The long-term effects of chronic recreational ketamine use on cognition and subjective experiences

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Overview

This thesis examines the chronic recreational use of the N-Methyl-D-Aspartate Receptor (NMDA-R) antagonist, ketamine, and its long-term effects on cognition and subjective experiences.

In Part 1, the context to the thesis is provided with information on the emergence and prevalence of recreational ketamine use, the NMDA-receptor hypofunction model of schizophrenia and the management of substance misuse. Thereafter, the literature is reviewed culminating in the following findings: chronic ketamine use (i) acutely impairs working, episodic and semantic memory, and induces dissociation and schizotypal symptoms; (ii) may produce residual effects in the days following acute use, and (iii) has long-term effects on the semantic store and episodic memory. From the existing literature, it is unclear whether chronic ketamine use is a useful model of chronic schizophrenia. Nonetheless, it is important to communicate the effects of chronic ketamine use to recreational users.

Part 2 reports an investigation of the long-term effects of recreational chronic ketamine use on semantic processing and subjective experiences with forty-six participants, aged 18 to 46 years. An independent groups design was used to compare ketamine, poly-drug and non-drug users. Ketamine users were higher in schizotypy than non-drug users. In general, the three groups performed similarly on semantic processing tasks, though ketamine users were impaired relative to other groups in processing high (compared to low)

frequency words. However, the absence of indirect priming effects across the three groups limits the conclusions that can be drawn and methodological reasons for this are discussed. Part 3 of this thesis presents a critical reflection on this research.

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In memory of my father KEG.

With special thanks to

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Part 1: Literature Review

Long-term effects of chronic ketamine use on cognition and subjective experience

Abstract

Rationale: A review of the chronic recreational ketamine research is needed because of (i) increases in recreational ketamine use in the past five years, and (ii) its application to the N-Methyl-D-Aspartate-Receptor ('NMDA-R') hypofunction model of psychosis.

Method: PsychInfo and Pubmed databases were searched using the following terms: 'ketamine', 'frequent', 'regular', 'repeated', 'chronic', and 'long-term'. The search was limited to human populations and English language journals. Relevant papers were entered into ISI Web of Science to broaden the search. In total eight studies were found.

Findings: Chronic ketamine use (i) acutely impairs working, episodic and semantic memory; and elevates dissociation and schizotypal symptoms, sedation, and other subjective and somatic effects. Further, there are suggestions of (ii) residual dissociative, schizotypal, sedative, and subjective and somatic effects, and (iii) long-term, but possibly reversible, effects on the semantic store, and persisting deficits in the manipulation of contextual information in episodic memory.

Conclusions: It is unclear whether chronic ketamine use is a useful model of chronic schizophrenia. Nonetheless, it is importance to communicate the effects of chronic ketamine use to recreational users. Methodological limitations of the research are discussed.

And then: eyes-open.
But they've been open.
You're in the K-hole now.
When you focus, you look around the room - but is it the same room? It may seem ultra clear, or hot and shadowy, or '50's kitschy... and then it changes.
The set changes...
a quick turn of the floor and...
There's a Moroccan influence, or a slick and modern approach, then it blends back into what it is - until it shifts again.
K is a displacer - you are outside of your head, and everything, everything, is new. You must look at that couch for the first time - define what it is - make a connection –and that's hard.
For some strange reason, that couch looks like a dancing tree frog. Not literally, like an acid hallucination... but subtly, so you can see both, the couch and the tree frog existing at once.
Now if you face the hallucination, and acknowledge it, you can change that frog into, say, a can of corn. The couch is still there, but now it looks just like a can of corn.
It's the damnedest thing.
The room changes, quickly, and... where was I?
Eye's closed, because something wondrous is happening. The universe is decoding itself to you, and even though nothing makes sense, it all comes together - and if you try to think about it, it's gone again and you're back on the ceiling sitting on your can of corn.
Welcome to the land of K.

From Disco Bloodbath: A Fabulous But True Tale of Murder in Clubland.
(St. James, 1999)

Introduction

This review draws together the emerging findings on the recreational and chronic use of the non-competitive N-Methyl-D-Aspartate Receptor ('NMDA-R') antagonist, ketamine, and its effects on cognitive functioning and subjective experience in humans. This field of research is important because of (i) its application to the NMDA-R hypofunction model of psychosis, which connects ketamine use, psychotic symptoms and cognitive deficits, and (ii) reported increases in recreational ketamine use.

Anecdotal reports and evidence from controlled studies of acute ketamine use have demonstrated that ketamine induces reversible schizophrenia-like and dissociative symptoms in humans (e.g., Jansen, 1990; Krystal et al., 1994; Morgan, Rossell et al., 2006; Olney, Newcomer & Farber, 1999). Ketamine mimics symptoms of schizophrenia more closely than any other drug (Newcomber & Krystal, 2001). Moreover, ketamine administered to people with a diagnosis of schizophrenia in remission has resulted in a "dose-dependent, short-lasting, but reproducible, increase in psychotic symptoms" (Lahti, Koffel, LaPorte & Tamminga, 1995, p. 16). These symptoms were qualitatively very similar to those that each individual experienced in the acute phase of their illness.

Ketamine is a less powerful analogue of Phencyclidine (PCP; 'angel dust'). Historically, abuse of PCP resulted in the emergence of 'PCP psychosis' with symptoms such as "thought disorder, blunted affect and cognitive impairments..." (Krystal, D'Souza, Mathalon, Belger & Hoffman, 2003, p. 218). Furthermore, PCP psychosis is difficult to differentiate from symptoms characteristic of people with a diagnosis of schizophrenia (Yesavage & Freeman, 1978; cited in Newcomer et al., 1999).

Acute ketamine also impairs cognitive systems, with pronounced yet reversible effects on, for example, attention (e.g., Umbricht, Koller, Vollenweider & Schmid, 2000), source memory (e.g., Morgan, Riccelli, Maitland & Curran, 2004) and semantic memory (e.g., Morgan, Rossell et al., 2006). Semantic processing deficits have been observed in people with a

diagnosis of schizophrenia (for a review, see Neely, 1991) and have been suggested by some to be central to the cognitive deficits observed in these individuals (e.g., Moritz et al., 2001; Rossell, Shapleske & David, 2000). These include the classic loosening of associations manifest in confused thought and speech (Bleuler, 1911; cited from Stotz-Ingenlath, 2000).

The N-Methyl-D-Aspartate Receptor (NMDA-R) hypofunction model of psychosis

The resemblance of the psychotomimetic and cognitive effects seen in people who ingest ketamine, to symptoms manifest in people with a diagnosis of schizophrenia has meant that ketamine is currently being investigated as a pharmacological model of psychotic symptoms in schizophrenia, i.e., the NMDA-R hypofunction model of psychosis (e.g., Krystal et al., 2003; Morgan, Rossell et al., 2006; Newcomer et al., 1999). The emerging body of evidence for the effects of an acute dose of ketamine has led some authors to suggest that acute ketamine administration may be a good model of the acute stages of schizophrenia (e.g., Krystal et al., 2003; Morgan, Rossell et al., 2006).

There is limited research on the effects of repeated ketamine dosing in humans. Despite this restricted knowledge base, researchers have proposed that the effects of chronic ketamine use may be better placed to model later stages of the development of schizophrenic symptoms (e.g., Jentsch & Roth, 1999; Phillips & Silverstein, 2003).

Ketamine abuse and management

Long-term ketamine use can have serious physical side-effects, such as stomach ulcers. However, it is unclear whether ketamine does (Critchlow, 2006) or does not result in physical dependence (Ricaurte & McCann, 2005). Nonetheless, its psychological properties are seductive, especially as the 'high' experienced from ketamine is relatively short lived and tends not to result in a 'hang-over'. Hence, its prevalence may result in some problematic use. This is especially pertinent to people who use ketamine on an almost daily basis. It is unclear whether drugs services within the NHS have the resources to support people in managing ketamine use, as resources tend to be directed towards heroin and crack-cocaine abuse and dependence. Whether voluntary sector services will be able to support this potential need remains to be seen.

Structure of review

To facilitate reading this review, central concepts are defined (see Box 1) and information on the current use of ketamine, and its pharmacological actions, is provided. To contextualise the discussion of chronic ketamine use reference is made, where appropriate, to the effects of an acute dose of ketamine. Thereafter, the literature is critiqued, and areas for future research presented. The methodology of the literature search is provided (see Box 2, page 20).

Box 1.1. Terms and definitions

Poly-drug use: use of more than one type of psychoactive drug.
Chronic or repeated use: use of a psychoactive drug(s) at least twice a month for at least one year.

Ketamine group: poly-drug users who use ketamine.
Poly-drug control group: poly-drug users who do not use ketamine.
Drug free control group: participants with no reported psychoactive drug history.

Acute effects: effects that occur soon after, and are attributed to, drug ingestion.
Residual effects: effects that occur a short period of time (e.g., hours or days) after drug ingestion, and are attributed to recent drug use.
Long-term effects: effects that occur days or months after drug ingestion.
Reversible effects: effects that dissipate after reduction or cessation of drug use.
Persistent effects: effects that continue after reduction or cessation of drug use.

Recreational ketamine use in context

The emergence of recreational ketamine use

Ketamine was synthesised in 1962 in the search for a replacement to PCP and was subsequently patented for use in human and veterinary anaesthesia. It is documented to have become used recreationally (i.e., non-medically) by the 1970s (Dotson, Ackerman & West, 1995) and personal accounts of its use were published in 'Journeys in to the Bright World' (Moore & Alltounian, 1978) and 'The Scientist' (Lilly, 3rd Ed., 1996).

It is thought that ketamine might have been introduced into the United Kingdom (UK) club scene as a result of having been 'cut' into 3, 4-methylenedioxymethamphetamine (MDMA, Ecstasy) (Dalgarno & Shewan, 1996) that people were using in the late 1980s and early 1990s. Ketamine

then became integrated into the 'acid house' music scene (Dotson et al., 1995). Today, recreational ketamine use occurs amongst a predominantly 'clubbing' sub-culture and at squat- and private-parties (Curran & Monaghan, 2001; Curran & Morgan, 2000).

The prevalence of recreational ketamine use

Recreational ketamine use has been reported in, amongst other places, Australia (e.g., Topp et al., 1998), China (e.g., Zhao et al., 2004), Denmark (e.g., Sorensen, 2005), Singapore (e.g., Lim, 2003), Taiwan (e.g., Li, Liu & Yu, 2005), the UK (e.g., Bolding, Hart, Sherr & Elford, 2006; Deehan & Saville, 2003; Riley, James, Gregory, Dingle & Cadger, 2001) and the United States of America (USA) (e.g., Lankenau & Clatts, 2005). Thus, ketamine is a widely used drug.

It is difficult to estimate the population prevalence rate for recreational ketamine use as most countries do not collect information on ketamine in national censuses. However, ketamine use in the general population is thought to be relatively low. For example, in the USA, ketamine use prevalence rates for students in grades 8, 10 and 12 were 0.6%, 1.0% and 1.6%, respectively (Johnston, O'Malley, Bachman & Schulenberg, 2006). It is interesting to note that the prevalence rate increases with age.

There is more, although still limited, data on the prevalence of ketamine use within 'clubbing' sub-cultures. In the mid 1990s, 32% of respondents to a UK clubbers survey disclosed having tried ketamine (Release, 1997). In 2000, a

similar UK survey reported a lifetime prevalence rate of 47% (Mixmag, 2001). However, only 12% of clubbers in a Scottish club survey reported ketamine use (Riley et al., 2001).

Prevalence rates of regular (e.g., monthly) ketamine use have also increased. Approximately 4% of respondents to a UK national clubbing survey used ketamine regularly in 1999 (Mixmag, 2000) increasing steadily to approximately 36% in 2005 (Mixmag, 2006). Bolding et al. (2006) found that in their survey of 1307 London based gay men, 32% had used ketamine within the last year; approximately half of these men used ketamine at least once or twice a month in the preceding year. Of those who had used ketamine within the last 12 months only three of them had not used any other recreational drugs; ketamine and ecstasy (96%) followed by ketamine and cocaine (88%) were the most common poly-drug combinations. Another study investigated the drug patterns of gay men in New York and reported that 41% used a combination of GHB and ketamine (Halkitis & Palamar, 2006). In China, there have been reports of heroin users using ketamine (Zhao et al., 2004). Australian studies have reported an increased lifetime-prevalence of ketamine use amongst ecstasy users (Breen et al., 2004; Topp et al., 1998). This pattern of poly-drug use is normative (Riley et al., 2001).

In sum, general population prevalence of ketamine is thought to be relatively low. However, there appears to have been an increase in clubber's lifetime prevalence and regular use of ketamine, both nationally and internationally.

Further, ketamine is generally used as one element in a complex pattern of poly-drug use.

Cost

A recent survey of 15 drug agencies found that ketamine could be purchased from £15 to £50 per gram depending on geographical location (Druglink, 2005); thus, it is a comparatively cheap recreational drug.

Legal status

In January 2006, the UK government classified ketamine as a Class C drug under the Drugs Act 2005. This means that possession of, or intention to supply, ketamine could result in a two year prison sentence or a maximum of 14 years imprisonment and a fine, respectively. Ketamine is also a controlled substance in Australia and the USA.

The pharmacological action of ketamine

"There are approximately 12,000,000,000 neurons in the brain, with between 10 and 100,000 synaptic connections each, creating an almost unlimited number of associations among them" (Cozolino, 2002, p. 68). As each neuron 'fires' an electrical message is sent along its axon, across the synapse via (mostly) chemical neurotransmitters, and along the dendrites of another neuron, whereby the process may be repeated. Neurotransmitters have either an excitatory or inhibitory effect on the post-synaptic cell, thus regulating the overall activity of the brain. There are three main categories of

neurotransmitters (amino acids, peptides and monoamines) each with a number of different chemicals, which are involved in different mental processes.

Ketamine is a non-competitive NMDA receptor antagonist, which interferes with the action of the amino acid class of neurotransmitters. Glutamate is the most prevalent excitatory amino acid (EAA), playing a key role in cortico-cortical and cortico-subcortical interactions, as well as long-term potentiation (LTP). NMDA receptors are densely located in the cerebral cortex and hippocampus areas, which are involved in executive functions and memory systems. Thus, it is not surprising that the processes of learning and memory, facilitated by glutamate transmission from one cell to another, are disrupted by ketamine.

Acutely, ketamine also produces an increase in dopamine release in the nucleus accumbens (Smith et al., 1998), an action common to virtually all drugs of abuse. This dopamine action may therefore underpin some of the reinforcing effects of ketamine.

Little is known about chronic ketamine use in humans. In animals, repeated doses of ketamine can produce neurotoxicity (Wozniak, McEwen, Sesma, Olen & Fix, 1993). Only one brain imaging study has been carried out with human chronic ketamine users. Narendran et al. (2005) showed that repeated ketamine use is associated with "up regulation of D1 receptors" (p. 2357) in the dorsolateral prefrontal cortex.

Methodological considerations in chronic ketamine research

Ketamine is an anaesthetic and thus only given medically on a single dose basis, hence, it is not ethical to conduct controlled studies of its effects after repeated dosing. A naturalistic population, i.e., those who self-administer recreationally, is therefore the only way to determine ketamine's chronic effects on humans.

People who use drugs recreationally are generally poly drug users, thus, to try to isolate the effects of ketamine, comparisons can be made between poly-drug users who use ketamine and (i) poly-drug users who do not use ketamine, and/or (ii) participants who report no previous or current drug history. An experimental design used in the studies discussed in this review is the assessment of recreational drug users under the acute effects of drugs (Day 0), and again three days later (Day 3) when not under the acute effects of drugs. Thus, acute-on-chronic (i.e., the acute effects in chronic users), residual and longer-term effects can be investigated.

The vast majority of the studies investigating chronic ketamine use and its effects have been conducted by the Clinical Psychopharmacology Unit, within the Sub-Department of Clinical Health Psychology, University College London. The limitations of the majority of chronic ketamine research being carried out by one research team are acknowledged.

When reflecting upon the findings reported forthwith, it may be useful for the reader to consider the following questions:

- Are the findings reporting group differences due to pre-existing differences between the groups studied?
- Are the reported effects residual or long-term effects of repeated ketamine use?
- Are the effects reversible or persistent?

Chronic ketamine use and its effects on cognition

Ketamine, working memory and executive attention processes

Working memory is the memory system "that 'holds' the [information] input' while an interpretation of it is worked out" (Reber, 1985, p. 431). It enables humans to bring together different pieces of information and synthesize them, enabling, for example, problem solving and planning for the future. Within the 'executive' component of working memory there are a number of attentional mechanisms. Attention is defined as "a state of mental clarity in which one aspect of mind is more vivid than others" (Reber, 1985, p.64). Thus, it facilitates activities such as reading a book in a noisy environment, or playing a computer game.

Ketamine and working memory

Research into the effects of an acute dose of ketamine on working memory in healthy volunteers has produced inconsistent results. Some studies have found that acute ketamine impairs working memory (e.g., Morgan, Mofeez,

Box 1.2. Methodology of search

Databases searched: Psychinfo and Pubmed up to June 2007.

Search terms: 'ketamine', 'frequent', 'regular', 'repeated', 'chronic', and 'long-term'. The search was limited to human populations and English language journals.

Results: Six studies investigated the effects of recreational ketamine use in humans on cognitive systems and/or mental state. Two further studies assessed the effects of repeated participation in ketamine studies. All papers were entered into ISI Web of Science, however, no further relevant papers were identified.

Brandner, Bromley & Curran, 2004) whilst others find no impairment (e.g., Newcomer et al., 1999). Morgan and Curran (2006) proposed that these different findings may be, amongst other reasons, related to task difficulty. In general the consensus is that acute ketamine preserves the processes that maintain material in working memory, but impairs processes that enable the manipulation of that material in working memory (Fletcher & Honey, 2006; Morgan & Curran, 2006).

Curran and Morgan's (2000) study of the effects of recreational ketamine use on working memory utilised the 'serial sevens' task. In this task participants are given a three digit number and asked to subtract sevens sequentially as many times as possible for 90 seconds. At the time of ketamine ingestion, the ketamine group were significantly impaired on the serial sevens task compared to a poly-drug control group. They generated less than half the number of subtractions as the poly-drug control group; when errors were accounted for the ketamine group's performance deteriorated comparatively. However, there were no group differences three days later. Thus, ketamine was found to impair working memory acutely, but not three days later.

The effect of infrequent (<3 times per month) versus frequent (≥3 times per month) recreational ketamine use on working memory was investigated by Curran & Monaghan (2001). The authors replicated the design of Curran and Morgan (2000) and found that the performance of frequent and infrequent users on the serial sevens task was significantly impaired at the time of ketamine ingestion compared to three days later. However, there was no significant difference between the two groups at either time. Thus, this study supported previous findings (Curran & Morgan) that ketamine affects working memory acutely, but not three days later.

Morgan, Monaghan and Curran (2004) investigated the effects of a reduction, or cessation, of ketamine use on working memory. They reassessed a number of participants from their previous studies (Curran & Monaghan, 2001; Curran & Morgan, 2000) who had reduced their ketamine use, on average, by 88.3%; eight participants had not used ketamine for six months. They compared the data from Day 3 (in the original studies) to data collected three to four years later. They reported that there were no significant differences between the ketamine group and the poly-drug controls on the serial sevens task at either time point. Additionally, there was no change over time for either group. This implies that working memory functioning returns to normal within three days of ketamine abstention.

An interesting study by Narendran et al. (2005) compared people who reported (almost exclusive) recreational ketamine use to non-drug controls. Participants were administered a battery of neurocognitive tests (from the

Clinical Antipsychotic Trials of Intervention Effectiveness) which included a measure of working memory. They concluded that there was no difference in working memory between the two groups after two days of ketamine abstention.

In sum, of the four studies that have investigated the effects of recreational ketamine use on working memory, two found that ketamine acutely impairs working memory (Curran & Monaghan, 2001; Curran & Morgan, 2000). These findings are in line with some controlled studies (e.g., Adler, Goldberg, Malhotra & Breier, 1998; Morgan, Mofeez et al., 2004). This impairment in working memory was found to be isolated to the acute effects of the drug and not to be present two to three days later (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan, Monaghan et al., 2004; Narendran et al., 2005).

Ketamine and attentional processes in working memory

Few studies have investigated the effects of a single administered dose of ketamine in healthy volunteers on attentional processes in working memory. Morgan and Curran's (2006) review distinguished between research into sustained and selective attention. They reported inconsistent findings for an acute induced deficit in sustained attention. However, they found that there was a trend for selective attention to be left preserved by ketamine. They also reported that when attention deficits have been statistically controlled for memory deficits persisted (e.g., Malhotra et al., 1996).

Only three studies have investigated the effects of chronic ketamine use and selective attention. Each of these studies has utilised the 'digit cancellation task', where the participant's task is to delete a specified number from a sheet of other random numbers. There are clear limitations to the use of this simple task which involves more than attention, for example, visual scanning and selectivity, hand eye co-ordination, motor speed. Overall, the research indicates that chronic ketamine use acutely impairs selective attention (Curran & Monaghan, 2001; Morgan, Monaghan et al., 2004; Curran & Morgan, 2000). However, with respect to longer term effects, the evidence is inconclusive.

Ketamine and episodic memory

Episodic memory is a "form of memory in which information is stored with 'mental tags' about where, when and how the information was" learnt (Reber, 1985, p. 429). It has been characterised by the phrases 'I remember when...' and 'mental time travel' (Wheeler, Stuss & Tulving, 1997). Tulving's view of episodic memory allows mental time travel not only into one's past but also to help predict one's future.

Morgan and Curran's (2006) review concluded that an acute dose of ketamine administered to healthy volunteers impairs performance on tasks that tap episodic memory, possibly in a dose dependent fashion (Morgan, Mofeez et al., 2004). They reported that encoding, not retrieval, processes are central to this episodic memory deficit (Morgan & Curran). Further, evidence from source memory studies suggests that it is particularly the

encoding of contextual information that is disrupted by acute ketamine (e.g., Morgan, Mofeez et al., 2004). Fletcher and Honey's (2006) review of the effects of acute ketamine on healthy volunteer's episodic memory was more tentative in its conclusion, stating that "this area requires further exploration" (p.170).

To investigate the effects of repeated ketamine use on episodic memory, Curran and Morgan (2000) used the immediate and delayed prose recall task from the Rivermead Behavioural Memory Test (Wilson, Cockburn & Baddeley, 1985). They found that participants in the recreational ketamine group were impaired, compared to the poly-drug users, on this task when under the acute effects of ketamine. Three days later, despite improvement by both groups on the recall tasks, the ketamine group remained significantly impaired on delayed recall. The authors proposed that the Day 3, delayed recall impairment was partly due to the amnesic properties of the drug, i.e., a lack of memory for the task on Day 1 reduced practice effects and impaired subsequent explicit recall of this information. Thus, Curran and Morgan concluded that repeated ketamine use impaired episodic memory acutely, but that there was inconclusive evidence regarding persisting impairments.

Curran and Monaghan's (2001) comparison of frequent and infrequent ketamine users found the two groups had similar performances on immediate and delayed recall tasks whilst under the acute effects of ketamine. However, three days later the infrequent ketamine group's performance had improved on both tasks, whereas the frequent ketamine group's performance

had remained relatively stable. When years of ketamine use and ketamine dose on Day 0 were controlled for this impairment remained. This implies that only ketamine use above a certain threshold has persisting detrimental effects on episodic memory. Additionally, the authors claimed that it meant that the day three effects were not residual effects of the drugs (as both groups would have exhibited them) but persisting effects from repeated ketamine use.

Subsequent research by Morgan, Riccelli et al. (2004) proposed previous research investigating episodic memory was limited by the task used. They stated that the prose recall task only required participants to recall information learnt, not to explicitly remember information about the encoding context. In response to this they adopted a source memory task (Wilding & Rugg, 1996) that required participants to identify whether they had previously heard a word (i.e., recognition) and if so, what gender it had been spoken by (i.e., contextual, source information).

The ketamine group performed more poorly than the poly-drug control group on both item recognition and source memory on Day 0. On Day 3 the ketamine users' performance had improved; there was no longer a difference between the groups on item recognition, however, there was still a difference on source memory. Morgan, Riccelli et al. (2004) concluded that repeated ketamine use globally impaired episodic memory functions acutely. However, its persisting effects selectively impaired the memory of contextual information, hence, a Day 3 impairment on source memory only.

Morgan, Riccelli et al's (2004) finding supports Curran and Monaghan's (2001) conclusion of persisting impairments in episodic memory; further, it specifies that this effect is due to ketamine's interference with the ability to either encode, store or access contextual information. The degree of Day 0 and Day 3 impairment in the ketamine group was comparable to that found in drug-naive participants who were administered the same task under a 0.8mg/kg, and 0.4mg/kg dose of ketamine, respectively (Morgan, Mofeez et al., 2004). These doses approximate to 56mg and 28mg respectively, in an average 70kg adult. As participants in Morgan, Riccelli et al's study were estimated to be taking a mean dose of 1420mg ketamine per session it can be inferred that they had developed tolerance to its episodic impairing effects.

Morgan, Monaghan et al's (2004) three-year follow-up study on people who had markedly reduced or ceased their ketamine use utilised the prose recall task to tap episodic memory so that comparisons could be made to their earlier studies (i.e., Curran & Monaghan, 2001; Curran & Morgan, 2000). The ketamine group's performances on both the immediate and delayed prose recall tasks were relatively stable three to four years later; further, they performed significantly worse than the poly-drug control group at both baseline and follow up. Thus, despite a reduction in ketamine use there appeared to be a persisting impairment in episodic memory. As participants in the two groups were matched on demographic variables, and were roughly

matched on drug use, it was suggested that these findings imply chronic effects of ketamine, rather than pre-existing group differences.

In sum, four studies have investigated the effect of chronic ketamine use on episodic memory. Three studies assessed the acute effects of ketamine and found it to be acutely detrimental to episodic memory (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan, Riccelli et al., 2004) in line with controlled studies. There is evidence for persisting deficits in episodic memory three days after ingestion of the drug in frequent users (Curran & Monaghan, 2001), and deficits persisting despite a marked reduction in ketamine use (Morgan, Monaghan et al., 2004). Use of a 'source task' (Morgan, Riccelli et al., 2004) identified that this persisting impairment is likely to be due to selective difficulties in the manipulation of contextual information. In conclusion, there is evidence that ketamine impairs both item and source memory acutely, and in the longer-term source memory effects may be persisting even after cessation of ketamine use.

Ketamine and semantic memory

Semantic memory is our "memory for meanings" (Reber, 1985, p. 431). In contrast to episodic memory ('I remember') semantic memory can be characterised by the phrase, 'I know'. It helps people to make connections between 'things' and therefore make sense of the world around them. In lay-mans terms, semantic memory is general knowledge.

In respect to the effect of an acute dose of ketamine on semantic memory in healthy volunteers, Morgan and Curran's (2006) review observed that there is inconsistent evidence, with some studies reporting impairment (e.g., Krystal et al, 1994) whilst others report it remains intact (e.g., Ghoneim, Hinrichs, Mewaldt & Peterson, 1985). The authors tentatively concluded that ketamine does acutely affect semantic memory, however, this appears to be specific to controlled semantic processes (Morgan, Rossell et al., 2006).

To assess repeated ketamine use and semantic memory functioning Curran and Morgan (2000) used the verbal fluency and category generation tasks and the speed of comprehension test (Baddeley, Emslie & Nimmo-Smith, 1992). In the fluency generation task, participants are required to generate as many words as possible beginning with a specific letter (e.g., 'B') in 60 seconds. The category generation task requires participants to name as many members of a category (e.g., 'vegetables') as possible in 60 seconds. The speed of comprehension test requires participants to read as many sentences as possible in a two minute period, and judge them as either correct or incorrect sentences. Recreational ketamine users were acutely impaired on all three tasks compared to poly-drug users, and remained impaired on category fluency and speed of comprehension three days later. In addition, the ketamine group's Day 3 score on the speed of comprehension task was significantly poorer than the poly-drug control group's Day 0 score. This implies that ketamine acutely impairs semantic memory, with deficits lasting up to three days later.

To explore whether these Day 3 deficits in semantic memory were due to pre-existing group differences, residual effects or were persisting effects from repeated ketamine use, Curran and Monaghan (2001) used the same measures of semantic memory with infrequent and frequent ketamine users. Frequent and infrequent users were impaired in tasks tapping semantic memory at the time of drug ingestion compared to three days later, with some indication that the more heavily ketamine was used the more detrimental its acute effects. In addition, frequent ketamine users were impaired compared to infrequent ketamine users three days later. When dose of ketamine and years of ketamine use were controlled for these differences remained. The authors concluded that these Day 3 effects most likely demonstrated chronic effects; if they were residual they would have been evident in both groups. In respect to pre-existing differences, the groups were well matched on non-ketamine drug use, and relatively well matched for demographic variables.

Morgan, Monaghan et al. (2004) investigated the effects of a marked reduction in recreational ketamine use on the tasks previously used to assess semantic memory. The ketamine group performed more poorly than poly-drug controls on the category generation and speed of comprehension tasks at baseline (i.e., three days after ingestion), but groups did not differ on the verbal fluency task. At follow up, three to four years later, the ketamine group performed more poorly on the speed of comprehension task only. The improvement in category generation scores was significantly negatively correlated with reduction in ketamine use, and time since last ketamine use.

Thus, there appeared to be a deficit in aspects of semantic memory three days after ingesting ketamine, which was partially reversible following a marked reduction in the use of the drug. In light of these findings, earlier studies can be interpreted as demonstrating impairments in semantic memory due to repeated ketamine use, and not due to pre-existing group differences, or residual effects.

However, the category generation task, as well as other 'semantic' tasks used in these studies, makes demands on sustained attention and working memory both of which are acutely impaired by ketamine. Thus, to determine whether ketamine impairs semantic memory Morgan, Rossell et al. (2006) utilised the semantic priming paradigm. Semantic priming is a "form of memory that involves a change in a person's ability to identify, produce or classify an item as a result of a previous encounter with that item or a related item" (Schacter, Dobbins & Schnyer, 2004, p. 853). Semantic priming draws on several processes, however, these can be teased apart via manipulation within the semantic priming task.

The semantic priming task involves the presentation of a prime word (e.g., bird) followed by a target word that is either related (e.g., fly) or unrelated (e.g., hat) to the prime word, or a pseudo word (e.g., frut) (See Figure 1). The participants' task is to decide as quickly as possible whether the target word is a real or pseudo word. In general, presentation of a prime word that is semantically related to a target word results in a faster and more accurate identification of the target word, than if the prime and target are not related.

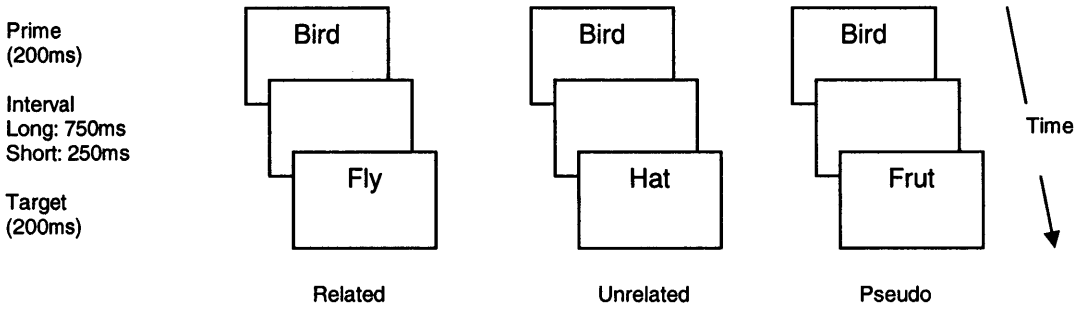

Figure 1.1. Semantic priming task (adapted from Rossell, Price & Nobre, 2003)

Manipulation of the time between the presentation of the prime and target words can elicit understanding about whether ketamine impairs unconscious or conscious processes involved in semantic memory. Short (250msec) and long (750msec) intervals are indicative of unconscious and conscious processes, respectively (Neely, 1991). Additionally, using low and high frequency English language words can aid understanding of whether the impairment to semantic memory is characterised by predominately a storage or access problem (Nickels & Howard, 1995; Warrington & Cipolotti, 1996). Longer reaction times and/or greater errors to low frequency words, compared to high frequency words, implies decay of these low frequency words in the semantic store. However, if there is no difference between the reaction times for low and high frequency words, this implies difficulty in accessing the semantic store.

Morgan, Rossell et al. (2006) conducted two experiments using the semantic priming paradigm, one with healthy volunteers administered ketamine, and one with chronic recreational ketamine users. In their 'healthy volunteers' study, they found that when the amount of time between presentation of the

prime and target words was long enough to facilitate activation of conscious processes, ketamine impaired semantic memory in a dose-dependent fashion. Thus, response times to the related target word were slower the greater the dose of ketamine ingested. Interestingly, this impairment occurred to such an extent that related words were responded to more slowly than, albeit as accurately as, unrelated words, i.e., an inverse priming effect. That reaction times did not differ for low and high frequency English language words indicates that an acute dose of ketamine disrupts *access* to the semantic store rather than damaging the semantic store per se (Nickels & Howard, 1995; Warrington & Shallice, 1979).

In their chronic ketamine study, Morgan, Rossell et al. (2006) found that ketamine users demonstrated greater priming effects to high frequency English language words than poly-drug users. However, when the priming task used low frequency words and was slowed down to facilitate activation of conscious processes, ketamine impaired performance to such an extent that related words were responded to more slowly than unrelated words, i.e., an inverse priming effect. This suggests a storage problem, that is, decay of words in the semantic store (Warrington & Cipolotti, 1996; Lambon-Ralph et al., 1998). Morgan, Rossell et al. note that the pattern of priming observed is similar to people with a probable diagnosis of Alzheimer's Disease (Giffard et al., 2002).

Interestingly, Morgan, Rossell et al's (2006) poly-drug controls demonstrated longer reaction times to priming than placebo controls (in the healthy

volunteers study) for high frequency words when priming was slowed down to facilitate the activation of conscious processes, i.e., a relative impairment in accessing the semantic store during conscious processing. Thus, the authors questioned the impact of recreational drugs other than ketamine on semantic processing.

In sum, the literature suggests that chronic ketamine use impairs aspects of semantic memory acutely and three days later. This Day 3 effect may be due to chronic use. However, there is evidence to suggest that these effects are reversible following a marked reduction in ketamine use. Further, one study has been interpreted to suggest that chronic ketamine use may specifically damage the semantic store. In conclusion, chronic ketamine use has long-term but seemingly specific and possibly reversible effects on semantic memory.

Summary of the effects of chronic ketamine use on cognition

Research into chronic ketamine use corroborates findings from healthy volunteer studies, suggesting that ketamine acutely impairs working memory and associated attention processes, episodic and semantic memory. Further, it is possible that ketamine has specific long-term and possibly reversible detrimental effects on the semantic store. There is a suggestion of long-term and persisting deficits in the manipulation of contextual information in episodic memory.

Chronic ketamine use and its effects on subjective experiences

Ketamine and dissociative experiences

The term 'dissociation' is used to "characterise the process (or its result) whereby a coordinated set of activities, thoughts, attitudes or emotions becomes separated from the rest of the person's personality and functions independently" (Reber, 1985, p. 208). It is often considered a mechanism whereby the aim is to protect the individual from distressing experiences.

Studies of acute ketamine administration in healthy volunteers have found that ketamine acutely induces dissociative experiences (e.g., Pomarol-Clotet et al., 2006). Some studies have reported a dose-response effect (e.g., Morgan, Mofeez et al., 2004).

In the majority of the studies discussed below, dissociation was assessed using the Adapted Dissociative States Scale (Curran & Morgan, 2000; adapted from The Clinician Administered Dissociative States Scale, Bremner et al., 1998).

At the time of drug ingestion recreational ketamine users scored higher on measures of dissociation than poly-drug controls in two studies (Curran & Morgan, 2000; Morgan, Riccelli et al., 2004). Three days after drug ingestion ketamine users exhibited higher levels of dissociative symptomatology than poly-drug controls in one study (Curran & Morgan, 2000). Infrequent and frequent users of ketamine were found to have comparable levels of

dissociative symptomatology at drug ingestion and three days later, although both groups reported significant reductions over time. All studies reported (albeit non-significant in some studies) reductions in dissociative symptomatology three days after ketamine ingestion (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan, Ricelli et al., 2004). After marked reduction, or cessation, of ketamine use, and three to four years after the original assessment, there was a main effect of time, i.e., a reduction in dissociative symptoms for both groups; there was no significant difference between the two groups (Morgan, Monaghan et al., 2004).

In a review of the effect of repeated participation in acute ketamine studies, Cho et al. (2005, p. 140) concluded that there was "no evidence... [for] perceptual changes resembling dissociation" (using the Clinician Administered Dissociative States Scale; Bremner et al. 1998). Nonetheless, they reflected that their participants had only been administered ketamine a maximum of 11 times, and that their results might not be generalisable to people who use more frequently or at higher doses.

To conclude, there is evidence that repeated ketamine use acutely increases dissociative symptomatology, but little evidence of dissociation persisting beyond acute use.

Ketamine and schizotypal experiences

Schizotypal experiences are those which resemble, to a lesser degree, symptoms present in a person with a diagnosis of schizophrenia, for

example, disturbances in thought, speech and behaviour. Schizotypy is a "personality construct that is currently used to refer to the multidimensional continuities assumed to connect normal sets of behaviours and experiences to the sets of behaviours and experiences which characterise persons with a [diagnosis of] schizophrenia" (Kravetz, Faust & Edelman, 1997, p. 857).

In general, acute ketamine studies have found that healthy volunteers exhibit schizotypal symptoms such as "partially held delusions of reference" (Pomarol-Clotet et al., 2006, p. 177) and suspiciousness (Lahti, Weller, Michaelidis, Parwarni, Tamminga, 2001). Morgan, Mofeez et al. (2004) found no significant difference in schizotypy between healthy volunteers administered a low and high dose of ketamine.

In most chronic ketamine studies schizotypy symptomatology was assessed using the Schizotypal Symptomatology Questionnaire (Curran & Morgan, 2000) which was adapted from the Schizotypal Personality Questionnaire (Claridge & Broks, 1984) and the Magical Ideation Scale (Eckbald & Chapman, 1983).

At the time of drug ingestion, schizotypy symptomatology was higher in recreational ketamine users than poly-drug controls (Curran & Morgan, 2000; Morgan, Riccelli et al., 2004). Assessment of healthy volunteer controls implies that administered ketamine may induce schizotypy properties in a dose-response fashion (Morgan, Rossell et al., 2006). However, frequent and infrequent ketamine users had similar levels of schizotypy

symptomatology despite ingestion of different doses of ketamine (Curran & Monaghan, 2001). It is possible that the frequent recreational ketamine users in the study demonstrated a tolerance, rather than a sensitization, to the acute schizotypy effects of repeated ketamine use. It is also possible that ketamine users show ceiling effects on schizotypy scales.

Two studies found that chronic ketamine users reported higher levels of schizotypy symptoms than poly-drug users three days after drug ingestion (Curran & Morgan, 2000; Morgan, Monaghan et al., 2004) whilst two others did not (Morgan, Riccelli et al., 2004; Morgan, Rossell et al., 2006). Despite the higher levels found at Day 3, there was a trend for a reduction in schizotypy symptomatology in Curran and Morgan's study. Further, the schizotypy symptoms reported by frequent and infrequent ketamine users declined in the three days following ingestion and were comparable to each other (Curran & Monaghan, 2001). Comparability between infrequent and frequent users implies that the day three effects are residual, rather than chronic (which would be implied if the frequent group had significantly higher levels than the infrequent group three days after drug ingestion).

Cho et al's (2005) study on the effects of healthy volunteers' repeated participation in acute ketamine research (a maximum of 11 times, over a non-specified period) did not find any persisting adverse positive or negative symptoms (as recorded by the Brief Psychiatric Rating Scale, BPRS; Overall & Gorham, 1962). These results indicate a need to use ketamine at a greater frequency, and/or dosage than in acute studies, for any longer term

detriments. Similarly, Lahti, Warfel et al. (2001) carried out a long-term follow up of patients with a diagnosis of schizophrenia who received ketamine during research ("up to four subanaesthetic doses... usually over a two week period", p. 870). They did not find any changes in patients' BPRS scores over time, or compared to a patient control group. Despite the low level of ketamine dose and frequency use reported by Lahti, Warfel et al., compared to recreational users, these results indicate that there are no long-term effects for people already susceptible to psychotic experiences.

In contrast to other findings, Morgan, Monaghan et al. (2004) found that despite marked reduction in ketamine use, ketamine users' schizotypy scores were higher than poly-drug users' at long-term follow-up. This suggests either that chronic ketamine use may result in elevated, persisting and non-reversible schizotypy effects or that individuals who are higher in schizotypy are more likely to use ketamine.

In sum, there is evidence to suggest that repeated ketamine use acutely produces schizotypal symptoms. However, research is inconclusive about whether repeated ketamine use elevates schizotypy symptoms in the long-term and whether this is reversible or not.

Ketamine and mood, somatic and other subjective effects

A recent randomised control trial concluded that acutely, ketamine has fast acting anti-depressant properties (Zarate et al., 2006). In general, most acute ketamine studies show little difference in depression scores. Curran

and Morgan (2000) found that their chronic ketamine group scored significantly higher (i.e., more depressed) than poly-drug controls on the depression factor of the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) on Day 0 and Day 3. However, ketamine users were not within the clinical range. Studies consistently report that ketamine and poly-drug users do not differ in their subjective ratings of depression after drug ingestion or three days later (Curran & Morgan, 2000; Morgan, Monaghan et al., 2004; Morgan, Riccelli et al., 2004).

Ketamine and poly-drug users reported comparable levels of contentedness and calmness (using a 16 item visual analogue scale; Bond & Lader, 1984) after drug ingestion, with only a trend for improved scores three days after drug ingestion (for both groups) (Curran & Morgan, 2000). There were no differences between the groups three to four years later following a marked reduction in ketamine use (Morgan et al., 2004). Cho et al's (2005) review found no differences in anxiety levels between people involved in up to 11 ketamine studies and controls. Thus, there is no evidence for chronic ketamine use resulting in elevated anxiety levels acutely or in the long-term.

Chronic ketamine users have been found to be significantly less alert (i.e., more drowsy) than poly-drug controls at the time of drug ingestion, but not three days later (Morgan, Riccelli et al., 2004) or after marked reduction in ketamine use (Morgan, Monaghan et al., 2004). Frequent ketamine users, ingesting higher doses, were drowsier than infrequent ketamine users at the time of drug ingestion and three days later; both groups were less drowsy on

Day 3 (Curran & Monaghan, 2001). This implies a dose-response effect, which has face validity given ketamine's anaesthetic properties. However, one study reported no differences in alertness between ketamine and poly-drug users at drug ingestion or three days later (Curran & Morgan, 2000).

Other subjective and somatic effects of ketamine use, for example bodily numbness, altered reality and time perception, have been assessed using visual analogue scales (Curran & Monaghan, 2001; Curran & Morgan, 2000; Morgan, Monaghan et al., 2004; Morgan, Riccelli et al., 2004). In general, ketamine users rate themselves more highly on these scales after drug ingestion, but not three days later, when compared to poly-drug users (Curran & Morgan, 2000; Morgan, Riccelli et al., 2004). However, frequent ketamine users reported impaired memory and concentration, and higher levels of nausea compared to infrequent ketamine users, three days after drug ingestion (Curran & Monaghan, 2001). These memory findings are consistent with anecdotal reports of memory difficulties in ketamine users (Jansen, 1990) and may reflect chronic effects. Despite a marked reduction in ketamine use, ketamine users scored higher than poly-drug controls on factors assessing perceptual distortion, bodily symptoms and cognitive and mental state (Morgan, Monaghan et al., 2004).

In sum, repeated ketamine use does not appear to induce low mood or anxiety either acutely or long-term. There is a suggestion of reduced alertness acutely. Ketamine users report acute somatic and other subjective

effects typical of ketamine use, however, there is inconsistent evidence regarding whether these effects continue beyond acute drug ingestion or not.

Summary of the effects of chronic ketamine use on subjective experiences

In sum, evidence from studies into chronic ketamine use supports findings from controlled studies: repeated ketamine use acutely produces dissociative and schizotypal symptoms, somatic and other subjective effects. Chronic ketamine users may also experience residual dissociative, sedative, somatic and other subjective effects. It is unclear whether schizotypal symptoms occur beyond acute ketamine ingestion, and if so whether they persist despite a reduction or cessation in ketamine use.

Discussion

Main findings

This is the first time that the effect of chronic recreational ketamine use on both cognitive functioning and subjective experience has been reviewed. The main conclusions drawn from the research are that chronic ketamine use (i) acutely impairs working, episodic and semantic memory. Further, it (ii) acutely elevates and may induce residual dissociative, schizotypal, sedative, somatic and other subjective symptoms. Additionally, there may be (iii) long-term but possibly reversible effects on the semantic store, and persisting deficits in the manipulation of contextual information in episodic memory.

The acute cognitive and mental experiences of people who repeatedly use ketamine concur with findings from many of the controlled studies investigating the effects of an acute dose of ketamine in healthy volunteers. This demonstrates the validity of naturalistic studies of ketamine use, despite methodological limitations (discussed below). The longer-term effects of chronic ketamine use extend the current evidence base and are applicable to both the fields of substance misuse, and pharmacological models of psychosis.

Limitations of research

There are a number of important limitations to the studies reviewed, which are discussed below:

Reported drug use

In each of the studies run by the Clinical Psychopharmacology Unit, past and current drug use was assessed via a structured interview. It is likely that there is 'measurement error' present, thus reducing the reliability of the information gathered. Difficulties in obtaining a true estimate of drug use can be attributed to a number of different factors, for example, participants' lack of knowledge about drug quantities, the purity of drugs purchased, inaccurate recall of quantities and dates used, and social desirability effects, leading to over- or under-estimation of drug use. Whilst, Narendran et al's (2005) study utilised hair analysis to verify a three month drug history, prior drug use was unaccounted for. However, it is noted that as ketamine is often diverted from

legal medical or veterinary supplies its purity is often higher than other recreational drugs.

Independent group design

Studies in this review have tended to use independent group designs and have therefore attempted to match different participant groups on a number of variables, including age, years of education, pre-morbid IQ, and non-ketamine current drug use. The premise underlying matching is to (i) treat the groups as equivalents and (ii) to minimise the impact of confounding variables thus isolating the effect of the independent variable, i.e., ketamine present or absent. Matching current drug use is problematic, for the reasons outlined above. It may not be sufficient to match on variables such as 'pre-morbid IQ' and 'years of education' as robust indicators of an individual's cognitive functioning. Further, there are many variables that participants could be matched on. For example, Curran (2000) highlights the probable increased levels of "impulsiveness and sensation seeking" in people who use certain recreational drugs over others.

Representativeness of sample

The sample sizes reported in the studies reviewed are not large, varying between 28 and 40 participants. Narendran et al. (2005) reported that their sample of (mostly) exclusive ketamine users may not be representative of the ketamine using population as most people who use ketamine are poly-drug users. Studies by the Clinical Psychopharmacology Unit at UCL employed a 'snowballing' recruitment procedure and participants tended to be recruited at

clubs, squat- and private-parties. Individuals who combine ketamine use with other non-recreational drugs, for example heroin (Zhao et al., 2004), may not be represented in these samples. Further, none of the studies report sexual orientation, which prevalence studies (e.g., Bolding et al., 2006) indicate is useful information to collect. An important further consideration is the current prohibition of ketamine and other recreational drugs, which may disproportionately inhibit participation from members of some groups of society more than others.

Measures of cognition and mental state

It is important to bear in mind that whilst a cognitive assessment tool may draw preferentially on one cognitive system any single task generally taps into a number of systems (Wheeler et al., 1997). This makes it difficult to isolate the effects of repeated ketamine use of cognitive functioning. It is also important to try and separate any direct effects of ketamine on cognition from any indirect effects via, for example, increased schizotypy or fatigue. Some of the earlier Clinical Psychopharmacology Unit studies were compromised by the nature of the tasks that they employed; however, subsequent studies enabled a re-examination of findings with superior tasks which tended to support and extend previous findings. Similarly, there are limitations to the measurement of mental phenomena via questionnaires. Curran and Morgan acknowledge that their Schizotypal Symptomatology Questionnaire (adapted fm Schizotypal Personality Questionnaire (Claridge & Broks, 1984) and the Magical Ideation Scale (Eckblad & Chapman, 1983))

may tap into schizotypal personality traits rather than an acute state. Future studies may benefit from utilising clinical interviews.

Applications to the NMDA-R hypofunction model of psychosis

The chronic effects of ketamine reported herein resemble the positive, negative and cognitive symptoms often experienced by people with a diagnosis of schizophrenia. However there are differences, for example, ketamine users do not frequently report auditory hallucinations. Conversely, the enjoyment derived from dissociative type experiences after ketamine ingestion is not frequently reported by people with a diagnosis of schizophrenia. It is widely acknowledged that drug models of clinical disorders have only partial validity (e.g., Fletcher & Honey, 2006; Morgan & Curran, 2006). This is especially pertinent to schizophrenia with its heterogeneous nature.

Nonetheless, the chronic ketamine research can be considered within the context of the NMDA-R hypofunction model of psychosis. As the acute effects of both an administered and recreationally ingested dose of ketamine are comparable, it could be argued that there is no need to investigate both acute and chronic ketamine models of psychosis. However, another narrative is that more research is required to fully understand the acute effects of repeated ketamine use. For example, Fletcher and Honey (2006) report that working memory deficits in schizophrenia are primarily due to deficits in manipulation, not maintenance, of material. Acute ketamine studies on healthy volunteers have replicated this finding. However, chronic

ketamine studies are yet to investigate these two processes whilst recreational users experience the acute effects of ketamine ingestion. Further, as stated in the introduction, some authors have suggested that chronic ketamine use, and thus chronic NMDA-R hypofunction, is a more appropriate model for chronic schizophrenia. The finding that repeated ketamine use appears to result in long-term deficits in semantic and episodic memory, some of which may not be reversible, suggests potentially fruitful avenues for investigating the mechanisms underlying the chronic cognitive deficits evident in some people with a diagnosis of schizophrenia. At the present time however, further research is required to substantiate this claim.

Applications to the management of ketamine use

It is important to consider that repeated ketamine use has a number of longer-term effects, some of which may not be reversible upon reduction or cessation. Although the life time prevalence of ketamine use is likely to be low within the UK general population, there is a reported increase in both lifetime prevalence and regular ketamine use within sub-populations, such as clubbers within both the heterosexual and gay communities. It is important that the effects of repeated ketamine use are disseminated in a non-sensationalist and readily accessible way. For example, collaborating with specialist dance focused publications may facilitate informed drug taking decisions and harm minimisation practices. Additionally, information distributed to relevant health care professionals within the statutory and voluntary sectors may enable better detection of the side effects of chronic

ketamine use. In the long-term it may facilitate differential diagnosis with dementias such as Korsakoff's Syndrome and Alzheimer's Disease.

Future research

As previously stated, research into chronic ketamine use is in its infancy and is hampered by a number of methodological issues which need to be addressed. The evidence base will become more reliable as existing findings are replicated using different and more specific measures of cognition and mental state.

It is important that this field of research conducts planned longitudinal studies to assess the effects of increases, decreases and the cessation of ketamine use. It would also be fruitful to gain an understanding into the antecedents of ketamine use, as well as its continuation and cessation. This information may help health care practitioners support people who seek help for problematic ketamine use.

In order to examine the relationship between cognitive functioning and schizophrenia-like symptoms the semantic priming paradigm can be further utilised. Extrapolating from research with people with a diagnosis of schizophrenia, indirect semantic priming may provide a more sensitive and accurate measure of impaired semantic processing in people who use ketamine chronically (Moritz et al., 2001). This may further understanding between semantic processing and symptoms such as thought disorder. It may also be beneficial to undertake studies in which people with a diagnosis

of schizophrenia (first episode and chronic) are directly compared to people who use ketamine (acutely and repeatedly).

To further our knowledge in understanding the mechanisms underlying cognitive and mental phenomena, functional magnetic resonance imaging techniques may also prove fruitful as demonstrated in acute ketamine studies (Fletcher & Honey, 2006).

Conclusions

This review has examined the emerging body of evidence for the effects of chronic recreational ketamine use on cognitive functioning and subjective experience. Whilst the field is subject to methodological limitations its findings are vindicated to some extent by their comparability to controlled studies. Findings of note are long-term but possibly reversible effects on the semantic store, and persisting deficits in the manipulation of contextual information in episodic memory. Replication of findings is required, as well as an expansion of the existing work. Further, findings need to be sensibly communicated to relevant and interested parties.

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Part 2: Empirical paper

An investigation into the long-term effects of recreational chronic ketamine use on semantic processing and subjective experiences

Abstract

Background: There has been an increase in the prevalence of recreational ketamine use over the past five years. Due to ketamine's cognitive and psychotomimetic effects it is being investigated as a pharmacological model for psychosis.

Problem under investigation: To investigate the long-term effects of chronic recreational ketamine use on indirect and direct semantic priming, general semantic processing and subjective experiences.

Participants: Forty-six participants, aged 18 to 46 years, completed the study, 24 male and 22 female.

Design: An independent groups design was used to compare three groups: 16 ketamine users (people who use ketamine and other recreational drugs), 14 poly-drug users (people who use recreational drugs, but not ketamine) and 16 non-drug users (people who have not and do not use illicit drugs). Participants completed computer tasks which assessed semantic memory and pen and paper questionnaires that assessed subjective experiences.

Results: The ketamine group scored higher than the non-drug group on a measure of schizotypy. Semantic processing was found to be similar across the groups, although the ketamine group had significantly longer reaction times to

high frequency words than to low frequency words on the direct semantic priming task, whereas the two control groups showed no significant differences.

Conclusions: The ketamine group were impaired relative to the other two groups in their processing of high frequency words compared to low frequency words, and were higher in schizotypy than non-drug users. However, the absence of indirect priming effects across the three groups limits the conclusions that can be drawn and methodological reasons for this are discussed.

Key words: chronic effects, drug abuse, ketamine, schizotypy, semantic priming, semantic memory.

Introduction

Ketamine, an N-Methyl-D-Aspartate Receptor (NMDA-R) receptor antagonist used medically as an anaesthetic, has become increasingly used as a recreational drug for its psychoactive effects in the past five years (Mixmag, 2006). This increase in recreational ketamine use is reflected in an increase in life time prevalence and regular usage, mostly by people who go 'clubbing' (Mixmag, 2000, 2001, 2006). Ketamine also has pronounced psychotomimetic properties and it is therefore being investigated as a model for schizophrenia.

There are two main avenues of research in to ketamine's effects on cognition and subjective experiences. Firstly, there are controlled 'acute' studies that have administered a dose of ketamine to healthy volunteers who have not used ketamine previously. Secondly, there are naturalistic studies that have examined the effects of ketamine in recreational users. Naturalistic studies have facilitated the examination of the 'acute on chronic' and 'chronic' effects of repeated recreational ketamine use. Acute on chronic effects are those that occur shortly after ingestion of ketamine by recreational users, e.g., hours or days. Chronic ketamine effects are those that occur in recreational users days or months after ketamine ingestion. Within the recreational ketamine using population there is a range of usage, from once or twice a week, to daily use.

Ketamine use and cognition

Chronic recreational ketamine users experience a range of acute cognitive impairments, which are comparable to those experienced acutely by healthy volunteers after a single administered dose of ketamine. These include deficits in working (e.g., Curran & Monaghan, 2001; Curran & Morgan, 2000), episodic (e.g., Morgan, Riccelli, Maitland & Curran, 2004) and semantic memory (e.g., Curran & Monaghan, 2001). However, while the cognitive deficits induced acutely in healthy controls are reversible, chronic recreational users have been found to exhibit long-term and persisting deficits in aspects of episodic memory (Morgan, Riccelli et al., 2004) and specific yet possibly reversible effects on semantic memory (Morgan, Rossell et al., 2006).

Semantic memory is a "memory for meanings" (Reber, 1985, pp. 431). It stores a person's knowledge about language and the world around them, enabling them to make sense of it. The long-term effects of chronic recreational ketamine use on semantic memory were initially investigated via the fluency tasks and the speed of comprehension task. Fluency tasks require participants to name out loud as many words as they can think of, in 60 seconds, that begin with a specified letter (i.e., verbal fluency) or belong to a specified category (i.e., category fluency). The speed of comprehension test requires participants to read as many sentences as possible in a two minute period, and judge them as either correct or incorrect sentences. Performance on all three tasks was found to be impaired acutely; performance on category generation and speed of comprehension was impaired three days after ketamine ingestion (Curran &

Morgan, 2000). Deficits were pronounced for frequent compared to non-frequent ketamine users (Curran & Monaghan, 2001). Following a marked reduction in recreational ketamine use, improved performance on the category generation task correlated with ketamine reduction and days since last ketamine use (Morgan, Monaghan & Curran, 2004). Thus, the authors concluded that chronic ketamine use leads to long-term, yet possibly reversible, deficits in aspects of semantic processing.

However, Morgan, Rossell et al. (2006) proposed that these findings may not be valid as the tasks used make demands on other cognitive systems that are also acutely impaired by ketamine use, such as sustained attention and working memory. Therefore, Morgan, Rossell et al. utilised the semantic priming paradigm to assess semantic processing in chronic recreational ketamine users.

The semantic priming task involves the presentation of a prime word (e.g., shoe) followed by a second target word that is either related (e.g., handbag) or unrelated (e.g., sky) to the prime word, or a pseudo word (e.g., gomp). The participant is required to decide whether the target word is a real or pseudo word (i.e., lexical decision procedure), responding quickly and accurately on a keyboard. The semantic priming task draws on cognitive connectionist models of semantic associations, which propose that semantic memory is a network of interconnected nodes, storing information about the world (e.g., Neely, 1977; cited from Neely, Keefe & Ross, 1989). This task provides the opportunity to

indirectly measure the speed and accuracy at which semantic associations pass through the semantic network.

The semantic priming task draws on three processes: 1) word stimulus-node activation, 2) expectancy effects and 3) semantic matching. The presentation of the word stimulus (i.e., the prime word) results in the activation of a node within the semantic network, which in turn activates related nodes, etc. Collins and Loftus (1975) proposed that the activation of a prime-related node reduces its threshold for subsequent recognition, resulting in faster response times. Hence, if the subsequent target word matches a previously activated node it will result in faster participant responding. This is considered to be an automatic/unconscious process (Neely, 1991).

Subsequent to the word stimulus-node activation process, it is proposed that two conscious processes occur: one pre lexical (expectancy effects) and one post-lexical (semantic matching) (Neely et al., 1989). The expectancy effect is the process whereby a set of potential targets is generated by the prime, and the processing of any word outside that potential set is inhibited. Thus, if the presented target word matches a word from the set of potential targets it should be processed more quickly (as evidenced by faster response times) than a target word that does not match a potential target. Semantic matching refers to the extent of semantic similarity between the prime and target words, and provides information about the lexical status of the word (Chwilla, Hagoort &

Brown, 1998). The greater the degree of semantic matching between the prime and the target, the faster the respondents' reaction time.

It is possible to separate out the effects of these three processes as the automatic, unconscious process of stimulus-node activation occurs prior to the two later conscious processes. Short and long intervals between the presentation of the prime and target words, a period of time known as stimulus onset asynchrony (SOA), facilitate the examination of unconscious and conscious processes, respectively. It is generally considered that an SOA below 500ms reflects unconscious processing, whilst longer SOAs reflect conscious processing (Neely, 1991).

Recent research has demonstrated that three days after acute ketamine ingestion, chronic ketamine users are specifically impaired in priming at a long SOA, suggesting deficits in controlled semantic processing (Morgan, Rossell et al., 2006). The pattern of priming observed at this SOA was particularly interesting in that it suggested not only impaired but inverse priming. That is, ketamine users were faster at processing unrelated word pairs than related word pairs. The authors suggested that this may be due to a deficit in semantic matching, i.e., an impairment in the ability to process the stimuli in terms of it's meaning, and thus assess the degree of semantic relatedness between the prime and target. In order to explore this further the current study uses an indirect semantic priming task.

The indirect semantic priming task examines the response to two words that are related by an absent mediating term. For example, the prime presented may be 'lemon' and the target 'sweet' which are both indirectly related by the word 'sour'. If semantic matching is impaired then one would hypothesise that priming for indirectly related word pairs would be affected to a much greater degree in ketamine users than that for directly related word pairs. However, neural network models of NMDA-R assemblies suggest that ketamine use may be associated with a reduction in the ability to inhibit previously activated nodes in the semantic network (Nestor et al., 2001). This could lead to competition between related semantic nodes resulting in a disruption in priming. If this, and not a semantic matching deficit, is responsible for the reduction in priming at a long SOA, then indirect priming may be less affected by chronic ketamine use than direct priming.

The inverse priming previously observed in ketamine users (Morgan, Rossell et al., 2006) was particularly apparent for low frequency words. The authors suggested that this indicates a problem in the storage of, rather than access to, semantic information. The rationale for this hypothesis is that an access disorder, such as that found in aphasic patients (Nickels & Howard, 1995; Warrington & Shallice, 1979), is indicated by individuals having equivalent difficulties in naming both high and low frequency English language words. However, a storage disorder such as that found in semantic dementia (Warrington & Cipolotti, 1996; Lambon-Ralph, Graham, Ellis & Hodges., 1998), is indicated by greater difficulty in naming low compared to high frequency

words. The current study intends to further investigate this deficit in processing low frequency words by using an extended battery of other semantic tasks that manipulate word frequency. This will examine if Morgan, Rossell et al's storage problem is a priming specific effect, as has recently been demonstrated in persons high in schizotypy (Morgan, Bedford, McPhee & Rossell et al., in prep; Morgan, Bedford, Rossell., 2006), or if it is indicative of more pervasive problems with the storage of semantic information.

In summary, the present study aims to replicate and further investigate priming deficits, by controlling for semantic distance, i.e., the degree to which two exemplars of a category are semantically related. A further aim is to characterise the effects of chronic recreational ketamine use on semantic memory using a variety of measures that enables the differentiation of access and storage problems. No previous study of ketamine users has used an indirect priming task or used the measures of semantic processing that this study will use.

Ketamine use and schizophrenia-like symptoms

Acute administration of ketamine to healthy controls produces psychotomimetic effects, i.e., it induces psychotic symptoms (Morgan, Rossell et al., 2006; Olney, Newcomer & Farber, 1999). Evidence from naturalistic studies into chronic ketamine use validates these findings, in that repeated ketamine use acutely produces dissociative and schizotypal symptoms (e.g., Curran & Morgan, 2000; Morgan, Riccelli et al., 2004). Morgan, Rossell et al. found that after acute drug

ingestion chronic ketamine users reported schizotypal and dissociative symptoms comparable to healthy controls after being administered ketamine (200ng/ml) in laboratory studies. Further, in recreational users there is some evidence for residual dissociative, sedative and somatic effects three days after acute ketamine ingestion (Curran & Monaghan, 2001; Curran & Morgan, 2000). As yet, there is inconclusive evidence as to whether schizotypal symptoms persist beyond this, and if so whether they are permanent or reversible (Curran & Morgan, 2000; Morgan, Monaghan et al., 2004; Morgan, Riccelli et al., 2004; Morgan, Rossell et al., 2006).

Due to the similarity of these psychotomimetic effects to symptoms manifest in people with a diagnosis of schizophrenia, ketamine is being investigated as a pharmacological model of schizophrenia (Morgan, Rossell et al., 2006; Krystal et al., 1994; Olney et al., 1999). Morgan, Rossell et al. proposed that acute ketamine administration may be a better model of the acute stages of schizophrenia, whilst studying the effects of chronic ketamine use may aid understanding of the symptoms of chronic schizophrenia.

The relationship between cognitive functioning and schizophrenia-like symptoms

Semantic processing deficits have been repeatedly observed in people with a diagnosis of psychotic symptoms in schizophrenia (for a review, see Neely, 1991) and have been suggested to be central to the cognitive deficits observed in these individuals (Moritz et al., 2001; Rossell, Shapleske & David, 2000).

These include the classic loosening of associations manifest in confused speech and thought which contribute to delusional ideas (Bleuler, 1911; cited from Stotz-Ingenlath, 2000).

Aims and hypotheses

Theoretically, if semantic deficits are central features of schizophrenia, and ketamine is a valid model of schizophrenia, then any semantic deficits in ketamine users should correlate with their schizophrenia-like symptoms. Therefore, this study aimed to compare chronic ketamine users to poly-drug and non-drug using controls on an indirect and direct semantic priming task, and on measures of psychotic symptoms. It also aimed to compare the groups on other measures of semantic processing that manipulate frequency, to investigate the possibility of deficits in the storage of semantic information.

On the basis of Morgan, Rossell et al. (2006) it is predicted that recreational ketamine users will display a long-term inverse priming effect in the direct priming task, for low frequency words at a long SOA, whereas other groups will show standard priming. It is also expected that ketamine users will be impaired on the category, but not verbal, fluency task compared to the other groups, as found by Curran and Morgan (2000), Curran and Monaghan (2001) and Morgan, Monaghan et al. (2004). As no study on recreational chronic ketamine use has explored indirect semantic priming, or the other semantic processing tasks employed in this study, these aspects of the present research are exploratory.

It is predicted that recreational ketamine users will display persisting increased levels of schizotypy than the poly- and non-drug-controls, as found by Curran and Morgan (2000) and Morgan, Monaghan et al. (2004). No study has explored delusion related beliefs, however, due to their similarity to overall schizotypy experiences it is speculated that the ketamine group will also exhibit persisting increased levels compared to the control groups. Further, based on Morgan, Riccelli et al. (2004) and Morgan, Monaghan et al., it is expected that there will be no group differences in long-term levels of dissociative symptomatology.

Method

Participants, design and setting

Participants were recruited via the internet, the researcher's contacts, snowball sampling (Solowij, Hall, Lee, 1992) and the UCL psychology subject pool. Inclusion criteria for all participants were 1) aged at least 18 years; 2) English as a first language; 3) absence of current or past epilepsy, head injury, neurological and/or psychiatric conditions; 4) not more than 50 units of alcohol consumed per week; 5) absence of regular heroin use; 6) non-participation in other studies investigating recreational ketamine use, carried out by the Clinical Psychopharmacology Unit.

An independent groups design was used to compare three groups. Participants in the ketamine group used ketamine at least twice a month for at least one

year. Participants in the poly-drug control group used recreational drugs at least twice a month for at least one year; they had not used ketamine more than three times in total and not within the last two years. Participants in the non-drug control group had not used cannabis more than 10 times in total and not within the last two years; they had no other illicit drug history.

Previous studies on the target population have recruited samples of 28 to 40 participants, with between 14 to 20 participants in different groups; these studies have reported significant findings. Therefore, the current study aimed to recruit 48 participants, with 16 participants in each group. Forty-six participants completed the study: 40 in laboratories at the Clinical Psychopharmacology Unit, six in a quiet room at either the participant's (one) or the investigator's (five) home.

Ethics

This study was approved by the UCL Research Ethics Committee (Appendix A) and all participants provided written, witnessed, informed consent.

Procedure

Volunteers who met the relevant criteria were provided with an information sheet (Appendix B) and a consent form (Appendix C). If willing to participate, they provided written, witnessed, informed consent. An index of pre-morbid IQ was obtained using the 'spot the word' test (Baddeley, Emslie & Nimmo-Smith, 1993). Participants were then administered a test battery that comprised

Box 2.1. Order of presentation of tasks

1 Spot the Word
2 Semantic Priming (in/direct)*[1]
3 Dissociative Experiences Scale (DES)
4 Nonsense sentences*
5 Oxford-Liverpool Inventory of Feelings and Experiences (O-Life)
6 Drug history
7 Fluency
8 Categories*
9 Peter's Delusions Inventory (PDI)
10 Demographics
11 Semantic Priming (in/direct)*[1]

*Computer task, [1]Order of direct and indirect priming tasks were counterbalanced across participants and within groups.

computer based tasks which assessed semantic memory, and pen and paper questionnaires that assessed personal experiences (see Box 2.1 for order of presentation). All instructions were read aloud by the researcher, and for each computer task there was a practice period before the main task. A drug history and urine sample was taken. The drug history was taken in the middle of the testing session so that it provided a break from the other tasks. The average time taken to complete the experiment for members of the ketamine and poly-drug groups was 1hr 45min, and for the non-drug group the average time was 1hr 30min; the difference in time to complete the study was due to the length of the drug history. Participants were paid £15 to compensate them for their time.

Measures

Semantic processing

Five tasks assessed semantic processing. All stimuli for computer based tasks were programmed and presented using DMDX software, and appeared in lower

case letters, Times New Roman, font size 18, in the centre of the screen. Trial presentation was randomised, and participants were required to respond quickly and accurately on a keyboard.

Semantic priming. In both of the semantic priming tasks the prime was presented for 200ms, followed by a blank screen (of 50ms [short SOA] or 550ms [long SOA]), followed by the target word for 200ms; there was a blank screen for 2000ms preceding the next trial. Word pairs were not used more than once and were unique to each task. The participants' task was to decide whether the target word was a real or pseudo word (i.e., lexical decision procedure). These tasks indirectly assess the role of semantic relatedness, unconscious and conscious processing, and access and storage difficulties in semantic memory.

Indirect. Stimuli were 332 words (274 concrete nouns and 58 pseudo words). Words were arranged into indirectly related (bird-aeroplane [46]), unrelated (caterpillar-hat [62]) and pseudo (iguana-frut [58 pairs]) word pair conditions.

Direct. Stimuli were 480 words (360 concrete nouns and 120 pseudo words). Words were arranged into related (book-story [60]), unrelated (stereo-hamster [60]) and pseudo (cat-frut [120 pairs]) word pair conditions. Half of the words were high frequency English language words (>30 words per million) and half of the words were low frequency English language words (1-30 words per million).

Categories (Rossell & David, 2006). Stimuli were 90 category name and category exemplar pairs. There were five categories, with pairs arranged into one of five category name-category exemplar pair types: correct-high frequency (e.g., sport-football), correct-low frequency (e.g., sport-polo), borderline (e.g., sport-dancing), incorrect-related (e.g., sport-chess) or incorrect-unrelated (e.g., sport-ruler). The category name was presented for 1000ms, followed by a delay of 550ms, followed by the category exemplar for 200ms; there was a blank screen for 2000ms preceding the next trial. The participants' task was to decide whether the category exemplar was a correct example of the category name or not. This task explicitly assesses hierarchical/categorical organisation within semantic memory.

Nonsense sentences (Morgan, Bedford, et al., in prep.). Stimuli were 96 short sentences. Sentences were either true (e.g., skeletons are bones [32]), possible/unlikely (e.g., scientists turn grass blue [32]) or false (e.g., camels attack people with hammers [32]), and either neutral (48) or emotional (persecutory [12], grandiose [12], religious [12], somatic [12]) in content. Sentences were presented for 1200ms, followed by a delay of 1200ms before the next trial. The participants' task was to decide whether the sentence was true, possibly true or false. This task provides an assessment of emotional and semantic processing, and is sensitive to delusions.

Fluency – verbal and category. Verbal: participants were given the letter 'B' and asked to say aloud as many English language words as possible starting with that letter within 1min. They were not allowed to use real nouns (i.e., names of people or places) or successive words beginning with the same prefix (e.g., dis-). Category: participants were given the category 'fruit' and asked to say aloud as many exemplars of that category as possible within 1min. These tasks tap speeded retrieval from semantic memory as well as tapping executive function.

Subjective experiences

Oxford-Liverpool Inventory of Feelings and Experiences (O-Life, short version; Mason, Linney & Claridge, 2005). A 43 item bi-modal questionnaire that provides an overall schizotypy score and has four factors: unusual experiences, cognitive disorganisation, introvertive anhedonia and impulsive nonconformity.

Peters et al. Delusions Inventory (PDI; Peters, Joseph & Garety, 1999). A 21 item bi-modal (yes, no) scale with each positive response requiring participants to answer three further questions on a Likert scale from 1 (low) to 5 (high). It has been used to measure delusion-related beliefs and vivid mental experiences in the normal population.

Dissociative Experiences Scale (DES; Burnstein & Putnam, 1986). A 28 item Likert scale ranging from 0 - 100 that assesses dissociative symptoms.

Analysis

Data were analysed using SPSS 11.5. Reaction times (RTs) and error rates (ERs) that were more than 2.5 standard deviations (sd) from each participant's mean score were trimmed. Participants whose RTs and ERs were more than 2.5sd from their group mean were excluded. In all analyses the between subjects factor Group had three levels (ketamine, poly-drug and non-drug). Data from the indirect semantic priming task were analysed by a 3 x 2 x 2 Repeated Measures Analysis of Variance (RMANOVA), with Group and two within subjects factors: Relatedness (indirectly related, unrelated) and SOA (short, long). Data from the direct semantic priming task were analysed by a 3 x 2 x 2 x 2 RMANOVA, with Group and three within subjects factors: Relatedness (directly related, unrelated), SOA (short, long) and Frequency (high, low). Data from the nonsense sentences task were analysed by a 3 x 3 x 2 RMANOVA, with Group and two within subjects factors: Type (true, unlikely, nonsense) and Valence (neutral, emotional). Data from the categories task were analysed by a 3 x 5 RMANOVA, with Group and one within subjects factor: Relatedness (high, borderline, low, related, unrelated). Where the sphericity assumption was violated Greenhouse Geisser statistics are reported. Data from the fluency tasks and questionnaires were analysed by 1-way ANOVA. Post-hoc tests were Bonferroni corrected to reduce the likelihood of Type I errors.

Results

Demographics and drug use (Table 2.1)

There were no significant differences between the three groups in age, gender, years in education, Spot the Word performance and alcohol use. The ketamine group had a longer period of regular cannabis use than the poly-drug group ($t(22) = 2.682$, $p = .014$); there were no other significant group differences in drug use.

Urinalysis detected the following drugs in the ketamine group: ketamine or nor-ketamine (10), cannabis (0), cocaine (1), amphetamines (1), opiates (0). In the poly-drug group the following drugs were detected: ketamine or nor- ketamine (0), cannabis (6), cocaine (2), amphetamines (2), opiates (0). Amphetamine was detected in one participant in the non-drug group.

Semantic processing

Indirect semantic priming (Table 2.2)

Reaction times (RTs). There was a trend for a main effect of group ($F(1, 42) = 2.65$, $p = .08$), with the ketamine group tending to have shorter RTs than the poly-drug group ($p = .081$). There was a significant main effect of SOA ($F(1, 42) = 5.50$, $p = .024$) with longer RTs at the short SOA than the long SOA. There was also a main effect of relatedness ($F(1, 42) = 5.483$, $p = .024$) with longer RTs for indirectly related words than unrelated words.

Table 2.1

Group means (sd) for demographics and current drug use

	Ketamine	Poly-drug	Non-drug
N	16	14	16
Age, years	26.88 (6.22)	24.50 (6.82)	26.56 (5.68)
Years in education	14.88 (3.22)	14.86 (3.39)	15.94 (2.24)
Spot the word, No. of words	50.00 (3.95)	51.00 (2.66)	50.31 (4.67)
Right handed (%)	68.75	78.57	93.75
Males (%)	50.00	57.00	50.00
Heterosexual (%)	68.75	71.43	100.00
Caucasian (%)	100.00	92.86	68.75
Current drug use			
Ketamine, grams per session	1.91 (1.17)		
days per month	7.97 (7.45)		
months used	44.25 (25.91)		
Cannabis, days to smoke 1/8 ounce	17.17 (23.63)	30.00 (29.85)	
days per month	3.06 (6.02)	6.93 (7.36)	
months used	40.36 (18.80)*	21.00 (16.57)*	
Ecstasy, pills per session	2.56 (2.38)	3.00 (1.68)	
days per month	1.86 (2.06)	2.03 (1.90)	
months used	42.56 (26.85)	25.33 (29.52)	
Cocaine, grams per session	0.53 (0.76)	0.36 (0.58)	
days per month	0.75 (0.83)	1.41 (2.23)	
months used	26.80 (25.24)	20.17 (16.07)	
Amphetamine, grams per session	0.26 (0.35)	0.54 (1.86)	
days per month	0.31 (0.35)	0.76 (2.12)	
months used	20.40 (16.05)	20.43 (23.52)	
Alcohol, units per session	6.16 (2.98)	6.75 (4.59)	4.56 (3.65)
days per month	8.81 (8.55)	10.5 (8.46)	8.31 (7.61)
months used	56.50 (48.57)	48.5 (49.49)	43.5 (46.93)

Note. sd = standard deviation

*p<0.05

Table 2.2

Group means (sd) for indirect and direct priming tasks

	Ketamine	Poly	Non-drug
Indirect priming– reaction times (ms)			
Related word, short SOA	651.15 (108.41)	750.54 (127.90)	691.95 (109.30)
long SOA	650.66 (122.75)	734.64 (134.22)	679.91 (116.45)
Unrelated, short SOA	653.11 (103.38)	739.21 (135.14)	686.93 (102.72)
long SOA	624.50 (99.53)	733.64 (132.04)	664.99 (105.49)
Indirect priming– error rates (%)			
Related word, short SOA	1.33 (3.03)	1.492 (2.99)	1.86 (4.27)
long SOA	1.05 (2.17)	0.00 (0.00)	0.69 (1.85)
Unrelated, short SOA	1.59 (2.57)	2.66 (3.80)	2.21 (3.39)
long SOA	2.33 (4.78)	1.67 (2.89)	0.73 (1.95)
Direct priming– reaction times (ms)			
Related word, short SOA, high frequency	761.76 (96.23)	786.400 (126.62)	719.42 (148.44)
low frequency	672.38 (88.83)	772.09 (128.57)	681.94 (90.01)
Related word, long SOA, high frequency	731.59 (91.41)	771.01 (117.78)	687.83 (96.79)
low frequency	693.95 (110.01)	757.06 (135.93)	667.39 (109.14)
Unrelated, short SOA, high frequency	696.99 (93.81)	765.18 (138.00)	667.35 (97.95)
low frequency	778.88 (127.73)	770.75 (158.23)	682.28 (97.60)
Unrelated, long SOA, high frequency	743.27 (91.08)	801.02 (138.09)	717.47 (100.83)
low frequency	708.67 (74.75)	796.34 (127.99)	702.21 (109.24)
Direct priming– error rates (%)			
Related word, short SOA, high frequency	9.14 (7.69)	14.87 (7.76)	9.29 (8.67)
low frequency	1.21 (3.20)	4.71 (5.80)	3.04 (4.46)
Related word, long SOA, high frequency	1.67 (4.40)	2.39 (6.12)	2.74 (4.71)
low frequency	0.67 (2.35)	2.95 (6.01)	1.11 (2.92)
Unrelated, short SOA, high frequency	2.81 (6.40)	5.35 (6.13)	0.00 (0.00)
low frequency	5.57 (6.56)	10.65 (7.06)	3.29 (4.83)
Unrelated, long SOA, high frequency	4.15 (6.55)	3.65 (4.82)	4.47 (6.99)
low frequency	5.45 (7.75)	5.66 (6.93)	3.42 (6.62)

Note. sd = standard deviation

Priming scores. To explore actual priming effects, priming scores were calculated (RT unrelated – RT indirect) for both SOAs. One sample t-tests were performed with the priming scores to analyse if priming was significantly different from zero. Significant priming was only observed at the long SOA ($t(44) = 2.17$, $p = .035$). The mean priming score at the long SOA across groups was negative (-14.58 ± 45.05) indicating faster responses to unrelated than indirectly related words. A 2 x 2 RMANOVA (group x SOA) of the priming scores did not yield any significant interactions or main effects.

Error rates (ERs). There was a significant main effect of relatedness ($F(1, 40) = 4.188$, $p = .047$) with higher ERs for unrelated than indirectly related words.

Direct semantic priming (Table 2.2)

Reaction times (RTs). There was a significant group x frequency interaction ($F(2, 43) = 3.64$, $p = .035$). This interaction was analysed using Bonferroni corrected paired samples t-tests, which demonstrated significantly longer RTs to high frequency words than low frequency words in the ketamine group ($p < 0.001$) but not in the other two groups (see Figure 2.1). The following interactions were also significant: relatedness x SOA ($F(1, 43) = 20.18$, $p < .0005$), with longer RTs to unrelated words at the long SOA than the short SOA; relatedness x frequency ($F(1, 43) = 7.987$, $p = .007$), with longer RTs to related, high frequency words than related, low frequency words; relatedness x SOA x frequency ($F(1, 43) = 7.91$, $p = .007$), reflecting longer RTs to related, high frequency words at the short SOA than related, low frequency words at the short

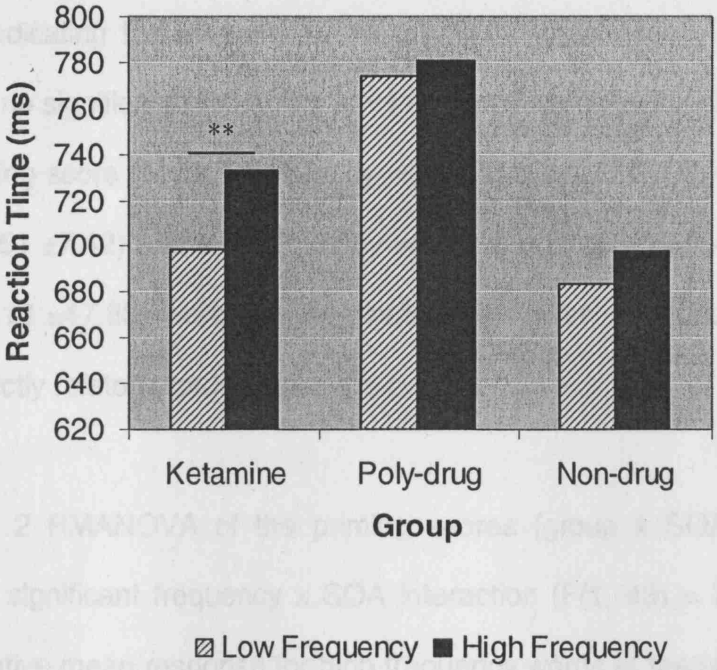

Figure 2.1. Group mean reaction time (ms) to high and low frequency words in the direct semantic priming task.
**p < 0.01

SOA. There was a trend for a main effect of group ($F(2, 43) = 2.78$, $p = .073$), with shorter RTs in the non-drug group than the poly drug group ($p = .077$). There was a main effect of frequency ($F(1, 43) = 17.839$, $p < .0005$) with longer RTs to high frequency words than low frequency words.

Priming scores. To analyse priming effects priming scores were again calculated (RT unrelated – RT directly related), for both levels of frequency (high and low) and SOA (long and short). One-sample t-tests revealed that there was significant priming across three of the four conditions. High frequency words at

a short SOA ($t(45) = 3.64$, $p = 0.001$) had a negative mean priming score (-47.40 ± 73.67) indicating faster responses to unrelated than directly related words. There was no significant priming for low frequency words at the short SOA. The mean priming score for high frequency words at a long SOA ($t(45) = 2.94$, $p = 0.005$) (23.51 ±7.42) and low frequency words at a long SOA ($t(45) = 3.15$, $p = 0.003$) (29.18 ±47.83) were positive, indicating slower responses to unrelated than to directly related words across the groups.

A 3 x 2 x 2 RMANOVA of the priming scores (group x SOA x frequency) revealed a significant frequency x SOA interaction ($F(1, 43) = 7.91$, $p = .007$) with a negative mean response for high frequency words at the short but not the long SOA. There was a main effect of frequency ($F(1, 43) = 7.987$, $p = .007$) with a negative mean response for high frequency words. There was also a main effect of SOA ($F(1, 43) = 20.181$, $p < .0005$), with a negative mean response for words at the short SOA.

Correlations. There was a significant positive correlation between days since last ketamine use and RT to high frequency word pairs in the ketamine group ($r = .534$, $p = .033$). No significant correlations emerged between total O-Life schizotypy score and RTs to high and low frequency word pairs in the ketamine group.

Error rates (ERs). There was a significant SOA x group interaction ($F(2, 40) = 5.874$, $p = .006$). This interaction was analysed using Bonferroni corrected

paired samples t-tests, which demonstrated significantly more errors to words at the short SOA than to the long SOA for the poly drug group ($p < .0005$) but not in the other two groups. Other significant interactions were: relatedness x SOA ($F(1, 40) = 16.255$, $p < .0005$), with higher ERs for related words at the short SOA than at the long SOA; relatedness x frequency ($F(1, 40) = 31.346$, $p < .0005$) with higher ERs for related high frequency words than related low frequency words; frequency x relatedness x SOA ($F(1, 40) = 14.035$, $p = .001$) with higher ERs for high frequency, related words at the short SOA, than for low frequency, related words at the short SOA. There was a significant main effect of group ($F(2, 40) = 6.772$, $p = .003$), with higher ERs in the poly-drug group than in the ketamine ($p = .016$) and non-drug groups ($p = .004$). There was a significant main effect of SOA ($F(1, 40) = 24.798$, $p < .0005$) with higher ERs at the short SOA than the long SOA.

Categories (Table 2.3)

Reaction times (RTs). There was a main effect of type of category exemplar ($F(4, 172) = 69.31$, $p < .0005$). Participant's RTs to exemplars of the 'borderline' and 'non-category but related' types were longer than the 'low frequency' and 'non-category and non-related' types; RTs for these conditions were all longer than for the 'high frequency' exemplar type.

Error rates (ERs). There was a trend for a group x type of category exemplar interaction ($F(8, 172) = 2.181$, $p = .082$). A Bonferroni corrected post-hoc test revealed lower ERs on the borderline type by the non-drug group than the

Table 2.3

Group means (sd) for measures of semantic processing

	Ketamine	Poly	Non-drug
Categories – reaction times (ms)			
High frequency	812.30 (128.25)	889.96 (145.32)	852.71 (159.82)
Low frequency	926.39 (104.46)	954.14 (139.15)	937.08 (156.77)
Borderline frequency	995.37 (105.90)	1109.99 (153.84)	1076.31 (184.53)
Non-category and related	1050.71 (175.68)	1160.49 (169.56)	1133.29 (161.38)
Non-category and unrelated	857.35 (140.25)	990.15 (156.97)	933.45 (161.83)
Categories – error rates (%)			
High frequency	3.10 (4.35)	3.51 (4.25)	2.39 (3.20)
Low frequency	9.48 (7.83)	10.13 (8.29)	8.41 (8.09)
Borderline frequency	39.54 (15.72)	39.22 (16.84)	25.62 (11.96)
Non-category and related	29.79 (16.93)	38.12 (18.91)	34.78 (17.75)
Non-category and unrelated	3.80 (5.90)	3.61 (5.39)	7.76 (7.88)
Nonsense sentences – reaction times (ms)			
True sentences, neutral valence	1155.15 (125.95)	1261.71 (130.07)	1180.15 (167.76)
emotional valence	1266.82 (107.42)	1302.69 (129.83)	1247.32 (156.58)
Unlikely sentences, neutral valence	1379.01 (128.50)	1428.74 (120.34)	1374.64 (126.09)
emotional valence	1346.20 (165.91)	1443.77 (168.08)	1441.97 (160.00)
Untrue sentences, neutral valence	1258.49 (143.20)	1369.38 (138.58)	1265.71 (130.59)
emotional valence	1311.94 (112.02)	1415.98 (125.67)	1338.43 (102.29)
Nonsense sentences – error rates (%)			
True sentences, neutral valence	3.09 (5.73)	3.78 (6.92)	4.30 (6.57)
emotional valence	4.22 (10.35)	4.93 (7.82)	3.04 (6.14)
Unlikely sentences, neutral valence	56.20 (19.71)	49.06 (19.76)	52.12 (20.33)
emotional valence	67.93 (16.37)	62.94 (27.11)	55.40 (21.07)
Untrue sentences, neutral valence	5.88 (8.56)	17.75 (18.90)	9.11 (9.78)
emotional valence	9.94 (7.10)	15.26 (14.85)	9.28 (9.55)
Verbal Fluency – correct (n)	16.44 (4.43)	16.64 (4.38)	14.38 (3.48)
Category Fluency – correct (n)	17.94 (3.59)	18.86 (4.22)	16.50 (2.71)

Note. sd = standard deviation

ketamine (p = .034) and poly-drug groups (p = .049). There was a main effect of type of category exemplar (F(4, 172) = 85.891, p < .0005). Participant's ERs for the 'borderline' and 'non-category and related' exemplar types were higher than

for 'low frequency'; ERs for these conditions were all higher than for 'non-category and non-related' and 'high frequency' exemplar types.

Correlations. As both drug groups had similar ERs on the borderline condition of the Categories task, cannabis use was correlated with this aspect of performance, however no significant correlations were observed. In addition, the total O-Life schizotypy score did not correlate with error rates in this condition.

Nonsense sentences (Table 2.3)

Reaction times (RTs). There was a trend for main effect of group ($F(2, 41) = 2.648$, $p = .083$), with the ketamine group tending to have shorter RTs than the non-drug group and the poly-drug group ($p = .093$). There was a significant main effect of sentence type ($F(1.715, 41) = 40.188$, $p < .0005$), with shorter RTs for true sentences, followed by untrue sentences and then unlikely sentences. There was a significant main effect for valence ($F(1, 41) = 28.19$, $p < 0.0005$), with faster RTs to neutral sentences than to emotional sentences.

Error rates (ERs). There was a significant sentence type x valence interaction ($F(2, 84) = 7.209$, $p = .001$) with higher ERs for unlikely sentences with emotional content than to unlikely sentences with neutral content. There was a significant main effect of sentence type ($F(1.166, 48.966_{GG}) = 223.008$, $p < 0.0005$) with higher ERs for unlikely sentences followed by untrue sentences and then true sentences. There was a significant main effect of valence (F(1,

42) = 6.609, p = .014) with higher ERs for emotional sentences than for neutral sentences.

Fluency (Table 2.3)

There were no significant differences between the groups in the number of correct responses on the verbal fluency and category fluency tasks. Error rates were at floor and were therefore not analysed.

Subjective experiences (Table 2.4)

O-Life

There was a significant group difference in total O-Life scores (F(2, 43) = 3.807, p = .03) which reflects the ketamine group scoring higher than the non-drug control group (p = .029). Further, there was a group difference on the unusual experiences factor of the O-Life (F(2, 43) = 4.818, p = .013), reflecting higher scores by the ketamine group than the non-drug control group (p = .01). There was a trend for a significant group difference in impulsive non-conformity (F(2, 45) = 2.659, p = .082) with the ketamine group tending to score higher than the non-drug group (p = .092).

Correlations. To explore the group difference, current cannabis use in the ketamine and poly-drug groups was correlated with the overall O-Life schizotypy score. No significant correlations emerged.

Table 2.4

Group means (sd) on O-Life, PDI and DES

	Ketamine	Poly-drug	Non-drug
O-Life – total score	16.69 (5.99)*	14.71 (6.76)	10.56 (6.47)*
unusual experiences	5.25 (2.32)**	4.00 (2.25)	2.69 (2.41)**
cognitive distortions	5.44 (2.71)	4.86 (3.37)	3.19 (2.99)
introverted anhedonia	1.06 (1.12)	1.36 (1.34)	1.38 (2.03)
impulsive non-conformity	4.94 (2.52)	4.5 (2.28)	3.31 (1.14)
PDI – total score	7.19 (2.99)	8.64 (2.95)*	5.19 (3.31)*
distress	1.86 (0.65)	2.20 (0.84)	1.80 (0.75)
pre-occupation	2.09 (0.71)	2.17 (0.77)	1.61 (0.77)
conviction	2.71 (0.56)	2.94 (0.50)	2.81 (0.50)
DES - total score	630.00 (485.39)	631.43 (409.8)	336.88 (221.38)

Note. sd = standard deviation; O-Life = Oxford-Liverpool Inventory of Feelings and Experiences; PDI = Peter's et al. Delusions Inventory; DES = Dissociative Experiences Scale.
*p<0.05, **p<0.01

PDI

There was a significant group difference in the total PDI scores (F(2, 45) = 4.73, p = .014), with post-hoc comparisons showing that the poly-drug group scored higher than the non-drug group (p = .012). There were no group differences on any of the PDI factors.

DES

There was a trend for a significant group difference (F(2, 43) = 3.002, p = .06) with the ketamine group scoring higher than the non-drug group, although post-hoc comparisons were non-significant (p = .114).

Discussion

Main findings

In general, chronic recreational ketamine users, poly-drug and non-drug users were found to perform similarly on semantic processing tasks. The hypothesis relating to ketamine use and semantic priming deficits was not supported. However, on the direct semantic priming task ketamine users responded significantly more quickly to low frequency words than to high frequency words; this was not observed in poly- and non-drug users. There were no group differences on other measures of semantic processing. The ketamine group rated themselves higher than non-drug users, but not poly-drug users, on a measure of schizotypy. The groups were well matched on demographic variables and pre-morbid functioning.

Semantic processing

The main group difference was on the direct semantic priming task. On this task the ketamine group exhibited an idiosyncratic pattern of faster reaction times to low frequency than high frequency words. This pattern is not demonstrative of an access or storage problem (Warrington & Shallice, 1979) and does not supply any direct evidence for whether there are semantic deficits in chronic ketamine users.

On the direct semantic priming task there was a tendency for impaired performance to related high frequency word pairs during unconscious

processing, compared to related low frequency words during conscious processing. This pattern of performance was also demonstrated in the error data. Additionally, there were higher error rates at the short SOA than long SOA, implying impaired unconscious processing.

On the indirect semantic priming task the three groups performed similarly. Importantly, there was no evidence for normal priming effects in any group on the indirect priming task, i.e., there were similar reaction times to indirectly related and unrelated word pairs. However, each of the groups exhibited inverse priming at the long SOA, i.e., during conscious processing. Despite the absence of priming for indirectly related words, there was a greater level of accuracy for indirectly related than unrelated words across groups.

In respect to the other tasks that tapped semantic processing, the most interesting finding was on the categories task. There was a trend for the ketamine and poly-drug users to make more errors on the borderline condition (e.g., sport-dancing) than the non-drug group. The borderline condition is the most complex condition in this task, thus it is possible that the current data reflects a very subtle change in the organisation of the semantic system. If this is the case, the differences cannot be attributed to chronic ketamine use as both the ketamine and poly-drug groups had similar error rates. However, there was no significant correlation between error rate and cannabis use in each of the groups.

On the other semantic processing tasks there were no group differences. Further, group performances did not demonstrate any access or storage problems.

Comparisons with existing literature

The ketamine specific deficit on the direct priming task, i.e., faster reaction times for low frequency words than high frequency words, has not been reported previously. An explanation that may account for this finding is based on connectionist models of semantic memory (e.g., Neely, 1977; cited from Neely, Keefe & Ross, 1989). Collins and Loftus (1975) proposed that the activation of a prime-related node reduces the necessary stimuli for subsequent recognition, thus resulting in faster response times. An extension of this process that fits the current data is that the presentation of high frequency words activated too many associated 'nodes' and overwhelmed the semantic network of chronic ketamine users, thus slowing down processing. A similar idea relates to neural network models of NMDA-R assemblies, which suggest ketamine may impair the ability to inhibit previously activated nodes, resulting in a disruption to priming (Nestor et al., 2001). High frequency words are, by definition, more likely to have 'their' node activated thus impairing performance. Both of these explanations relate to unconscious processes.

The absence of group differences in priming on the direct priming task is in contrast to Morgan, Rossell et al's (2006) recreational ketamine study. Interestingly, their ketamine specific pattern of inverse priming for low frequency

words at a long SOA is the opposite of the inverse priming evident across groups in the current study (i.e., inverse priming for high frequency words at the short SOA). Further, the current results are inconsistent with Morgan, Bedford et al's (2006) study of priming in people high and low in schizotypy, which did not find any frequency effects. Instead, they reported greater priming at the long SOA than the short SOA for people high in schizotypy and the reverse pattern for people low in schizotypy. On the other hand, Moritz et al. (1999) found that people with high-proneness to schizophrenia had enhanced priming effects at the short SOA than at the long SOA. Thus, a number of studies report conflicting results, with each supporting different aspects of theory, i.e., enhanced automatic processing (e.g., Moritz et al.) versus impaired conscious processing (e.g., Morgan, Rossell et al.; Morgan, Bedford et al.).

Methodological differences between the studies may account for the different findings. Whilst the structure of the direct semantic priming tasks used in the studies were comparable the word stimuli were different, and the current study used shorter SOA's. In contrast to Morgan, Rossell et al's (2006) recreational ketamine experiment, the current study did not stipulate that participants had to be three days abstinent. However, urinalysis revealed relatively low levels of drugs in the current participants.

This is the only study to have used an indirect semantic priming task with recreational ketamine users, and no group differences were found. Importantly, there was no evidence of normal priming by any of the groups on this task. This

calls into question the validity of the indirect priming task used in this study. To recapitulate, the rationale in using an indirect priming task is that the prime and target words are semantically related, but to a lesser degree than two directly related words. Hence, the conscious process of semantic matching can be assessed. A lack of normal priming can be interpreted in three ways. Firstly, that semantic matching was impaired in each of the groups; this is not very plausible. Secondly, it is suggestive of an absence of a semantic relationship between the two words, because they are too distantly related, i.e., they are processed as unrelated word pairs. Thirdly, it can be argued that some people will always be able to develop an association between two words, even technically unrelated word pairs. Thus, all word pairs may have been treated as indirectly related words. Due to the lack of priming the indirect priming stimuli were rated by the researcher as indirectly related, unrelated and pseudo word pairs, and compared to the original classifications. There was 82.6% agreement on the rating of indirectly related words. Thus, a number of words were so low in semantic strength that there was no agreement that they were indirectly related.

Considering the unusual findings from the two semantic priming tasks, it is important to consider the context of the participants' performances. Participants knew the purpose of the study, thus ketamine users may have been motivated to do well. Despite there being a pattern of alternating between semantic and other tasks, there may have been interference between the tasks. This possibility is enhanced as most participation occurred in the evening (i.e., after

work) and the length and nature of the experiment may have interacted to induce boredom and reduce concentration.

Rossell and Stefanovic's (2007) review of semantic priming effects in schizophrenia discusses experimental aspects of the priming task that may help to elucidate the current findings. They concluded that there is inconsistent evidence for a clear relationship between SOA and priming effects, thus the shorter SOAs employed in the current study may not be accountable for the lack of priming effects. However, it is possible to speculate that the short SOA in the current study was too short and that automatic processing was interrupted by the presentation of the target word. Rossell and Stefanovic also reported that if the proportion of related pairs to unrelated pairs is greater than 25%, priming is more likely. The current direct and indirect semantic priming tasks had 25% and 27.7% (a corrected figure accounting for inter-rater disagreement is 22.9%) related pairs, respectively, so may have had a marginal effect on priming.

The nature of the relationship between the prime and the target also impacts on priming effects. Ober, Vinogradov & Shenaut (1995) investigated horizontal/associated pairs (i.e., members of the same category, e.g., bird and cat) and vertical pairs (i.e., category superordinate and subordinate, e.g., bird and flamingo). They concluded that lack of a priming effect in people with a diagnosis of schizophrenia was more likely for horizontal than vertical pairs. The current priming tasks used horizontal pairs. This may account for the lack of normal priming in ketamine users in the indirect task, but not in either of the

control groups. Further, the direct priming task used horizontal pairs and there was priming, however, there were no group differences.

The similar group performances on the fluency tasks reflect a mixture of previous study findings: a ketamine induced long-term deficit has been reported for category but not verbal fluency (Curran & Morgan, 2000; Morgan, Monaghan et al., 2004).

The findings from the other semantic processing tasks are consistent with Morgan, Bedford et al's (in prep.) assessment of semantic processing in schizotypy. They reported a subtle "idiosyncratic organisation of semantic information... [that makes] them less effective on..." (p.19) the categories task. They reported an absence of global semantic impairments as assessed by other tasks.

Subjective experiences

The ketamine group scored higher in schizotypy, as assessed by the total O-Life score and the unusual experiences factor of the O-Life, than the non-drug control group. However, there were no differences between the ketamine and poly-drug groups. Unusual experiences reflect 'positive' symptoms of psychosis, such as "perceptual, hallucinatory and magical thinking" (Mason, Claridge & Jackson, 1995, p. 7). This data can be interpreted in three ways. Firstly, that chronic ketamine use results in elevated schizotypy. Secondly, that people high in schizotypy are more likely to use ketamine and other recreational

drugs. Thirdly, the lack of statistical difference between ketamine and poly-drug users' schizotypy scores implies that other drug use may contribute, mostly reflecting 'positive' experiences. However, the finding that current cannabis use did not correlate with overall schizotypy in either the ketamine or poly-drug group does not lend support to this latter interpretation.

Previous studies of recreational ketamine users have only made comparisons to poly-drug users and not to non-drug controls. Comparable schizotypy levels between ketamine and poly-drug users is in accordance with some previous research (e.g., Morgan, Riccelli et al., 2004; Morgan, Rossell et al., 2006) but not others (e.g., Curran & Morgan, 2000; Morgan, Monaghan et al., 2004). It is important to note that previous studies assessed schizotypy three days after drug use, whilst days since last drug use varied in the current study. Additionally, this is the first chronic ketamine study to have assessed schizotypy with the O-Life questionnaire.

Interestingly, the poly-drug group scored higher than the non-drug group on the PDI. Whilst this was unexpected, there was no difference between the poly-drug and ketamine groups' scores. It is important to consider the similarity of the constructs that are measured by the O-Life, particularly the unusual experiences construct, and the PDI. That the ketamine group scored higher on the O-Life, and the poly-drug group scored higher on the PDI, calls into question the reliability of the data. Although the data is meant to capture experiences in 'normal day to day life', it is possible that participant's self-ratings also capture

their 'on drug' experience. It is impossible to discern the extent to which the results may reflect the effects of a range of drugs, or pre-existing group differences.

As predicted, there were no group differences on the measure of dissociation.

Limitations of the study

The current sample of 46 participants is the largest in the chronic ketamine literature. Nonetheless, it is not a large sample, and was divided amongst three (compared to the usual two) groups of participants, which may have reduced the study's power. Whilst the majority of drug using participants were recruited via a number of similar internet forums, recruitment did not benefit from substantial 'snowballing'. Further, the non-drug group tended to be recruited via the researcher's contacts. Thus, despite the groups being well matched on age, years of education, pre-morbid functioning and non-ketamine current drug use, they may have been a heterogeneous sample and differed in other ways, e.g., impulsiveness (Curran, 2000). Recreational drug research is complicated by the difficulty in recruiting participants, and this subsequently impacts on the representativeness of study samples. Pertinent to all recreational drug research is the prohibition of the entity that is being investigated, which may disproportionately inhibit participation from members of some groups of society more than others.

Scientific and clinical implications

The findings herein suggest that twice weekly ketamine use for a period of approximately 3.5 years does not impair semantic memory. It is important to consider that although this sample were chronic ketamine users, their use tended to reflect weekend clubbing, i.e., recreational. However, there were a few participants who used ketamine daily, illustrating the broad range of ketamine use. In light of very heavy ketamine use, and of recent reports of ketamine dependence (Critchlow, 2006), it may prove fruitful for researchers to separate out the effects of recreational and daily ketamine use. It is possible that greater frequency, and more chronic use, of ketamine has more detrimental effects.

The absence of a normal priming effect in the indirect semantic priming task raises the issue of whether it was an adequate task. The results from the direct priming task contrast with those previously found (Morgan, Rossell et al., 2006). This highlights the inconsistent findings from a vast number of studies into semantic memory in the fields of schizophrenia and schizotypy, and may question the validity of the semantic priming paradigm. Alternatively, the current pattern of results between the ketamine and poly-drug groups, especially for the subjective findings, may be suggestive of either (i) something unique about the current sample, or that (ii) other long-term substance use can elevate schizotypal and delusional experiences.

Conclusion

The current study employed a comprehensive range of semantic processing tasks that have not previously been used with chronic recreational ketamine users. No overall semantic processing deficits were found, although the ketamine group responded to low frequency words more quickly than high frequency words. They also scored higher on a measure of schizotypy. Further, there were no correlations between performances on cognitive and subjective measures. The findings do not lend support to the NMDA-R hypo-function model of schizophrenia.

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Part 3: Critical Appraisal

Introduction

This critique presents an opportunity to reflect upon my experience of carrying out this piece of research. I have focused on the following areas: conducting research in the context of a Doctorate in Clinical Psychology; the phenomenon of naturalistic drug studies generally, and specific methodological considerations and clinical implications of the current study.

Research in the context of a Doctorate in Clinical Psychology

On my first day of the Doctorate in Clinical Psychology at UCL I can remember another trainee clinical psychologist telling me the topic of their thesis research, and asking me the topic of mine. I did not have an answer, in fact I was clueless. Further, I was surprised that someone else had already made their choice, and was sceptical about whether they would remain true to their early conviction. In contrast, I decided that I would keep my options open; options that I was confident would be delivered via clinical placements and visiting lecturers.

During my first year I was interested in two areas of research: attention deficits in children with HIV/AIDS, and the effects of recreational drug use on cognition. I investigated both of these areas, speaking to different researchers and potential supervisors. I became aware of a need to strike a balance between my own research interests and the other demands of the training course. In

particular, I had to 'fit' my thesis into one or two days a week, within a two year period. In respect to time, there is a stark contrast between carrying out a thesis in the context of a Doctorate in Clinical Psychology and a standard PhD; on the other hand, the thesis is a smaller scale piece of work. Additionally, being on a course with 41 other trainees in my year meant that internal supervisors were not at a premium; this could be counterbalanced by finding an external supervisor who had enough research experience and was used to supervising doctoral theses. Hence, there was a tension between doing exactly what I wanted (if I could work that out!) and conducting a piece of research that was feasible.

We were encouraged to work in teams and although I was happy to do this I carried out this piece of work independently, with support from my supervisors. At times I would have enjoyed the company and support of a fellow trainee, especially in recruiting participants; this proved to be the greatest challenge in executing the study. However, in hindsight, and having heard tales from other trainees, I am glad that I worked on my own! From the beginning it meant that I had to assume full responsibility and thus control of the project. I was able to set my own deadlines for completing different tasks of the project, which was important given the narrow time margins.

In respect to writing-up the thesis, there were a number of challenges. The literature review is based on a limited number of studies, reflecting the almost embryonic stage of research into the long-term effects of chronic ketamine use.

Whilst at times I thought that this would make the review an easy process, the opposite was true. I had to combine the information in a way that I hoped would enliven the reader and guide them through the intricacies of the research, rather than induce tedium through a potentially repetitive naming of the same studies. However, the greatest challenge for me was in understanding the unique data set that I collected, which painted a different picture to the one that was predicted. In trying to sift through the potential meanings, I had to remind myself of the importance of staying close to the hypotheses, and therefore restrain myself from 'fishing' for statistically significant findings.

Upon reflection, many of the constraints and challenges that were present during the current experience are comparable, or identical, to the challenges present in research in general. There will always be a tendency towards a struggle between research interests and available resources; between the need to answer the questions posed and the desire to look for something of significance, and between writing an article that contains enough information to facilitate understanding and replication, without its value becoming misplaced due to its brevity or length. I have experienced these tensions in previous research settings, and I hope to be more prepared for them the next time they arise.

Reflections on the phenomenon of naturalistic drug studies

Naturalistic drug studies are compromised by a number of factors, such as poly-drug use, study design and recruitment difficulties, which are discussed below.

Ethical approval will not be granted to repeatedly administer a pure dose of ketamine to a drug naive participant. It can be argued that studies should recruit people who only use ketamine (e.g., Narendran et al., 2005). However, it would be very difficult to recruit a sample and it would not be representative of most ketamine users. Therefore, an especially important consideration in interpreting the findings from drug studies is the normative nature of poly-drug use; each person has their own unique history of drugs and drug mixtures with unknown interactions and effects. Additionally, naturalistic drug studies tend to use independent group designs, which introduce their own set of problems such as matching participants. Unfortunately it is very difficult to apply more sophisticated designs such as double-blind designs, as participants know their own drug history and therefore which group they are in.

Some of the difficulties relating to participant recruitment are illustrated in the following extract from a website interview (that was not broadcast) which I took part in to aid recruitment:

> Interviewer: Why do you think so few people have come forward? Do you think it's a legal issue or are people embarrassed or ashamed of their drug use? Do

you think a period of decriminalisation is necessary to encourage honest and in-depth scientific research into drug use and its short- and long-term effects?

Justin: Ideally we want to create a situation where people can be honest to enable researchers to give informed answers.

A good number of people have made contact but not all have turned into... participants. That could be for a number of reasons. [I] send people more information and they often don't want to do it. People worry about confidentiality, and some may not fulfil the criteria, for example, if they're under eighteen [years]. Some do arrange a date, then... [I] don't hear back.

Overall I'm quite impressed by the response. If all contacts turned into volunteers I'd be done and dusted! ...I've actually met about 20 people and only one didn't turn up. So those who commit do follow through! I can completely understand people who don't want to take part, and I am relying on someone's goodwill. You need to allow between 1.5 and 2 hours for testing, then there's travel time, so although we're paying £15, it's just a token really. Some people do it for the money, some because they find it interesting and important. ...[the study will] be written up and submitted to the university. I will be able to post... information about the main findings as it's important to keep people in the loop and informed...

The criminalisation of drugs means that drug use is often shrouded in secrecy. Thus, potential volunteers are often and rightly concerned about confidentiality. Some people are reassured by a researcher's steps to ensure anonymity and confidentiality, however, many are not. Evident in recruitment for the current

study was an air of paranoia, with people on websites sometimes concerned that I was an undercover policeman.

Another factor linked to the prohibition of drugs is the shame that some people may experience as a result of their recreational drug use. This may be especially pertinent for people who have unsuccessfully tried to reduce their drug use. Additionally, several participants told me that they knew people who did not want to take part in the study because they did not want to know about any possible adverse effects of their drug use.

Further, due to the level of payment offered to people, it is likely that recreational drug studies are "inherently biased towards attracting participants on a low income and with time to spare" (Participant 'A'). In the current study participants were paid £15 to compensate them for their time. For the average member of the ketamine and poly-drug groups this payment equated to £8.57 per hour. However when travel time is included, estimated at 1.5hours for a return journey, the hourly rate is £4.62. Thus, participants were paid below the minimum wage (i.e., £5.35 per hour for someone aged 22 years and older). Additionally, some participants had to pay their travel costs as they did not have Transport for London travel cards. Although the participant payment is only meant to be a 'contribution', it highlights the fact that successful recruitment (for many studies) relies upon participant 'altruism'.

It is likely that the above factors lead to a disproportionate representation of some groups in society taking part in recreational drug studies, thus affecting the validity of their findings.

Methodological considerations of the current study

Outlined and discussed below are a number of study specific methodological limitations.

Days since last drug use

In some previous studies into the effects of ketamine use participants were assessed immediately after drug ingestion and three days later (e.g. Curran & Morgan, 2000). In general, these studies reported no, or minimal, drug use between the two assessment sessions. In the current study assessment took place at one time point, when participants were free from the influence of drugs only. However, the time period between drug ingestion and assessment was not stipulated. One participant commented that participating in the study on a Monday, compared to later in the week, would result in a poorer performance; this could have been due to a variety of factors, for example, drugs still being in the body, a 'hang over' or sleep deprivation.

Accuracy of drug history

Asking participants to provide details of their drug history is problematic, as their account may be subject to several biases, including: social desirability, memory

inaccuracies and a lack of knowledge of drug weights (e.g., an ounce versus an eighth). To minimise the error in estimating drug usage, 'current days used per month' was used in some analyses instead of 'quantity used per session' as the former is likely to be more accurately recalled by participants. Additionally, it is not possible to know the purity of a drug. Indeed, ketamine has been suggested to have entered the UK clubbing scene as a result of having been cut in to into 3, 4-methylenedioxymethamphetamine (MDMA, Ecstasy) (Dalgarno & Shewan, 1996). Thus, it is possible that participants in the poly-drug group had unknowingly consumed small amounts of ketamine.

Drug screening

In the current study participants provided a urine sample for analysis of recent drug use; this provided an objective test of recent drug use. A limitation of urinalysis is that it only provides a record of drug consumption in the last few hours or days. Ketamine has a short half life (Ricaurte & McCann, 2005) meaning that it leaves the body in approximately 8 hours. Thus, urine analysis cannot provide an accurate picture of long-term drug use. An alternative, although vastly more costly, procedure is hair analysis. Hair provides a record of drug use for the period of time that a piece of hair has been growing. For example, in Narendran et al's (2005) study, participants were required to have at least 3cm of hair which enabled assessment of drug use for at least three months. The reason for not using hair analysis in the current study was cost.

Length of the study

The length of time taken by participants to complete the study varied from approximately 1hr 30min to 1hr 45min. Thus, participants were required to concentrate for a fairly long period of time; a number of participants commented that they were aware that they made more acquiescence errors as they progressed through the study. To protect the data from being subject to fatigue effects the study procedure incorporated the following methods: (i) the first and last tasks were counterbalanced across group and participant, (ii) order of presentation alternated between pen and paper tasks and computer tasks, (iii) the structured interview to collect participant's drug history took place in the middle of the procedure, providing a break, and additionally, (iv) participants were able to take a break at any point during the study. When the study procedure was initially thought about, complete counterbalancing was considered. However, counterbalancing presents its own problems, e.g., possible *variable* task interference effects, and error-proneness in administering tasks. It may have been useful to have used a measure of fatigue to identify if it co-varied with task performance.

Use of British English language words

The study was based on British English language words and participants were required to have English as their first language, although this did not exclude people who were bilingual. In the current study three participants were fluent in Afrikaans and informed me that the English non-word 'kolp' is slang for 'to hit' in Afrikaans. Further, another participant noted that some of the English non-

words were correctly spelt in American English, for example, 'color'. Although no participants were of American origin, it is possible a participant might have had difficulty differentiating between American English and British English spelling. Whilst I do not think that this had an effect on the overall findings, I would recommend that future studies consider removing words that are real words in other languages.

Fluency tasks

This study utilised the category generation and letter fluency tasks in its assessment of semantic processing. However, it did not incorporate the category switching task, i.e., alternating between generating exemplars of two different categories. For example, a participant might be asked to alternate between generating examples of the category 'furniture' followed by the category 'fruit' followed by the category 'furniture', and so on. Participant's performance is measured on the number of correct switches between categories as well as correct exemplars generated for each category. The ability to switch between categories is a more difficult and complex task than generating examples from a single category. Thus, it is thought to be more sensitive to frontal lobe activity. A consequence of not using the switching task is being unable to ascertain a person's level of cognitive flexibility, thus participants with minor impairments in semantic processing may have been missed. However, other tasks in the study were probably more sensitive than these, such as semantic priming.

Measures of mood

The current study did not assess participant's mood. The rationale for this was that, with the exception of one study (Curran & Morgan, 2000), ketamine and poly-drug users were not found to have differences in affect. Additionally, due to the length of the study compromises were made. Further, the exclusion criteria of a history of, or current, psychiatric condition is likely to have minimised the possibility of mood as a confounding variable.

Religiosity

In the Peters et al. Delusions Inventory (PDI) a number of questions (numbers 8, 11, 12 & 14) are likely to be scored more highly by people who are religious, or from particular cultural backgrounds. It is possible that the scoring of the PDI misinterprets and misrepresents an individual's religious or cultural convictions as indicative of delusional beliefs. This may have been pertinent in the finding that the poly-drug group scored more highly than non-drug controls, but not the ketamine users, on the total PDI score. Future studies using the PDI may benefit from recording data on participants religious beliefs.

Clinical implications

The empirical paper noted the broad range in the frequency of ketamine use, from weekend to daily use. Furthermore, there is increasing evidence of ketamine being used outside of its original 'clubbing' domain. For example, Lankenau et al. (2007) reported on the practices of ketamine injecting drug

users in the USA. Several participants in the current study had been using ketamine for more than seven years, which is twice as long as the group mean. Additionally, a number of participants told me that they had tried unsuccessfully to stop their ketamine use. Thus, there is evidence for an emerging population of dependent and problematic ketamine users.

Within my capacity as a trainee clinical psychologist in a substance misuse service, I worked with someone who was psychologically dependent on ketamine. Their ketamine use occurred in the context of a long history of poly-drug use and mental health problems; this is a common pattern in people who access substance misuse services. If I had not been an additional resource in the service they would have been directed towards voluntary sector services. However, some voluntary sector services that receive funding for this type of work are already stretched to capacity working with people with, for example, heroin and crack-cocaine problems. It is important that there is scope for supporting people with ketamine use difficulties. Escalating and prolonged problematic ketamine use may carry consequences in terms of cognitive and subjective experiences, as well as exacerbating other difficulties.

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Appendices

Appendix A

Approved ethics application form

Amendment Approval Request Form

1. ID Number:	Name and Address of Principal Investigator:
0052/001	Clinical Health Psychology, UCL

2. Title of Project:
The determinants and psychological consequences of ketamine use (v 2)

3. Information about the amendment:

(a) Is the amendment purely administrative? YES

(b) Has the Participant Information Sheet/Consent Form been changed as a result of the amendment? YES If yes, please enclose a copy - enclosed

4. Summarise the issues contained in the amendment. Mr Justin Grayer, a postgraduate student (on the UCL Doctorate in Clinical Psychology), will be using a different psychological test (indirect semantic priming) with three of the groups involved in the main project (ketamine users, polydrug users and drug naive controls). He will recruit new participants who are not involved in the main project. The test of semantic priming asks participants to determine whether each of a series of stimuli is a real English word or not. Priming is indexed by reaction times to words which follow semantically related words. It is a widely used 20 minute test which does not produce any distress or fatigue. Mr Grayer will also be administering some of the questionnaires used in study 0052/001.

5. Please give any other information you feel may be necessary:
As in the main study, participants will be paid £7.50 per hour to compensate for their time and inconvenience. They will also be asked to provide a urine sample to screen for recent drug use (this project does not have the funding of the main project to analyse saliva and hair). There will be 16 volunteers in each of the three groups.

Signature of Principal Investigator: **Date of Submission: 2nd December 2005**

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been ....Approved.... **by the Research Ethics Committee.**

Chair's Signature: **Date:** 7/12/05.

Please return completed form to:
Secretary of the UCL Research Ethics Committee
Graduate School, North Cloisters, Wilkins Building
Gower Street, London WC1E 6BT

Appendix B

Participant Information Sheet

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY

UCL

VOLUNTEER INFORMATION SHEET

The determinants and psychological consequences of ketamine use (version 2) - An investigation of the long term effects of an NMDA-receptor antagonist on semantic processing and mental state

Investigators:

Purpose of the study:
To determine the long term effects of recreational ketamine use on mental processing.

INFORMATION LEAFLET FOR VOLUNTEERS

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY?

We are interested in the effects of recreational ketamine use on mental functioning and personal experiences.

SOME BACKGROUND TO THE RESEARCH

Ketamine as a drug has been shown in laboratory studies to have effects in brain areas important for memory and mental state. With many other drugs there are also long term effects; for instance people who drink lots of alcohol often find their memories are not as good as they were. This can often be affected by factors such as the length of time they have been drinking and the quantity that they drink. The present study aims to find out what the long-term effects of using ketamine may be, by examining how any changes in cognitive functioning are related to changes in drug use.

WHAT WILL BE STUDIED?

We will be looking at memory as well as mood and mental state in people who take ketamine, people who take other drugs but not ketamine and people who do not take any recreational drugs.

Appendix C

Participant Consent Sheet

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY

CONSENT FORM

CONFIDENTIAL

Title of study: The determinants and psychological consequences of ketamine use (version 2) - An investigation of the long term effects of an NMDA-receptor antagonist on semantic processing and mental state

Investigators: Justin Grayer, Celia Morgan, H. Valerie Curran

Please complete the following: *delete as necessary*

1. Have you read the information sheet ? YES / NO
2. Have you had an opportunity to ask questions and discuss this study ? YES / NO
3. Have you received satisfactory answers to all your questions ? YES / NO
4. Have you received enough information about this study ? YES /NO
5. Which investigator have you spoken to about this study ? .....
6. Do you understand that you are free to withdraw from this study:
   * at any time YES / NO
   * without giving a reason for withdrawing YES / NO
7. Do you agree to take part in this study ? YES/ NO

Signed..... Date.....

Name (please print) .....

Investigator.....