbol-Coding	92.8 ± 15.7	79.3 ± 17.0[c]	82.7 ± 16.5[c]	<0.001	0.142	0.249
WAIS III Arithmetic	15.9 ± 3.4[c]	13.0 ± 4.1 [c]	13.2 ± 4.1 [c]	<0.001	0.142	0.223
WAIS III Information	14.8 ± 4.6	11.0 ± 4.2 [c]	10.6 ± 4.2 [c]	<0.001	0.078	0.353
WAIS III Digit Span (Forward)	15.2 ± 1.5	15.5 ± 1.0	15.1 ± 1.3	0.169	0.037	0.021
WAIS III Digit Span (Backward)	9.3 ± 3.1	8.3 ± 3.3	8.8 ± 3.2	0.090	0.120	0.096
WMS III Logical Memory: immediate recall	26.1 ± 6.9	17.7 ± 8.7 [cd]	20.5 ± 7.7 [c]	<0.001	**0.001**	0.262
WMS III Logical Memory: delayed recall	22.9 ± 7.1	14.7 ± 8.8 [c]	17.0 ± 7.8 [c]	<0.001	**<0.001**	0.233
WMS III Logical Memory: recognition	24.6 ± 2.9	22.3 ± 3.8 [c]	23.2 ± 3.4[c]	<0.001	0.118	0.181
WMS III Logical Memory: retention	85.5 ± 17.0	80.4 ± 26.5	79.8 ± 18.1	0.107	0.188	0.005
WMS III word list: first total recall	33.4 ± 5.4	30.0 ± 5.8 [c]	31.1 ± 6.1[c]	<0.001	0.078	0.104
WMS III word list: delayed recall	8.4 ± 2.1	7.4 ± 2.4[c]	7.6 ± 2.4	0.007	0.147	0.071
WMS III word list: recognition	23.3 ± 1.0	22.8 ± 1.7 [c]	23.1 ± 1.4	0.043	0.213	0.060
WMS III word list: retention	82.8 ± 15.7	78.8 ± 24.9	80.2 ± 18.9	0.360	0.597	0.004
ROCF: copy	33.6 ± 2.2	32.7 ± 3.2	32.9 ± 2.9	0.071	0.230	0.040
ROCF: immediate recall	23.6 ± 6.8	19.2 ± 7.4 [c]	18.5 ± 7.5 [c]	<0.001	0.026	0.123
ROCF: delayed recall	24.1 ± 6.1	19.3 ± 7.3 [c]	18.6 ± 7.7 [c]	<0.001	0.003	0.144
ROCF: savings	71.7 ± 17.3	58.4 ± 20.6 [c]	56.4 ± 22.4 [c]	<0.001	0.005	0.139
WCST: total attempts	89.2 ± 19.5	96.8 ± 20.6	98.9 ± 20.6	0.002	0.711	0.099
WCST: category completed	5.6 ± 0.9	5.4 ± 1.5	5.4 ± 1.5	0.133	0.657	0.078
WCST: preservative errors	9.6 ± 8.0	13.2 ± 11.1 [c]	12.8 ± 12.2	0.031	0.853	0.089
Stroop Test: interference (seconds)	20.7 ± 7.1	24.4 ± 7.0 [c]	23.5 ± 6.8 [c]	0.000	0.306	0.083
Stroop Test: total reaction time (seconds)	51.5 ± 14.1	56.3 ± 15.3	55.3 ± 13.5	0.043	0.649	0.050
Stroop Test: total errors	1.7 ± 1.8	2.7 ± 2.3 [c]	1.7 ± 1.8 [c]	0.003	0.907	0.093
Verbal Fluency: total correct responses	45.0 ± 9.1	40.9 ± 8.9 [c]	39.3 ± 8.8 [c]	<0.001	0.367	0.186
Language	14.8 ± 0.5	14.6 ± 0.7 [c]	14.7 ± 0.5	0.010	0.163	0.030

[a] ANOVA; [b] MANCOVA, adjusted for age, sex, level of education, and BDI total score; [c] Post hoc comparisons, significantly different from HC, significance level = 0.017; [d] Post hoc, significantly different from poly K, significance level = 0.017.

HC: health control group; poly K: poly-ketamine group; ROCF: the Rey-Osterrieth Complex Figure; primarily K: primarily ketamine group; WAIS III: Wechsler Adult Intelligence scale - Third Edition; WCST: Wisconsin Card Sorting test; WMS III: Wechsler Memory scale - Third Edition.

In the primarily K group, the days of ketamine use in the recent month and the duration of abstinence were significantly correlated with 4 and 3 memory variables, respectively. The duration of ketamine use related exclusively with Logical Memory immediate recall while the number of days of ketamine use in the previous 2 years did not relate with any of the memory variables (Table 8). A standardization of the scores for Logical Memory immediate and

delayed recall and ROCF immediate and delayed recall were performed and the total memory score was generated by summing up the 4 standard scores.

Table 8 Correlation of drug use patterns and memory in primarily K group

		Duration of ketamine use (months)	Ketamine use in previous 2 years (days)	Ketamine use in recent month (day)	Duration of abstinence (day)
WMS III Logical Memory: immediate recall	r	-0.210	-0.077	-0.297	0.185
	p	*0.036*	*0.447*	*0.003*	*0.065*
WMS III Logical Memory: delayed recall	r	-0.145	-0.051	-0.291	0.259
	p	*0.149*	*0.617*	*0.003*	*0.009*
ROCF: immediate recall	r	-0.048	0.057	-0.263	0.243
	p	*0.634*	*0.575*	*0.008*	*0.015*
ROCF: delayed recall	r	-0.015	0.052	-0.211	0.232
	p	*0.881*	*0.605*	*0.035*	*0.020*

ROCF: The Rey-Osterrieth Complex Figure; WMS III: Wechsler Memory scale - Third Edition.

Cognitive functions in current primarily ketamine (CK) and ex-primarily ketamine (EK) users

To clarify the reversibility of ketamine's effects, a comparison between current and ex-ketamine users was performed. The definition of an ex-user in the primarily K group is an individual who stopped using ketamine and all of the other drugs mentioned in the poly K group for at least one month [Morgan et al. 2009]. Primarily ketamine users were further categorized based on their abstinence status, with 49 of the participants classified as ex-ketamine users (EK) and 51 as current ketamine users (CK). ANOVA revealed that both CK and EK were older and less educated compared to the participants in the HC group (P=0.003 and P<0.001, respectively). Ketamine use patterns were similar between CK and EK regarding age of first exposure, total frequency in the previous two years, duration of ketamine use, SDS score, and level of other drug use (Tables 9 and 10). CK had a significantly higher BDI score than EK (20.6 ± 10.1 vs. 11.8 ± 9.1, $p < 0.001$, respectively) and compared to the HC group (20.6 ± 10.1 vs. 9.1 ± 8.1, $p < 0.001$) (Table 9).

Table 9 Demographic variables and reported estimates of ketamine use across the three groups

	CK [a]	EK[a]	HC[a]	P-value[b]
	N = 51	N = 49	N = 100	

Male, n (%)	29 (56.9)	24 (49.0)	58 (58.0)	0.567[c]
Age, years	22.8 ± 4.3[d]	22.0 ± 4.0	20.6 ± 3.6	0.003
Education, years	9.7 ± 1.9[d]	9.5 ± 1.7[d]	11.7 ± 2.4	<0.001
Age first used ketamine, (range) years	17.2 ± 3.2 (11-25)	16.6 ± 3.0 (12-26)	-	0.280[e]
Total years of ketamine use	5.3 ± 2.8	4.7 ± 3.0	-	0.336[e]
Frequency of ketamine use in previous two years, days per month [f]	19.8 ± 10.6	19.8 ± 11.5	-	0.997[e]
Current frequency of ketamine use, days per month	17.4 ± 10.9	-	-	-
Days since last use of ketamine (range) days	3.4 ± 8.3 (0-30)	196.6 ± 163.1 (31-639)	-	<0.001[e]
SDS score	8.2 ± 3.1	7.4 ± 3.8	-	0.249
BDI score	20.6 ± 10.1[d,h]	11.8 ± 9.1	9.1 ± 8.1	<0.001
BDI score >/= 15	37 (72.5)[d,h]	15 (30.6)	20 (20.0)	<0.001[c]

[a] Mean ± standard deviation unless otherwise specified; [b] ANOVA unless otherwise specified; [c] Chi Square test; [d] Post hoc comparison, significantly different from controls; [e] T test; [f] Frequency of use just before stopping in ex-users; 1 month before stopping in ex-users; [h] Post hoc comparison, significantly different from EK.

BDI: Beck Depression Inventory; CPK: current poly-ketamine group; EPK: ex-poly-ketamine group; HC: health control group; SDS: Severity of Dependence scale.

Table 10 Reported estimates of drug use apart from ketamine in CK and EK

	CK [a] N = 51	EK[a] N = 49	P-value[b]
Cocaine			
Age first used, years	19.1 ± 3.7	18.5 ± 3.3	0.569
Total years of use	0.9 ± 1.9	0.9 ± 2.1	0.920
Frequency of use in previous two years, days per month [c]	2.0 ± 2.7	6.7 ± 10.4	0.089
Current frequency of use, days per month	0.5 ± 1.1	0.1 ± 0.6	0.080
Days since last use, days	138 ± 347	371 ± 582	0.150
Ecstasy			
Age first used, years	17.1 ± 2.9	15.4 ± 2.1	0.076
Total years of use	1.0 ± 2.0	1.0 ± 2.3	0.996
Frequency of use in previous two years, days per month [c]	8.9 ± 10.2	8.4 ± 10.7	0.901
Current frequency of use, days per month	0.2 ± 1.0	0.9 ± 2.3	0.073
Days since last use, days	913 ± 1129	806 ± 1071	0.801
Methamphetamine			
Age first used, years	18.9 ± 4.2	16.0 ± 2.5	0.038
Total years of use	0.2 ± 1.0	0.9 ± 2.3	0.073
Frequency of use in previous two years, days per month [c]	3.0 ± 3.4	5.9 ± 8.7	0.326

Current frequency of use, days per month	0.07 ± 4.2	0.02 ± 0.8	0.413
Days since last use, days	133 ± 280	823 ± 953	0.024
Sedatives and Hypnotics			
Age first used, years	16.7 ± 3.4	16.2 ± 2.6	0.653
Total years of use	0.7 ± 1.7	1.0 ± 3.0	0.513
Frequency of use in previous two years, days per month [c]	5.4 ± 9.3	8.3 ± 11.2	0.549
Current frequency of use, days per month	0.02 ± 0.14	0.0 ± 0.0	0.329
Days since last use, days	334 ± 503	866 ± 1096	0.144
Cannabis			
Age first used, years	15.6 ± 2.3	14.4 ± 1.5	0.129
Total years of use	0.7 ± 2.0	1.5 ± 3.7	0.162
Frequency of use in previous two years, days per month [c]	1.2 ± 1.1	1.8 ± 2.3	0.467
Current frequency of use, days per month	0.0 ± 0.0	0.0 ± 0.0	-
Days since last use, days	470 ± 735	882 ± 1026	0.366
Alcohol			
Age first used, years	14.2 ± 4.8	14.3 ± 3.5	0.948
Total years of use	7.1 ± 6.0	6.4 ± 5.1	0.825

[a] Mean ± standard deviation; [b] T test; [c] Frequency of use just before stopping in ex-users.

CK: current primarily ketamine users; EK: ex-primarily ketamine users.

After adjusting for age, sex, level of education, and BDI score, the HC group displayed significantly better performance than CK in WAIS Digit Symbol-Coding, WAIS Logical Memory (immediate recall, delayed recall, and recognition), ROCF (copy, immediate recall, delayed recall, and savings), Stroop test total reaction time, and modified VF test, but not in the others (Table 11). In addition, CK also performed worse than EK in a similar profile, except that they performed equally on Logical Memory recognition and CK was worse on Logical Memory retention. The only significant differences between EK and the participants in the HC group in the cognitive tests were on Digit Span Forward (P=0.004) (Table 11). A correlational analysis indicated that BDI scores were negatively correlated with Digit Symbol-Coding, arithmetic, backward digit span, and logical memory scores (immediate recall). This trend also suggests that the BDI scores were negatively related to other logical memory (delayed recall and recognition) and ROCF (immediate recall, saving) scores with borderline significance (Table 12).

Table 11 Group scores on cognitive assessments comparing CK, EK, and HC

	CK [a] N = 51	EK[a] N = 49	HC[a] N = 100	P-value [b]	P-value [e]
WAIS III Digit Symbol-Coding	73.9 ± 14.6[c,d,f,g]	85.1 ± 17.9	92.9 ± 15.8	<0.001	0.003
WAIS III Arithmetic	12.5 ± 4.1[c]	13.4 ± 4.0	15.9 ± 3.4	0.008	0.138
WAIS III Digit Span (Forward)	15.3 ± 1.1	15.6 ± 0.9[f]	15.2 ± 1.5	0.066	0.039
WAIS III Digit Span (Backward)	7.4 ± 3.0[c,d]	9.3 ± 3.3	9.3 ± 3.1	0.001	0.075
WMS III Logical Memory: immediate recall	21.0 ± 10.7[c,d,f,g]	31.5 ± 12.9	38.2 ± 10.2	<0.001	<0.001

WMS III Logical Memory: delayed recall	11.2 ± 6.9[c,d,f,g]	18.4 ± 9.0	22.9 ± 7.1	<0.001	<0.001
WMS III Logical Memory: recognition	21.1 ± 3.9[c,d,f]	23.5 ± 3.4	24.6 ± 2.9	<0.001	0.029
WMS III Logical Memory: retention	74.7 ± 26.3[d,g]	86.3 ± 25.8	85.5 ± 17.0	0.020	0.012
ROCF: copy	32.0 ± 3.5[c,d,f,g]	33.5 ± 2.7	33.6 ± 2.2	0.003	0.002
ROCF: immediate recall	16.4 ± 7.7[c,d,f,g]	22.1 ± 5.9	23.6 ± 6.8	<0.001	<0.001
ROCF: delayed recall	17.0 ± 7.7[c,d,f,g]	21.8 ± 6.2	24.1 ± 6.1	<0.001	<0.001
ROCF: savings	52.5 ± 22.5[c,d,f,g]	64.6 ± 16.6	71.7 ± 17.3	<0.001	0.001
Stroop test: interference (seconds)	25.3 ± 8.2[c]	23.5 ± 5.5	20.7 ± 7.1	<0.001	0.269
Stroop test: total reaction time (seconds)	61.9 ± 17.2[c,d,f,g]	50.5 + 10.5	51.5 + 14.1	<0.001	0.002
Stroop test: total errors	2.5 ± 2.1	2.7 ± 2.3	1.7 ± 1.8	0.540	0.458
Modified Verbal Fluency test	37.9 ± 7.5[c,d,f,g]	44.0 ± 9.2	45.0 ± 9.1	<0.001	0.006

[a]Mean ± standard deviation unless otherwise specified; [b]Adjusted for age, gender, and level of education; [c] Post hoc comparison, significantly different from controls; [d] Post hoc comparison, significantly different from EK. Adjusted significance level is 0.017 for post hoc comparisons.

[e]Adjusted for age, gender, level of education and BDI score; [f] Post hoc comparison, significantly different from controls; [g] Post hoc comparison, significantly different from EK.

BDI: Beck Depression Inventory; CPK: current poly-ketamine group; EPK: ex-poly-ketamine group; HC: health control group; ROCF: the Rey-Osterrieth Complex Figure; SDS: Severity of Dependence scale; WAIS III: Wechsler Adult Intelligence scale – Third Edition; WCST: Wisconsin Card Sorting Test; WMS III: Wechsler Memory scale - Third Edition.

Table 12 Correlations between BDI and cognitive assessment scores in CK (N = 51)

	Pearson's correlations	P-value
WAIS III Digit Symbol-Coding	-0.311	0.026
WAIS III Arithmetic	-0.347	0.012
WAIS III Digit Span (Forward)	0.063	0.660
WAIS III Digit Span (Backward)	-0.335	0.016
WMS III Logical Memory: immediate recall	-0.284	0.043
WMS III Logical Memory: delayed recall	-0.251	0.076
WMS III Logical Memory: recognition	-0.256	0.070
WMS III Logical Memory: retention	0.069	0.628
ROCF: copy	0.111	0.439
ROCF: immediate recall	-0.272	0.053
ROCF: delayed recall	-0.212	0.136
ROCF: savings	-0.241	0.088
Stroop test: time (seconds)	0.126	0.384
Stroop test: total errors	0.147	0.307
Modified Verbal Fluency test	-0.174	0.221

BDI: Beck Depression Inventory; ROCF: the Rey-Osterrieth Complex Figure; WAIS III: Wechsler Adult Intelligence scale – Third Edition; WCST: Wisconsin Card Sorting test; WMS III: Wechsler Memory scale - Third Edition.

Cognitive functions in current poly ketamine (CPK) and ex-poly ketamine (EPK) groups

Table 13 presents the comparisons between poly-ketamine users and healthy controls. Poly-ketamine users were further categorized into ex- (EK) and current (CK) users. The participants in the poly K group had a lower overall level of education and higher BDI total score compared to the HC group. Moreover, the BDI total score for the CPK group was higher than it was for the EPK group. There was no difference in SDS scores or the total frequency of any drugs. The total frequency of each drug was also comparable between the CPK and EPK groups, with the exception of ice (p = 0.039). Regarding cognitive function, after adjusting for age, sex, level of education, and BDI score, the CPK group had lower scores in logical memory delayed recall and word list delayed recall than the HC group and also tended to score lower in logical memory retention (p = 0.072), word list recognition (p = 0.069), word list retention (p = 0.056), and ROCF delayed recall (p = 0.040) and saving (p = 0.045). The EPK group revealed significantly lower scores in ROCF immediate (p = 0.016) and delayed (p = 0.003) recall and saving (p = 0.004) compared to the HC group. In addition, the EPK group also had lower scores in logical memory delayed recall compared to the HC group (17.1 ± 8.7 vs. 22.9 ± 7.1, respectively), although the difference did not reach a significant level. However, the CPK and EPK groups had similar scores in memory variables, with the CPK group tending to score lower in the modified VF test than the EPK group after controlling for the BDI score (p = 0.018).

Table 13 Group scores on cognitive assessments comparing the EPK, CPK, and HC groups

	EPK [a] N = 56	CPK [a] N =44	HC [a] N = 100	P-value [d]
Age	20.8 ± 3.7	20.1 ± 4.1	20.6 ± 3.6	0.626 [b]
Male, N (%)	32 (57.1)	24 (54.5)	58 (58.0)	0.928 [c]
Level of education (years)	9.3 ± 1.8	9.2 ± 2.1	11.7 ± 2.4	<0.001 [b]
BDI	13.2 ± 10.1	22.1 ± 11.5 (P < 0.001**)	9.1 ± 8.13	<0.001 [b]
SDS	7.2 ± 4.3	7.2 ± 3.6	-	0.957**
Total frequency (days in previous 2 years)				
Any drug	536.3 ± 242.2	526.8 ± 236.5	-	0.935** [f]
Cocaine	118.0 ± 172.0	101.6 ± 166.0	-	0.563** [f]
Ice	43.1 ± 133.9	77.3 ± 124.0	-	0.039** [f]
Cannabis	23.5 ± 107.3	29.3 ± 76.5	-	0.240** [f]
Ecstasy	18.5 ± 43.5	19.8 ± 68.2	-	0.525** [f]
Hypnotics	45.0 ± 91.2	51.3 ± 164.3	-	0.106** [f]
Ketamine	374.7 ± 234.3	351.2 ± 242.7	-	0.588** [f]
Opioids	6.5 ± 48.8	0.0 ± 0.0	-	0.375** [f]

WAIS III Digit Symbol-Coding	84.0±16.8	81.1 ± 16.3	92.8 ± 15.7	0.949
WAIS III Arithmetic	13.7 ± 4.2	12.7 ± 4.1	15.9 ± 3.4	0.386
WAIS III Information	10.7 ± 4.5	10.5 ± 4.0	14.8 ± 4.6	0.106
WAIS III Digit Span: Forward	15.2 ± 1.5	15.1 ± 1.4	15.2 ± 1.5	0.330
WAIS III Digit Span: Backward	9.3 ± 3.1	9.2 ±3.2	9.3 ± 3.1	0.323
WMS III Logical Memory: immediate recall	29.5 ± 13.1	30.3 ± 9.7	38.2 ± 10.2	0.136
WMS III Logical Memory: delayed recall	17.1 ± 8.7	16.8 ± 6.5 (p = 0.007*[d])	22.9 ± 7.1	0.021
WMS III Logical Memory: recognition	23.4 ± 3.5	23.0 ± 3.3	24.6 ± 2.9	0.686
WMS III Logical Memory: retention	79.3 ± 17.9	80.5 ± 18.4 (p = 0.072*[d])	85.5 ± 17.0	0.198
WMS III Word list: immediate recall	5.2 ± 1.7	5.3 ± 1.5	5.8 ± 1.5	0.430
WMS III Word list: delayed recall	7.8 ± 2.4	7.3 ± 2.5 (p = 0.016*[d])	8.4 ± 2.1	0.136
WMS III Word list: recognition	23.1 ± 1.4	23.0 ± 1.4 (p = 0.069*[d])	23.3 ± 1.0	0.285
WMS III Word list: retention	82.7 ± 17.7	77.0 ± 20.2 (p = 0.056*[d])	82.8 ± 15.7	0.228
ROCF: copy	32.9 ± 2.7	32.8 ± 3.1	33.6 ± 2.2	0.664
ROCF: immediate recall	18.3 ± 7.7 (p = 0.016*[d])	18.8 ± 7.3	23.6 ± 6.8	0.037
ROCF: delayed recall	18.6 ±7.7 (p = 0.003*[d])	18.5 ±7.8 (p = 0.040*[d])	24.1 ± 6.1	0.009
ROCF: savings	56.5 ± 22.6 (p = 0.004*[d])	56.2 ± 22.3 (p = 0.045*[d])	71.7 ± 17.3	0.010
WCST: number of attempts administered	98.1 ± 21.0	100.0 ± 20.4	89.2 ± 19.5	0.842
WCST: percent of error	11.3 ± 9.6	15.6 ± 14.8	9.6 ± 8.0	0.342
WCST: number of categories completed	5.5 ± 0.9	5.2 ± 1.7	5.7 ± 0.9	0.355
Stroop Test: interference (seconds)	22.7 ± 6.3	24.5 ± 7.4	20.7 ± 7.1	0.440
Stroop Test: total reaction time (seconds)	53.9 ± 13.0	57.2 ± 14.0	51.5 ±14.1	0.875
Stroop Test: total errors	2.3 ± 2.1	3.0 ± 2.5	1.7 ± 1.8	0.203
Modified VF test	41.2 ± 8.6	36.9 ± 8.5 (p = 0.065*[d]) (p = 0.018**[e])	45.0 ± 9.1	0.055

[a] Mean ± standard deviation unless otherwise specified; [b] ANOVA; [c] Chi-Square test; [d] UNCOVA, adjusted for level of education and BDI score.

*Compared to the HC group and ** Compared to the EPK group after controlling for the BDI score. Significance level for post hoc comparisons is 0.017.

CPK: current poly-ketamine group; EPK: ex-poly-ketamine group; HC: health control group; BDI: Beck Depression Inventory; ROCF: the Rey-Osterrieth Complex Figure; SDS: Severity of Dependence scale; WAIS III: Wechsler Adult Intelligence scale – Third Edition; WCST: Wisconsin Card Sorting test; WMS III: Wechsler Memory scale - Third Edition.

Cognitive functions in current primarily ketamine (CK) and current poly-ketamine (CPK) users

The current primarily ketamine users (CK) in this study were older than the current poly-ketamine users (CPK) (P=0.001) and the participants in the HC group (p = 0.001). Both of the drug groups had higher BDI scores than the HC group (both P < 0.001), but there were no differences between the CK and CPK users in relation to sex, level of education, or BDI score. As for drug use patterns, CK and CPK users revealed no difference regarding their total days of drug use in the previous month or the 2 previous years while the CK users reported more days of ketamine use both in the previous month (p <0.001) and in the previous 2 years (p = 0.017). The CK users also had a shorter mean interval between their last use of ketamine and the date of assessment compared to the CPK users (p <0.001). Moreover, the CK users had higher SDS scores than the CPK users (p = 0.045) (Table 14).

After adjusting for age, sex, level of education, and BDI score, differences across the three groups were revealed in relation to the following: Digit Symbol-Coding, all four indexes for the Logical Memory and ROCF tests, word list recognition, and the modified VF test. In post hoc comparison, the CK users had lower scores in Logical Memory immediate and delayed recall compared to the CPK users (P=0.001 and P=0.002, respectively) (Table 15).

Table 14 Comparisons of demographics and drug use patterns among CK, CPK, and HC participants

	CK [a] N = 51	CPK [a] N =44	HC [a] N = 100	P-value
Age	22.8 ± 4.3 (p = 0.001*) (P = 0.001**)	20.1 ± 4.1	20.6 ± 3.6	0.001 [b]
Male, N (%)	29 (56.9)	24 (54.5)	58 (58.0)	0.928 [d]
Level of education (years)	9.7 ± 1.9 (p < 0.001*)	9.2 ± 2.1 (p < 0.001*)	11.7 ± 2.4	<0.001 [b]
BDI	20.6 ± 10.1 (p < 0.001*)	22.1 ± 11.5 (p < 0.001*)	9.1 ± 8.13	<0.001 [b]
SDS	8.2 ± 3.1	7.2 ± 3.6	-	0.045 [c]
Days since last use of ketamine (range) days	3.4 ± 8.3	54.6 ± 111.0	-	<0.001 [e]
Ketamine use in previous month (days)	17.4 ± 10.9	9.7 ± 11.8	-	<0.001 [e]
Total drug use in previous month (days)	19.1 ± 10.6	17.2 ± 19.5	-	0.152 [e]
Total drug use in previous 2 years (days)				
Ketamine	464.4 ± 216.4	351.2 ± 242.7	-	0.017 [e]
Any drug	477.3 ± 216.8	526.8 ± 236.5	-	0.110 [e]

Cocaine	7.6 ± 15.0	101.6 ± 166.0	-	<0.001 [e]
Ice	2.0 ± 6.5	77.3 ± 124.0	-	<0.001 [e]
Cannabis	1.4 ± 5.0	29.3 ± 76.5	-	0.005 [e]
Ecstasy	1.1 ± 4.9	19.8 ± 68.2	-	0.008 [e]
Hypnotics	16 ± 4.8	51.3 ± 164.3	-	0.131 [e]
Opioids	0.0 ± 0.0	0.0 ± 0.0	-	1.000 [e]

[a] Mean ± standard deviation unless otherwise specified; [b] T test; [c] ANOVA; [d] Chi-Square test; [e] poly K compared to K; [f] comparison among 3 groups; [g] UNCOVA, controlled for age and total frequency, unless otherwise specified; [h] UNCOVA, controlled for age, sex, level of education, and BDI total score.

*Post hoc comparison with HC group. Significance level for post hoc comparisons is 0.017.

BDI: Beck Depression Inventory; CPK: current poly-ketamine group; EPK: ex-poly-ketamine group; HC: health control group; SDS: Severity of Dependence scale.

Table 15 Comparison of cognitive function among CK, CPK, and HC participants

	CK [a] N = 51	CPK [a] N =44	HC [a] N = 100	P-value [b]
WAIS III Digit Symbol-Coding	73.9 ± 14.6 (p = 0.003* [b])	81.1 ± 16.3	92.8 ± 15.7	0.008
WAIS III Arithmetic	12.5 ± 4.1 (p = 0.048*[b])	12.7 ± 4.1	15.9 ± 3.4	0.072
WAIS III Information	10.5 ± 3.9	10.5 ± 4.0	14.8 ± 4.6	0.126
WAIS III Digit Span: Forward	15.3 ± 1.1 (p = 0.068*[b])	15.1 ± 1.4	15.2 ± 1.5	0.334
WAIS III Digit Span: Backward	7.4 ± 3.0	9.2 ±3.2	9.3 ± 3.1	0.054
WMS III S Logical Memory: immediate recall	21.0 ± 10.7 (p < 0.001* [b]) (p = 0.001**[c])	30.3 ± 9.7 (p < 0.001*[b])	38.2 ± 10.2	0.000
WMS III Logical Memory: delayed recall	11.2 ± 6.9 (p<0.001*[b]) (p=0.002**[c])	16.8 ± 6.5 (p = 0.007*[b])	22.9 ± 7.1	0.000
WMS III Logical Memory: recognition	21.1 ± 3.9 (p = 0.033*[b]) (p = 0.064**[c])	23.0 ± 3.3	24.6 ± 2.9	0.005
WMS III Logical Memory: retention	74.7 ± 26.3 (p = 0.072*[b])	80.5 ± 18.4 (p = 0.072*[b])	85.5 ± 17.0	0.017
WMS III Word list: immediate recall	4.6 ± 1.5 (p = 0.077*[b])	53 ± 1.5	5.8 ± 1.5	0.106
WMS III Word list: delayed recall	6.8 ± 2.6	7.3 ± 2.5 (p = 0.016*[b])	8.4 ± 2.1	0.083
WMS III Word list: recognition	22.5 ± 2.1	23.0 ± 1.4 (p = 0.069*[b])	23.3 ± 1.0	0.046

WMS III Word list: retention	80.0 ± 24.8	77.0 ± 20.2 (p = 0.056*[b])	82.8 ± 15.7	0.318
ROCF: copy	32.0 ± 3.5 (p = 0.008* [b])	32.8 ± 3.1	33.6 ± 2.2	0.038
ROCF: immediate recall	16.4 ± 7.7 (p = 0.005* [b])	18.8 ± 7.3	23.6 ± 6.8	0.012
ROCF: delayed recall	17.0 ± 7.7 (p = 0.002*[b])	18.5 ±7.8 (p = 0.040*[b])	24.1 ± 6.1	0.007
ROCF: savings	52.5 ± 22.5 (p = 0.006*[b])	56.2 ± 22.3 (p = 0.045*[b])	71.7 ± 17.3	0.022
WCST-trial	102.2 ± 20.1	100.0 ± 20.4	89.2 ± 19.5	0.481
WCST-PE	15.2 ± 12.6	15.6 ± 14.8	9.6 ± 8.0	0.799
WCST-category	5.1 ± 1.6	5.2 ± 1.7	5.7 ± 0.9	0.801
Stroop Test: interference (seconds)	25.3 ± 8.2	24.5 ± 7.4	20.7 ± 7.1	0.327
Stroop Test: total reaction time (seconds)	61.9 ± 17.2 (p = 0.041* [b])	57.2 ± 14.0	51.5 ±14.1	0.060
Stroop Test: total errors	2.5 ± 2.1	3.0 ± 2.5	1.7 ± 1.8	0.721
Modified VF test	37.9 ± 7.5 (p = 0.087* [b])	36.9 ± 8.5 (p = 0.065*[b])	45.0 ± 9.1	0.047

[a] Mean ± standard deviation unless otherwise specified; [b] UNCOVA, adjusted for age, sex, level of education, and BDI score; [c] UNCOVA, adjusted for age.

*Compared to the HC group and ** Compared to the CPK and EPK groups. The significance level for post hoc comparisons is 0.017.

BDI: Beck Depression Inventory; CPK: current poly-ketamine group; EPK: ex-poly-ketamine group; HC: health control group; ROCF: the Rey-Osterrieth Complex Figure; SDS: Severity of Dependence scale; WAIS III: Wechsler Adult Intelligence scale – Third Edition; WCST: Wisconsin Card Sorting test; WMS III: Wechsler Memory scale – Third Edition.

Discussion

Demographics and drug use patterns

The drug preferences among the youths in this study are consistent with the latest government report and a local study [Narcotics Division 2012; Tang et al. 2011a]. Ketamine is the most preferred drug to abuse, followed by cocaine, ice, and hypnotics. Ecstasy, cannabis, and opioids are ranked last on the list shown in Table 3. The mean SDS scores for the primarily K and poly K groups were 7.8 and 7.2, respectively, which indicates a severe level of addiction [Cuenca-Royo et al. 2012]. The same scores varied from 3 to 4 for cannabis, amphetamine, and cocaine users [Gossop et al. 1995; Martin et al. 2006]. A cut-off point of 3/4 in the SDS for drug dependence screening was commonly recommended [Kaye et al. 2002; Martin et al. 2006;

Topp et al. 1997]. A cut-off score of 8 had a specificity of 98% in detecting the DSM-IV dependence diagnoses [Topp et al. 1997].

The participants in this study were teenagers or young adults who started their drug use at a middle school age. They were generally less educated, with an average education level of Form 3. In addition, approximately 50% of them were unable to find (or maintain) a job and their incomes were significantly less than those of the normal controls. These demographic characteristics are in line with the most recent local report [Narcotics Division 2012] and the majority of studies in broad areas [Degenhardt et al. 2008; Reynaud-Maurupt et al. 2007]. The onset age of cannabis use was the earliest among the drugs studied, which has also commonly been seen as an initiation into increased drug use in other epidemical investigations [Fergusson et al. 2006; Kandel et al. 2006]. An association between ketamine use and the use of other psychotropic drugs has been discovered [Degenhardt et al. 2008]. The participants in this study preferred to use drugs at home or in the homes of their peers, which differs from an earlier local study, which reported that discos and bars were the common environment of choice [Chen et al. 2005b]. This shift may reflect a trend of drug abuse in youths becoming an increasingly "hidden" activity [Narcotics Division 2012]. The common administration route for ketamine is still nasal inhalation in Hong Kong. However, ketamine has been increasingly reported as an injectable substance [Lankenau et al. 2007a; Lankenau et al. 2007b]. Although these data are limited to a subgroup of injection drug users, they remain noteworthy.

Effects of ketamine on psychological health

The strict criteria used to refer participants for psychiatric interview may explain the relatively low attendance rate in all three groups. In this study, a cutoff point of 8 in BDI and 4 in HADSA were used to screen for potential mood and anxiety disorders. However, these cutoff points are lower than those recommended elsewhere [Brennan et al. 2010; Viinamaki et al. 2004]. In addition, participants with any suspected psychotic symptoms were referred to a psychiatrist for further diagnosis of psychotic disorders. The results suggest that the BDI and HADSA scores were lower in those who attended the interviews, but these differences were not statistically significant.

The number of drug users who received clinical diagnoses did not differ significantly from normal youths, but the trend of more severe comorbid psychiatric disorders among the drug users was notable – both pre- and post-drug use. A comparison of the ketamine and normal control groups reveals that the ketamine groups had higher BDI scores. This result is in keeping with abundant evidence that affective disorders and substance use disorders are all comorbid disorders [Chen et al. 2005b; Compton et al. 2007; Kessler et al. 1996; Tang et al. 2011a; Tang et al. 2011b]. Psychotic disorders, however, were rare in the current sample.

Only 3% of all of the drug users studied were diagnosed with psychotic disorders, compared to a higher rate of 6.3% in a local study [Chen et al. 2005b]. Considering that half of

the participants did not participate in the second interview, the reported percentage of psychotic disorders might be lower than that reported elsewhere.

Effects of ketamine on cognitive functions

Effect of primarily ketamine on memory

This study's findings support its proposed hypothesis; that is, both the primarily K and poly K groups showed impaired cognitive function in a range of domains when potential confounding factors were not adjusted. However, compelling evidence suggests that cognitive function is altered by a number of confounding variables, such as depression and education. Depression is strongly related to cognitive deficit in patients with major depressive disorders [Lee et al. 2011], poly-drug abusers [Stevens et al. 2007], and people with substance use disorders [Latvala et al. 2009; Tarter et al. 1995]. Evidence also suggests that low levels of basic education account for lower verbal intellectual ability and contribute to cognitive deficits indicative of substance use disorders [Latvala et al. 2009; Tarter et al. 1995]. Consequently, to obtain convincing results, such factors were added into the multivariate analyses.

After adjusting for age, sex, level of education, and BDI score, ketamine proved to have a unitary influence on memory that is strikingly consistent with previous studies of the acute or chronic effects of ketamine. Episodic, visual, verbal, short- and long-term memories were all affected in chronic ketamine users. Substantial evidence from healthy volunteers has documented that one-off doses of ketamine mainly effect the encoding of information, which presents as difficulty recalling both verbal [Morgan et al. 2004b] and visual [Oye et al. 1992] information that was shown right before the infusion of ketamine. The pattern of memory impairment found in this study could also be thought of as an impairment of the encoding process of episodic memory [Morgan et al. 2006].

This study also finds that recent ketamine use was independently related to episodic memory impairment. The duration of ketamine use, represented in this study by the number of days of ketamine use in the previous two years, did not contribute to memory impairment after adjustments for confounding factors. The relation of memory impairment to ketamine use was dependent on the extent of ketamine use reported previously [Curran et al. 2001; Morgan et al. 2004b]. However, the absence of an accumulated effect of ketamine on memory impairment suggests the possibility of recovery once ketamine use has been reduced or stopped. Therefore, to test this assumption, a subgroup analysis comparing current ketamine users and ex-ketamine users was performed.

In the primarily ketamine group, the current users displayed impaired memory compared to both ex-users and the health controls, whereas no difference was found between the latter two groups. These findings are in line with studies that have found evidence of impairments in working memory, verbal memory, visual memory, and executive function

[Curran et al. 2001; Morgan et al. 2004c; Morgan et al. 2009]. The results of this study also indicate the impairment of mental motor speed. As presented earlier, cognitive impairment remained even after adjusting for level of education, which seemed to be confined to current users and hence, would make it less likely that pre-existing differences in education or intellectual ability alone would explain these findings. An alternative explanation is that the direct acute and/or chronic effects of ketamine cause cognitive deficits [Morgan et al. 2006]. The absence of impairment in ex-users also suggests that cognitive impairments may be reversible upon cessation of drug use [Morgan et al. 2009]. A 3-year longitudinal study suggested that semantic memory impairments are reversible, whereas episodic memory and attention deficits are not [Morgan et al. 2006]. A recent follow up study found a correlation between changes in ketamine use and memory function, but not in relation to other cognitive functions [Morgan et al. 2010]. The reversibility of cognitive impairments may be related to the observed reversible neurotoxicity of N-methyl-D-aspartate (NMDA)-receptor antagonists in animal models [Jevtovic-Todorovic et al. 2001]. Recovery of cognitive deficits was also observed within the first month of abstinence in a group of heavy alcohol drinkers [Dingwall et al. 2011].

Recent neuroimaging studies have begun to provide the physiological bases of ketamine-induced cognitive impairment. Liao (2011) conducted a structural magnetic resonance imaging study that demonstrated a reduction in frontal gray matter volume in patients who were chronic ketamine users [Liao et al. 2011]. A recent diffusion tensor imaging study also found abnormalities of the white matter in the bilateral frontal and left temporoparietal regions following chronic ketamine use [Liao et al. 2010]. Another functional magnetic resonance imaging study revealed ketamine-induced acute changes to the frontal and temporal cortices [Deakin et al. 2008]. A positron emission tomography scan showed that chronic ketamine users exhibited an up-regulation of dopamine D1 receptors in the dorsolateral prefrontal cortex [Narendran et al. 2005]. All these changes may provide a structural and functional basis for the memory impairment observed in this study, but neuroimaging evidence of the reversibility of the effects of ketamine use remains absent.

Effect of primarily ketamine on executive function

The analyses conducted in the primarily ketamine user group collected for this study reveal that working memory and other executive function components, such as shifting and inhibition, remain intact after considering the potentiate interference of education and depression. However, a weak difference was found in a subgroup of current ketamine users in relation to working memory (arithmetic test) and the modified VF test compared to the healthy control group. These results are nowhere near significant enough to prove the effects of ketamine on executive function. As previously mentioned, the semantic fluency test is also related to semantic memory in addition to executive function [Henry et al. 2004]. In fact, this study's results regarding the effects of ketamine on executive function were far less consistent. For example, ketamine users displayed the intact function required to perform the Stroop test [Rowland et al. 2005], continuous performance tasks [Newcomer et al. 1999], and trailmaking and 0-back [Morgan et al. 2004a], but revealed impairment in the WCST [Krystal et al. 2000], continuous performance tasks [Krystal et al. 1994], and the Hayling test [Morgan et al. 2004b]. There is not currently enough evidence to prove the impact of ketamine on executive processes and one explanation for the current discrepancy is that executive function tests commonly tap memory function and their results may subsequently be affected by ketamine. However, some researchers have argued that ketamine also influences learning [Krystal et al. 2000; Morgan et al. 2006].

Effect of poly-ketamine on cognitive function

One issue generated by this study's hypothesis is that poly-drug ketamine users did not show additional impairment in any cognition domain compared to primarily ketamine users. Moreover, in subgroup analysis, current primarily ketamine users showed more severe memory impairment than current poly-ketamine users. Although differences in drug use patterns may partially explain why the poly-ketamine group had more abstainers and used less ketamine in the month before recruitment, another explanation would be that the severity of the detrimental effects of ketamine might also present as the effect duration of those effects. Again, this hypothesis was tested via subgroup comparisons between current poly-ketamine users and ex-poly-ketamine users. Unlike the comparisons between current and ex-primarily ketamine users, both current and ex-poly-ketamine users showed episodic memory impairment (verbal memory impairment in current poly-ketamine users and visual memory impairment in ex-poly-ketamine users), which indicates the absence of memory improvement after abstinence in poly-ketamine users. Consistent with this study, other research has documented abstinent ecstasy users who continued to show memory impairment at 2 months [Yip et al. 2005], 1 year [Hoshi et al. 2007], and even as long as 2.5 years [Thomasius et al. 2006] after abstinence. Furthermore, cocaine [van Gorp et al. 1999], amphetamine [van Holst et al. 2011], and poly drug [Hoshi et al. 2007] users also show continuous detrimental effects on memory after abstinence. The suggestion that ketamine causes reversible memory impairment in primary users and sustained impairment in a poly drug use context, together with the evidence of

sustained memory deficiency in other drug abstainers, leads to the speculation that cognition improvement after ketamine abstinence is the result of ketamine's reversible effect on NMDA receptors.

Conclusions

In conclusion, cocaine and ice were the most abused drugs in the ketamine-using sample. Primarily and poly-ketamine users displayed similar ketamine use patterns. The most common comorbid psychiatric disorder was depressive disorder. In univariate analyses, both primarily and poly-ketamine users showed impairments in verbal memory, visual memory, executive function, language, and motor speed compared to health controls. After adjusting for age, sex, level of education, and BDI score, differences among the three groups regarding verbal and visual memory remained. Primarily and poly-ketamine groups performed these cognition tests similarly. Recent use of ketamine is the independent predictor of impaired memory function. In subanalyses, the primarily ketamine group was further divided into ex- and current ketamine users. Current ketamine users displayed worse visual memory, verbal memory, executive function, and motor speed compared to both the ex-ketamine and health control groups. Meanwhile, ex-ketamine users were comparable with the health control group. The analogue profile was not repeated on poly-ketamine users, such that both ex- and current poly-ketamine users showed similar impaired memory along with other impaired cognitive functions compared to the health control group. Moreover, the current primarily ketamine users performed poorly on verbal memory tests compared to poly-ketamine users. Longitudinal or prospect design studies will help strengthen the evidence of the reversibility of memory impairment caused by ketamine and research into the mechanisms of this reversal will also require future work.

Limitations

First, this is a cross-sectional study and the possibility of pre-existing differences in cognitive function or depressive symptoms cannot be ruled out. Similarly, the reversibility of cognitive and mood changes is also uncertain. Prospective studies of participants at high risk for ketamine use or participants who become abstinent from ketamine will shed additional light on the abovementioned issue. Second, although the extent of alternate drug use in addition to ketamine was relatively low, we cannot rule out the effects of these compounds on our findings. Third, there were differences between the ketamine users and controls in terms of age and education level that were only partially solved by statistical adjustments. Finally, the status of participants' ketamine and additional drug use is based exclusively on self-reporting.

References

Alvarez J A and Emory E. (2006) Executive function and the frontal lobes: a meta-analytic review. Neuropsychology review. 16(1):17-42.

American Psychiatric Association. (2000) Diagnostic and Statistical Manual of Mental Disorders. 4th ed. . Washington, DC: American Psychiatric Association;

Axelrod B N, Ryan J J and Ward L C. (2001) Evaluation of seven-subtest short forms of the Wechsler Adult Intelligence Scale-III in a referred sample. Arch Clin Neuropsychol. 16(1):1-8.

Baddeley A and Hitch G. (1974) Working memory. In: G H Bower, editors. The psychology of learning and motivation: Advances in research and theory (Vol. 8). ed. New York: Academic Press.;

Blyler C R, Gold J M, Iannone V N and Buchanan R W. (2000) Short form of the WAIS-III for use with patients with schizophrenia. Schizophr Res. 46(2-3):209-215.

Brennan C, Worrall-Davies A, Mcmillan D, Gilbody S and House A. (2010) The Hospital Anxiety and Depression Scale: a diagnostic meta-analysis of case-finding ability. J Psychosom Res. 69(4):371-378.

Bunevicius A, Peceliuniene J, Mickuviene N, Valius L and Bunevicius R. (2007) Screening for depression and anxiety disorders in primary care patients. Depression and anxiety. 24(7):455-460.

Cacciola J S, Alterman A I, Mclellan A T, Lin Y T and Lynch K G. (2007) Initial evidence for the reliability and validity of a "Lite" version of the Addiction Severity Index. Drug Alcohol Depend. 87(2-3):297-302.

Carroll J B. (2005) The Three-Stratum theory of cognitive abilities. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press;

Chan E L S, Chen E Y H and Chan R C K. (2005) Three-subtest short form of the Wechsler Adult Intelligence Scale-III for patients with psychotic disorders: A preliminary report. Hong Kong Journal of Psychiatry 15(39-42.

Chan R C K. (2004) Development of a Chinese verbal fluency test for the Hong Kong psychiatric setting. Hong Kong J Psychiatry. 4(2):8.

Chan R C K, Wong M, Chen E Y H and Lam L C W. (2003) Semantic Categorisation and Verbal Fluency Performance in a Community Population in Hong Kong: a Preliminary Report. Hong Kong J Psychiatry. 13(4):14-20.

Chen J Q and Gardner H. (2005a) Assessment based on Multiple-Intelligence theory. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press;

Chen R Y, Chan R C K, Chen E Y H and Tang S W. (2005b) Research Report on a Study on the Cognitive Impairment and Other Harmful Effects Caused by Ketamine Abuse. arcotics Division, Security Bureau. http://www.nd.gov.hk/research_reports.htm.

Chen R Y, Chan R C K, Chen E Y H and Tang S W (2005c) Research Report on a Study on the Cognitive Impairment and Other Harmful Effects Caused by Ketamine Abuse. Hong Kong Narcotics Division, Security Bureau

Chiu H F, Chan C K, Lam L C, Ng K O, Li S W, Wong M and Chan W F. (1997) The modified Fuld Verbal Fluency Test: a validation study in Hong Kong. The journals of gerontology. Series B, Psychological sciences and social sciences. 52(5):P247-250.
Cianciolo A T and Sternberg R J. (2004) Intelligence: a brief history. Malden, MA Blackwell Publishing;
Compton W M, Thomas Y F, Stinson F S and Grant B F. (2007) Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry. 64(5):566-576.
Critchlow D G. (2006) A case of ketamine dependence with discontinuation symptoms. Addiction. 101(8):1212-1213.
Cuenca-Royo A M, Sanchez-Niubo A, Forero C G, Torrens M, Suelves J M and Domingo-Salvany A. (2012) Psychometric properties of the CAST and SDS scales in young adult cannabis users. Addict Behav.
Curran H V and Monaghan L. (2001) In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction. 96(5):749-760.
Curran H V and Morgan C. (2000) Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction. 95(4):575-590.
Davis S T, Donald H S and Zhu J J. (2003) Revising a standard: an evaluation of the original and development of the WAIS-III. In: S T Davis, Donald H S, et al., editors. Clinical interpretation of the WAIS-III and WMS-III. 1 ed. San Diego: Academic Press; 44-85.
Deakin J F, Lees J, Mckie S, Hallak J E, Williams S R and Dursun S M. (2008) Glutamate and the neural basis of the subjective effects of ketamine: a pharmaco-magnetic resonance imaging study. Arch Gen Psychiatry. 65(2):154-164.
Degenhardt L and Dunn M. (2008) The epidemiology of GHB and ketamine use in an Australian household survey. Int J Drug Policy. 19(4):311-316.
Dingwall K M, Maruff P and Cairney S. (2011) Similar profile of cognitive impairment and recovery for Aboriginal Australians in treatment for episodic or chronic alcohol use. Addiction. 106(8):1419-1426.
Eling P, Derckx K and Maes R. (2008) On the historical and conceptual background of the Wisconsin Card Sorting Test. Brain and cognition. 67(3):247-253.
Fergusson D M, Boden J M and Horwood L J. (2006) Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction. 101(4):556-569.
Golden J C. (1976) Identification of brain disorders by the Stroop color and word test. Journal of clinical psychology. 32(654 - 658.
Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W and Strang J. (1995) The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction. 90(5):607-614.
Heaton R K, Chelune G J, Talley J L, Kay G G and Curtiss G. (1993) Wisconsin Card Sorting Test manual revised and expanded. USA: Psychological Assessment Resources, Inc
Henry J D and Crawford J R. (2004) A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology. 18(2):284-295.

Hetem L A, Danion J M, Diemunsch P and Brandt C. (2000) Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. Psychopharmacology (Berl). 152(3):283-288.
Hoshi R, Mullins K, Boundy C, Brignell C, Piccini P and Curran H V. (2007) Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naive controls. Psychopharmacology (Berl). 194(3):371-379.
Hua M S, Chang B S, Lin K N, Yang J M, Lu S R and Chen S Y. (2005) Wechsler memory scale. 3rd ed. (Chinese) [Manual]. Taipei: Chinese Behavioral Science Corp;
Jevtovic-Todorovic V, Wozniak D F, Benshoff N D and Olney J W. (2001) A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Res. 895(1-2):264-267.
Jurado M B and Rosselli M. (2007) The elusive nature of executive functions: a review of our current understanding. Neuropsychology review. 17(3):213-233.
Kamphaus R W, Winsor Pierce A, Rowe E W and Kim S. (2005) A history of intelligence test interpretation. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press;
Kandel D B, Yamaguchi K and Klein L C. (2006) Testing the Gateway Hypothesis. Addiction. 101(4):470-472; discussion 474-476.
Kane M J and Engle R W. (2003) Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to Stroop interference. J Exp Psychol Gen. 132(1):47-70.
Kaufman A S and Kaufman N L. (1993) Manual for the Kaufman Adolescent and Adult Intelligence Test (KAIT). . Circle Pines, MN: American Guidance Service;
Kaufman J C, Kaufman A S, Kaufamn-Singer J and Kaufman N L. (2005) The Kaufman Assessment Battery for Children-Second Edition and the Kaufman Adolescent and Adult Intelligence Test. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press; 344-370.
Kaye S and Darke S. (2002) Determining a diagnostic cut-off on the Severity of Dependence Scale (SDS) for cocaine dependence. Addiction. 97(6):727-731.
Kessler R C, Nelson C B, Mcgonagle K A, Edlund M J, Frank R G and Leaf P J. (1996) The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. Am J Orthopsychiatry. 66(1):17-31.
Krystal J H, Abi-Saab W, Perry E, D'souza D C, Liu N, Gueorguieva R, Mcdougall L, Hunsberger T, Belger A, Levine L and Breier A. (2005) Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl). 179(1):303-309.
Krystal J H, Bennett A, Abi-Saab D, Belger A, Karper L P, D'souza D C, Lipschitz D, Abi-Dargham A and Charney D S. (2000) Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. Biol Psychiatry. 47(2):137-143.
Krystal J H, D'souza D C, Karper L P, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers M B, Jr., Vegso S, Heninger G R and Charney D S. (1999) Interactive effects of

subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl). 145(2):193-204.
Krystal J H, Karper L P, Seibyl J P, Freeman G K, Delaney R, Bremner J D, Heninger G R, Bowers M B, Jr. and Charney D S. (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 51(3):199-214.
Lankenau S E and Sanders B. (2007a) Patterns of ketamine use among young injection drug users. J Psychoactive Drugs. 39(1):21-29.
Lankenau S E, Sanders B, Bloom J J, Hathazi D, Alarcon E, Tortu S and Clatts M C. (2007b) First injection of ketamine among young injection drug users (IDUs) in three U.S. cities. Drug Alcohol Depend. 87(2-3):183-193.
Latvala A, Castaneda A E, Perala J, Saarni S I, Aalto-Setala T, Lonnqvist J, Kaprio J, Suvisaari J and Tuulio-Henriksson A. (2009) Cognitive functioning in substance abuse and dependence: a population-based study of young adults. Addiction. 104(9):1558-1568.
Lee D T, Yip A S, Chiu H F, Leung T Y and Chung T K. (2001) Screening for postnatal depression: are specific instruments mandatory? Journal of affective disorders. 63(1-3):233-238.
Lee R S, Hermens D F, Porter M A and Redoblado-Hodge M A. (2011) A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. Journal of affective disorders.
Lee T M and Chan C C. (2000) Stroop interference in Chinese and English. J Clin Exp Neuropsychol. 22(4):465-471.
Leshner A I. (2001) Hallucinogens and dissociative drugs including LSD, PCP, ketamine, dextromethorphan. National institute on drug abuse research report series.
Leung C M, Ho S, Kan C S, Hung C H and Chen C N. (1993) Evaluation of the Chinese version of the Hospital Anxiety and Depression Scale. A cross-cultural perspective. International journal of psychosomatics : official publication of the International Psychosomatics Institute. 40(1-4):29-34.
Lezak M D. (1995) Neruopsychological assessment (3rd ed.). New York: Oxford University Press.;
Liao Y, Tang J, Corlett P R, Wang X, Yang M, Chen H, Liu T, Chen X, Hao W and Fletcher P C. (2011) Reduced dorsal prefrontal gray matter after chronic ketamine use. Biol Psychiatry. 69(1):42-48.
Liao Y, Tang J, Ma M, Wu Z, Yang M, Wang X, Liu T, Chen X, Fletcher P C and Hao W. (2010) Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. Brain. 133(Pt 7):2115-2122.
Ludwig C, Borella E, Tettamanti M and De Ribaupierre A. (2010) Adult age differences in the Color Stroop Test: a comparison between an Item-by-item and a Blocked version. Arch Gerontol Geriatr. 51(2):135-142.
Lukoff D, Liberman R P and Nuechterlein K H. (1986) Symptom monitoring in the rehabilitation of schizophrenic patients. Schizophrenia bulletin. 12(4):578-602.
Martin G, Copeland J, Gates P and Gilmour S. (2006) The Severity of Dependence Scale (SDS) in an adolescent population of cannabis users: reliability, validity and diagnostic cut-off. Drug Alcohol Depend. 83(1):90-93.
Matlin M W. (2005) Cognition. New York: J. Wiley & Sons;

Mcgrew K S. (2005) The Cattell-Horn-Carroll theory of cognitive ability past, present and future. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press; 136-182.
Mcgrew K S and Woodcock R W. (2001) Technical manual. Woodcock-Johnson III. . Itasca, IL: Riverside;
Mclellan A T, Cacciola J C, Alterman A I, Rikoon S H and Carise D. (2006) The Addiction Severity Index at 25: origins, contributions and transitions. Am J Addict. 15(2):113-124.
Milner B. (1963) Effects of different brain lesions on card sorting: The role of the frontal lobes. Archives of Neurology. 9(100-110.
Morgan C J and Curran H V. (2006) Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl). 188(4):408-424.
Morgan C J, Mofeez A, Brandner B, Bromley L and Curran H V. (2004a) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology. 29(1):208-218.
Morgan C J, Mofeez A, Brandner B, Bromley L and Curran H V. (2004b) Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose-response study. Psychopharmacology (Berl). 172(3):298-308.
Morgan C J, Monaghan L and Curran H V. (2004c) Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. Addiction. 99(11):1450-1461.
Morgan C J, Muetzelfeldt L and Curran H V. (2009) Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. Addiction. 104(1):77-87.
Morgan C J, Muetzelfeldt L and Curran H V. (2010) Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction. 105(1):121-133.
Morgan C J, Riccelli M, Maitland C H and Curran H V. (2004d) Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. Drug Alcohol Depend. 75(3):301-308.
Naglieri J A and Das J P. (2005) Planing, Attention, Simultaneous, and Successive (PASS) theory In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press; 120-135.
Narcotics Division S B (2012) CRDA and Drug Statistics Hong Kong
Narendran R, Frankle W G, Keefe R, Gil R, Martinez D, Slifstein M, Kegeles L S, Talbot P S, Huang Y, Hwang D R, Khenissi L, Cooper T B, Laruelle M and Abi-Dargham A. (2005) Altered prefrontal dopaminergic function in chronic recreational ketamine users. Am J Psychiatry. 162(12):2352-2359.
National Institute on Durg Abuse. (2010). Club Drugs (GHB, Ketamine, and Rohypnol) (InfoFacts). InfoFacts. Retrieved from http://www.drugabuse.gov/publications/infofacts/club-drugs-ghb-ketamine-rohypnol
Newcomer J W, Farber N B, Jevtovic-Todorovic V, Selke G, Melson A K, Hershey T, Craft S and Olney J W. (1999) Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology. 20(2):106-118.

Nyhus E and Barcelo F. (2009) The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: a critical update. Brain and Cogntion. 71(3):437-451.
Osterrieth P A. (1944) Le test de copie d'une figure complex: Contribution a l'etude de la perception et de la memoire [The Complex Figure Test: Contribution to the study of perception and memory]. Archives of Psychology. 28(1021 - 1034.
Oye I, Paulsen O and Maurset A. (1992) Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther. 260(3):1209-1213.
Parwani A, Weiler M A, Blaxton T A, Warfel D, Hardin M, Frey K and Lahti A C. (2005) The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology (Berl). 183(3):265-274.
Perret E. (1974) The left frontal lobe of man and the suppression of habitual responses in verbal categorical behavior. Neuropsychologia. 12(323-330.
Rabin L A, Barr W B and Burton L A. (2005) Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members. Arch Clin Neuropsychol. 20(1):33-65.
Regard M. (1981) Cognitive rigidity and flexibility: A neuropsychological study. . British Columbia: University of Victoria
Reynaud-Maurupt C, Bello P Y, Akoka S and Toufik A. (2007) Characteristics and behaviors of ketamine users in France in 2003. J Psychoactive Drugs. 39(1):1-11.
Reynolds C R and Kamphaus R W. (2005) Introduction to the Reynolds Intelligence Assessment Scales and the Reynolds Intellectual Screening Test. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press;
Roid G H. (2003) Stanford-Binet Intelligence Scales, Fifth Edition. Itasca, IL: Riverside;
Roid G H and Pomplun M. (2005) Interpreting the Stanford-Binet Intelligence Scales, Fifth Edition. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press; 325-343.
Ross S and Peselow E. (2009) The neurobiology of addictive disorders. Clin Neuropharmacol. 32(5):269-276.
Rowland L M, Astur R S, Jung R E, Bustillo J R, Lauriello J and Yeo R A. (2005) Selective cognitive impairments associated with NMDA receptor blockade in humans. Neuropsychopharmacology. 30(3):633-639.
Schrank F A. (2005) Woodcock-Johnson III Test of cognitive ability. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press; 371-401.
Schwartz B L. (2011) Memory: foundations and applications. Thousand Oaks, California: SAGE Publications, Inc.;
Shek D T. (1990) Reliability and factorial structure of the Chinese version of the Beck Depression Inventory. Journal of clinical psychology. 46(1):35-43.
So E, Kam I, Leung C M, Chung D, Liu Z and Fong S. (2003a) The Chinese-bilingual SCID-I/P Project: stage 1- reliability for mood disorders and schizophrenia. Hong Kong Journal of Psychiatry. 13:7-18.

So E, Kam I, Leung C M, Pang A and Lam L. (2003b) The Chinese-bilingual SCID-I/P Project: stage 2 – Reliability for anxiety disorders, adjustment disorders, and "no diagnosis". Hong Kong Journal of Psychiatry. 13:19-25.
Squire L R. (1987) Memory and brain. New York Oxford University Press; 3.
Sternberg R J. (2005) The Triarchic Theory of Successful Intelligence. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press;
Stevens A, Peschk I and Schwarz J. (2007) Implicit learning, executive function and hedonic activity in chronic polydrug abusers, currently abstinent polydrug abusers and controls. Addiction. 102(6):937-946.
Stroop J R. (1935) Studies of interference in serial verbal reactions. Journal of Experimental Psychology. 18:643-662.
Stuss D T. (2011) Functions of the frontal lobes: relation to executive functions. Journal of the International Neuropsychological Society : JINS. 17(5):759-765.
Tang A, Cheung R Y, Liang H J, Ungvari G S and Tang W K. (2011a) Psychiatric morbidity at a female residential drug treatment centre in Hong Kong. East Asian Arch Psychiatry. 21(1):28-31.
Tang A, Liang H J, Ungvari G S and Tang W K. (2011b) Referral patterns and clinical characteristics of subjects referred to substance abuse clinic of a regional hospital in Hong Kong. East Asian Arch Psychiatry. 21(1):22-27.
Tarter R E, Mezzich A C, Hsieh Y C and Parks S M. (1995) Cognitive capacity in female adolescent substance abusers. Drug Alcohol Depend. 39(1):15-21.
Taylor E M. (1959) Psychological appraisal of children with cerebral defects. Cambridge: MA: Harvard University Press;
The Psychological Corporation. (2002) The WAIS-III–WMS-III technical manual: Update. San Antonio: The Psychological corporation;
Thomasius R, Zapletalova P, Petersen K, Buchert R, Andresen B, Wartberg L, Nebeling B and Schmoldt A. (2006) Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. J Psychopharmacol. 20(2):211-225.
Topp L and Mattick R P. (1997) Choosing a cut-off on the Severity of Dependence Scale (SDS) for amphetamine users. Addiction. 92(7):839-845.
Tulsky D S. (2004) A new look at the WMS-III: new research to guide clinical practice. J Clin Exp Neuropsychol. 26(4):453-458.
Tulsky D S, Chelune G J and Price L R. (2004) Development of a new Delayed Memory Index for the WMS-III. J Clin Exp Neuropsychol. 26(4):563-576.
Umphress T B. (2008) A comparison of low IQ scores from the Reynolds Intellectual Assessment Scales and the Wechsler Adult Intelligence Scale-Third Edition. Intellect Dev Disabil. 46(3):229-233.
Van Gorp W G, Wilkins J N, Hinkin C H, Moore L H, Hull J, Horner M D and Plotkin D. (1999) Declarative and procedural memory functioning in abstinent cocaine abusers. Arch Gen Psychiatry. 56(1):85-89.
Van Holst R J and Schilt T. (2011) Drug-related decrease in neuropsychological functions of abstinent drug users. Curr Drug Abuse Rev. 4(1):42-56.

Viinamaki H, Tanskanen A, Honkalampi K, Koivumaa-Honkanen H, Haatainen K, Kaustio O and Hintikka J. (2004) Is the Beck Depression Inventory suitable for screening major depression in different phases of the disease? Nord J Psychiatry. 58(1):49-53.
Wasserman J D and Tulsky D S. (2005) A history of intelligence assessment. In: D P Flanagan and Harrison P L, editors. Contemporary intellectual assessment: theories, tests and issues. ed. New York: The Guilford Press; 3-23.
Wechsler D. (1939) The messurement of adult intelligence. Baltimore: Williams & Wilkins; 3.
Wechsler D. (1997a) Wais-III Administration and Scoring Manual. 3rd. San Antonio: TX: The Psychological Corporation.;
Wechsler D. (1997b) Wechsler Memory Scale- Third Edition San Antonio,: TX: The Psychological Corporation.;
Wolff K and Winstock A R. (2006) Ketamine : from medicine to misuse. CNS Drugs. 20(3):199-218.
Yip J T and Lee T M. (2005) Effect of ecstasy use on neuropsychological function: a study in Hong Kong. Psychopharmacology (Berl). 179(3):620-628.