NEUROCOGNITIVE FUNCTION IN RECREATIONAL KETAMINE: A SCOPING REVIEW

FUNCIONAMIENTO NEUROCOGNITIVO EN EL USO RECREATIVO DE LA DE KETAMINA: UNA REVISIÓN DE ALCANCE

Carolina Bellas-Arnosi
Facultad de Psicología, Universidad de Santiago de Compostela.
https://orcid.org/0000-0002-2948-7874

Socorro Rodríguez-Holguín
Facultad de Psicología, Universidad de Santiago de Compostela.
https://orcid.org/0000-0003-1502-987X

Marta Beranuy
Facultad de Ciencias de la Salud, Universidad Pública de Navarra.Grupo de Investigación en Ciberp-sicología, Universidad Internacional de La Rioja.
https://orcid.org/0000-0003-3226-9082

Fran Calvo
Departament de Pedagogia, Institut de Recerca sobre Qualitat de Vida, Universitat de Girona.
https://orcid.org/0000-0002-0300-8548

Contact information of corresponding author

Marta Beranuy
Adress: Campus Arrosadia, Calle Cataluña, s/n, 31006, Pamplona (Navarra), Spain.
Telephone number: +34 948 169 000
Email: marta.beranuy@unavarra.es

Resumen

Introducción: La ketamina es un anestésico disociativo que actúa como antagonista de los receptores NMDA, que desempeñan un papel crucial en el fortalecimiento del aprendizaje y la memoria. No es de extrañar que su uso repetido pueda estar asociado al deterioro de las funciones cognitivas. **Objetivo:** El objetivo de este trabajo es realizar una revisión de alcance de los efectos neurocognitivos del uso re- creativo de la ketamina. **Método:** Se realizó una búsqueda bibliográfica en PyscINFO, PubMed, Scopus y Web of Science para el periodo 2000-2020. Finalmente, se incluyeron en la revisión 25 artículos originales. **Resultados y conclusiones:** Los resultados revelan que 1) el consumo agudo de ketamina produce déficits en la memoria de trabajo, la memoria semántica y la memoria episódica, 2) el consumo frecuente de ketamina se ha aso- ciado con el deterioro de la memoria episódica y, posiblemente, del aprendizaje, la función ejecutiva, la atención y la memoria semántica, 3) las personas diagnosticadas con trastorno por consumo de ketamina presentan déficits en la memoria episódica visual y verbal, la memoria de trabajo y la atención, 4) los déficits detectados pueden mejorar e incluso revertir tras un periodo de abstinencia.

Palabras clave

Ketamina, neurocognitivo, uso de sustancias, abstinencia, revisión narrativa.

Abstract

Introduction: Ketamine is a dissociative anesthetic that acts as an antagonist to NMDA receptors, which play a crucial role in strengthening learning and memory. Not surprisingly, its repeated use may be associated with impaired cognitive functions. **Objective:** The aim of this paper is to carry out a scoping review of the scientific literature on the neurocognitive effects of recreational ketamine use. **Method:** A bibliographic search was conducted in PyscINFO, PubMed, Scopus and Web of Science for the period 2000-2020. Eventually, 25 original articles were included in the review. **Results and conclusions:** The findings reveal that 1) acute ketamine use produces deficits in working memory, se- mantic memory, and episodic memory, 2) frequent ketamine use has been associated with impairment in episodic memory and possibly in learning, executive function, attention, and semantic memory, 3) people diagnosed with ketamine use disorder have deficits in visual and verbal episodic memory, working memory and attention, 4) deficits detected may improve and even be reverted after a period of abstinence.

Keywords

Ketamine, neurocognitive, drug use, abstinence, narrative review.

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Ketamine is a dissociative anesthetic used mainly in veterinary and human medicine with limited use in humans due to side effects such as hallucinations and vivid dreams. Such effects have been reported by patients that undergo surgical procedures where ketamine is used as an anesthetic (Muetzelfeldt et al., 2008).

Its consideration as a dissociative anesthetic is due to the fact that the substance produces a functional and electrophysiological dissociation between the limbic and thalamocortical systems, depressing the thalamocortical pathways and activating the limbic system, although some studies have suggested that excitation occurs in both systems (Cruz et al., 2009). Pharmacologically, ketamine acts as a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors. In addition to binding to these, it also interacts with central and spinal opioid receptors and with cholinergic muscarinic receptors, noradrenergic receptors and serotonergic receptors (Centro de información de Medicamentos, 2020). However, both its analgesic action and effects at a psychological level are associated with its activity on NMDA glutamatergic receptors. Such receptors are known for their role as mediators of sensory inputs at spinal, cortical and thalamic levels, and as moderators of emotional responses, learning and memory (Sassano-Higgins et al., 2016).

Ketamine is causing high concern because of its use in Asia (during the period 2013-2017, 89% of global ketamine was seized in Asia) and its increasing use in other regions(United Nations Office on Drugs and Crime, 2019). Although in the European framework its use is less frequent when compared to other substances, over the last few years it has increased in countries such as the Czech Republic, Spain and the United Kingdom. In Spain, the rate of lifetime ketamine use is 0.9 per 100 inhabitants (in the population aged 15-64). The prevalence increases up to 1.7% in the 25-34 age group (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2019).

The increase in the prevalence of the use of this substance outside the clinical setting makes it essential to evaluate its short- and long-term effects, in order to understand the risks to which users may be exposed. The main acute effects caused by ketamine are: numbness, loss of balance and dizziness that can result in potentially dangerous falls for the user (Jansen, 2000) ; at a psychological level, it can transiently induce symptoms similar to schizophrenia. The long-term effects of its use seem to especially affect the urinary system, where it can produce ulcerative cystitis, and the gastrointestinal system, giving rise to "K cramps" or abdominal pains derived from the use of the substance (Sassano-Higgins et al., 2016). At a psychiatric level, its prolonged use can induce depressive symptomatology and delusional thinking (Morgan & Curran, 2012; Sassano-Higgins et al., 2016). Lastly, at a cognitive level, its use is associated with the impairment of memory, learning and some executive functions (Tang et al., 2019).

The increasing trend that appears to be observed in recreational ketamine use may constitute a public health problem that should be managed with the support of existing scientific evidence. Given that no reviews have been found in recent years on the neurocognitive effects derived from recreational ketamine use, it is essential to update this information. Thus, the aim of the present work is to perform a scoping review of the scientific literature available from 2000 to 2020, on the neurocognitive effects of recreational ketamine use.
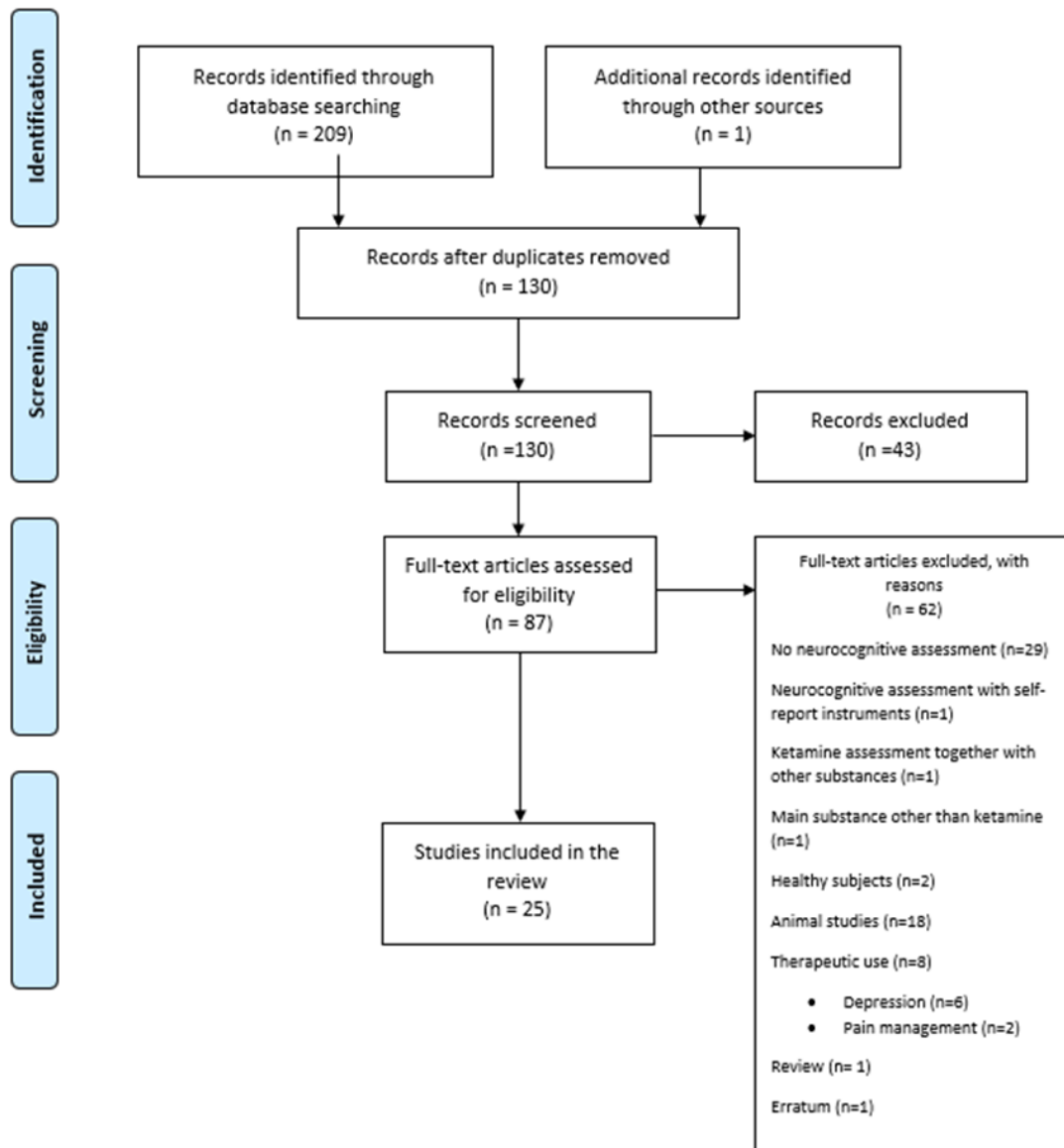
Method

The bibliographic search for this scoping review was performed using the following databases: PyscINFO, Scopus, Web of Science (WOS) and PubMed. The search strategy included the following terms: "ketamine" AND "abuse" AND "cognitive". The term "cognitive" was selected instead of "neurocognitive" due to the fact that it yielded a larger number of articles and also included all results pertaining to the second term. The three selected terms had to be included in all fields (Psicinfo), in the title, abstract or keywords (Scopus and WOS) or in the title and abstract (PubMed). The search covered publications between 1st January 2000 and 31st December 2020, in English or Spanish. The final search strategy used in PubMed was ("Ketamine"[Title/Abstract] AND "Abuse"[Title/Abstract] AND "Cognitive"[Title/Abstract] AND 2002/01/01:2020/12/31[Date - Publication]) AND ("Ketamine"[Title/Abstract] AND "Abuse"[Title/Abstract] AND "Cognitive"[Title/Abstract]) AND 2002/01/01:2020/12/31[Date - Publication].

Inclusion criteria were: 1) empirical studies with human subjects, 2) exploration of neurocognitive functioning using neuropsychological assessment techniques, and 3) in samples of recreational ketamine users (frequent, infrequent, polydrug users, with ketamine use disorder or former users). Exclusion criteria were: 1) review articles and grey

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literature, 2) studies not assessing neurocognitive functioning or assessing neurocognitive functioning by self-report, and 3) studies that did not to explore the effects of recreational ketamine use (e.g. studies on schizophrenia or on the therapeutic and controlled use of ketamine). Figure 1 shows the search strategy and article selection.

Figure 1. Flow chart, following the different phases of the review.

Identification

Records identified through database searching (n = 209)

Additional records identified through other sources (n = 1)

Records after duplicates removed (n = 130)

Screening

Records screened (n =130)

Records excluded (n =43)

Eligibility

Full-text articles assessed for eligibility (n = 87)

Full-text articles excluded, with reasons (n = 62)

No neurocognitive assessment (n=29)

Neurocognitive assessment with self-report instruments (n=1)

Ketamine assessment together with other substances (n=1)

Main substance other than ketamine (n=1)

Healthy subjects (n=2)

Animal studies (n=18)

Therapeutic use (n=8)

- Depression (n=6)
- Pain management (n=2)

Review (n= 1)

Erratum (n=1)

Included

Studies included in the review (n = 25)

Results

A total of 209 articles were initially selected (43 in PsycINFO, 18 in PubMED, 69 in Web of Science and 79 in Scopus). After removing duplicates, the number was narrowed down to 130, of which 43 were excluded in the first screening as they did not fit the objective of the study. This left 87 articles, 62 of which were excluded because they did not meet the inclusion criteria. In the end, 25 original articles were included.

All 25 articles were published in English. The temporal distribution of the results is homogeneous over the 20-year period that the present study considers, with years 2018 and 2013 standing out with six and three articles, respectively. The manuscripts were published in 11 different journals. "Addiction" was the most used source. The studies were conducted in three different countries: 12 in China, 11 in the UK and two in Taiwan. The articles were

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classified according to the characteristics of the sample used in each study (table 1); publications that studied frequent keta- mine users make up the largest category (n=12).

The variables related to the ketamine use of participants in the 25 studies are heterogeneous. The most common criterion employed to classify frequent ketamine users (FKU) was having used ketamine 24 times or more over a six month period in the last two years (Liang et al., 2020; Liang et al., 2013; Liang et al., 2014; Tang et al., 2013; Zhang et al., 2018, 2020), followed by having done so more than four times a week (Morgan et al., 2009, 2010; Morgan et al., 2008). The most frequently used criterion for selecting non-frequent users of ketamine was to use less than four times a week (Morgan et al., 2009, 2010). The most frequently used criterion to constitute groups of former ketamine users (EKU) was sustained abstinence for at least one month (Morgan et al., 2009, 2010; Tang et al., 2013). Three studies were conducted with subjects that had been diagnosed with ketamine use disorder (KUD) according to the diagnostic criteria set by the DSM-IV-TR for substance dependence (Cheng et al., 2018; Ke et al., 2018; Wang et al., 2018) or by using a dependence test (Morgan et al., 2012) (Severity Dependence Scale, SDS).

One aspect that should be taken into account is the fact that four of the cross-sectional studies that were reviewed (Liang et al., 2020; Liang et al., 2013; Liang et al., 2014; Zhang et al., 2018) did not include a clinical diagnosis (KUD) as a requirement to be part of the sample. However, it was assessed using the SDS, and the mean scores exceeded the cut-off point considered for dependence by Morgan et al. (2012).

A wide variety of instruments were used to assess episodic (visual and verbal) declarative memory and its different sub-processes (recall and familiarity) (e.g., Wechsler Memory Scale -WMS III-, Rey-Osterrieth Complex Figure test -ROCF-, Chinese Auditory-Verbal Learning Test -CAVLT-, Continuous Visual Memory Test -CVMT-, source memory task, prose recall task), semantic memory (e.g., Verbal Fluency test), attention (Digit Span Test -DVT- or the arithmetic subtest of the WAIS-III), and executive functions such as working memory (Digit Span Task, the Spatial Working Memory of the CANTAB or the 2-back task), response inhibition (Stroop test) or concept formation skills and cognitive flexibility (Wisconsin Card Sorting Task -WCST). Processing speed (Symbols and Digits Test -SDMT-) and implicit memory (priming tasks) were also assessed. Table 1 shows the tests in more detail and Table 2 presents the results of the studies.

The twenty-five articles that were reviewed explore, using neuropsychological tests, neurocognitive functioning associated with acute, frequent, and prolonged ketamine use.

The reviewed papers explored episodic (recall and familiarity) and semantic declarative memory, attention, and executive functions (working memory, response inhibition and planning, among others). Other processes such as processing speed and implicit memory were also assessed to a lesser extent. Special emphasis was placed on declarative memory, since it seems to be the most affected dimension, as already indicated by previous reviews (Morgan & Curran, 2006). The role of the NMDA receptor in memory and learning processes could explain this impact (Tsien et al., 1996).

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Table 1. *Author information, aims, sample characteristics and methods of the articles included in the review.*

Author/s	Aim	Sample characteristics	Methods
Acute ketamine use			
Curran and Morgan (2000)	To examine the acute and residual effects of ketamine on cognitive function and schizotypal and dissociative symptomatology in recreational users.	Total (n=39) KU (n=20, consumption in the last 30 minutes); CGP (n=19).	Prose recall; Verbal fluency;Speed of comprehension test; Serial sevens; Digit cancellation task; Word-stem completion task; Word-subtraction task;
Curran and Monaghan (2001)	Examine whether frequent use of ketamine produces chronic effects (ensure that they are chronic and not persistent).	Total (n=37, polydrug users, ketamine use 30 minutes before): FKKU (n=18, >2 times per month); NFKU (n=19, ≤2 times per month).	Prose recall; Verbal fluency; Speed of comprehension test; Serial sevens task; Digit cancellation task.
Morgan, Ricelli et al. (2004)	To determine whether ketamine use is associated with deficits in episodic memory.	Total (n=40) KU (n=20, ketamine use in the last 10 minutes); CGP (n=20)	Source memory task
Uhlhaas et al. (2007)	To determine whether repeat users have deficits in perceptual organisation.	Total (n=32) KU (n=16, consumption in the last 15 minutes); CGP (n=16).	*Contour integration test*
Frequent users			
Morgan et al. (2006)	Examining semantic priming following repeated self-administration by recreational ketamine users	Total (n=32) KU (n=16, ≥2 times per month); CGP (n=16).	Semantic priming task with a manipulation of frequency (high and low) and stimulus onset asynchrony (SOA: short-200 msec, long-750 msec).
Morgan et al. (2008)	To explore the attentional biases of different populations of ketamine users with respect to incentive stimuli.	Total (n=150) FKU (n=30, >4 times/week); NFKU (n=30, <4 times/week, but ≥1 time/month); EKU (n=30, abstinent ≥3 months); CGP (n=30); CG (n=30))	Dot-probe task; Two times of stimulus presentation (200 and 2000ms); 2 types of stimuli: drug-related or money-related..
Morgan et al. (2009)*	To determine how variations in ketamine use (including abstinence) affect neurocognitive function.	Total (n=150) FKU (n=30, >4 times/week); NFKU (n=30, <4 times/week, but ≥1 time per month); EKU (n=30, abstinent ≥1 month); CGP (n=30); CG (n=30)	Tasks from the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB): Pattern Recognition Memory (PRM), Spatial Working Memory (SWM), Stockings of Cambridge (SOC). Source memory task; Prose recall (Rivermead Behavioural Memory Test); Fluency tasks (verbal and category); Hayling test.
Stefanovic et al. (2009)	Experiment 2. To assess cognitive functioning at the level of semantic processing in a group of ketamine users.	FKU (n=22, ≥1 time/month for at least 1 year) CGP (n= 26) CG (n= 48)	Direct semantic priming task (SOA: automatic-250 msec, strategic 750 msec).
Chan et al. (2013)	To investigate the effects of repeated ketamine self-	Total (n=55)	Symbol Digit Modalities Test (SDMT); Digit Vigilance Test (DVT);

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	administration on frontal fluency, attention, learning, and both verbal and non verbal memory.	KU (n=25, ≥1 time/month in the last 2 years); CG (n=30)	Stroop Color–Word Test (Stroop; Lee & Chan, 2000); Chinese Auditory-Verbal Learning Test (CAVLT); Continuous Visual Memory Test (CVMT); Verbal Fluency Test (VFT); Ruff Figural Fluency Test (RFFT)
Liang et al. (2013)*	To compare the cognitive functioning of current and former polydrug users of ketamine with individuals who do not use illicit drugs.	Total (n=200) PKU [n=100, PKU (≥24 times over 6 months in the last 2 years), ECKP (abstinent ≥ 30 days)]; CG (n= 100).	Logical Memory and Word List subtests (WMS-III); Rey-Osterrieth Complex Figure Test (ROCF); Stroop Test; Wisconsin Card Sorting Test (WCST); Modified Verbal Fluency Test (MVFT); Digit Span Backwards Test (DSB).
Liang et al. (2014)	To explore gender differences in the effects of ketamine on cognitive functions in ketamine users.	Total (n=200) KU (n=100, ≥24 times over 6 months in the last 2 years, 47♀ and 53♂); CG (n=100, 42♀ and 58♂)	Logical Memory and Word List subtests (WMS-III); Stroop Test; Modified Verbal Fluency Test (MVFT); Wisconsin Card Sorting Test (WCST); Digit Span backwards task (DSB); ROCF Test.
Tang et al. (2013)*	Examining the cognitive functions of young ketamine users.	Total (n=200) FKU (n=100, ≥24 times over 6 months in the last 2 years): FKU (n=51, in the last month) and ECKF (n=49, abstinent ≥1 month). CG (n=100).	Digit-symbol coding subtest (WAIS-III); Arithmetic subtest (WAIS-III); Digit span subtest (WAIS-III); Logical memory subtest (WMS-III); ROCF test; Stroop test.
Zeng et al. (2016)	To compare ketamine, methadone and non-users on its impulsivity, antisocial personality and cognitive skills.	Total (n=170) KU (n=51); MU (n=59); CG (n=60).	Stop-signal test; Stroop test; 2-back task; Iowa Gambling Task.
Zhang et al. (2018)	To examine cognitive deficits in chronic ketamine users. To explore synergistic effects between ketamine and other drugs.	Total (n=829) FKU (n= 565, ≥24 times over 6 months in the last 2 years): KU (n=286) and PKU (n=279). CG (n=261).	Digit Span Subtest (WMS-III); Logical Memory Subtest (WMS-III); ROCF Test; Stroop Test; Wisconsin Card Sorting Test (WCST).
Liang et al. (2020)	To measure white matter volume and its relationship with cognitive and depressive symptoms in KU (FKF or PKU) compared to CG.	FKU (n=39, K ≥24 times over 6 months in the last 2 years, other substances <1 time per month in the last 2 years). PKU (n=41, K+other substances ≥24 times over 6 months in the last 2 years). CG (n=46).	WAIS-III (Digit Span Forward and Backward, Arithmetic); WMS-III Logic Memory delay recall, retention and recognition; WMS-III Word List delay recall and retention; Rey-Osterrieth Complex Figure test Learning (WMS-III Logic Memory immediate recall, WMS-III Word List immediate recall; Modified Verbal Fluency Test; Stroop interference; Wisconsin Card Sorting Test; Digit Symbol Coding; Modified Boston Naming test.
Zhang et al. (2020)	To assess the cognitive functioning of chronic ketamine users and to examine whether there is a relationship between these and early treatment dropout.	Total (n=397). FKU (n=286, K ≥24 times over 6 months in the last 2 years, other drugs <24 times over 6 months in the last 2 years): Completers (n=165); Dropouts (n=121).	Digit Span Subtest (WMS-III); Logical Memory Subtest (WMS-III); ROCF Test; Stroop Test; Wisconsin Card Sorting Test (WCST).

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		CG (n=111).	
Ketamine use disorder			
Morgan et al. (2012)	To assess neurocognitive functioning in people dependent on ketamine, cannabis and cocaine.	Total (n=130) KUD (n=21); ACAN (n=29); CANUD (n=22); PDU - cannabis, cocaine and ketamine - (n=28); CG (n=30).	Prose recall; Digit span (forward and backwards); Verbal fluency; Category fluency.
Cheng et al. (2018)	To compare neurocognitive functioning, in relation to symptoms of psychosis, in KUD with psychosis with that of KUD without psychosis and people with a schizophrenia diagnosis.	Total (n=149) KUD No psychosis (n=51), KUD Psychosis (23), SZ (n=75) (SZ=schizophrenia diagnosis)	Cogstate Battery: Detection Task, Identification Task, One Back Task, Two Back Task, International shopping List Task and Delayed Recall Task, Groton Maze Learning Task and Delayed Recall Task, Social Emotional Cognition Task
Ke et al. (2018)	To examine the cognitive functioning of chronic ketamine users.	Total (n=128) KUD (n=63); CG (n=65).	Immediate/Delayed Visual Reproduction Test (WMS-RC); Immediate/Delayed Logical Memory Test (WMS-RC); Stroop Test; WCST; Continuous Performance Test (CPT).
Siu et al. (2018)	Evaluating the impact of a short-term inpatient and community support programme for ketamine abusers.	Total (n= 118) KUD treatment (n=84) No KUD treatment (n=34)	The Montreal Cognitive Assessment (MoCA)
Wang et al. (2018)	To assess the long-term consequences of chronic ketamine use	Total (n=165) KUD (n=58); MAUD (n=49); CG (n=58)	*Brief Assessment of Cognition in Schizophrenia (BACS)*
Prospective studies on ketamine use			
Morgan, Monaghan et al. (2004)	Follow-up of a cohort assessed 3 years earlier; analyse deficits observed 3 days after use.	Total (n=28) KU (n=18); CGP (n=10)	Speed of comprehension; Semantic (category) fluency; Prose recall; Digit cancellation task; Serial sevens task; Phonological (verbal) fluency.
Morgan et al. (2010)*	To assess the cognitive consequences of long-term ketamine use (1-year follow-up).	Total (n=150) FKU (n=30, ≥ 4 times a week); NFKU (n=30, < 4 times a week and minimum one month); EKU (n=30, ≥1 month of abstinence); CGP (n=30); CG (n=30).	Tasks from the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB): Pattern Recognition Memory (PRM), Spatial Working Memory (SWM), Stockings of Cambridge (SOC). Source memory task; Prose recall (Rivermead Behavioural Memory Test); Fluency tasks (verbal and category).
Abstinent users			
Tang et al. (2019)	Investigating changes in cognitive function of abstinent ketamine users.	KU in 12-week abstinence (n=114, use of ketamine or ketamine with any other illicit substance ≥24 times / 6 months).	Stroop Test; WCST; Digit Span (WAIS-III); Logical Memory (WMS-III); ROCFT Test.
Man (2020)	To evaluate the cognitive and vocational impact of 3 interventions [Virtual Reality, Mentored Coaching and Waiting List (CG)] with ketamine users.	KU in abstinence and treatment or waiting list (n=90, ≥24 times over 6 months in the last 2 years, no other drug use 1 or more times over the last 2 years). Does not specify length of abstinence.	Digit Vigilance Test (DVT); Rivermead Behavioural Memory Test (RBMT); Wisconsin Card Sorting Test (WCST).

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Table 2. *Results and conclusions of the articles included in the review*

Study	Results and conclusions
Curran and Morgan (2000)	Day 0: lower CK performance in Prose Recall, Verbal Fluency, Category Generation, Comprehension Speed, Serial Subtraction Task, Digit Cancellation Task than GCP.
	Day 3: CK improvement in Prose recall, Verbal fluency, Serial subtraction task. Similar speed KU and CGP in Digit Cancellation Task. No improvement in Category generation. Word-stem completion task: No differences between groups.
	Ketamine appears to induce acute deficits in working, episodic and semantic memory. Three days after use, recreational users show impairments in semantic memory.
Curran and Monaghan (2001)	Day 0: similar score on prose recall, category generation, FKU lower performance than NFKU on verbal fluency and speed of comprehension.
	Day 3: NFKU performs better than FK on prose recall, category generation. Both groups perform better than Day 0 on speed of comprehension.
	No between-group differences in serial subtraction task and digit cancellation. Frequent ketamine use produces long-term impairments in episodic memory and in aspects of semantic memory retrieval.
Morgan, Ricelli et al. (2004)	Day 3: KU show persistent deficits in source memory, but not in item recognition.
	Repeated ketamine use may produce chronic deficits in episodic memory.
	Day 0: KU made more errors.
Uhlhaas et al. (2007)	Day 3: errors made by both groups were similar (both made fewer errors).
	On the night of consumption, ketamine produces a dysfunction in contour integration, but this did not occur 3 days later, when participants were not under the effects of the drug.
	KU showed inverse priming for low-frequency words in the long SOA and significantly less than CGP.
Morgan et al. (2006)	Significant correlation of KU: days per month of consumption and the effect of short/long SOA on priming.
	The effect of reverse priming is indicative of alterations in processing. Decreased priming for low-frequency words suggests that long-term ketamine use may impair semantic storage.
Morgan et al. (2008)	CKF showed an attentional bias to both types of incentive stimuli in the short stimulus presentation interval, which correlated significantly with the degree of ketamine consumption.
	No attentional bias was observed in any of the other groups.
	All groups rated money-related stimuli as more pleasant than neutral stimuli.
	FKU is associated with deficits in working memory, episodic memory and aspects of executive functioning.
	NFKU does not appear to produce neurocognitive deficits.
Morgan et al. (2009)*	No significant worsening in KUD (possible reversibility of deficits in frequent users).
	FKU group worse performance in PRM, SWM, SOC and source memory task.
	No between-group differences in prose recall task, fluency tasks and Hayling test.
	Results showed that FKUs were impaired in working memory, episodic memory and aspects of executive functioning (planning). Non-frequent

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	recreational use did not appear to be related to any cognitive impairment.
Stefanovic et al. (2009)	KFU do not reduce the difference between automatic and strategic semantic priming.
	There are no significant differences in semantic priming between FKU and CG.
	KU have deficits in verbal fluency, cognitive processing speed and verbal learning, the latter correlating with years of consumption. No deficits were found in figurative fluency, selective attention, sustained attention, visual learning or verbal/non-verbal episodic memory.
Chan et al. (2013)	Higher ketamine use is associated with poorer performance on learning and memory tasks.
	The study suggests that repeated ketamine use causes differential impairment of multiple domains of frontal and medial temporal functioning, possibly specific to verbal information processing.
	PKUs and EPKUs score lower than CGs in Logical Memory and ROCF.
Liang et al. (2013)*	There are no significant differences between PKU and EPKU cognitive functioning. There are no differences in executive functions between the groups. PKU and EPKU: deficits in visual and verbal memory.
	FKUs showed deficits mainly in verbal and visual episodic memory, but not in working memory or executive functioning.
	KU♀ higher risk of visual memory deficits than KU♂. No significant differences in WCTS.
Liang et al. (2014)	KU lower performance in Logical memory and ROCF (immediate and delayed recall) than CG.
	KU♀ significantly lower performance in ROCF (delayed recall) than CG♀.
Tang et al. (2013)*	Cognitive deficits in current FKU were found in the domains of mental and motor speed, visual and verbal memory and executive functions. Current FKU is associated with cognitive impairment.
	2 back task: KU and MU scored significantly lower than CG, but there were no significant differences between the two.
	Response inhibition: MU significantly lower performance than the rest of the groups, except in Stop signal errors.
Zeng et al. (2016)	*Stroop test: KU lower performance than MU and CG.*
	IGT: no significant differences between groups.
	KU do not present deficits in decision-making, they present lower response inhibition and working memory, with levels similar to MU.
Cheng et al. (2018)	KUD Psychosis and SZ show greater deficits in spatial problem solving and verbal memory compared to KUD Non-psychosis.
	KUD No psychosis present less severe cognitive impairment than KUD Psychosis and SZ.
Siu et al. (2018)	FKU significantly improved cognitive functioning as assessed with the MoCA.
	The MoCA score does not point to cognitive impairment compared to the validated score in the Chinese and Korean population.
	No significant differences between groups in WCST, Digit Span, and Stroop test.
	Significant differences in Logical memory and ROCF (lower performance).
Zhang et al. (2018)	Concomitant use of other drugs does not seem to have an impact on cognitive performance.
	KU: days of ketamine use in the previous month correlated negatively with ROCF immediate and delayed recall.
	PKU: g/day correlates negatively with logical memory score (immediate recall).
	FKU have deficits in visual and verbal memory.
Morgan et al. (2012)	Prose recall: All consumer groups performed lower than CG in immediate recall. In delayed recall only CANUD performed worse.

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	Fluency: Lower total number of words produced by CANUD and KUD.
	Direct and inverse digits: No significant differences in direct digits, but in the inverse digit task where KUD and PDU had lower scores.
	KUD and ACAN were the most cognitively impaired. Worse frontal functioning in KUD.
	KUD and PDU have difficulties manipulating information in working memory.
Ke et al. (2018)	KUD have deficits in visual immediate memory, verbal memory (immediate and delayed), selective attention and response inhibition and sustained auditory attention.
	KUD worse performance on verbal memory, motor speed, verbal fluency, attention and processing speed and on the battery composite score than CG.
Wang et al. (2018)	AMA lower performance in motor speed, verbal fluency and attention and processing speed than CG.
	KUD worse than AMA on verbal memory, working memory, attention and processing speed and on the battery composite score.
	KUD have impaired cognitive functioning and AMA have intermediate performance (between KUD and CG).
	Category generation: KU performance was lower at the day 3 assessment in the original study, but there were no differences between groups 3 years later.
Morgan, Monaghan et al. (2004)	Episodic Memory, Comprehension Speed and Digit Cancellation: Lower KU performance at both time points (baseline and follow-up) compared to CGP.
	Serial subtraction task and verbal fluency: No significant differences between CGP and KU at either time point.
	KU reduced consumption by 88.3%. Their performance on semantic memory tasks had improved (correlation with reduced consumption). Impairments in episodic memory and attentional functioning seem to persist in the long term..
	FKKU lower performance in SWM, PRM (compared to NFKU and CGP), Source Memory (vs. ECK and CGP) and Verbal Fluency.
	FKU higher performance in SOC at follow-up.
	ECK lower performance in Verbal Fluency and tendency to score better in PRM than CGP and CG.
Morgan et al. (2010)*	All groups score lower in delayed recall (Prose Recall Task).
	Higher NFKU performance in Category Fluency at follow-up.
	Cognitive deficits are observed mainly in FKU.
	Increasing ketamine use over the years correlates with decreased performance in spatial working memory and pattern recognition tasks.
Tang et al. (2019)	After 12 weeks of abstinence: Significant improvement in visual memory (immediate and delayed recall on the Rey Osterrieth Complex Figure Test) and verbal memory (delayed and immediate recall on the Logical Memory). Improved performance of executive functions (completed Stroop test significantly faster; fewer attempts and perseverative errors on the WCST).
	Cognitive deficits may be reversible after 12 weeks of abstinence.
Man (2020)	Virtual Reality treatment: significant improvement in attention and memory over time.
	All three groups (abstinent) have an improvement in executive functions (WCTS) and non-verbal intelligence (TONI-III).
Liang et al. (2020)	FKU performed lower than CG in working memory (arithmetic), verbal memory (retention and recognition of logical memory) and learning

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	(immediate recall of logical memory and immediate recall of FCR).
	Significant differences between participants in Digit Span Backward, WMS III Logical Memory: immediate recall, recognition, ROCF: immediate recall, delayed recall and WCST: total attempts.
Zhang et al. (2020)	FKU have more cognitive deficits than CG in verbal/visual episodic memory and executive functioning.
	Deficits in executive functioning correlated significantly with treatment dropout at 3 months.

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Acute ketamine use

It is agreed that acute recreational ketamine use produces impairments affecting semantic and episodic memory, as well as working memory (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan, Riccelli, et al., 2004; Uhlhaas et al., 2007), which is consistent with laboratory studies with healthy individuals (Krystal et al., 1994; Malhotra et al., 1996). It should be mentioned that research on the therapeutic use of ketamine for treatment-resistant depression has found positive effects on neurocognitive functioning, referred to as procognitive, affecting mainly visual memory, simple working memory, and complex working memory (Lee et al. 2016). However, these results have been obtained in controlled clinical studies, using doses and routes of administration that may vary from those used by recreational users (Downing 2002).

Studies assessing the effects of recreational ketamine use three days after use conclude that at least some of these effects may not only be residual, but persistent (referred to as chronic). Forasmuch as ketamine has a very short half-life (2-4 h) (Zanos et al., 2018) the lower performance levels observed three days after its use cannot be attributed to a mere residual effect of acute intoxication. Thus, the deficits in episodic (recall) (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan, Riccelli, et al., 2004) and semantic memory (Curran & Monaghan, 2001; Curran & Morgan, 2000) that have been observed after three-day abstinence periods are conceived as persistent.

Frequent ketamine use

Frequent ketamine use is associated with deficits in episodic memory, both visual (Liang et al., 2020; Liang et al., 2013; Morgan et al., 2009, 2010) and verbal (Liang et al., 2013; Tang et al., 2013; Zhang et al., 2018, 2020), and in both (immediate and delayed) recall sub-processes (Liang et al., 2020; Liang et al., 2013; Tang et al., 2013; Zhang et al., 2018, 2020) and recognition (Liang et al., 2020; Liang et al., 2013; Morgan et al., 2009, 2010; Morgan, Monaghan, et al., 2004; Zhang et al., 2018, 2020). Nevertheless, Chan et al. (2013) and Morgan et al. (2009) did not find impaired recall processing. Verbal fluency has been used as an indicator to assess semantic memory performance. Some researchers found deficits at this level (Chan et al., 2013; Liang et al., 2013; Morgan et al., 2010; Tang et al., 2013), but others did not (Morgan et al., 2009; Morgan, Monaghan, et al., 2004). Chan et al. (2013) and Liang et al. (2020) have also found impaired learning, the latter interpreting learning performance based on the results obtained in an episodic memory test. All in all, these studies support the idea that FKUs show greater impairment in declarative memory and learning than non-frequent users.

Only two studies assessed implicit memory through a semantic priming task. The results of Morgan et al. (2006) showed that ketamine users experienced a decrease in priming for low-frequency words, which, according to the authors, suggests that in the long term, ketamine use may impair semantic storage. However, Stefanovic et al. (2009) found no differences in semantic priming compared to the control group. Likewise, perceptual priming was assessed in one study (Curran & Morgan, 2000) that does not support the existence of impairment in implicit memory either. The fact that priming (implicit memory) is not affected by K in the same way as declarative memory is not surprising, as these are different memory systems (Squire & Dede, 2015). Unlike hippocampal-dependent explicit memory, the synaptic plasticity mechanisms underlying implicit memory have not been associated with NMDA receptor activity (Bailey et al., 2015).

Regarding executive function, the reviewed studies show greater variability. Working memory, inhibitory control, cognitive flexibility, concept formation and planning have been explored. Working memory was assessed through a variety of instruments; impairment of the central executive system was found in several studies (Liang et al., 2020; Tang et al., 2013; Zeng et al., 2016; Zhang et al., 2020) but not in others (Liang et al., 2013; Zhang et al., 2018); three studies found storage impairment (Morgan et al., 2009, 2010; Tang et al., 2013) while three others did not (Liang et al., 2020; Zhang et al., 2018, 2020). Inhibitory control was not affected in six of the eight studies that explored it (Chan et al., 2013; Liang et al., 2020; Liang et al., 2013; Morgan et al., 2009; Zhang et al., 2018, 2020). Concept formation and cognitive flexibility skills have not been found to be impaired (Liang et al., 2013; Zhang et al., 2018) although a recent study did (Zhang et al., 2020). Planning ability was impaired in the only study that assessed it (Morgan et al., 2009); and decision-making, also assessed in only one paper, was unaffected (Zeng et al., 2016). It is worth mentioning that the study by Zhang et al. (2020) found a correlation between early treatment dropout and

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impaired executive functions, so future research should further investigate this issue.

Two of the cross-sectional studies that assessed processing speed found it to be impaired in ketamine users (Chan et al., 2013; Tang et al., 2013).

In terms of attention, the only cross-sectional study that assessed sustained attention found no deficits (Chan et al., 2013). Likewise, only Morgan et al. (2008) explored the existence of attentional biases towards ketamine-associated stimuli, finding them present in frequent users. Bechara (2005) has already postulated that these biases constitute one of the mechanisms mediating the development and consolidation of a substance use disorder (SUD), and it is suggested that this process should be explored in the future.

The gender perspective was not widely explored. Only one study considered this matter, and it found that deficits in visual episodic memory appear to be more pronounced in biological women (Liang et al., 2014), which may be related to the influence of sex hormones (Gómez-Gil et al., 2009; Lee et al., 2000). However, further studies are required to draw any conclusions.

Ketamine use disorder

Studies that explore subjects with KUD also show that its use had an impact on memory and executive functioning. Deficits were found in visual episodic memory (immediate recall) (Ke et al., 2018), which could be linked to reduced hippocampal activity (Honey et al., 2005; Morgan et al., 2014). Deficits in verbal episodic memory (immediate and delayed recall) were also found (Ke et al., 2018; Morgan et al., 2012; Wang et al., 2018) with this impairment being more pronounced in those with KUD and persistent psychosis compared to those without psychosis (Cheng et al., 2018). Impairment was also observed in semantic memory (verbal fluency), working memory, attention, and processing and motor speed (Cheng et al., 2018; Ke et al., 2018; Morgan et al., 2012; Wang et al., 2018), although other studies did not support the findings on executive function (Ke et al., 2018; Wang et al., 2018). The study by Siu et al. (2018) was the only one that did not find cognitive impairment compared to the reference population; this may be due to the employment of an instrument (MoCA cognitive screening test, designed for the identification of dementia) with low sensitivity for detecting impairment in young and non-clinical populations.

Several studies assessed the extent of ketamine dependence in their participants using the Severity Dependence Scale (SDS), but the presence of a KUD was not a requirement for study inclusion. However, these subjects obtained similar scores to the participants of studies included in the KUD category. Likewise, results obtained in those studies also supported the hypothesis that KUs have deficits in visual and verbal episodic memory (Liang et al., 2020; Liang et al., 2013; Liang et al., 2014; Zhang et al., 2018). Some neuroimaging studies support the existence of deficits in visual and verbal episodic memory in chronic users. These studies (Liao et al., 2010, 2011) have observed a reduction in grey matter volume in the prefrontal cortex and changes in white matter volume in the bilateral frontal cortex and left temporoparietal cortex, consistent with impairment of these functions.

In terms of the temporality of the deficits, some were maintained despite cessation. These were found to be in episodic memory (visual and verbal, delayed, recall and recognition) and attention (Liang et al., 2013; Morgan et al., 2010; Morgan, Monaghan, et al., 2004). Other deficits, however, could be temporary and even reverted after a period of abstinence or decreased use (semantic memory, episodic memory, executive functioning, attention) (Man, 2020; Morgan et al., 2009; Morgan, Monaghan, et al., 2004; Tang et al., 2019; Tang et al., 2013). These findings are supported by the study by Morgan et al. (2010), which indicated that EKUs performed better than current users in visuospatial working memory and visual episodic memory, suggesting that there would be an improvement in cognitive functioning. Even though further longitudinal studies to confirm these conclusions are pending, the findings suggest that the deficits may be temporary.

It is relevant to point out that a recent review (Strous et al. 2022) explored brain changes associated with long-term ketamine use that could help understanding the cognitive impairments found by the present review. According to

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this study, deficits found in memory could be related to impairment of regions such as the hippocampal complex, prefrontal and temporoparietal cortex. Likewise, the deficits observed in executive functioning could be related to fronto-striatal disturbances. To find out whether these alterations are related, future longitudinal research should analyse the brain changes by combining neuroanatomical and cognitive measurement techniques.

The fact that there are inconsistencies in the results of the reviewed studies may be due to several factors. One of them is the large variability in the duration of abstinence periods. Although the inclusion criterion was one month of abstinence, except for the study by Tang et al. (2019), the descriptive data of the samples indicate that, in the majority of the studies, these periods lasted longer (between 189 and 343 days on average).

Another variable that may lead to discrepancies in the results on the reversibility of the impairment found in FKU may be the existence of polydrug use (Zhang et al., 2018), as recreational ketamine use is often associated with the use of other substances(Delegación del Gobierno para el Plan Nacional sobre Drogas, 2019; Liang et al., 2015). Given that drug use has also been associated with deficits in cognitive functioning (Schilt et al., 2008; Vonmoos et al., 2013), it is possible that concomitant use of ketamine with other substances affects cognitive functioning. However, the only study to analyse this issue found that the use of other substances was not synergistic with ketamine in causing cognitive impairment (Zhang et al., 2018). Still, given the frequency of poly-drug use, research is needed to study the effects that the use of other drugs in combination with ketamine might have on cognitive function.

Frequency of use could influence the level of impairment in cognitive functioning. The reviewed studies use very heterogeneous inclusion criteria to categorise their participants, which may lead to discrepancies in the results. Thus, for example, in order to be considered a FKU, ketamine use had to occur at least once a month within the last two years, 24 times over six months in the last two years, or more than four times a week.

Considering the results and despite the limitations, we can conclude that ketamine use has an impact on various aspects of neurocognitive functioning, particularly declarative (episodic and semantic) memory and also on some executive functions. Given the increase in recreational ketamine use over the last few years, it is necessary to raise awareness among users of the risks that it may entail. It is also important for health professionals to be aware of the cognitive impairment associated with frequent use. Moreover, its recent use in the treatment of depression in clinical practice (Bahji et al., 2021), highlights the need to further explore the adverse effects of its use.

Furthermore, the findings regarding the possible reversibility of cognitive deficits associated with ketamine use are encouraging, as they may help to improve the quality of life of EKU and motivate them to remain abstinent.

Conclusions

Based on the findings presented by the reviewed literature, it can be said that:

1. Acute ketamine use produces deficits in working memory, semantic memory and episodic memory.

2. Frequent ketamine use is associated with cognitive impairment. There is evidence that episodic memory is affected, and that possibly learning and semantic memory are equally affected. Regarding the existence of deficits in attentional and executive functioning, the results are less consistent, although there is some evidence that working memory may be impaired.

3. Most studies assessing participants diagnosed with KUD indicate that they have deficits in visual and verbal episodic memory, working memory and attentional functioning.

4. Deficits in ketamine users may improve and may even be reversible after a period of abstinence.

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References

Bahji, A., Vazquez, G. H., & Zarate, C. A., Jr. (2021). Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *Journal of Affective Disorders, 278,* 542–555.

Bailey, C. H., Kandel, E. R., & Harris, K. M. (2015). Structural Components of Synaptic Plasticity and Memory Consolidation. *Cold Spring Harbor Perspectives in Biology*, *7*(7). https://doi.org/10.1101/cshperspect.a021758

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience*, *8*(11), 1458–1463.

Chan, K. W. S., Lee, T. M. C., Siu, A. M. H., Wong, D. P. L., Kam, C.-M., Tsang, S. K. M., & Chan, C. C. H. (2013). Effects of chronic ketamine use on frontal and medial temporal cognition. *Addictive Behaviors*, *38*(5), 2128–2132. https://doi.org/10.1016/j.addbeh.2013.01.014

Cheng, W.-J., Chen, C.-H., Chen, C.-K., Huang, M.-C., Pietrzak, R. H., Krystal, J. H., & Xu, K. (2018). Similar psychotic and cognitive profile between ketamine dependence with persistent psychosis and schizophrenia. *Schizophrenia Research*, *199*, 313–318. https://doi.org/10.1016/j.schres.2018.02.049

Centro de información de Medicamentos. (2020). Ketolar, ficha técnica. Agencia Española de Medicamentos y Productos Sanitarios. https://cima.aemps.es/cima/pdfs/es/ft/47034/FT_47034.pdf

Cruz, J. M., Giraldo, C. E., Fernández, E. F., & Tovar, O. E. (2009). Farmacología y uso clínico de la ketamina. *CES Medicina Veterinaria y Zootecnia*, *4*(1), 68–79.

Curran, H. V., & 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. https://doi.org/10.1046/j.1360-0443.2001.96574910.x

Curran, H. V., & 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. https://doi.org/10.1046/j.1360-0443.2000.9545759

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2019). *Encuesta sobre alcohol y otras drogas en España (EDADES).* https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2019_Estadisticas_EDADES.pdf

Downing, E. H. (2002). Revisión del uso recreacional de la ketamina. *Adicciones, 14*(2), 177–189.

Gómez-Gil, E., Cañizares, S., Torres, A., la Torre, F. de, Halperin, I., & Salamero, M. (2009). Androgen treatment effects on memory in female-to-male transsexuals. *Psychoneuroendocrinology*, *34*(1), 110–117. https://doi.org/10.1016/j.psyneuen.2008.08.017

Honey, G. D., a. E. Honey, R., O'Loughlin, C., Sharar, S. R., Kumaran, D., Suckling, J., Menon, D. K., Sleator, C., Bullmore, E. T., & Fletcher, P. C. (2005). Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: an fMRI study. *Cerebral Cortex* , *15*(6), 749–759. https://doi.org/10.1093/cercor/bhh176

Jansen, K. L. (2000). A review of the nonmedical use of ketamine: use, users and consequences. *Journal of Psychoactive Drugs*, *32*(4), 419–433. https://doi.org/10.1080/02791072.2000.10400244

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Ke, X., Ding, Y., Xu, K., He, H., Wang, D., Deng, X., Zhang, X., Zhou, Y., Zhou, C., Liu, Y., Ning, Y., & Fan, N. (2018). The profile of cognitive impairments in chronic ketamine users. *Psychiatry Research*, *266*, 124–131. https://doi.org/10.1016/j.psychres.2018.05.050

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., Heninger, G. R., Bowers, M. B., & Charney, D. S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry*, *51*(3), 199–214. https://doi.org/10.1001/archpsyc.1994.03950030035004

Lee, C. J., Do, B. R., Kim, J. K., & Yoon, Y. D. (2000). Pentobarbital and ketamine suppress serum concentrations of sex hormones in the female rat. *Journal of Anesthesia, 14*(4), 187–190. https://doi.org/10.1007/s005400070003

Lee, Y., Syeda, K., Maruschak, N. A., Cha, D. S., Mansur, R. B., Wium-Andersen, I. K., Woldeyohannes, H. O., Rosenblat, J. D., & McIntyre, R. S. (2016). A New Perspective on the Anti-Suicide Effects With Ketamine Treatment: A Pro- cognitive Effect. *Journal of Clinical Psychopharmacology, 36*(1), 50–56.

Liang, H. J., Lau, C. G., Tang, A., Chan, F., Ungvari, G. S., & Tang, W. K. (2013). Cognitive impairments in poly-drug ketamine users. *Addictive Behaviors*, *38*(11), 2661–2666. https://doi.org/10.1016/j.addbeh.2013.06.017

Liang, H. J., Lau, C. G., Tang, K. L. A., Chan, F., Ungvari, G. S., & Tang, W. K. (2014). Are Sexes Affected Differently by Ketamine? An Exploratory Study in Ketamine Users. *Substance Use & Misuse*, *49*(4), 395–404. https://doi.org/10.3109/10826084.2013.841248

Liang, H. J., Tang, K. L., Chan, F., Ungvari, G. S., & Tang, W. K. (2015). Ketamine users have high rates of psychosis and/ or depression. *Journal of Addictions Nursing*, *26*(1), 8–13. https://doi.org/10.1097/jan.0000000000000060

Liang, H., Tang, W. K., Chu, W. C. W., Ernst, T., Chen, R., & Chang, L. (2020). Striatal and white matter volumes in chronic ketamine users with or without recent regular stimulant use. *Drug and Alcohol Dependence*, *213*, 108063. https://doi.org/10.1016/j.drugalcdep.2020.108063

Liao, Y., Tang, J., Corlett, P. R., Wang, X., Yang, M., Chen, H., Liu, T., Chen, X., Hao, W., & Fletcher, P. C. (2011). Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biological Psychiatry*, *69*(1), 42–48. https://doi.org/10.1016/j.biopsych.2010.08.030

Liao, Y., Tang, J., Ma, M., Wu, Z., Yang, M., Wang, X., Liu, T., Chen, X., Fletcher, P. C., & Hao, W. (2010). Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. *Brain: A Journal of Neurology*, *133*(Pt 7), 2115–2122. https://doi.org/10.1093/brain/awq131

Malhotra, A. K., Pinals, D. A., Weingartner, H., Sirocco, K., Missar, C. D., Pickar, D., & Breier, A. (1996). NMDA Receptor Function and Human Cognition: The Effects of Ketamine in Healthy Volunteers. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *14*(5), 301–307. https://doi.org/10.1016/0893-133x(95)00137-3

Man, D. W. K. (2020). Virtual reality-based cognitive training for drug abusers: A randomised controlled trial. *Neuropsychological Rehabilitation*, *30*(2), 315–332. https://doi.org/10.1080/09602011.2018.1468271

Morgan, C. J. A., & Curran, H. V. (2006). Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology*, *188*(4), 408–424. https://doi.org/10.1007/s00213-006-0572-3

Morgan, C. J. A., & Curran, H. V. (2012). Ketamine use: a review. *Addiction* , *107*(1), 27–38.

https://doi.org/10.1111/j.1360-0443.2011.03576.x

Morgan, C. J. A., Dodds, C. M., Furby, H., Pepper, F., Fam, J., Freeman, T. P., Hughes, E., Doeller, C., King, J., Howes, O., & Stone, J. M. (2014). Long-Term Heavy Ketamine Use is Associated with Spatial Memory Impairment and Altered Hippocampal Activation. *Frontiers in Psychiatry / Frontiers Research Foundation*, *0*. https://doi.org/10.3389/fpsyt.2014.00149

Morgan, C. J. A., Monaghan, L., & Curran, H. V. (2004). 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. https://doi.org/10.1111/j.1360-0443.2004.00879.x

Morgan, C. J. A., Muetzelfeldt, L., & 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. https://doi.org/10.1111/j.1360-0443.2008.02394.x

Morgan, C. J. A., Muetzelfeldt, L., & 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. https://doi.org/10.1111/j.1360-0443.2009.02761.x

Morgan, C. J. A., Rees, H., & Curran, H. V. (2008). Attentional bias to incentive stimuli in frequent ketamine users. *Psychological Medicine*, *38*(9), 1331–1340. https://doi.org/10.1017/s0033291707002450

Morgan, C. J. A., Riccelli, M., Maitland, C. H., & Curran, H. V. (2004). Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. *Drug and Alcohol Dependence*, *75*(3), 301–308. https://doi.org/10.1016/j.drugalcdep.2004.03.006

Morgan, C. J. A., Rossell, S. L., Pepper, F., Smart, J., Blackburn, J., Brandner, B., & Curran, H. V. (2006). Semantic Priming after Ketamine Acutely in Healthy Volunteers and Following Chronic Self-Administration in Substance Users. *Biological Psychiatry*, *59*(3), 265–272. https://doi.org/10.1016/j.biopsych.2005.06.018

Morgan, C. J., Duffin, S., Hunt, S., Monaghan, L., Mason, O., & Curran, H. V. (2012). Neurocognitive Function and Schizophrenia-Proneness in Individuals Dependent on Ketamine, on High Potency Cannabis ("Skunk") or on Cocaine. In *Pharmacopsychiatry* (Vol. 45, Issue 07, p. 269). https://doi.org/10.1055/s-0032-1306310

Muetzelfeldt, L., Kamboj, S. K., Rees, H., Taylor, J., Morgan, C. J. A., & Curran, H. V. (2008). Journey through the K-hole: phenomenological aspects of ketamine use. *Drug and Alcohol Dependence*, *95*(3), 219–229. https://doi.org/10.1016/j.drugalcdep.2008.01.024

Sassano-Higgins, S., Baron, D., Juarez, G., Esmaili, N., & Gold, M. (2016). A review of ketamine abuse and diversion. *Depression and Anxiety*, *33*(8), 718–727. https://doi.org/10.1002/da.22536

Schilt, T., de Win, M. M. L., Jager, G., Koeter, M. W., Ramsey, N. F., Schmand, B., & van den Brink, W. (2008). Specific effects of ecstasy and other illicit drugs on cognition in poly-substance users. *Psychological Medicine*, *38*(9), 1309–1317. https://doi.org/10.1017/s0033291707002140

Siu, A. M. H., Ko, F. S. L., & Mak, S. K. (2018). Outcome Evaluation of a Short-Term Hospitalization and Community Support Program for People Who Abuse Ketamine. *Frontiers in Psychiatry / Frontiers Research Foundation*, *9*, 313. https://doi.org/10.3389/fpsyt.2018.00313

Squire, L. R., & Dede, A. J. O. (2015). Conscious and Unconscious Memory Systems. *Cold Spring Harbor Perspectives*

Health and Addictions / Salud y Drogas**.** Vol. 24 (1) 111-129 2024.

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in Biology, *7*(3). https://doi.org/10.1101/cshperspect.a021667

Stefanovic, A., Brandner, B., Klaassen, E., Cregg, R., Nagaratnam, M., Bromley, L. M., Das, R. K., Rossell, S. L., Morgan, C. J. A., & Curran, H. V. (2009). Acute and chronic effects of ketamine on semantic priming: modeling schizophrenia? *Journal of Clinical Psychopharmacology*, *29*(2), 124–133. https://doi.org/10.1097/jcp.0b013e31819a4b91

Strous, J. F. M., Weeland, C. J., van der Draai, F. A., Daams, J. G., Denys, D., Lok, A., Schoevers, R. A., & Figee, M. (2022). Brain Changes Associated With Long-Term Ketamine Abuse, A Systematic Review. *Frontiers in Neuroanatomy, 16*, 795231.

Tang, W. K., Lau, C. G., Ungvari, G. S., Lin, S.-K., & Lane, H.-Y. (2019). Recovery of cognitive functioning following abstinence from ketamine. *Addictive Behaviors*, *99*, 106081. https://doi.org/10.1016/j.addbeh.2019.106081

Tang, W. K., Liang, H. J., Lau, C. G., Tang, A., & Ungvari, G. S. (2013). Relationship between cognitive impairment and depressive symptoms in current ketamine users. *Journal of Studies on Alcohol and Drugs*, *74*(3), 460–468. https://doi.org/10.15288/jsad.2013.74.460

Tsien, J. Z., Huerta, P. T., & Tonegawa, S. (1996). The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell*, *87*(7), 1327–1338. https://doi.org/10.1016/s0092-8674(00)81827-9

Uhlhaas, P. J., Millard, I., Muetzelfeldt, L., Curran, H. V., & Morgan, C. J. A. (2007). Perceptual organization in ketamine users: preliminary evidence of deficits on night of drug use but not 3 days later. *Journal of Psychopharmacology*, *21*(3), 347–352. https://doi.org/10.1177/0269881107077739

United Nations Office on Drugs and Crime. (2019). *World Drug Report. Cannabis and hallucinogens*. UN.

Vonmoos, M., Hulka, L. M., Preller, K. H., Jenni, D., Baumgartner, M. R., Stohler, R., Bolla, K. I., & Quednow, B. B. (2013). Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. *The British Journal of Psychiatry: The Journal of Mental Science*, *203*(1), 35–43. https://doi.org/10.1192/bjp.bp.112.118091

Wang, L.-J., Chen, C.-K., Lin, S.-K., Chen, Y.-C., Xu, K., & Huang, M.-C. (2018). Cognitive profile of ketamine-dependent patients compared with methamphetamine-dependent patients and healthy controls. In *Psychopharmacology* (Vol. 235, Issue 7, p. 2113). https://doi.org/10.1007/s00213-018-4910-z

Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F. R., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., & Gould, T. D. (2018). Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological Reviews*, *70*(3), 621–660. https://doi.org/10.1124/pr.117.015198

Zeng, H., Su, D., Jiang, X., Zhu, L., & Ye, H. (2016). The similarities and differences in impulsivity and cognitive ability among ketamine, methadone, and non-drug users. *Psychiatry Research*, *243*, 109–114. https://doi.org/10.1016/j.psychres.2016.04.095

Zhang, C., Tang, W. K., Liang, H. J., Ungvari, G. S., & Lin, S.-K. (2018). Other drug use does not impact cognitive impairments in chronic ketamine users. *Drug and Alcohol Dependence*, *186*, 1–8. https://doi.org/10.1016/j.drugalcdep.2018.01.007

Zhang, C., Xu, Y., Zhang, B., Hao, W., & Tang, W. K. (2020). Cognitive impairment in chronic ketamine abusers. *Psychiatry Research*, *291*, 113206. https://doi.org/10.1016/j.psychres.2020.113206

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