Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2009.02761.x

Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study

Celia J. A. Morgan, Leslie Muetzelfeldt & H. Valerie Curran

Clinical Psychopharmacology Unit, University College London, London, UK

ABSTRACT

Background 'Recreational' use of ketamine is spreading rapidly among young people. In healthy individuals an acute dose of the N-methyl D-aspartate (NMDA) receptor antagonist ketamine induces marked psychosis-like effects and cognitive impairments, but little is known about the long-term effects of the drug. **Aims** To evaluate the long-term neuropsychiatric or cognitive consequences. **Methods** A total of 150 individuals were assessed, 30 in each of five groups: frequent ketamine users, infrequent ketamine users, abstinent users, polydrug controls and non-users of illicit drugs. Twelve months later, 80% of these individuals were re-tested. **Results** Cognitive deficits were mainly observed only in frequent users. In this group, increasing ketamine use over the year was correlated with decreasing performance on spatial working memory and pattern recognition memory tasks. Assessments of psychological wellbeing showed greater dissociative symptoms in frequent users and a dose–response effect on delusional symptoms, with frequent users scoring higher than infrequent, abstinent users and non-users, respectively. Both frequent and abstinent using groups showed increased depression scores over the 12 months. **Conclusions** These findings imply that heavy use of ketamine is harmful to aspects of both cognitive function and psychological wellbeing. Health education campaigns need to raise awareness among young people and clinicians about these negative consequences of ketamine use.

Keywords Chronic use, cognition, depression, glutamate, addiction and substance abuse, ketamine, learning and memory, dependence, longitudinal, NMDA receptor antagonist, recreational use.

Correspondence to: Celia Morgan, Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, Gower Street, London WC1E 6BT, UK. E-mail: c.morgan@ucl.ac.uk
Submitted 3 March 2009; initial review completed 27 April 2009; final version accepted 28 July 2009

INTRODUCTION

Ketamine, a drug once known only in certain subcultures, has now become a mainstream club drug. Internationally, the increased use of this drug is reflected in the critical review of ketamine being carried out currently by the World Health Organization's Expert Committee on Drug Dependence and the concern expressed about ketamine's impact on individual and social wellbeing by the recent UN Commission on Narcotic Drugs in 2007. In the United Kingdom alone, surveys of nightclub goers from 1999 to 2003 showed that prevalence rates rose from 25% to 40% [1].

Ketamine is an N-methyl-D-aspartate (NMDA: ecstasy) receptor antagonist which is used medically as an anaesthetic. It has the potential to cause marked changes acutely in cognitive function and psychological wellbeing, both through the dense population of NMDA receptors located throughout the cerebral cortex and hippocampus and via its effects on the transmission of modulatory, ascending monoamines such as dopamine (DA) and serotonin (5-HT) in the striatum and cortex [2,3]. Numerous studies have shown that a single, acute intravenous dose of ketamine produces schizophrenia-like symptoms, dissociative effects and broad-ranging cognitive dysfunction in healthy, ketamine-naive volunteers [4,5]. These healthy volunteers also show increased ratings of 'liking' and 'wanting more' ketamine [6]. The key question is what are the consequences of this psychotomimetic, cognitively impairing and subjectively

reinforcing drug for the increasing numbers of recreational users who take this drug repeatedly over months or years?

Controlled human studies of repeated doses of ketamine are precluded because it would be unethical to give an anaesthetic with these pronounced side effects more than once or twice. Therefore ketamine abusers themselves provide the only window on the consequences of repeated ketamine use.

In three studies, ketamine users (and controls) were tested on the night they took the drug and then again 3 days later when they were drug-free [7–9]. The acute effects of ketamine on the night of use mimicked those observed in laboratory studies showing impairment of performance on tasks tapping working, episodic and semantic memory. However, marked episodic memory impairments were also found in ketamine users when they were drug-free and these were related to the extent that individuals used ketamine.

Recently, in a larger-scale study, Morgan *et al.* [10] compared groups (each of 30 individuals) who used ketamine frequently (an average of 20 days per month) with infrequent (3.25 days/month), abstinent users of ketamine, polydrug users matched for other drug use except ketamine and people who did not use illicit drugs. The main findings in terms of psychopathology were that frequent ketamine users exhibited higher levels of schizophrenia-like, dissociative and depressive symptoms than the other groups. Infrequent ketamine users also showed evidence of elevated levels of dissociative and schizophrenia-like symptoms and abstinent users showed evidence of elevated delusions. In terms of cognitive function, impairments appeared confined to those who use the drug heavily. Frequent users showed impairments in verbal recognition memory, working memory and planning but not prose recall, response inhibition or retrieval from semantic memory. No differences were observed on neuropsychological tests in 'recreational' ketamine users or abstinent ketamine users compared to the polydrug and non-drug-using groups.

Cross-sectional studies have clear limitations in allowing any causal links to be drawn, as it is always possible that observed group differences in cognitive function and psychological wellbeing may have pre-dated drug-use. We reasoned that one way to address causation is through the rapid tolerance that develops to ketamine over time. For example, from the first 2 months of use to current use, frequent users report a six- to eightfold increase in dosage and infrequent users a threefold increase [11]. We hypothesized, first, that this increased use would result in increasing cognitive impairment and elevated schizophrenia-like and dissociative symptoms over time. Secondly, if ketamine-induced effects are reversible, reduced use of the drug should be reflected in improved cognitive function and abstinent users of the drug should show reduced delusional symptoms over time.

The present study aimed therefore to determine longitudinal changes in neurocognitive function and psychological wellbeing in groups of frequent, infrequent and abstinent users of ketamine over a 1-year period. We also aimed to determine associations between changes in ketamine use and changes in cognitive and psychological wellbeing. Rather than rely on self-reported drug use, we also used objective hair analytical techniques to determine drug use at both time-points.

MATERIALS AND METHODS

Participants and design

Participants were recruited initially via our existing drug-user database at UCL's Clinical Psychopharmacology Unit using a 'snowball' sampling technique [12] and were selected to be in one of five groups:

- frequent ketamine users (using the drug more than four times a week);
- infrequent ketamine users (using the drug less than four times a week but at least once a month);
- abstinent ketamine users (abstinent for a minimum of 1 month);
- polydrug users who were matched with the current ketamine-using groups for use of other drugs; and
- non-drug users who did not take illicit recreational drugs.

Drug users were required to abstain from psychotropic drug use for at least 24 hours prior to testing, to have no history of head injury, psychiatric illness or organic brain damage and to have English as their native language. The Cut-down, Annoyed, Guilt, Eye-opener (CAGE) screening instrument was used to assess ketamine dependence (adapted for ketamine from Brown & Rounds [13]). The study was approved by the UCL Graduate School ethics committee and all participants were paid for their participation.

The 30 participants in each of the five groups were re-contacted 12 months following their initial participation in the study. In all, 80% of the study population were re-assessed successfully: 25 frequent ketamine users, 27 infrequent, 24 abstinent ketamine users, 23 polydrug and 20 non-drug-users. The mean time between initial testing and re-testing was 366.6 (±92.11) days. For those cognitive tests that had two versions [all except for the Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks], these were counterbalanced across baseline and 12-month testing sessions within each group.

Procedure

For both testing sessions the procedure remained the same. At the start of the testing session participants gave written informed consent, a drug history was taken and then urine samples were analysed (Medscreen, London, UK). Hair (3 cm per participant) and urine samples were collected to verify participants' reports of drug use and confirm their inclusion in the respective groups (Trichotech, Cardiff, UK). The participants underwent a semi-structured interview and these qualitative data on the phenomenology associated with ketamine use is reported elsewhere [11]. They then completed the quantitative assessments of neurocognitive function and psychological wellbeing detailed below. The testing battery took between 1.5 and 2 hours to complete with two 10-minute breaks.

Assessments

Neurocognitive assessments

Tasks from the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB): three tests were used [14].

1 Pattern Recognition Memory (PRM): this taps visual recognition memory. Participants were shown a series of 12 patterns and told to try to remember them. At the end they were shown the same 12 patterns paired with previously unpresented patterns were required to choose the pattern they had seen before. The score is the total number of correct recognitions.
2 Spatial Working Memory (SWM): participants were required to search for blue tokens hidden in boxes on the screen. They were told that once they have found a blue token in a box, it would not be in that box again for the rest of that set. Thus they must maintain in working memory the previous locations of boxes. Scores are total number of errors and strategy.
3 Stockings of Cambridge (SOC:): based on the Tower of London, this assesses spatial planning and provides an index of frontal lobe functioning. Participants were required to use the balls in the lower display to copy the pattern in the upper display. The outcome measure reported here was number of problems solved in the minimum number of moves.
4 Source Memory Task [15]: this task was chosen as an index of episodic memory, i.e. awareness of when and where a stimulus was encoded. Stimuli consisted of 80 low-frequency words which were divided randomly into two study lists of 40 words. In each study list half the words were spoken in a female voice and half in a male voice (allocation was determined randomly). All study words were presented to participants aurally; participants listened to each word, repeated it aloud and then, depending upon the gender of the voice in which it is presented, rated the word as either 'pleasant/unpleasant' or 'abstract/concrete'. After a filled delay of 6 minutes, participants were given a recognition test list which combined the study list with the unpresented list. Participants said aloud whether each word was one that they had heard before and if so, whether it had been presented in a male or female voice.
5 Prose recall subtest of the Rivermead Behavioural Memory Test [16]: participants listened to a pre-recorded passage of prose (similar to a news bulletin on a radio). They were then asked to recall verbally as much as they could remember (i) immediately after presentation and then (ii) after a short delay of approximately 10 minutes filled with other tasks. Scoring was standard.
6 Fluency: semantic and phonological tasks were chosen to tap executive functioning and retrieval from semantic memory. In semantic fluency, participants were provided with a superordinate category member (fruit or vegetables) and asked to generate as many members of that category as possible in 90 seconds. Categories were matched for frequency of examples [17]. In phonological fluency, participants were provided with a single-letter prompt (M or B) and were required to generate as many words beginning with that letter in 90 seconds. Letters were matched for number of occurrences in the Oxford Mini-Dictionary (OUP, 1984). Number of category members and errors were recorded for both tasks.
7 Spot the Word [18]: this test was used as an index of pre-morbid IQ as scores on this test correlate well with other measures [e.g. National Adult Reading Test (NART)].

Psychological wellbeing

1 Short O-LIFE questionnaire [19]: this assesses schizophrenic symptoms in a normal population.
2 Peter's Delusion Inventor (PDI) [20]: this assesses delusional symptoms in the normal population. Participants also rate the degree of distress, preoccupation and conviction they have for each delusion reported.
3 Dissociative Experiences Scale (DES) [21]: this indexes dissociative symptoms ranging from everyday (e.g. the experience of riding in a car and not remembering all the trip) to more pathological (e.g. the experience of standing outside your body watching yourself).
4 The Beck Depression Inventory (BDI) [22]and Spielberger Trait Anxiety Inventory (STAI) [23] were used as measures of depression and anxiety.
5 Life Events Scale (LES) [24]: the life events scale is a self-report measure that taps positive and negative life events experienced over the previous year, and the perceived stress associated with those events. The 42 items

Table 1 Group means (standard deviation) for demographic data.

	Frequent ketamine	*Infrequent ketamine*	*Ex-ketamine users*	*Polydrug users*	*Non-drug users*
Age	25.68 (9.32)	27.5 (6.98)	27.26 (3.84)	31.29 (9.47)	25.05 (6.67)
Years in education	12.2 (4.91)	15.23 (2.67)	15.24 (3.35)	14.38 (2.77)	15.0 (2.75)
Spot the word score	46.25 (3.56)	51.54 (3.92)	50.57 (3.88)	51.125 (4.86)	49.29 (5.67)
Gender (male/female)	15/10	21/5	15/8	17/7	14/7

were chosen to represent life changes experienced frequently by individuals in the general population and participants had the option of adding a further four events if they had not been listed previously.

Statistical analyses

Demographic data were analysed with a series of one-way analyses of variance (ANOVAs) or Kruskal–Wallis tests where data were non-parametric and χ^2 tests where data were categorical. Drug use data were analysed with a series of repeated-measures ANOVAs with time (initial, follow-up) as the within-subjects factor and group as the between-subjects factor, with varying levels dependent upon the substance.

To assess the cumulative effects of ketamine over time, and because there was little change in drug use in the group, repeated-measures analyses of variance (RMANOVAs) were conducted with one within-subjects factors of time (initial testing, follow-up) and one between-subjects factor of group (frequent, infrequent, ex, polydrug, non-drug). *Post-hoc* tests were Bonferroni comparisons where there were main effect of groups, or a series of within-subjects paired sampled *t*-tests (corrected for multiple comparisons) where there were interactions.

Where clear effects of group emerged, correlations between amount of ketamine used and change in cognitive function and psychological wellbeing were conducted, significance levels were corrected to $P < 0.01$ to reduce the likelihood of Type 1 errors and with outliers [>3 standard deviations (SD) from the mean] removed.

As alcohol and pre-morbid IQ data differed across groups, these were correlated with variables where group differences were found: the only correlation to emerge was with d′ recognition memory data and pre-morbid IQ; therefore, we included this as a covariate in the subsequent analyses. Covarying for the time since first testing in days did not affect the outcome of the analyses, therefore the analyses of covariance (ANCOVAs) are not reported.

RESULTS

Demographics (Table 1)

There were no group differences in age or gender among the participants retained. There were significant group differences in years in education ($F_{(4,114)} = 3.47$, $P = 0.01$) and Spot the Word score ($F_{(4,114)} = 2.95$, $P = 0.023$). *Post-hoc* tests demonstrated fewer years in education in the frequent ketamine users compared to the infrequent and ex-ketamine users ($P < 0.05$), but no other differences. *Post-hoc* tests of the Spot the Word data demonstrated a poorer Spot the Word score in the frequent ketamine users compared to the infrequent ketamine-using group ($P < 0.05$), but no other group differences.

Ketamine use (Table 2)

There were expected significant main effects of group in frequency ($F_{(1,50)} = 47.81$, $P < 0.001$) and amount ($F_{(1,51)} = 11.61$, $P = 0.001$) of ketamine used, reflecting greater use in the frequent ketamine-using group. There were no main effects of time or interactions. Within the three ketamine-using groups there was a significant difference in the number of years of regular use (frequent: 6.67 ± 6.21; infrequent: 4.69 ± 1.99; abstinent users: 6.89 ± 2.39 years; $\chi^2_{(2)} = 12.9$, $P = 0.002$), attributable to fewer years of regular use in the infrequent compared to ex-users ($P < 0.01$). There was also a significant difference in the duration of abstinence at follow-up (frequent: 2.2 ± 2.81; infrequent: 11.03 ± 9.72; ex 540.54 ± 691.19 days; $\chi^2_{(2)} = 55.84$, $P < 0.001$)] reflecting a significantly greater number of days since ketamine was last used in the ex-users compared to both other groups ($P < 0.001$). CAGE scores were: frequent users (3.12 ± 1.14), infrequent users (1.76 ± 1.46) and ex-users (1.60 ± 1.10).

Other drug use (Table 2)

Drug use data for cannabis, 3,4-methylenedioxymethamphetamine (MDMA: ecstasy) and cocaine were analysed with a series of 4×2 repeated-measures ANOVAs with group (frequent, infrequent, abstinent ketamine and polydrug users) × time (initial, follow-up testing). Alcohol data were analysed by a 5×2 repeated-measures ANOVA, including the non-drug-using group.

There were no significant main effects or interactions for frequency or amount of cannabis used. For frequency of ecstasy use, there was a main effect of group

Table 2 Numbers of regular users and group means ± standard deviation (range) for subjective estimates of drug use across the two time-points.

		Frequent		*Infrequent*		*Ex-ketamine*		*Polydrug control*		*Non-drug control*	
		Initial, n = 30	*Follow-up, n = 25*	*Initial, n = 30*	*Follow-up, n = 27*	*Initial, n = 30*	*Follow-up, n = 23*	*Initial, n = 30*	*Follow up, n = 24*	*Initial, n = 30*	*Follow-up, n = 21*
Ketamine	No. regular users	30	22	30	23	0	3	0	0	0	0
	Amount used (no. grams)	2.77 ± 2.42 (2–4)	2.18 ± 1.82 (1–3)	1.26 ± 1.11 (1–2)	1.11 ± 1.06 (1–2)		0.6 ± 0.71 (0–1)	0	0	0	0
	Current use (days per month) max = 28	20.08 ± 7.41 (17–23)	16.0 ± 10.01 (1–28)	3.37 ± 2.08 (3–4)	4.70 ± 6.48 (2–7)		2.63 ± 5.91 (0–8)	0	0	0	0
	Days since last used (whole sample)	2 ± 2.60 (1–14)	35.44 ± 94.59 (1–340)	11.30 ± 9.36 (1–28)	26.46 ± 61.82 (1–308)		34.71 ± 50.49 (0–140)	0	0	0	0
Cannabis	No. regular users	21	17	20	17	18	13	28	16	0	0
	Amount used (no. days an eighth lasts)	4.75 ± 7.34 (0.5–9)	5.65 ± 7.97 (0–11)	5.58 ± 3.35 (2–9)	2.33 ± 1.03 (1–3)	7.75 ± 5.65 (3–12)	4.74 ± 2.58 (2–7)	5.76 ± 3.73 (4–8)	6.85 ± 5.91 (3–10)		0
	Current use (days per month)	21.86 ± 9.36 (16–27)	17.0 ± 12.12 (8–26)	27.33 ± 1.63 (26–29)	28 ± 0 (28–28)	27.43 ± 1.51 (26–29)	25.14 ± 7.56 (18–32)	26.00 ± 3.24 (24–28)	21.38 ± 10.56 (15–28)	0	0
	Days since last used (whole sample)	12.24 ± 37.80 (1–192)	10.50 ± 26.11 (1–112)	14 ± 35.97 (1–170)	26.55 ± 43.31 (1–168)	9.81 ± 15.62 (1–56)	33.28 ± 56.69 (0–168)	12.30 ± 30.47 (1–145)	33.61 ± 65.03 (1–224)		
Ecstasy	No. regular users	20	14	22	17	11	11	17	9	0	0
	Amount used (tablets per occasion)	2.44 ± 2.91 (1–4)	3.35 ± 3.21 (2–5)	2.67 ± 1.63 (2–3)	2.84 ± 1.53 (2–3)	2.45 ± 1.45 (2–3)	2.34 ± 1.57 (1–3)	3.85 ± 2.19 (3–5)	5.68 ± 14.52 (0–14)	0	0
	Current use (days per month)	0.83 ± 0.97 (0.4–1.2)	0.86 ± 0.79 (0.5–1)	1.72 ± 1.76 (1–2)	1.26 ± 1.29 (1–2)	0.87 ± 0.89 (0–1)	1.18 ± 1.34 (0.5–2)	1.91 ± 1.04 (1–3)	1.38 ± 1.37 (0.5–2)	0	0
	Days since last used (whole–sample)	27.91 ± 24.46 (2–84)	36.10 ± 41.44 (4–168)	26.30 ± 29.28 (1–116)	47.38 ± 68.33 (2–280)	42.13 ± 39.33 (1–118)	54.88 ± 68.04 (2–244)	11.31 ± 10 (1–42)	25.56 ± 25.19 (0–84)		
Cocaine	No. regular users	20	13	19	15	20	12	20	8	0	2
	Amount used (grams per occasion)	0.55 ± 0.49 (0.35–0.75)	0.55 ± 0.41 (0.3–1)	0.56 ± 0.39 (0.39–0.072)	0.44 ± 0.35 (0.3–1)	0.74 ± 0.60 (0.41–1.09)	0.81 ± 0.49 (0.5–1)	0.66 ± 0.46 (0.43–0.89)	0.62 ± 0.55 (0.3–1)	0	0.33 ± 0.58 (0–2)
	Current use (days per month)	2.25 ± 3.16 (1–4)	1.32 ± 1.35 (0–2)	2.21 ± 5.71 (0–5)	0.85 ± 1.05 (0.4–1)	1.73 ± 1.88 (1–3)	1.60 ± 1.51 (1–2)	4.22 ± 6.61 (1–7.5)	0.87 ± 0.82 (0.4–1)	0	0.67 ± 1.15 (0–4)
	Days since last used (whole sample)	21.59 ± 36.37 (1–183)	26.84 ± 23.76 (1–84)	30.08 ± 33.18 (1–116)	45.04 ± 57.98 (1–196)	31.26 ± 44.39 (1–185)	50.76 ± 68.56 (1–244)	28.05 ± 36.66 (1–112)	36.38 ± 63.17 (0–196)		
Alcohol	No. regular users	23	17	25	24	22	17	25	17	27	15
	Amount used (units per occasion)	11.96 ± 9.04 (8–16)	7.71 ± 4.47 (6–10)	8.64 ± 5.97 (6–11)	8.12 ± 4.99 (6–10)	9.34 ± 6.42 (6–12)	8.35 ± 6.03 (6–11)	11.62 ± 5.03 (9–14)	9.74 ± 6.70 (7–13)	10.50 ± 5.30 (8–13)	7.40 ± 4.65 (5–10)
	Current use (days per month)	13.81 ± 10.47 (9–18)	11.50 ± 10.71 (7–16)	9.57 ± 7.01 (7–12)	15.08 ± 8.59 (11–19)	13.16 ± 10.33 (9–18)	9.16 ± 6.97 (6–13)	13.14 ± 7.62 (10–17)	9.61 ± 8.66 (5–14)	10.40 ± 4.81 (8–13)	8.03 ± 6.58 (5–11)
	Days since last used (whole sample)	5.17 ± 16.27 (1–90)	4.12 ± 4.55 (1–14)	8.13 ± 23 (1–116)	1.84 ± 1.70 (1–7)	4.19 ± 5.96 (1–21)	14.10 ± 48.35 (1–224)	2.88 ± 4.42 (1–20)	3.71 ± 5.51 (1–21)	4.62 ± 4.55 (1–21)	3.90 ± 3.99 (1–14)

'Regular' use is defined as a minimum of once per month, but once per week for alcohol.

($F_{(3, 61)} = 3.12$, $P = 0.033$), but *post-hoc* tests revealed no further group differences. There were no significant effects of time or group on the number of ecstasy tablets taken per session. For the frequency of use of cocaine, there was a main effect of time ($F_{(1,64)} = 8.53$, $P = 0.005$) attributable to a reduction in cocaine use across all the drug-using groups over the year of the study. There was a also a main effect of time on the amount of cocaine used ($F_{(1,64)} = 8.79$, $P = 0.004$), again attributable to lower amounts of cocaine used in all groups over the course of the study.

Analysis of the frequency of alcohol use revealed a highly significant group × time interaction ($F_{(4,97)} = 6.21$, $P < 0.001$) and a trend for a main effect of time ($F_{(1,97)} = 2.84$, $P = 0.095$). Further analysis of the interaction with Bonferroni-corrected paired-samples *t*-tests revealed a significant increase in alcohol use among the infrequent ketamine users ($P < 0.001$) and a trend for a reduction in alcohol use in the abstinent ketamine users ($P = 0.023$).

Hair analysis

Hair analysis was used to confirm group membership. Ketamine levels in the three groups at baseline were: frequent users: 295.90 ± 635.27; infrequent users: 21.82 ± 46.27; abstinent ketamine 4.92 ± 16.32 ng/mg. Ketamine levels at follow-up were: frequent users 241.50 ± 550.72; infrequent users: 48.43 ± 104.56; abstinent users 14.89 ± 63.17; polydrug controls 1.63 ± 6.34 ng/mg.

Cognitive assessments (Table 3)

Spatial Working Memory task

Total number of errors. A 2 × 5 repeated-measures ANOVA of the data for total number of errors yielded a main effect of group ($F_{(4,108)} = 4.16$, $P = 0.04$). Bonferroni post-hoc tests demonstrated significant differences between the frequent ketamine-using group who made more errors than all other groups ($P < 0.05$), but no other differences between the groups.

Strategy. The 2 × 5 repeated-measures ANOVA for the strategy score revealed a significant time × group interaction ($F_{(4,108)} = 2.59$, $P = 0.041$), but no main effects. Post-hoc paired-samples t-tests revealed significantly lower strategy scores (i.e. better strategy) at follow-up in the frequent ketamine users ($P = 0.003$), but no other differences between the groups.

Stockings of Cambridge task

The 2 × 5 repeated-measures ANOVA on the problems solved in the minimum number of moves data demonstrated a significant main effect of time ($F_{(1,108)} = 9.73$, $P = 0.002$). There were also trends for both a main effect of group ($F_{(4,108)} = 2.30$, $P = 0.064$) and a time × group interaction ($F_{(4,108)} = 2.14$, $P = 0.081$). The trend for the interaction of time × group reflected better performance in the frequent ketamine users at 1-year follow-up than initial assessment ($P = 0.003$), but no changes across time for any other group.

Pattern recognition memory

A 2 × 5 repeated-measures ANOVA revealed a main effect of group for percentage correct on the pattern recognition memory task ($F_{(1,108)} = 4.429$, $P = 0.002$). This reflected poorer scores in the frequent ketamine users compared to the infrequent and ex-ketamine users ($P < 0.01$) and a trend for better scores in the abstinent ketamine users also compared poly-drug and non-drug-using groups ($P < 0.05$).

Prose recall

A 2 × 2 × 5 repeated-measures ANOVA, with the additional within-subjects factor of recall time (immediate, delayed) found a time × delay interaction ($F_{(1,113)} = 6.37$, $P = 0.013$) and main effects of time ($F_{(1,113)} = 6.26$, $P = 0.014$) and delay ($F_{(1,113)} = 124.34$, $P < 0.001$). All participants recalled less following a delay, but this effect was more pronounced at follow-up than initial testing ($P < 0.05$).

Source memory task

Recognition

A 2 × 5 repeated-measures ANCOVA of the d′ (index of discriminability), covarying for pre-morbid intelligence quotient (IQ) revealed a main effect of time ($F_{(1,108)} = 14.14$, $P < 0.001$) and a trend for a main effect of group ($F_{(4,108)} = 2.42$, $P = 0.055$). Poorer performance of all groups at follow-up was responsible for the main effect of time and the main effect of group reflected poorer performance in the frequent users compared to abstinent ketamine users ($P = 0.002$) and polydrug users ($P = 0.003$) and a trend when frequent users were compared to non-drug-users ($P = 0.090$). A similar analysis of the scores on C (bias) revealed a main effect of time ($F_{(1, 108)} = 28.74$, $P < 0.001$) as a result of greater bias in all groups at follow-up.

Source memory

Analysis of the proportion correct on the source memory task found a main effect of time ($F_{(1,113)} = 67.48$, $P < 0.001$). All groups had a greater proportion correct at follow-up.

Table 3 Group means (standard deviation) on cognitive assessments.

	Frequent		*Infrequent*		*Ex-ketamine*		*Polydrug control*		*Non-drug control*	
	Initial	*Follow-up*	*Initial*	*Follow-up*	*Initial*	*Follow-up*	*Initial*	*Follow-up*	*Initial*	*Follow-up*
Spatial working memory, total–errors	29.58 ± 19.93	19.92 ± 17.56	12.04 ± 9.15	13.04 ± 10.96	11.48 ± 12.66	12.48 ± 9.58	17.42 ± 17.35	15.5 ± 13.31	18.32 ± 19.40	15.89 ± 16.30
Spatial working memory, strategy	31.63 ± 5.31	27.33 ± 6.33	25.88 ± 5.63	26.24 ± 6.60	27.71 ± 4.63	27.86 ± 5.70	29.00 ± 5.74	30.25 ± 5.98	27.89 ± 7.10	27.37 ± 7.85
Stockings of Cambridge	7.67 ± 1.74	9.50 ± 1.89	9.42 ± 1.53	9.63 ± 1.79	8.95 ± 1.50	9.33 ± 1.56	9.48 ± 1.62	9.87 ± 1.87	9.00 ± 2.00	9.47 ± 1.92
Pattern recognition, % correct	83.68 ± 10.27	89.04 ± 7.24	91.84 ± 8.47	90.92 ± 9.89	95.63 ± 5.01	93.38 ± 7.14	90.53 ± 8.15	88.41 ± 9.69	90.79 ± 8.28	89.58 ± 10.35
D prime recognition memory	2.28 ± 0.80	2.02 ± 0.85	2.68 ± 0.71	2.42 ± 0.85	3.00 ± 0.67	2.76 ± 0.55	2.96 ± 0.78	2.82 ± 0.66	2.62 ± 0.84	2.67 ± 0.87
C, bias in recognition memory	0.45 ± 0.35	0.54 ± 0.32	0.30 ± 0.32	0.60 ± 0.32	0.41 ± 0.31	0.58 ± 0.29	0.32 ± 0.27	0.59 ± 0.25	0.36 ± 0.30	0.56 ± 0.32
Proportion of source memory errors	0.85 ± 0.11	0.71 ± 0.17	0.88 ± 0.12	0.79 ± 0.11	0.89 ± 0.11	0.78 ± 0.12	0.87 ± 0.13	0.74 ± 0.19	0.89 ± 0.10	0.68 ± 0.16
Verbal fluency	16.38 ± 4.89	13.48 ± 4.08	15.21 ± 3.22	17.25 ± 4.14	17.36 ± 5.71	15.12 ± 4.38	17.33 ± 4.00	15.25 ± 5.79	16.32 ± 4.10	14.53 ± 5.24
Category fluency	17.14 ± 4.67	15.57 ± 4.47	15.58 ± 4.35	18.75 ± 4.26	16.92 ± 3.54	17.36 ± 0.98	16.46 ± 3.56	15.83 ± 3.36	15.32 ± 4.12	15.53 ± 5.82
Prose recall immediate	8.12 ± 2.30	6.60 ± 2.46	8.56 ± 2.59	8.42 ± 3.05	8.38 ± 3.32	7.38 ± 3.4	8.10 ± 2.57	8.42 ± 3.12	8.58 ± 2.91	7.53 ± 3.32
Prose recall delayed	7.48 ± 2.36	5.84 ± 2.37	7.72 ± 2.73	7.42 ± 2.81	7.75 ± 3.19	5.81 ± 2.83	7.02 ± 2.58	6.90 ± 3.01	7.98 ± 3.07	6.4 ± 3.80

D prime was calculated as $d' = [z(\mathrm{Ht}') - z(\mathrm{Fa}')]$
The criterion C was calculated as $C = [z(\mathrm{Ht}') + (z(\mathrm{Fa}')]/2)$ where Ht = Hit and Fa = False Alarms.

Fluency

Verbal fluency

A 2 × 5 repeated-measures ANOVA found a significant time × group interaction ($F_{(4,108)} = 2.84$, $P = 0.027$) and a main effect of time ($F_{(1,108)} = 6.83$, $P = 0.01$). This reflected poorer performance at follow-up in the frequent ketamine users ($P = 0.046$) and the abstinent ketamine users ($P = 0.023$).

Category fluency

The repeated-measures ANOVA analysis for category fluency data demonstrated a trend for a time × group interaction ($F_{(4,108)} = 2.16$, $P = 0.078$). This reflected improved performance in the infrequent ketamine users at follow-up ($P = 0.022$).

Psychological wellbeing (Table 4)

O-LIFE

The 2 × 5 repeated-measures ANOVA for total scores on the O-LIFE yielded a significant time × group interaction ($F_{(4,105)} = 5.60$, $P < 0.001$) and significant main effects of both time ($F_{(1,105)} = 102.34$, $P < 0.001$) and group ($F_{(4,105)} = 2.63$, $P = 0.038$). This reflected a significant decrease in O-LIFE scores over time in all groups (infrequent, polydrug, non-drug all $P < 0.001$; abstinent ketamine $P = 0.014$), except the frequent ketamine users whose scores did not change over the year.

PDI (Fig. 1)

A 2 × 5 repeated-measures ANOVA demonstrated a main effect of group ($F_{(4,108)} = 4.16$, $P = 0.04$). This reflected significantly greater scores in the frequent ($P < 0.001$), infrequent ($P = 0.009$) and ex ($P = 0.016$) ketamine users compared to the non-drug controls. There was also a significant difference between frequent ketamine users and polydrug users ($P = 0.002$).

BDI

The analysis of depression scores found a significant group × time interaction ($F_{(4,110)} = 2.97$, $P = 0.022$). *Post-hoc* paired-samples *t*-tests demonstrated that the interaction was attributable to an increase in depression at follow-up both in the frequent ketamine users ($P = 0.041$) and the abstinent ketamine users ($P = 0.013$).

STAI

The 2 × 5 repeated-measures ANOVA demonstrated a significant main effect of time ($F_{(1,107)} = 4.10$ $P = 0.045$)

Table 4 Group means for measure of psychological wellbeing.

	Frequent		*Infrequent*		*Ex-ketamine*		*Polydrug control*		*Non-drug control*	
	Initial	*Follow-up*	*Initial*	*Follow-up*	*Initial*	*Follow-up*	*Initial*	*Follow-up*	*Initial*	*Follow-up*
O-LIFE total	19.76 ± 7.15	18.62 ± 7.06	22.00 ± 6.40	15.39 ± 7.76	21.14 ± 7.81	16.76 ± 7.34	20.29 ± 5.79	11.92 ± 6.01	18.10 ± 8.02	9.90 ± 7.70
PDI	8.39 ± 3.30	8.04 ± 4.24	6.92 ± 3.07	6.62 ± 3.57	7.00 ± 4.28	6.52 ± 4.48	5.63 ± 3.08	4.50 ± 2.89	3.90 ± 2.95	3.95 ± 3.58
BDI	7.08 ± 5.27	10.67 ± 7.99	10.04 ± 7.15	8.08 ± 7.38	4.96 ± 3.52	9.00 ± 8.48	6.42 ± 4.03	5.38 ± 4.95	7.45 ± 6.89	7.95 ± 7.28
DES	76.95 ± 38.46	75.09 ± 45.16	66.00 ± 37.17	66.92 ± 56.39	47.17 ± 25.73	52.26 ± 38.17	48.17 ± 33.75	41.74 ± 32.18	35.67 ± 38.44	47.00 ± 40.61
STAI	36.13 ± 7.65	33.67 ± 8.64	34.75 ± 8.93	30.21 ± 4.96	32.55 ± 6.65	32.41 ± 6.62	34.00 ± 6.95	30.83 ± 8.65	30.72 ± 7.85	31.89 ± 9.05
LES positive	11.52 ± 7.49	9.05 ± 7.99	7.57 ± 3.55	8.70 ± 7.71	11.83 ± 8.65	8.00 ± 5.55	8.13 ± 6.13	7.96 ± 5.43	5.89 ± 2.99	8.22 ± 7.33
LES negative	−12.71 ± 10.88	−7.95 ± 6.48	−4.83 ± 4.03	−5.91 ± 6.00	−7.70 ± 8.35	−6.04 ± 6.51	−5.50 ± 4.03	−5.13 ± 4.95	−4.72 ± 5.30	−4.33 ± 4.12

O-LIFE: Oxford Liverpool Inventory; PDI: Peters Delusion Inventory; BDI: Beck Depression Inventory; DES: Dissociative Experiences Scale; STAI: Spielberger Trait Anxiety Inventory; LES: Life Experience Scale.

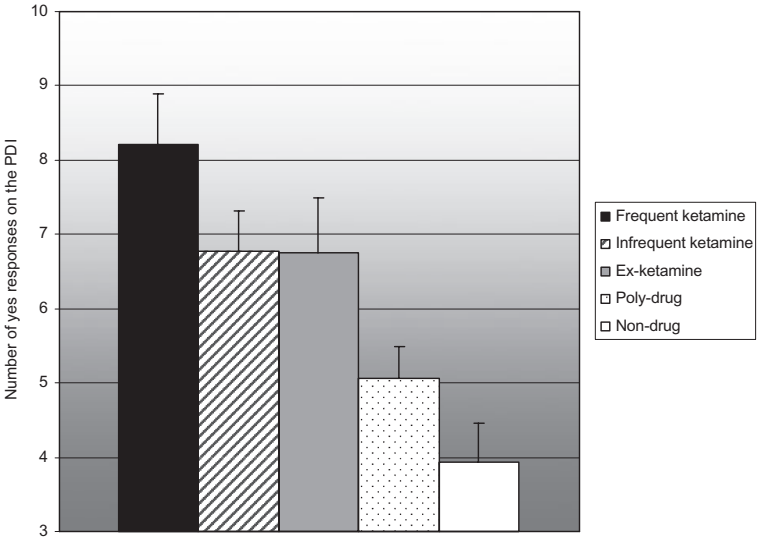

Figure 1 Mean Peters Delusion Inventory (PDI) scores across both testing sessions, by group

attributable to lower anxiety at follow-up than the first time of testing.

DES

A significant main effect of group ($F_{(4,106)} = 4.69$, $P = 0.002$) emerged for the DES scores. This was due to greater dissociation scores in frequent users compared to the poly-drug ($P = 0.015$) and non-drug ($P = 0.009$) groups.

LES

There were no differences in positive life experiences. For negative life experiences over the past 12 months there was a significant main effect of group ($F_{(4,104)} = 4.30$, $P = 0.003$), which reflected more negatively rated life events in the frequent ketamine users compared to infrequent ketamine ($P = 0.016$), polydrug ($P = 0.013$) and non-drug ($P = 0.006$) users.

Correlations between change in amount of ketamine use and other measures in frequent users (Fig. 2)

In the current ketamine-using groups, the change in amount of ketamine used (self-reported) over the year correlated (i) positively with change in number of errors on the spatial working memory task ($r = 0.623$, $P = 0.004$) and (ii) negatively with change in percentage correct for the pattern recognition memory task ($r = -0.732$, $P < 0.001$). No correlations emerged with frequency of cannabis use and cocaine use and key cognitive variables or measures of psychological wellbeing.

DISCUSSION

This is the first large-scale longitudinal study to investigate the effects of ketamine use on cognition and psychological wellbeing. We achieved a good retention rate (80%) in the study and the groups were broadly matched across relevant drug use and demographic variables.

Main findings

The cognitive deficits that emerged were confined mainly to those who used ketamine frequently. We found evidence of persisting decrements in frequent ketamine users compared to other groups in spatial working memory and pattern recognition memory and a trend for poorer performance in verbal recognition memory. For the two measures where there was significantly poorer performance in the frequent ketamine users, correlations emerged between change in ketamine use over the year and their performance on these tasks: increasing ketamine use in both cases correlated with poorer performance. Among frequent ketamine users compared to initial testing, they showed improved use of strategy on the spatial working memory task and better performance on the Stockings of Cambridge task. There was a decline over the same time-period in both the frequent and ex-ketamine users' performance on a verbal fluency task.

On measures of psychological wellbeing there was evidence of a dose–response effect on delusional symptomatology, with frequent users scoring highest followed by infrequent ketamine and abstinent users. Frequent users showed evidence of greater dissociative symptomatology than the non-drug group. Schizotypal symptom scores appeared to decrease in all groups across the year, with the exception of the frequent users, and there was evidence of an increase in depressive symptoms in both the frequent and abstinent ketamine users.

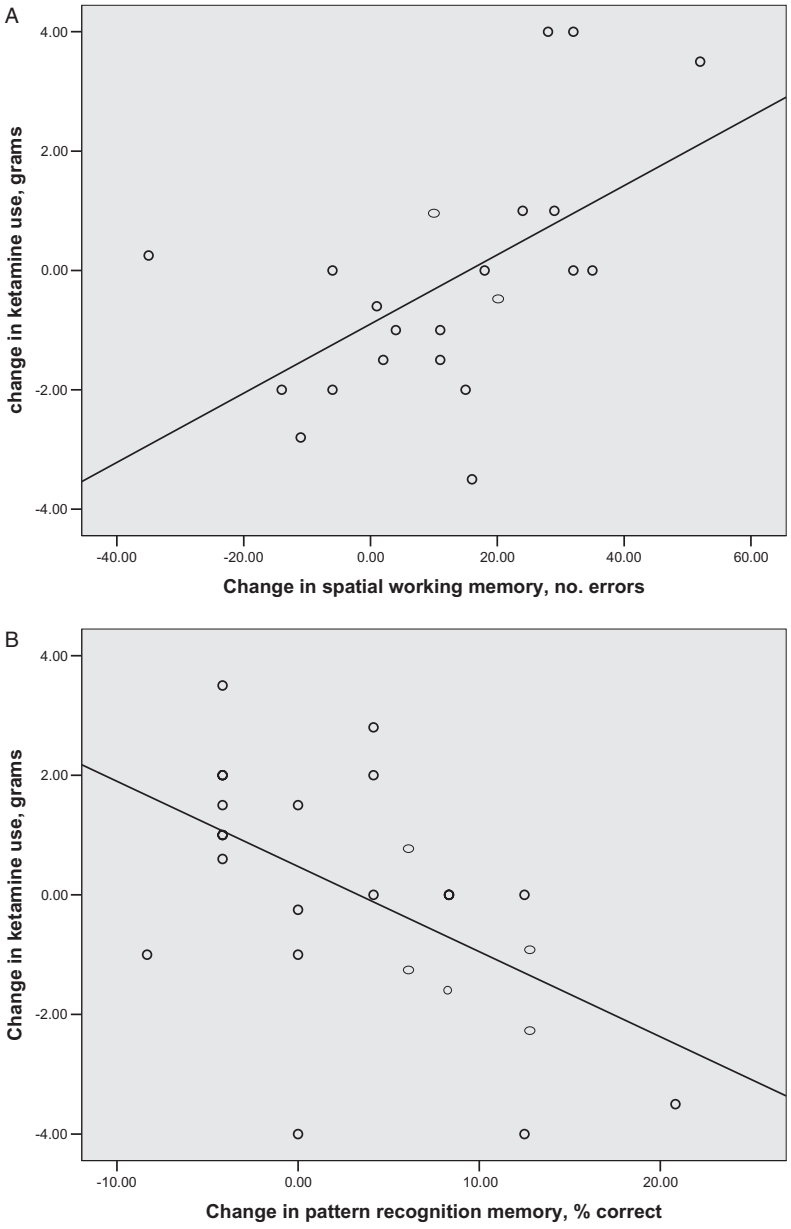

Figure 2 Scatterplots of (a) change in self-reported ketamine use and change in errors on the spatial working memory task (SWM); (b) pattern recognition memory percentage correct in the frequent ketamine-using group

Changing drug use over time

Contrary to our hypotheses, ketamine use in the two current ketamine-using groups did not escalate over the duration of the study in their subjective ratings. This is despite previous research demonstrating rapidly increasing use of the drug in these groups in the first 6 months of use and tachyphylaxis or developing tolerance rapidly in anaesthesia with ketamine [25]. This may be that because use had already stabilized in these individuals, tachyphylaxis may occur during the initiation of use. This said, however, some individuals did show marked increases in ketamine use and some decreases but not enough to facilitate statistically meaningful subgroup analyses. However, analyses did demonstrate that concentrations of ketamine in hair had doubled in recreational users at follow-up. Groups were well matched on other drug use, which remained relatively stable over time, with the exception of cocaine use which decreased across the year in all drug-using groups.

Cognitive function

There were clear correlations between change in ketamine use and change in performance on the spatial working memory and pattern recognition subtests of the CANTAB battery. An increase in ketamine use over the year was associated with a reduction in the percentage correct on the pattern recognition memory task and a greater number of errors on the spatial working memory task. Interestingly, the same task did not show an impairment in healthy volunteers following an acute dose of

ketamine [26]. This therefore appears to be a purely chronic effect and is reminiscent of similar impairments in chronic alcoholics [27]. Overall, the frequent ketamine users performed much more poorly than any other group on these measures, with a trend for poorer verbal recognition memory. That ketamine should have such profound effects on recognition memory is perhaps unsurprising, given the contribution of the NMDA-receptor to human memory encoding and consolidation [28]. In a small group of low-frequency ketamine users, Narendran *et al.* [29] found no evidence of cognitive impairment but altered dopaminergic functioning in the dorsolateral prefrontal cortex (DLPFC)—a key area involved in working memory. We also noted a suggestion of a progressive decline over the year in performance on a verbal fluency task in both frequent and abstinent ketamine users. This could again be related possibly to DLPFC functioning, but in the absence of any correlation with actual ketamine use it is as yet unclear whether it may be mediated by other factors such as the increase in depression in these two groups.

Improvements were observed in the frequent users' performance on the Stockings of Cambridge task and the strategy that they used in the spatial working memory task. These may partly reflect practice effects, as these tasks have only one version. Further, as frequent ketamine users performed particularly poorly on these tasks at baseline testing, they had more potential than the other groups to show improvement over the two testing sessions.

Psychological wellbeing

In accord with the suggestion that chronic ketamine administration may model aspects of psychosis [30], frequent and, to a lesser degree, infrequent and abstinent ketamine users showed evidence of mild delusional ideation. This replicates the findings of some previous studies [e.g. 10,31] and appears to be a relatively robust effect of repeated ketamine self-administration. It is also the only 'dose–response' effect to emerge from this study, suggesting a clear link with ketamine use *per se*. In infrequent ketamine users, these mild delusions occurred in the absence of cognitive deficits. Their neurochemical aetiology is unclear, but repeated ketamine use may induce changes in dopaminergic as well as glutamatergic function. It is also possible that while participants were asked explicitly to rate their day-to-day experiences when not under the influence of ketamine, their delusion formation occurs while on the drug [32] and then crystallizes and impinges onto their sober state. Interestingly, schizotypy scores decreased markedly following repeated testing in all groups except the frequent ketamine users. This may be a function of increased age, decreased cocaine use and/or a problem with repeated administration of the same measure over 12 months. That schizotypy scores remained constant in the frequent users supports the notion that repeated heavy ketamine use may induce some psychotic-like symptoms. Furthermore, frequent ketamine users showed evidence of increased dissociative states in everyday life which are also observed in psychotic disorders [33].

Frequent and ex-ketamine users both showed increased scores over the year on the BDI. Ketamine has been reported to be effective in alleviating depressive symptoms for up to a week following a single dose in treatment-resistant patients [34], so its effects on non-medical users of the drug are intriguing; the mechanism of the acute antidepressant and chronic depressant effects may be linked. Increased depression in frequent users could also reflect their increased dependency on ketamine, as depression is also commonly comorbid in opiate- and alcohol-dependent populations [35,36]. The frequent ketamine users had experienced more negative life events over the 12 months than other groups, due probably to their more chaotic life-styles, which may also feed into their depressive symptoms. Why abstinent ketamine users were more depressed is less clear, but may possibly reflect a change in life-style, as recreational drug use has been found in one previous prospective study to be associated with decreased depression [37].

Reversibility of impairments

Contrary to our original hypotheses, with the exception of a progressive decline in verbal fluency and increase in depressive symptoms, we found no evidence of improvements in cognitive function in abstinent users alongside their increasing abstinence from ketamine. At the same time, the abstinent ketamine users showed no cognitive deficits compared to non- or polydrug-using groups at either baseline or follow-up. The most plausible explanation is that this group had already recovered from any deficits. This population was the hardest to recruit and some individuals had been abstinent from ketamine for some time. Therefore, although impairments in ketamine users may be cumulative, perhaps they recover within a relatively short period following abstention, although these data cannot really speak to this issue. Future work should use prospective studies that follow the natural history of ketamine users into abstinence to address this question.

Methodological considerations

Methodological considerations common to all recreational drugs research apply to this study; for example, problems stemming from polydrug use and pre-existing group differences (see [38]). Some clear strengths of this study were our use of objective measures of drug use

(hair and urine) and a longitudinal design which circumvented some issues associated with cross-sectional studies. In hindsight, however, it may be that re-testing individuals after a year was not long enough to observe either progressive deficits or recovery of cognitive function. Few participants had changed their drug use patterns significantly over this time. Related to this point, while 150 volunteers was a relatively large study, especially in the field of recreational drugs research, it was not large enough to allow for much movement between groups or subgroup analyses. We were also unable to verify 24-hour abstinence with biological samples due to the duration at which ketamine stays in urine (between 1 and 2 days); however, along with the participants' self-report, the experimenters have extensive experience with testing this population, both intoxicated and unintoxicated, and reported that none appeared intoxicated at time of testing. Although we attempted to match our samples as closely as possible, there were demographic differences between the ketamine-using groups in years in education and pre-morbid IQ. Inevitably, daily users of ketamine who have used the drug for a number of years may represent a different population to those individuals who choose to use the drug once a month, reflecting either the causes or consequences of their heavy drug use.

The profile of a ketamine user

The psychological profile of a frequent ketamine user that has emerged from this research is of an individual with marked, profound cognitive impairments in short- and long-term memory, and someone who is mildly 'delusional' and distinctly dissociated in their day-to-day existence. Coupled with the marked dependency on ketamine observed in this group [39] and depressive symptoms that may be a consequence of the drug, we can conclude that repeated, heavy ketamine use is harmful to an individual's wellbeing in a variety of domains. Related to the harmful nature of ketamine, we feel it necessary to note that two of the volunteers in the frequent ketamine-using group were lost to follow-up due to their deaths during the year in ketamine-related accidents. In high doses the drug makes the user completely unresponsive to the world around them and renders them very vulnerable to physical dangers, such as drowning or crossing busy roads without checking for traffic. This clear danger of acute ketamine use should be emphasized to young people. On the other hand, infrequent or recreational ketamine use appears to be associated with no apparent cognitive impairments and only very mild delusional symptoms. Although our abstinent ketamine users did not use the drug as heavily as the frequent using group in this study, some had taken the drug daily and yet seemed to show no evidence of residual impairments following cessation of use of ketamine.

Despite the dramatic increase in ketamine use over the past decade, young people who use this drug are still largely unaware of its damaging properties and its potential for dependency. Health education campaigns and workers should target ketamine users to ensure that people are informed of the negative consequences of heavy ketamine use. Clinicians should also be aware of the adverse consequences of heavy use of ketamine, the symptoms of which may overlap with some forms of psychiatric disorders.

Acknowledgements

This study was funded by a grant to H.V.C. from the UK Economic and Social Research Council (RES-000-23-0945). The authors thank Huw Rees for assisting with data collection and all participants for their involvement.

Declarations of interest

None.

References

1. McCambridge J., Winstock A., Hunt N. 5-Year trends in use of hallucinogens and other adjunct drugs amongst UK dance drug users. *Eur Addict Res* 2007; **13**: 57–64.
2. Aalto S., Hirvonen J., Kajander J., Scheinin H., Kjell N., Vilkman H. *et al.* Ketamine does not decrease striatal dopamine D2 receptor binding in man. *Psychopharmacology* 2002; **164**: 401–6.
3. Breier A., Malhotra A. K., Pinals D. A., Weisenfeld B. S. E., Pickar D. Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *Am J Psychiatry* 1997; **154**: 805–11.
4. Fletcher P. C., Honey G. D. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn Sci* 2006; **10**: 167–74.
5. Morgan C. J., Curran H. V. Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology (Berl)* 2006; **188**: 408–24.
6. Morgan C. J. A., Mofeez A., Brandner B., Bromley L., Curran H. V. Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose–response study. *Psychopharmacology* 2004; **172**: 298–308.
7. Curran H. V., Morgan C. J. A. Cognitive, dissociative and psychotogenic effects of ketamine on recreational users on the night of drug use and 3 days later. *Addiction* 2000; **95**: 575–90.
8. Curran H. V., Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. *Addiction* 2001; **96**: 749–60.
9. Morgan C. J. A., Ricelli M., Maitland C. H., Curran H. V. Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. *Drug Alcohol Depend* 2004; **75**: 301–8.
10. Morgan C. J., Muetzelfeldt L., Curran H. V. Ketamine use, cognition and psychological wellbeing: a comparison of

frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction* 2009; **104**: 77–87.
11. Muetzelfeldt L., Kamboj S. K., Rees H., Taylor J., Morgan C. J., Curran H. V. Journey through the K-hole: phenomenological aspects of ketamine use. *Drug Alcohol Depend* 2008; **95**: 219–29.
12. Solowij N., Hall W., Lee N. Recreational MDMA use in Sydney: a profile of 'Ecstasy' users and their experience with the drug. *Br J Addict* 1992; **87**: 1161–72.
13. Brown R. L., Rounds L. A. Conjoint Screening Questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. *Wisc Med J* 1995; **94**: 135–40.
14. Sahakian B. J., Owen A. M. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *J R Soc Med* 1992; **85**: 399–402.
15. Wilding E. L., Rugg M. D. An event-related potential study of recognition memory with and without retrieval of source. *Brain* 1996; **119**: 889–905.
16. Wilson B., Cockburn J., Baddeley A. *The Rivermead Behavioural Memory Test*. Bury St Edmunds: Thames Valley Test Company; 1985.
17. Battig W. F., Montague W. E. Category norms of verbal items in 56 categories. A replication and extension of the Connecticut category norms. *J Exp Psychol* 1969; **80**: 1–46.
18. Baddeley A., Emslie H., Nimmo-Smith I. The spot the word test: a robust estimate of verbal intelligence based on lexical decision. *Br J Clin Psychol* 1993; **32**: 55–65.
19. Mason O., Linney Y., Claridge G. Short scales for measuring schizotypy. *Schizophr Res* 2005; **78**: 293–6.
20. Peters E. R., Joseph S. A., Garety P. A. Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). *Schizophr Bull* 1999; **25**: 553–76.
21. Bernstein E., Putnam F. W. Development, reliability and validity of a dissociation scale. *J Nerv Ment Dis* 1986; **174**: 727–35.
22. Beck A. T. *The Beck Depression Inventory (BDI)*. New York: The Psychological Corporation, Harcourt Brace Jovanovitz Inc; 1978.
23. Spielberger C. *State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Mind Garden; 1983.
24. Sarason I. G., Johnson J. H., Siegel J. M. Assessing the impact of life changes: development of the Life Experiences Survey. *J Consult Clin Psychol* 1978; **46**: 932–46.
25. Kofke W. A., Bloom M. J., Van Cott A., Brenner R. P. Electrographic tachyphylaxis to etomidate and ketamine used for refractory status epilepticus controlled with isoflurane. *J Neurosurg Anesthesiol* 1997; **9**: 269–72.
26. Honey R. A., Turner D. C., Honey G. D., Sharar S. R., Kumaran D., Pomarol-Clotet E. Subdissociative dose ketamine produces a deficit in manipulation but not maintenance of the contents of working memory. *Neuropsychopharmacology* 2003; **28**: 2037–44.
27. Pfefferbaum A., Desmond J. E., Galloway C., Menon V., Glover G. H., Sullivan E. V. Reorganization of frontal systems used by alcoholics for spatial working memory: an fMRI study. *Neuroimage* 2001; **14**: 7–20.
28. Morris R. G. M., Davis S., Butcher SP. Hippocampal synaptic plasticity and NMDA receptors: a role in information storage? *Philos Trans R Soc Lond B* 1990; **329**: 187–204.
29. Narendran R., Frankle W. G., Keefe R., Gil R., Martinez D., Slifstein M. *et al.* Altered prefrontal dopaminergic function in chronic recreational ketamine users. *Am J Psychiatry* 2005; **162**: 2352–9.
30. Jentsch J. D., Roth R. H. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1999; **30**: 201–25.
31. Uhlhaas P. J., Millard I., Muetzelfeldt L., Curran H. V., Morgan C. J. Perceptual organization in ketamine users: preliminary evidence of deficits on night of drug use but not 3 days later. *J Psychopharmacol* 2007; **21**: 347–52.
32. Corlett P. R., Honey G. D., Aitken M. R., Dickinson A., Shanks D. R., Absalom A. R. *et al.* Frontal responses during learning predict vulnerability to the psychotogenic effects of ketamine: linking cognition, brain activity, and psychosis. *Arch Gen Psychiatry* 2006; **63**: 611–21.
33. Foote B., Park J. Dissociative identity disorder and schizophrenia: differential diagnosis and theoretical issues. *Curr Psychiatry Rep* 2008; **10**: 217–22.
34. Zarate C. A. Jr, Singh J. B., Carlson P. J., Brutsche N. E., Ameli R., Luckenbaugh D. A. *et al.* A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; **63**: 856–64.
35. Watts M. Understanding the coexistence of alcohol misuse and depression. *Br J Nurs* 2008; **17**: 696–9.
36. Palomo T., Archer T., Kostrzewa R. M., Beninger R. J. Comorbidity of substance abuse with other psychiatric disorders. *Neurotox Res* 2007; **12**: 17–27.
37. de Win M. M., Reneman L., Jager G., Vlieger E. J., Olabarriaga S. D., Lavini C. *et al.* A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. *Neuropsychopharmacology* 2007; **32**: 458–70.
38. Curran HV. Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. *Neuropsychobiology* 2000; **42**: 34–41.
39. Morgan C. J. A., Rees H., Curran H. V. Attentional bias to incentive stimuli in frequent ketamine users. *Psychol Med* 2008; **38**: 1331–40.