Psychopharmacology (2006) 188:408–424
DOI 10.1007/s00213-006-0572-3

REVIEW

Acute and chronic effects of ketamine upon human memory: a review

Celia J. A. Morgan · H. Valerie Curran

Received: 20 April 2006 / Accepted: 9 August 2006 / Published online: 28 September 2006

Abstract
Introduction Ketamine is attracting increasing research interest not only because of its powerful amnestic effects but also as a putative model of schizophrenia and as a substance with an expanding following of recreational users.
Objective This article reviews the existing literature on the effects of acute ketamine on the memory of healthy volunteers and of repeated doses of ketamine in recreational users.
Current trends Although there have been relatively few, often methodologically diverse, studies to date of the mnemonic effects of ketamine, there is an emerging consensus that an acute dose of the drug impairs the manipulation of information in working memory and produces decrements in the encoding of information into episodic memory. Preliminary evidence suggests that ketamine may differ from other classic amnestic drugs in impairing aspects of semantic memory. Acute-on-chronic effects in ketamine users generally mimic the pattern seen in controlled studies with healthy volunteers. However, chronic ketamine use may be associated with a more specific pattern of memory decrements and with episodic memory impairment, which might not abate following cessation of use.
Future trends An important aim of future research should be to detail the specificity of ketamine's amnestic effects on both a neuropharmacological and a cognitive level.

C. J. A. Morgan (✉) · H. V. Curran
Clinical Psychopharmacology Unit,
Sub-department of Clinical Health Psychology,
University College London,
Gower Street,
London WC1E 6BT, UK
e-mail: c.morgan@ucl.ac.uk

Keywords Ketamine · NMDA · Working memory · Episodic memory · Semantic memory · Drug abuse · Glutamate

Introduction

The aim of this review is to explore the nature of memory and related impairments induced by ketamine. Characterising the cognitive effects of ketamine is important with respect to three broad areas of research: memory, schizophrenia and substance use. The effects of ketamine are relevant to memory research as its main action is as an antagonist of the *N*-methyl-*d*-aspartate receptor (NMDA-R), which is considered to be of vital importance in mechanisms of synaptic plasticity and neuronal learning such as long-term potentiation and long-term depression. It is also suggested that age-related decreases in NMDA receptor function may contribute to age-related memory decline (see Newcomer and Krystal 2001 for a review). Another of the intriguing properties of ketamine is its capacity to induce certain cognitive and negative symptoms which are similar to those observed in schizophrenia. Ketamine has thus been widely investigated as a potential pharmacological model of schizophrenia. Whilst the drug's effects on memory are given some consideration in the current review in the context of schizophrenia research, the reader is directed to another recent review (Fletcher and Honey 2006) for a more detailed discussion of this topic. Ketamine research is also pertinent to substance misuse as an increasing number of young people are now taking this drug recreationally (DrugScope 2005) and there is evidence that some users may develop dependence (Hurt and Richie 1994).

Ketamine is a potentially important research tool in exploring the overlap between memory impairment, schizo-

phrenia and substance use. For example, there is a high comorbidity between schizophrenia and substance use disorders (Chambers et al. 2001) and both schizophrenia and chronic substance use have been associated with impairments of memory and executive function (Goldstein and Volkow 2002). Even though human research on the mnemonic effects of ketamine is a young and currently expanding field, and studies are often methodologically diverse, it seemed timely to review and draw out implications for future research.

In this review, we first summarise the literature that has examined (1) the acute effects of ketamine on memory in laboratory studies with healthy volunteers and (2) chronic effects in recreational ketamine users. This part of the review will adopt a 'memory systems' approach as a theoretical scaffold and attempt to link together findings from different studies both within and across memory systems. Following this, we consider the specificity of ketamine's effects, both pharmacologically and cognitively. Finally, we consider the relationship between findings with acute and chronic ketamine and cognitive deficits in schizophrenia.

Memory systems and ketamine

In 1994, Schacter and Tulving published an influential essay on memory systems. Tulving defined a memory system in general as 'a set of correlated processes' (Tulving 1985 p 386; cf. Schacter 1999). Differing memory systems have been identified by their representation of different kinds of information, in addition to distinct neurobiological underpinnings. Separable—but interactive—memory systems were suggested to have different laws and principles characterising their operation and differences in their ontogenetic and phylogenetic development (Schacter 1999). The memory systems model was developed from the findings of cognitive, neuropsychological, psychopharmacological and, more recently, neuroimaging research.

The five proposed memory systems are episodic memory, semantic memory, working memory, procedural learning and the perceptual representation system (PRS). An important caveat to consider before examining research into ketamine's effects on memory systems is that no one task can tap a single memory system or process. The five systems to be discussed below are interactive and any one task may involve two or more memory systems. For example, immediate recall of a story may tap working memory, as one has to hold on line the first part of a story whilst processing the next part to get the overall semantic 'gist', as well as semantic memory. Another conceptual issue concerns the use of the term 'executive function', which refers to processes such as planning, sequencing and manipulating material. Working memory is an executive function but many other 'memory' tasks also require executive functions, including episodic and semantic memory tasks. With this in mind, the findings of studies reviewed below are summarised in Table 1 in terms of the principal system thought to be tapped by the task employed.

Some of the evidence for the existence of dissociable memory systems stems from the functional neuroimaging of memory. However, there is some considerable overlap in the neuroanatomical structures involved in each memory system, which also serves to reinforce the point that similar processes may be involved in different memory systems. A large body of evidence has investigated the neural correlates of memory and such findings will be but briefly summarised here. Encoding, i.e. the deposit of information into, in episodic memory is thought to be mediated by left pre-frontal and temporal regions, the anterior cingulate cortex (ACC) and the hippocampus. General retrieval (i.e. the process of attempting to remember information) from episodic memory is thought to be associated with activation in the right pre-frontal and bilateral temporal cortex, the ACC, cerebellum, precuneus and thalamus. Successful retrieval, i.e. correctly remembering information, is associated with activation in the pre-frontal cortex (PFC), precuneus and hippocampus (see Fletcher et al. 1997 for a review). Semantic memory retrieval, as encoding of information into semantic memory is rarely examined, is thought to be dependent on activation of the left pre-frontal and temporal regions and ACC (see Cabeza and Nyberg 2000 for a review). Working memory research has suggested that ventrolateral regions may perform simpler tasks within working memory such as maintenance of information, whilst mid-dorsal regions perform higher level functions such as manipulation (e.g. Petrides et al. 1993). Procedural learning is thought to be largely dependent on the basal ganglia and surrounding structures (see Hazeltine and Ivry 2003 for a review) and the PRS, in particular perceptual priming, has been found to be accompanied by a decrease in blood flow in regions of the extrastriate visual cortex (see Schacter 1999 for a review).

Neuroimaging evidence has thus been helpful in suggesting commonalities across memory systems, as discussed above, i.e. the involvement of the left inferior PFC in episodic, semantic and working memory. In addition, it has suggested different activations for different component processes, i.e. encoding and retrieval in episodic memory, maintenance and manipulation in working memory. Whilst the functional neuroimaging evidence as to the effects of ketamine on memory is at this stage quite limited, it is clear that this will be important in further delineating the effects of this drug on memory. In addition, this research is helpful in highlighting the overlap between different memory

Table 1 Findings of studies following an acute dose of ketamine in the laboratory, and acute-on-chronic and chronic effects in a recreational ketamine-using population summarised in terms of the 'memory systems' model

Principal memory system tapped	Task	Study	Acute	Acute-on-chronic	Chronic
Episodic memory	Immediate verbal recall	Ghoneim et al. (1985)	X		
		Krystal et al. (1994)	√		
		Harborne et al. (1996)	X		
		Malhotra et al. (1996)	X		
		Newcomer et al. (1999)	X		
		Hetem et al. (2000)	X		
		Curran and Morgan (2000)		X	X
	Delayed verbal recall	Ghoneim et al. (1985)	X		
		Krystal et al. (1994)	X		
	Verbal recognition	Ghoneim et al. (1985)	X		
		Malhotra et al. (1996)	X		
		Hetem et al. (2000)	X		
		Honey et al. (2006)	X		
		Honey et al. (2005b)	X		
		Morgan et al. (2004c)		X	√
	Source memory	Honey et al. (2005b)	X		
		Morgan et al. (2004a)	X		
		Honey et al. (2006) (agency)	X		
		Morgan et al. (2004c)		X	X
	Spatial memory	Rowland et al. (2005)	X		
	Associative memory	Harris et al. (1975)	X		
		Harborne et al. (1996)	X		
Semantic memory	Category fluency	Ghoneim et al. (1985)	√		
		Adler et al. (1998)	X		
		Morgan et al. (2004a)	√		
		Curran and Morgan (2000)		X	X
	Speed of comprehension	Morgan et al. (2004a)	X		
		Curran and Morgan (2000)		X	X
	Semantic priming	Morgan et al. (2006b)	X		X
Working memory	Digit span forwards	Ghoneim et al. (1985)	√		
		Honey et al. (2003)	√		
		Abel et al. (2003)	√		
		Rowland et al. (2005)	√		
	Digit span backwards	Harris et al. (1975)	√		
		Ghoneim et al. (1985)	√		
		Honey et al. (2003)	X		
		Abel et al. (2003)	X		
		Rowland et al. (2005)	√		
	Spatial span	Rowland et al. (2005)	√		
	Serial sevens	Curran and Morgan (2000)		X	√
	N-back–1-back, 2-back	Adler et al. (1998)	X		
		Morgan et al. (2004a)	X		√
		Narendran et al. (2005)			
	Spatial working memory (SDR)	Newcomer et al. (1999)	√		
Attention	CPT	Krystal et al. (1994)	X		
		Harborne et al. (1996)	√		
		Malhotra et al. (1996)	X		
		Adler et al. (1998)	√		
		Newcomer et al. (1999)	√		
		Umbricht et al. (2000)	X		
	N-back–0-back	Adler et al. (1998)	√		
		Morgan et al. (2004a)	√		
	Stroop	Harborne et al. (1996)	√		
		Newcomer et al. (1999)	√		
	DSST/SCT	Hetem et al. (2000)	X		

Table 1 (continued)

Principal memory system tapped	Task	Study	Acute	Acute-on-chronic	Chronic
Executive functioning	Verbal fluency	Krystal et al. (1994)	X		
		Krystal et al. (1998)	X		
		Adler et al. (1998)	X		
		Newcomer et al. (1999)	√		
		Krystal et al. (1998)	√		
		Abel et al. (2003)	√		
		Rowland et al. (2005)	√		
		Curran and Morgan (2000)		X	√
	Trailmaking (B-A)	Harborne et al. (1996)	√		
		Morgan et al. (2004a)	√		
	WCST	Krystal et al. (1994)	X		
		Krystal et al. (2000)	X		
	Tower of London	Honey et al. (2003)	√		
Procedural memory	Serial reaction time task	Morgan et al. (2004a)	X		
PRS	Perceptual priming	Morgan et al. (2004a)	√		
		Curran and Morgan (2000)	√		

SDR spatial delayed response task, *DSST* digital symbol substitution test, *SCT* symbol copy test

systems and again borne in mind when considering the effects of ketamine on memory.

Other factors that complicate comparisons between the studies reviewed below include (1) the wide variety of tasks used across the different studies; (2) the wide variety of doses, routes of administration and populations and (3) the variation in test times post-ketamine that memory has been assessed. Further differences have also been observed that are not accounted for by the above explanations (see Honey et al. 2003). These may be related to individual differences in drug response (e.g. Malhotra et al. 1998) or the use of different strategies to meet task demands that may vary from participant to participant (Honey et al. 2003). Despite this, however, there is sufficient commonality in the studies to allow some comparison and integration.

Acute effects of ketamine on human memory

Episodic memory

Episodic memory makes possible what Tulving (1998) terms ‘mental time travel’ back into a person’s past. Think of the last film you saw—you remember not only what the title of the film was but also whom you went with and whether you had popcorn or went for dinner afterwards. Episodic memory is thought to facilitate the acquisition and retrieval of information about specific personal experiences that occur at a particular time and place (Tulving 1985; Tulving and Markowitsch 1998). A large number of studies have consistently found ketamine-induced decrements across tasks which principally tap episodic memory at a range of doses (Hetem et al. 2000; Ghoneim et al. 1985; Krystal et al. 1994; Malhotra et al. 1997; Newcomer et al. 1999). In addition, these effects have been found across diverse measures, including recognition tasks (Hetem et al. 2000; Ghoneim et al. 1985; Honey et al. 2003); recall of passages of prose (Newcomer et al. 1999); recall of high- and low-frequency word lists (Hetem et al. 2000; Ghoneim et al. 1985; Malhotra et al. 1996); spatial learning paradigms (Rowland et al. 2005) and, of particular relevance to episodic memory, source memory tasks (Honey et al. 2005b, 2006; Morgan et al. 2004a).

Other studies have investigated the relative contributions of encoding (i.e. the process of acquiring information and placing it into memory) and retrieval (i.e. the recovery of previously encoded information from memory) to these verbal episodic memory deficits. Overall, research seems to suggest an impairment of memory for information studied on-drug, i.e. an encoding deficit, but not information studied before drug administration, i.e. intact retrieval. This encoding deficit has been noted on recognition memory tasks (Honey et al. 2005a; Hetem et al. 2000), recall tasks (Morgan et al. 2004b) and a virtual Morris water maze (Rowland et al. 2005). Pre-clinical support for ketamine-induced encoding impairment is provided by studies describing NMDA antagonist-induced deficits in acquisition (i.e. encoding) but not performance (i.e. retrieval) in spatial learning tasks (Ohno et al. 1994). Contradictory findings were observed in a recent study and this gave rise to the suggestion that ketamine may impair consolidation processes in memory (Parwani et al. 2005). Whilst this is a potentially interesting field for further research, issues with the design of the latter study, for example testing subjects

during differing levels of psychotic symptoms and the possibility of proactive interference, complicate the interpretation of the findings.

Another facet of verbal episodic memory, the conscious state associated with remembering, also appears to be affected by ketamine. Memory research has promoted the view that episodic memory may be characterised by the subjective awareness of recreating events and experiences and reliving these events and experiences mentally. Tulving (1985) termed this type of awareness 'autonoetic' awareness and contrasted it with 'noetic' awareness; that is, feelings of *familiarity* with an event or experience without conscious *recollection*. This can also be thought of as the difference between 'remembering' and 'knowing'. 'Remembering' refers to one's personal experience of the past that allows mental time travel and engages one's sense of self; 'knowing' denotes other experiences of the past—knowledge that we possess but in a self-independent manner. Source memory tasks are one way of examining such recollective or remember processes. Such tasks tap into not only our memory for information (e.g. the 'what' component of episodic memory) but also memory for contextual details surrounding the encoding episode (e.g. the 'where', 'who', 'how', etc.). Typically, such tasks involve a recognition component (where participants are simply asked to say whether they have seen a word before), and also a 'source' component, where they must recall some contextual details that were present at the encoding episode (e.g. whether the words were presented in a male or female voice). Ketamine impairs source memory and recognition memory (Morgan et al. 2004a; Honey et al. 2005b). Impairment of source memory suggests a disruption to recollection.

One special case of source memory is invoked in tasks where people are asked to remember 'agency'—whether it was themselves or another person who generated the information encoded at study. In the classic generation effect, people have very good memory for items they generated themselves as compared with items generated by another person (Slamecka and Graf 1978). Honey et al. (2006) showed that this generation effect was preserved after acute ketamine administration (100 ng/ml) but that memory for who generated it (source) was impaired. This impairment was evident by participants on ketamine more often reporting that they did not know who had generated the items. Interestingly, when they were then asked to guess who generated the items, participants on ketamine were less likely than controls to guess that it was an external source (i.e. the experimenter), which is an opposite pattern to that observed in individuals with schizophrenia (e.g. Danion et al. 1999).

Subsequent memory is thought to be facilitated when the meaning of information is processed at encoding compared to simple processing of physical attributes (Craik and Lockhart 1972); this is known as the 'levels of processing' effect. Ketamine has been found to disrupt recognition memory for words encoded at an intermediate (active/passive) but not at a deep (pleasant/unpleasant) or shallow semantic level (number of syllables) (Honey et al. 2005b). Recollective ('remember') processes are thought to be engaged when retrieving information that has been deeply processed. The latter findings may therefore again indicate ketamine's capacity to impair recollection. The deepest level of encoding in this study was thought to render information relatively invulnerable to the amnestic effects of ketamine.

Subsequent work, however, found memory for words generated via deep semantic processing was impaired compared to words generated using shallow processing (word stem completion) (Honey et al. 2006), which suggests that ketamine may have reduced the degree of semantic processing associated with the encoding or generate tasks. Another study did not find that ketamine's effect depended on depth of processing (Morgan et al. 2004a); thus, this area requires further investigation.

Further indirect evidence for impaired recollective processes following ketamine administration comes from neuroimaging studies. A reduction in hippocampal left PFC activation was observed when retrieving information encoded prior to ketamine infusion (Honey et al. 2005a). This may represent an inability to access the contextual details associated with a remembered stimulus, i.e. a failure to engage recollective processes. Similar findings are also observed in patients with schizophrenia (Heckers et al. 1998).

In summary, ketamine has been shown to produce robust episodic memory impairments. Specific task manipulations have enjoyed some success in delineating the processes involved in these deficits. The emergent findings would suggest that ketamine principally impairs the encoding of information into episodic memory. Any effects the drug exerts upon retrieval are much more subtle. In addition, evidence suggests that ketamine may impair the recollective or 'remember' aspects of episodic memory whilst leaving in tact familiarity or 'know' components.

Semantic memory

Semantic memory refers to a person's general knowledge about the world (Tulving 1972). It differs from episodic memory in that semantic information is not associated with a specific learning context. Semantic knowledge covers a range of organised information including concepts, vocabulary and facts. The majority of the work to date on semantic memory has looked at the effects of ketamine on fluency tasks, comparing semantic fluency (e.g. generate as many examples of 'fruit' as you can think of) with

phonemic fluency (e.g. generate words beginning with 'M') tasks. Findings have been inconsistent. Whilst some studies showed ketamine-induced impairments in category (Abel et al. 2003; Adler et al. 1998) and phonemic fluency (Adler et al. 1998; Krystal et al. 1994, 1999), others have found fluency to be intact (Abel et al. 2003; Newcomer et al. 1999; Rowland et al. 2005; Krystal et al. 1999). Clearly, both types of fluency tasks tap executive function, and impaired performance could reflect a failure to initiate or sustain the use of strategies. One way of minimising strategy use is to present semantic information simply for verification, as in sentence verification tasks (e.g. psychiatrists are made in factories; cuckoos have wings). Acutely, ketamine also impairs performance on this task (Morgan et al. 2004a), although this may reflect a generalised slowing of response.

A more appropriate way of assessing semantic processing is to use a semantic priming task. Semantic priming is seen when a response to a target word (e.g. chair) is facilitated when it is preceded by a semantically associated 'prime' (e.g. table) compared to an unrelated prime (e.g. finger). Recent research has found ketamine-induced deficits in semantic processing on these tasks (Morgan et al. 2006b). The semantic priming deficits were relatively specific in that they reflected reduced priming only when there was a longer (500 ms) interval between the presentation of the prime and the target. Semantic priming was intact when this interval was so brief (50 ms) as to allow only automatic processing. Because the priming deficit occurred only at the longer time interval, Morgan et al. argued that ketamine produces a specific impairment of controlled semantic processing.

Other evidence for semantic memory impairments stems indirectly from neuroimaging data. Compared to placebo, when encoding words in a deep encoding condition which were later successfully remembered, ketamine increased left frontal activity on a deep encoding task, as estimated by the blood-oxygenation-level-dependent (BOLD) signal (Honey et al. 2005a). The authors interpreted this finding as difficulties in selecting semantic attributes that are relevant to the semantic judgement that constituted the deep encoding task. Overall, ketamine has been found to disrupt semantic memory. However, this disruption appears to be of controlled semantic processes which may in turn be dependent on other executive functions.

Attention and executive functioning

As mentioned before, even with relatively specific task manipulations, cognitive tasks do not invoke memory systems in isolation. Perhaps the greatest confound of performance on tasks designed to examine episodic and semantic memory stems from concomitant deficits in attentional and executive processes. Some studies find ketamine-induced deficits in sustained attention on the continuous performance task (CPT; Krystal et al. 1994; Malhotra et al. 1996; Umbricht et al. 2000), but others report no deficits (Krystal et al. 1999; Newcomer et al. 1999). In contrast, studies that have examined selective attention using the Stroop paradigm have, in general, found that performance is unaffected by the drug (Harborne et al. 1996; Luby et al. 1959; Newcomer et al. 1999; Oranje et al. 2000; Rowland et al. 2005). Performance on the 0-back component of the N-back working memory task (discussed below), where participants are required to simply respond when they see a certain stimulus, has been found to be relatively unimpaired by ketamine (Morgan et al. 2004a; Adler et al. 1998). Whilst evidence of attentional deficits following ketamine administration is not consistent across different tasks and studies, it is plausible that such attentional difficulties may underpin some of the episodic and semantic memory problems observed following ketamine. However, Malhotra et al. (1996) covaried for attentional effects and found ketamine's effects on memory (free recall and recognition) were still significant. From the limited evidence available, it would appear that whilst attention does impact upon performance on episodic and semantic memory tasks, episodic memory deficits are not simply a by-product of concomitant attentional problems.

Executive functioning can be conceptualised as the selection, monitoring and integration of cognitive and behavioural processes and is sub-served by the frontal lobes. After ketamine administration, participants made more perseverative errors on the Wisconsin card-sorting task (WCST; Krystal et al. 1994), which is thought to tap executive functioning. Krystal et al. (2000) re-examined performance on the WCST by repeating the task following ketamine and placebo administration in a crossover design. Participants who had acquired the rules of the WCST whilst on ketamine performed worse in the task, whereas those who acquired the rules on placebo were relatively unimpaired. The authors suggested that general NMDA-R-mediated impairments to learning do not affect the cognitive functions necessary to carry out the WCST, such as mental set shifting, and that impairments on this task may reflect more general deficits in rule learning (Krystal et al. 2000). This may be of relevance for findings of the effects of ketamine on the Tower of London task, where no impairment was observed following ketamine (Honey et al. 2003). However, this task is not intended to be repeated, as strategies can be acquired and, in repeated-measures designs, complex order-by-drug interactions may occur. Executive functioning has been further examined with a simple trailmaking task and performance does appear to be intact once psychomotor slowing is controlled for (Harborne et al. 1996; Morgan et al. 2004a).

Response inhibition and suppression have been assessed following an acute dose of ketamine using the Hayling task (Morgan et al. 2004b) On the Hayling task, participants given 0.8 mg/kg of ketamine made more errors on part B of the task (where the are required to give a semantically incongruous ending to an incomplete sentence—e.g. 'He posted the letter without a...') but not on part A (where the congruous ending is required). This indicates disrupted response inhibition but not response initiation. However, on a more simplistic measure of response inhibition, the go/no-go task, participants given acute ketamine made fewer correct responses but showed no difference in the number of response inhibition errors, suggesting that inhibiting simple pre-potent responding was intact. Therefore, a more parsimonious explanation of the findings of the Hayling task may be that ketamine-induced strategic or semantic impairments render participants unable to generate contextually incongruous endings.

Error monitoring also comes under the umbrella term of executive processes. Neuroimaging studies have suggested that the ACC is involved in error monitoring (Honey et al. 2005a,b). After ketamine, ACC activation was reduced for incorrect responses (Honey et al. 2005a).

Overall, from these limited executive functioning data, although acute ketamine administration has little impact on executive processes, it appears to impair error monitoring. This relative absence of ketamine-induced executive impairment suggests again that semantic and episodic memory deficits are veridical and not secondary to problems in search and strategy processes. However, as error monitoring is also important in learning, and therefore, performance on episodic memory tasks, further work should examine the role that such deficits play in ketamine-induced encoding problems following.

Working memory

Working memory is proposed to facilitate the maintenance and manipulation of internal representations such that these representations can be used to guide future behaviour (Baddeley 1998). The most recent form of the model is comprised of four components: the phonological loop, the visual–spatial scratchpad, the central executive and the episodic buffer (Baddeley 2000). Baddeley suggests that the phonological loop is involved in rehearsal and temporary storage of auditory verbal information and that the visual–spatial scratchpad serves an analogous function for visual and spatial properties of a stimulus (these two are termed 'slave systems'). The central executive is thought to be a limited-capacity supervisory attentional mechanism (Shallice 1982) and the episodic buffer, the newest component of the model, is proposed to facilitate the integration of information from all of the above sources into long-term memory.

Forwards digit span, which involves repeating back a sequence of numbers, may be seen as an index of the phonological loop. Performance on this task is intact following ketamine administration (Ghoneim et al. 1985; Honey et al. 2003; Rowland et al. 2005; Abel et al. 2003). From the limited evidence available—one study examining forwards spatial span (Rowland et al. 2005) and a spatial delayed response task (Newcomer et al. 1999)—the operations of the visual–spatial scratchpad also seem to be unaffected by ketamine. Thus, ketamine does not impair the simple maintenance of material in working memory.

Ketamine's effects on integration and manipulation within working memory, i.e. the central executive, have also been investigated, although findings are less consistent than those relating to the slave systems. Preserved backwards digit span has been observed in some (Rowland et al. 2005; Ghoneim et al. 1985; Harris et al. 1975) but not all (Abel et al. 2003; Honey et al. 2003) studies. Neuroimaging work has demonstrated augmented BOLD response on ketamine in frontal–parietal regions for manipulation but not for maintenance of information (Honey et al. 2004). This suggests that, in the former studies, even when no behavioural differences are present, manipulation of information in working memory by the central executive is affected by ketamine, although again it is unclear what exactly this may reflect (i.e. augmented or decreased glutamatergic activity and/or performance).

The N-back has also been used to investigate working memory following ketamine administration. This involves an attentional component (0-back), where participants are required simply to respond to a particular number/letter, and then two further components with increasing working memory load. In the 1-back, participants are required to respond if the letter/number is the same as the one previously presented; in the 2-back, they must respond if the letter/number is the same as the one two before. Ketamine was associated with decreased scores on the one-back and two-back, but not the zero-back, components (Adler et al. 1998; Morgan et al. 2004a). Conversely, spatial working memory was preserved after ketamine administration (Honey et al. 2003). On the serial sevens task, where participants are required to count backwards in sevens from a three-digit number, which may also tap the episodic buffer, impaired performance after administration of the more potent NMDA antagonist, PCP, has been observed (Cohen et al. 1962; Luby et al. 1959). The inconsistency in findings may well reflect differences in the level of difficulty of the working memory tasks employed and strategy use by participants, as well as differences in

how ketamine was administered and whether steady-state plasma levels were achieved or not.

In summary, the majority of studies suggest that ketamine affects manipulation rather than maintenance of information in working memory. Such an inability to manipulate information on-line could also affect performance on episodic and semantic memory tasks, and so, the possibility remains that such deficits are related to general working memory problems. However, that such episodic and semantic memory impairments have been observed in studies that have found no evidence of working memory deficits would seem to suggest a dissociation.

Procedural learning and the PRS

Procedural learning and the PRS are non-declarative memory systems where retention is assessed indirectly or implicitly. Procedural learning pertains to the learning of motor and cognitive skills; 'real-world' examples may be learning to ride a bike or learning to read. Procedural learning is likely comprised of numerous sub-systems with the commonality between them being that they all consist of learning a new skill. On a repeated version of the WCST (Krystal et al. 1999), ketamine tended to impair acquisition, suggesting potential impairment of procedural *learning*, but not of the expression of the rules necessary to conduct the task. Perceptual priming was preserved following a single dose of ketamine and procedural learning (on a serial reaction time task) was impaired, although the latter finding may have been complicated by slower reaction times in the high-dose ketamine group (Morgan et al. 2004a). This dissociation is interesting as in a variety of disorders (e.g. organic amnesia, schizophrenia) it is explicit memory processes that are predominantly impaired and implicit processes that are preserved. However, following ketamine administration, two implicit processes appear differentially effected. The procedural learning task used required the encoding of contextual relations between a set of stimuli (i.e. a specific sequence of letters) to learn the sequence. In contrast, priming requires the simple encoding of stimulus features. It is possible then that the process of encoding contextual relations is impaired by the drug. It may be that the distinction between contextual and non-contextual memory (or associative and non-associative learning) may be more relevant to the memory impairing properties of ketamine than the implicit/explicit distinction. These findings are complementary to those on tasks such as the AX-CPT task, where response inhibition/sustained attention errors following ketamine have been found (Umbricht et al. 2000), but only on trials that require memory of transient contextual relations between stimuli.

Summary of acute effects of ketamine on memory

A relatively large body of work has now addressed the cognitive impairments associated with acute ketamine administration. Despite the heterogeneity in tasks, dosing regimens, etc., encoding of information into episodic memory is consistently impaired, whereas effects on retrieval are subtle at most. Evidence suggests that recollection is more disrupted by ketamine than by familiarity. Semantic retrieval deficits have also been observed, which is intriguing in the light of the observed preserved familiarity. Semantic and episodic memory deficits are unlikely to be simple by-products of executive deficits. Manipulation within working memory is impaired by ketamine, but the ability to maintain information online is intact. Of implicit memory processes, what little evidence currently exists suggests that perceptual priming is preserved whereas procedural learning is disrupted.

Chronic effects of NMDA-antagonists on memory and cognition

Although there have been few studies to date, initial evidence suggests that chronic administration of NMDA-R antagonists results in a different profile of deficits than acute exposure. Both chronic PCP (Sams-Dodd 1995, 1996; Steinpreis et al. 1994) and ketamine (Bernstein et al. 2003; Keilhoff et al. 2004) lead to decreased social interaction in rats. Jentsch et al. (1997) investigated the effects of sub-chronic administration of PCP on a spatial delayed alternation task in rats. Impairments were seen at longer delays but not after no delay, implying a working memory deficit. Chronic PCP exposure in monkeys also produced deficits on a response inhibition task (Jenstch et al. 2000). The executive functions investigated in these two studies have been linked to PFC. Thus, the preliminary results in this field suggest that this region may mediate the deficits induced by chronic PCP (the dorsolateral PFC in monkeys and the medial PFC in rats). Chronic PCP exposure has also been reported to reduce frontal lobe glucose utilisation in humans (Wu et al. 1991). On the basis of the selectivity of these deficits and evidence from PCP users, it has been suggested that chronic administration of NMDA-R antagonists may provide a better model of schizophrenia than acute antagonism (Jentsch and Roth 1999).

Chronic behavioural and cognitive effects of NMDA-R antagonists on human memory

As ketamine's medical use is as an anaesthetic, and given the range of its cognitive and psychotic-like side-effects, ethics precludes administering repeated doses to healthy

volunteers under laboratory conditions. Therefore, evidence of the chronic effects of ketamine and PCP in humans derives solely from abusing populations. This in turn means it is subject to the many limitations of naturalistic drug research (e.g. poly-drug use, pre-existing population differences, varying doses and purity of the drug).

In one of the few published studies of the cognitive effects of chronic PCP, Carlin et al. (1979) administered the Halstead–Reitan neuropsychological battery to 12 PCP abusers, 12 poly-drug users and 12 non-drug controls. They found the poly-drug group and the PCP group could not be differentiated from each other and both were impaired relative to controls. However, Ware (1979) compared eight hospitalised PCP users to eight poly-drug users and found differences on the revised Wechsler adult intelligence scale, but not the Halstead–Reitan. Cognitive impairments were found by Cosgrove and Newell (1991) in a group of 15 chronic PCP drug users. They found an overall impairment on a range of cognitive tasks (verbal fluency, trailmaking, verbal memory, block design). In this study, the PCP abusers ceased use of the drug for 4 weeks and then were re-tested. Verbal memory and trailmaking scores improved on cessation of PCP use.

Surveys of PCP users contain numerous reports of persistent problems with memory, speech and thinking (Fauman and Fauman 1978). An early survey of ketamine users also indicated the perceived cognitive effects of long-term use to be attentional dysfunction and decreased sociability (Siegel 1978). Feldman et al. (1997) described the chronic effects of PCP as leading to significant cognitive impairment characterised by confusion, thought disorder and severe memory loss referred to as 'burnout' by users. A single case report in the literature also indicates chronic memory impairments as a result of ketamine use (Jansen 1990).

Episodic memory

Several studies have used naturalistic designs to test the effects of ketamine in users shortly after they self-administer (i.e. acute-on-chronic effects) and then again a few days later when they are drug-free to gauge chronic effects. To control for use of other psychotropics, control participants are individuals who use a similar amount of other drugs but do not use ketamine. In general, the pattern of acute-on-chronic effects parallel those observed in laboratory studies with healthy volunteers. Prose recall was impaired in ketamine users 3 days after drug use (Curran and Morgan 2000; Curran and Monaghan 2001). In addition, item recognition and source memory were disrupted on the night of drug use; however, 3 days later, in ketamine users only, source memory was found to be impaired, in the presence of intact item recognition (Morgan et al. 2004d). The day 3, or 'chronic' results suggest that ketamine use impairs recollection in the face of relatively preserved familiarity. However, this could also reflect task difficulty, as prose and source recall are harder than simple item recognition.

As discussed above, the depth with which items are encoded is directly related to the probability of remembering them, so that semantically encoded words are recalled or recognised better than more superficially encoded words. One of the deepest levels of encoding is when individuals are asked to encode words (e.g. 'perfectionist'; 'extrovert') in relation to themselves. A recent study found that drug-free chronic ketamine users did not differ from poly-drug controls when recognising words that were self-referentially encoded, whereas they were significantly impaired when words were encoded (1) in relation to another person, (2) semantically (e.g. it is positive to be '...') or (3) superficially (how many syllables the word has). Thus, engineering the very deepest level of encoding can overcome episodic memory impairments apparent in ketamine users (Morgan and Curran, unpublished observations). This is turn suggests that observed impairments in episodic memory are, in part at least, due to failure to initiate deep encoding strategies.

Whilst any comparison can only be descriptive, the episodic memory impairment observed on the night of drug use in ketamine users tested in phase one of the Morgan et al. (2004d) study was similar to that observed following an acute dose of ketamine in healthy volunteers on the same task (Morgan et al. 2004a). However, given that doses reported by ketamine users were much higher (approximately 90–260% more) than the higher doses administered in controlled, acute studies, it is clear that users have developed some degree of tolerance to the effects of ketamine, including its amnestic effects. Tolerance to the effects of ketamine might theoretically be related to NMDA-R upregulation, which has been observed in animal models following repeated NMDA-R antagonist administration (Arvanov and Wang 1998). The contribution of pre-existing differences in memory in individuals who do and do not chose to use ketamine is a potential confound in these studies. However, a comparison of two groups who both used ketamine but differed in how frequently they used it found that memory impairment when they were drug-free was directly dependent on the extent of use of the drug (Curran and Monaghan 2001).

Semantic memory

Semantic memory impairments in ketamine users appear to be more profound than those seen after an acute dose of ketamine in healthy volunteers. On the speed of comprehension task, ketamine users completed fewer sentences and made more errors than poly-drug controls (Curran and

Morgan 2000), which indicates gross semantic impairments, as errors on this task are relatively difficult to elicit (Rossell et al. 2001). Ketamine users also generated fewer exemplars in category but not verbal fluency. The dissociation of performance on the above tasks may indicate impaired storage of, rather than access to, semantic knowledge (Allen et al. 1993). This is also supported by the only study to date examining semantic priming in ketamine users (Morgan et al. 2006b). Paralleling findings following acute administration to healthy volunteers using the same task, semantic priming was reduced at a long prime–target interval, indicating an impairment in controlled semantic processes as discussed above. Specifically, however, priming was lower only for low-frequency words. This may suggest that some degradation of the semantic store may have occurred in ketamine users and is reminiscent of some recent findings in individuals with schizophrenia (Rossell and David 2006).

Working memory, attention and executive functioning

In chronic ketamine users, an impairment to simple focused attention was evident by slower performance on the digit cancellation task (Curran and Morgan 2000). The absence of errors on this task suggests that simple vigilance may be preserved in ketamine users, but that monitoring of information was simply more effortful for these individuals. However, there is a need for more research on the attentional effects of repeated ketamine use.

In ketamine users, performance on the serial sevens was impaired on the night of drug use (i.e. an acute on chronic effect), but no impairment was evident 3 days after drug use (Curran and Morgan 2000). However, findings from this task may be influenced by baseline numeracy and working memory abilities. Performance on a verbal fluency task was intact; however, ketamine users tended to make more perseverative errors (Morgan et al. 2004c). On a go/no-go task, when participants were drug-free, there were no differences between ketamine users and poly-drug controls; however, on the night of drug use, ketamine users made more false alarms and fewer hits (Morgan and Curran, unpublished observations). This false alarm increase could signal response inhibition deficits; however, combined with fewer hits these data may indicate globally inaccurate performance. In contrast, the animal literature shows that chronic NMDA-antagonism is associated with deficits in both response inhibition and working memory (see Jentsch and Roth 1999 for a review).

It seems somewhat paradoxical that the changes following repeated antagonism of the NMDA-R may result in a similar, if not slightly more selective, profile of effects on cognitive functioning as acute antagonism (Krystal et al. 1999). However, neural network models suggest that, theoretically, both hypoglutamatergic states (reduced glutamatergic signal and associated excessive inhibition) and hyperglutamatergic states (heightened activation or inhibitory deficits) could produce similar cognitive disruptions (Lisman et al. 1998; Grossberg 1984). In addition, abnormal hippocampal neurogenesis has been observed in rats following repeated ketamine administration, along with a reduced sensitivity of GABA-ergic interneurons (Keilhoff et al. 2004), which again could theoretically produce disruptions in information processing similar to those described following acute ketamine. A recent study with ketamine users found an upregulation of D1 receptor availability in the dorsolateral PFC (Narendran et al. 2005). However, the cognitive impairments observed following repeated ketamine self-administration are less indicative of a dopaminergic (DA-ergic) mechanism, as, in general, DA-ergic dysfunction results in more wide-ranging deficits on executive functioning and working memory tasks (Paulus et al. 2002) than have been observed in the limited investigations to date. Narendran et al. found no difference between 14 ketamine users and cannabis-using controls on an N-back task, so the functional consequences of greater D1 availability in dorsolateral prefrontal cortex are unclear. It is worth noting also that the majority of the ketamine users in this study, however, were using <400 mg of ketamine per week, on average only a quarter as much as the users who have participated in other ketamine user studies.

Reversibility of impairments

Three years later, after reducing the use of ketamine considerably (88%), some semantic memory recovery has been demonstrated in a small opportunistic follow-up study of ketamine users (Morgan et al. 2004c). The improvement in semantic processing correlated with the reduction in ketamine use. It is not yet clear what the mechanism of this reversible semantic impairment may be. It could be a compensatory psychological mechanism, which has been adopted to deal with the semantic impairments experienced by ketamine users, or it could be reversible neurotoxicity similar to that observed in rats (Olney et al. 1989).

However, persisting episodic and attentional impairments were still evident in ketamine users when compared to poly-drug controls after reducing their use of the drug. This may relate to the irreversible cell death observed following repeated high doses of high-affinity NMDA-R antagonists (Olney et al. 1991). At this time, the exact mechanism remains unclear. Regardless, these persistent memory and attentional impairments have worrying implications for the growing population of ketamine users.

Specificity of the effects of ketamine on memory

Pharmacological/neurotransmitter specificity

Whilst the main action of ketamine, as discussed above, is considered to be via the blockade of NMDA-R on GABA-ergic interneurons, and consequent increase in glutamatergic availability an non-NMDA glutamatergic receptors (e.g. alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, kainate and metabotropic glutamate receptors), it is also known to affect a variety of other neurotransmitter systems. Animal studies show that low concentrations of ketamine antagonise NMDA-evoked DA release in the striatum (Moghaddam et al. 1997). However, many of the behavioural effects of ketamine and PCP resemble those of a DA agonist (e.g. psychotomimetic properties and stereotypy in rats). At sub-anaesthetic doses, NMDA-R antagonists increase extracellular DA concentrations in the rat PFC (Lindefors et al. 1997; Moghaddam et al. 1997). This increase in DA is associated with poorer performance on a working memory task (Verma and Moghaddam 1997). In humans, positron emission tomography (PET) studies suggest that ketamine stimulates the release of dopamine in the striatum (Smith et al. 1998).

PCP and ketamine have also been shown to inhibit NMDA-stimulated acetylcholine release from rat cerebral cortical and striatal slices at very low concentrations (nanomolar to micromolar) (Kegeles et al. 2002; Lodge and Johnston 1985). However, more recent animal studies also suggest an increase in cortical acetylcholine release with administration of acute and repeated doses of ketamine (Nelson et al. 2002). MK-801 and PCP have been shown to inhibit NMDA-induced cortical GABA release (Drejer and Honore 1987). Ketamine also interacts with μ-opioid receptors and with the non-opioid σ receptor site, although the affinities of the drug for these receptors are at least one order of magnitude lower than for the PCP site (Oye et al. 1992).

The interactive effects of ketamine with other compounds can give us valuable insights into the neuropharmacological mechanism by which the drug is cognitively impairing. Whilst the majority of such studies have concentrated on reversing psychotic symptoms, some have also examined the interactive effects of ketamine with other compounds on cognition. Pre-medication with diazepam (Kothary and Zsigmond 1977; Tucker et al. 1984), flunitrazepam (Freuchen et al. 1976), lorazepam (Dundee and Lilburn 1978) or midazolam (White et al. 1982; Renstall et al. 1988) has been shown to be effective in preventing dysphoria and psychotic symptoms upon emergence from ketamine anaesthesia (Zsigmond and Domino 1980). However, the interactive effects of benzodiazepines and ketamine were not formally investigated using double blind, placebo-controlled methods until Krystal et al. (1998) examined the interactive effects of lorazepam and ketamine. In this study, concomitant administration of lorazepam and ketamine reduced anxiety and depression ratings on the brief psychiatric rating scale (BPRS). Lorazepam did not, however, antagonise any of ketamine's other psychotomimetic or cognitive effects. In fact, lorazepam *potentiated* the amnestic and sedative actions of ketamine consistent with the anaesthesia literature (Freuchen et al. 1976). It is likely that this potentiation is at least partially responsible for the capacity of benzodiazepines to increase the clinical tolerability of ketamine. It may further suggest that the episodic memory-impairing effects of ketamine may be related to its blockade of NMDA-R on GABA-ergic interneurons and the resultant cortical disinhibition.

Other studies have investigated the effects of ketamine on the DA system. A [^{14}C]2-deoxyglucose (2-DG) uptake study in rodents demonstrated that haloperidol potentiated the uptake of 2-DG in specific brain regions following the administration of sub-anaesthetic doses of ketamine including the medial PFC, retrosplenial cortex, hippocampus, nucleus accumbens, basolateral amygdala and anterior ventral thalamic nucleus (Duncan et al. 2003). Krystal et al. (1999) examined the interactive effects of haloperidol and ketamine behaviourally in healthy volunteers. Their main finding was that haloperidol-reduced ketamine-induced impairments on tasks tapping executive functioning, such as the WCST and Gorham's proverb test, but did not attenuate impairments on any other tasks, including working memory. More recently, Krystal et al. (2005b) examined the interactive effects of ketamine and amphetamine. Amphetamine attenuated ketamine's effects on immediate recall on a word recall task (Hopkins) which involves both episodic and working memory. Unfortunately, common measures were not used across the two studies and, as such, whether there are distinct effects of D2 antagonism and D1 agonism on the cognitive effects of ketamine administration cannot be gauged. However, these studies do highlight the key role of DA-ergic mechanisms in some of the cognitively impairing properties of ketamine.

Pre-clinical microdialysis research would now suggest that the effects of NMDA-R antagonists are mediated by increased glutamate release in the PFC (Adams and Moghaddam 1998; Moghaddam et al. 1997). As discussed above, this implies that the neuropsychiatric effects of ketamine are mediated not by attenuation of glutamate activity at the NMDA-R but by increased glutamate activity at non-NMDA glutamate receptors. This concurs with evidence from post-mortem studies related to hyperglutamatergic functioning in schizophrenic brains, including an overabundance of glutamatergic synapses in the frontal cortex (Deakin and Simpson 1997). The hyperfunction hypothesis was tested in a study using the metabotropic

type II glutamate agonist LY3540740. The compound decreased the cognitive and motor effects of PCP in rats (Moghaddam et al. 1997). Moreover, the same compound attenuated ketamine-induced working memory deficits in humans (Krystal et al. 2005a). In addition, a study with healthy volunteers investigated the interactive effects of ketamine and lamotrigine (Anand et al. 2000). Lamotrigine decreased ketamine-induced positive and negative symptoms of schizophrenia as indexed by the BPRS, as well as attenuating perceptual distortions and impairments on the Hopkins word learning test.

In relation to the neuropharmacological specificity of ketamine, taken together, the above findings suggest that the effects of ketamine on executive functioning and working memory may be underpinned by its indirect DA-ergic properties. Episodic and semantic memory deficits may be mediated by ketamine's hyperglutamatergic properties, as is evidenced by using agents that act indirectly through GABA-ergic mechanisms or, more directly, on the glutamatergic system itself. Clearly these systems interact; for example, the notion that glutamate acts as a 'brake' or 'accelerator' of monaminergic systems (Carlsson et al. 1999), and whilst it is a difficult task, future work using sophisticated neuropharmacological manipulations should aim to understand how such interactions effect changes on a behavioural level.

In considering the pharmacological specificity of ketamine's mnemonic effects, it is helpful to compare these with effects of other psychotropics. Other centrally acting drugs can produce acute effects on memory comparable with those induced by ketamine. For example, benzodiazepines and anticholinergics like scopolamine robustly impair episodic memory as seen in impaired source memory (e.g. Mintzer and Griffiths 1999; Weingartner et al. 1998) and impaired recollection with relatively preserved familiarity (Curran 2000). Similarly, these drugs also generally leave maintenance in working memory intact but produce dose-dependent and task-difficulty-dependent impairments of manipulation of material within working memory (e.g. Rusted et al. 1991; Weingartner et al. 1998). However, anticholinergics and benzodiazepines do not impair performance on semantic fluency tasks or affect semantic processing in conceptual priming tasks. So, although research is at a very early stage, the potential mnemonic or cognitive distinctiveness of ketamine may lie in its effects on semantic processing and semantic memory. This dissociation of mnemonic effects of different drugs may provide clues as to the neurochemical basis of such memory systems.

Clearly, benzodiazepines and cholinergic blockers do not produce psychotomimetic effects and other drugs associated with psychotomimetic effects (e.g. amphetamine, LSD) do not produce the cognitive profile of ketamine. However, recent studies by D'Souza et al. (2004, 2005) suggest that another amnestic drug, tetrahydrocannabinol (the main active ingredient in cannabis), can produce some psychotic-like symptoms when injected intravenously in healthy volunteers and produces a re-emergence of acute symptoms in stabilised schizophrenics. In a thoughtful commentary, Fletcher and Honey (2006) have drawn out parallels between the memory and psychotomimetic effects of cannabis and ketamine. It may be that the cognitive effects that make psychotomimetic compounds such as ketamine distinct from other non-psychotomimetic drugs are those that may underpin, at least in part, its schizophrenia-like symptoms.

In terms of the research on chronic self-administration of ketamine reviewed here, the conclusions one may draw regarding pharmacological specificity become even more opaque. Not only, as discussed above, does ketamine have diffuse actions, but there is the possibility with this group of drug users that other drugs they are taking are partly responsible for the effects observed. Most of the studies reviewed here, however, have used well-matched 'poly-drug' control groups. The possibility remains, however, of interactive effects of ketamine with other drugs used.

Cognitive specificity

No centrally acting drug only affects memory. Ketamine reduces arousal, and this can impact globally on task performance, as too would drug-induced changes in motivation or effort. At the same time, most of the acute and chronic studies described above did not show across-the-board impairments. However, it is often the case that the degree of impairment observed seems to increase with the level of difficulty of the task. Tasks that can incrementally increase load or difficulty, as in some working memory tasks like the N-back, are helpful for elucidating the interaction of drug effects with task difficulty, but this is not feasible for some types of memory. Impairments in attention and working memory will impact on a variety of memory tasks, including encoding into episodic memory.

There also appear to be individual differences in the effects of ketamine which may reflect genetic differences (Petrakis et al. 2004), and a recent analysis suggests that there are subtle gender differences in ketamine's effects on verbal recall (Morgan et al. 2006a). There are clearly individual differences in recreational drug user's response to ketamine, with many anecdotal reports of people trying it once and never taking it again compared with others who use it frequently. In terms of the ketamine user studies, there is a strong possibility of pre-existing differences between ketamine users and non-users. Studies using a 'dose–response' methodology, by testing frequent and infrequent ketamine users, may circumvent this problem to some degree (Curran and Monaghan 2001),

although one cannot exclude the possibility that pre-existing differences predispose some people to use ketamine more than others. It may be that a synthesis of research that examines the factors that account for individual differences in response to ketamine in the laboratory my be able to inform research into factors that predispose people to ketamine use, especially in light of research suggesting a reduced dysphoric response to ketamine in unaffected relatives of alcoholics (Petrakis et al. 2004).

Doses of ketamine which induce psychotic symptoms will have performance effects, which may reflect the impact of these symptoms on task performance. This is partly an advantage of the drug model of psychosis. However, it remains unclear what the relative contributions of the pharmacological action (e.g. NMDA-R blockade) of the drug are, as opposed to the psychotic symptoms, which may include perceptual disturbances. Dose–response studies are critical if we are to understand such interactive effects. Recent studies using sub-psychotic doses of ketamine (e.g. Honey et al. 2005a,b) have also proved useful in addressing this question, as subtle effects on episodic and working memory are still evident at doses which do not induce psychotic symptoms (Honey et al. 2005a,b, 2006). The interpretation of data from the latter studies with those that evoke both psychotic and cognitive effects may also shed light on the cognitive causes and consequences of psychosis.

Ketamine and cognitive deficits in schizophrenia

All drug models of clinical disorders have only partial validity, mimicking some but not other symptoms, and this is especially the case with the heterogeneous disorder we call schizophrenia. Ketamine does not generally induce auditory hallucinations, which are common in schizophrenia. Or again, acute ketamine is subjectively rewarding and produces euphoria, phenomena not often associated with the illness.

The similarity of the cognitive profile of an acute dose of ketamine with that observed in schizophrenia has been thoughtfully considered in Fletcher's and Honey's (2006) review, and the reader is directed there for further discussion of this topic. However, in light of the cognitive effects of ketamine included in this review, it is interesting to consider whether an acute dose of ketamine or chronic self-administration provides a better model of the cognitive deficits in schizophrenia. Unsurprisingly, the findings thus far do not yield a clear answer. They suggest that, in terms of semantic and episodic memory, cognitive deficits following repeated self-administration of ketamine may be more similar to those observed in schizophrenia than those observed following acute doses of the drug. However, for working memory and aspects of executive functioning, acute ketamine may produce a more similar pattern of impairment. In schizophrenia, working memory deficits are thought to be the cognitive function least affected by atypical antipsychotic treatment (Harvey et al. 2003); therefore, in this respect, acute ketamine may prove to be a more useful model for investigation of novel pharmacotherapies. However, some researchers have argued that episodic and semantic memory impairments in schizophrenia are more profoundly affected (Tamlyn et al. 1992) and, of the range of cognitive impairments, are the best candidates for a differential deficit (e.g. Saykin et al. 1991). On this basis, chronic ketamine self-administration may be a better model.

If, as is increasingly suggested by the schizophrenia literature, chronic NMDA-R antagonism does occur endogenously in this disorder (see Krystal et al. 2000 for a review), then repeated ketamine administration may mimic the functional and neurodegenerative consequences of such persistent antagonism. Although no work exists as yet to indicate whether NMDA-R upregulation occurs in ketamine users, it seems reasonable to conclude that this is the case both from the animal literature (Keilhoff et al. 2004) and from knowledge of the general effects of repeated drug administration (Feldman et al. 1997). There is also a literature to suggest that this upregulation occurs in schizophrenia (Meador-Woodruff and Healy 2000). Thus, whilst not mimicking the aetiology or acute phases of the disorder, the ketamine-abusing population may depict later functional changes. Highly speculatively, the use of both chronic and acute models of schizophrenia may allow some dissociation of the original glutamatergic-induced causes and symptoms and the subsequent consequences of chronic psychotic symptoms.

Fletcher and Honey (2006) argue that acute ketamine may better reflect the cognitive disturbances seen in the prodromal phase of the disorder, prior to the emergence of the illness and initial diagnosis. They also suggest that it may reflect the more subtle difference seen in close relatives of those with the disorder. A promising strategy would be to focus on symptoms that the drug model does mimic—for example, delusional thinking and negative symptoms. From an ongoing study, we have preliminary data suggesting that delusional beliefs of chronic users increase proportionately with the extent to which they use ketamine.

Conclusions and future directions

The body of work summarised in the current review suggests that ketamine, both acutely and chronically, has

specific and yet wide-ranging effects on memory systems. Acute doses impair episodic memory, potentially affecting both recollective processes involved in retrieval and initial encoding of information. Semantic processing is also impaired, as is manipulation, but not maintenance of information in working memory. Data suggest that ketamine may disrupt performance not only on explicit, but also certain implicit memory tasks. In particular, it appears to disrupt those functions that require encoding and retrieval of contextual information. This may reflect a decrement in initiating encoding strategies (e.g. deeper semantic processing) which support later retrieval efforts. Functional neuroimaging suggests that ketamine's effects may be via a disruption of frontal processes involved in working and episodic memory. Chronically, ketamine has similar but yet more marked effects on semantic and episodic memory.

Research has begun to address the relationship between ketamine's modulation of other neurotransmitter systems and its memory-impairing effects suggesting contributions of GABA-ergic and DA-ergic effects, in addition to its glutamatergic properties. However, as ketamine is a neurochemically 'dirty' drug, this remains a challenging task. Future work may begin to utilise some of the more sophisticated cognitive methods in concert with neuropharmacological and imaging techniques to delineate the complex actions of ketamine. It may also prove fruitful to explore the relationship between the memory-impairing effects of ketamine and neurochemical changes, indexed by changes in receptor occupancy using the novel gluatamatergic ligands developed for PET and NMDA-R ligands being currently used in single photon emission computed tomography (e.g. Stone et al. 2006).

In addition, investigating some of the relatively unique effects of ketamine, for example on semantic memory, may provide clues as to the neurochemical basis of memory. It is worth emphasising that whilst using the memory system's framework may have been conceptually useful in this review, it may have obscured some of the common processes operating within these tasks. Ever more careful dissection of the cognitive components of each task will help to shed light on both the common and the distinct effects of ketamine. Related to the cognitive effects of chronic ketamine use, future work should address the neuroanatomical and neurochemical correlates of such impairments. Ketamine can impair memory and induce psychotic symptoms, as well as be subjectively reinforcing to both healthy volunteers and drug users. This triangle of effects may mean that it will prove to be a useful future tool with which to explore links between substance misuse, schizophrenia and cognitive function.

Acknowledgement This work was supported by a Medical Research Council to HVC (UK) Studentship to C.J.A. Morgan and by an Economic and Social Research Council.

References

Abel KM, Allin MPG, Hemsley DR, Geyer MA (2003) Low dose ketamine increases pre-pulse inhibition in healthy men. Neuropharmacology 44:729–737

Adams B, Moghaddam B (1998) Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine. J Neurosci 18:5545–5554

Adler CM, Goldberg TE, Malhotra AK, Breier A (1998) Effects of ketamine on thought disorder, working memory and semantic memory in healthy volunteers. Biol Psychiatry 43:811–816

Allen HA, Liddle PF, Frith CD (1993) Negative features, retrieval processes and verbal fluency in schizophrenia. British Journal of Psychiatry 163:769–775

Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH (2000) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine—support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 57:270–276

Arvanov VL, Wang RY (1998) Clozapine, but not haloperidol or raclopride, prevents functional hyperactivity of NMDA receptors in rat cortical neurons induced by subchronic administration of phencyclidine. Soc Neurosci Abstr 24:1827

Baddeley A (1998) Recent developments in working memory. Current opinion in neurobiology 8:234–238

Baddeley A (2000) The episdoic buffer: a new component of working memory? Trends in Cognitive Sciences 4:417–423

Bernstein HG, Becker A, Keilhoff G, Spilker C, Gorczyca WA, Braunewell KH, Grecksch G (2003) Brain region-specific changes in the expression of calcium sensor proteins after repeated applications of ketamine to rats. Neurosci Lett 339:95–98

Cabeza R, Nyberg L (2000) Neural bases of learning and memory: functional neuroimaging evidence. Curr Opin Neurol 13:415–421

Carlin AS, Grant I, Adams KM, Reed R (1979) Is phencyclidine (PCP) abuse associated with organic brain impairment? Am J Drug Alcohol Abuse 6:273–281

Carlsson A, Waters N, Carlsson ML (1999) Neurotransmitter interactions in schizophrenia—therapeutic implications. Biol Psychiatry 46:1388–1395

Chambers RA, Krystal JH, Self DW (2001) A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol Psychiatry 50:71–83

Cohen BD, Rosenbaum G, Luby ED, Gottlieb JS (1962) Comparison of phencyclidine hydrocholoride (sernyl) with other drugs. Arch Gen Psychiatry 6:395–401

Cosgrove J, Newell TG (1991) Recovery of neuropsychological functions during reduction in use of phencyclidine. J Clin Psychol 47:159–169

Craik FIM, Lockhart RS (1972) Levels of processing: a framework for memory research. Journal of Verbal Learning and Verbal Behavior 11:671–684

Curran HV (2000) Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. Neuropsychobiology 42:34–41

Curran HV, Monaghan L (2001) In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction 96:749–760

Curran HV, Morgan CJA (2000) Cognitive, dissociative and psychotogenic effects of ketamine on recreational users on the night of drug use and 3 days later. Addiction 95:575–590

Danion JM, Rizzo L, Bruant A (1999) Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. Archives of General Psychiatry 56:639–644

Deakin JF, Simpson MD (1997) A two-process theory of schizophrenia: evidence from studies in post-mortem brain. J Psychiatr Res 31:277–295

Drejer J, Honore T (1987) Phencyclidine analogues inhibit NMDA-stimulated [3H]GABA release from cultured cortex neurons. Eur J Pharmacol 143:287–290

DrugScope (2005) UK drug situation 2005. http://www.drugscope.org.uk/news_item.asp?intID=1241

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29:1558–1572

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry 57:594–608

Duncan GE, Miyamoto S, Lieberman JA (2003) Chronic administration of haloperidol and olanzapine attenuates ketamine-induced brain metabolic activation. J Clin Exp Ther 305:999–1005

Dundee JW, Lilburn JK (1978) Ketamine–lorazepam: attenuation of psychic sequelae of ketamine by lorazepam. Anaesthesia 33: 312–314

Fauman MA, Fauman BJ (1978) The psychiatric aspects of chronic phencyclidine use: a study of chronic PCP users. In: Stillman RC, Stillman RC (eds) Phencyclidine (PCP) abuse: an appraisal. National Institute on Drug Abuse, Rockville, MD, pp 66–118

Feldman RS, Meyer JS, Quenzer LF (1997) Principles of neuropsychopharmacology. Sinauer, Sunderland, MA

Fletcher PC, Frith CD, Rugg MD (1997) The functional neuroanatomy of episodic memory. Trends in Neurosciences 20:213–218

Fletcher PC, Honey GD (2006) Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. Trends Cogn Sci 10:167–174

Freuchen I, Ostergaard J, Kuhl JB, Mikkelsen BO (1976) Reduction of psychotomimetic side effects of Ketalar (ketamine) by Rohypnol (flunitrazepam). A randomized double-blind trial. Acta Anaesthesiol Scand 20:97–103

Ghoneim M, Hinrichs JV, Mewaldt SP, Peterson RC (1985) Ketamine: behavioural effects at subanesthetic doses. J Clin Psychopharmacol 5:70–77

Goldstein RZ, Volkow ND (2002) Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 159:1642–1652

Grossberg S (1984) Some normal and abnormal behavioral syndromes due to transmitter gating of opponent processes. Biol Psychiatry 19:1075–1118

Harborne GC, Watson FL, Healy DT, Groves L (1996) The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers. J Psychopharmacol 10:134–140

Harris JA, Biersner RJ, Edwards D, Bailey LW (1975) Attention, Learning and Personality During Ketamine Emergence: A Pilot Study. Anesthesia and Analgesia 54:169–172

Harvey PD, Green MF, McGurk SR, Meltzer HY (2003) Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. Psychopharmacology 169:404–411

Hazeltine E, Ivry RB (2003) Neural structures that support implicit sequence learning. In: Jiminez L (ed) John Benjamins, Amsterdam, pp 109–141

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM (1998) Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat Neurosci 1:318–323

Hetem LAB, Danion JM, Diemunsch P, Brandt C (2000) Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. Psychopharmacology 152:283–288

Honey RAE, Turner D, Honey GD, Sharar SR, Kumaran D, Pomarol-Clotet E, McKenna PJ, Sahakian B, Robbins TW, Fletcher PC (2003) Low dose ketamine produces a deficit in manipulation but not maintenance of the contents of working memory. Neuropsychopharmacology 28:2037–2044

Honey RA, Honey GD, O'loughlin C, Sharar SR, Kumaran D, Bullmore ET, Menon DK, Donovan T, Lupson VC, Bisbrown-Chippendale R, Fletcher PC (2004) Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: an FMRI study. Neuropsychopharmacology 29:1203–1214

Honey GD, Honey RA, O'loughlin C, Sharar SR, Kumaran D, Suckling J, Menon DK, Sleator C, Bullmore ET (2005a) Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: an FMRI study. Cereb Cortex 15:749–759

Honey G, Honey R, Sharar S, Turner D, Pomarol-Clotet E, Kumaran D, Simons J, Hu X, Rugg M, Bullmore E, Fletcher P (2005b) Impairment of specific episodic memory processes by subpsychotic doses of ketamine: the effects of levels of processing at encoding and of the subsequent retrieval task. Psychopharmacology 181:445–457

Honey GD, O'loughlin C, Turner DC, Pomarol-Clotet E, Corlett PR, Fletcher PC (2006) The effects of a subpsychotic dose of ketamine on recognition and source memory for agency: implications for pharmacological modelling of core symptoms of schizophrenia. Neuropsychopharmacology 31:413–423

Hurt PH, Ritchie EC (1994) A case of ketamine dependence. American Journal of Psychiatry 151:779

Jansen KLR (1990) Ketamine: can chronic use impair memory? Int J Addict 25:133–139

Jentsch JD, Tran A, Le D, Youngren KD, Roth RH (1997) Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. Neuropsychopharmacology 17:99

Jentsch JD, Roth RH (1999) The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 30:201–225

Jenstch JD, Roth RH, Taylor JR (2000) Object retrieval/detour deficits in monkeys produced by prior subchronic phencyclidine administration: evidence for cognitive impulsivity. Biol Psychiatry 48:415–424

Kegeles LS, Martinez D, Kochan LD, Hwang DR, Huang Y, Mawlawi O, Suckow RF, Van-Heertum RL, Laurelle M (2002) NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. Synapse 43:19–29

Keilhoff G, Bernstein HG, Becker A, Grecksch G, Wolf G (2004) Increased neurogenesis in a rat ketamine model of schizophrenia. Biol Psychiatry 56:317–322

Kothary SP, Zsigmond EK (1977) A double-blind study of the effective antihallucinatory doses of diazepam prior to ketamine anesthesia. Clin Pharmacol Ther 21:108–109

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Charney DS (1994) Subanesthetic effects of the non-competitive NMDA-antagonist, ketamine, in humans. Arch Gen Psychiatry 51:199–214

Krystal JH, Karper LP, Bennett A, D'Souza DC, Abi-Dargham A, Morrisey K, Charney DS (1998) Interactive effects of sub-

anesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology 135:213–299

Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers MB, Vegso S, Heninger GR, Charney DS (1999) Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology 145:193–204

Krystal JH, Bennett A, Abi-Saab D, Belger A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS (2000) Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. Biol Psychiatry 47:137–143

Krystal JH, Abi-Saab W, Perry E, D'Souza C, Liu N, Gueorguieva R, McDougall L, Hunsberger T, Belger A, Levine L, Breier (2005a) Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology 179:303–309

Krystal JH, Perry EB Jr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, MacDougall L, Abi-Saab W, D'Souza DC (2005b) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 62:985–994

Lindefors N, Barati S, O'Connor WT (1997) Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in the rat medial prefrontal cortex. Brain Research 759:205–212

Lisman JE, Fellous J, Wang X (1998) A role for NMDA-receptor channels in working memory. Nat Neurosci 1:273–275

Lodge D, Johnston GA (1985) Effect of ketamine on amino acid-evoked release of acetylcholine from rat cerebral cortex in vitro. Neurosci Lett 56:371–375

Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R (1959) Study of a new schizophrenomimetic drug—sernyl. AMA Arch Neurol Psych 81:363–369

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 14:301–307

Malhotra A, Adler CM, Kennison SD, Elman I, Pickar D, Breier A (1997) Clozapine blunts N-methyl-D-aspartate antagonist induced psychosis: a study with ketamine. Biol Psychiatry 42:664–668

Malhotra AK, Breier A, Goldman D, Picken L, Pickar D (1998) The apolipoprotein E epsilon 4 allele is associated with blunting of ketamine-induced psychosis in schizophrenia. A preliminary report. Neuropsychopharmacology 19:445–448

Meador-Woodruff JH, Healy DJ (2000) Glutamate receptor expression in schizophrenic brain. Brain Res Rev 31:288–294

Mintzer MZ, Griffiths RR (1999) Triazolam and zolpidem: effects on human memory and attentional processes. Psychopharmacology (Berl) 144:8–19

Moghaddam B, Adams B, Verma A, Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 17:2921–2927

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV (2004a) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29:208–218

Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV (2004b) Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose response study. Psychopharmacology 172:298–308

Morgan CJA, Monaghan L, Curran HV (2004c) Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. Addiction 99:1450–1461

Morgan CJA, Ricelli M, Maitland CH, Curran HV (2004d) Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. Drug Alcohol Depend 75:301–308

Morgan CJA, Rossell SL, Pepper F, Smart J, Blackburn J, Brandner B, Curran HV (2006a) Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. Biol Psychiatry 59:265–272

Morgan CJA, Perry EB, Cho HS, Krystal JH, D'Souza DC (2006b) Greater vulnerability to the amnestic effects of ketamine in males. Psychopharmacology (Berl) 187:405–414

Narendran R, Frankle WG, Keefe R, Gil R, Martinez D, Slifstein M, Kegeles LS, Talbot PS, Huang Y, Hwang DR, Khenissi L, Cooper TB, Laruelle M, Abi-Dargham A (2005) Altered prefrontal dopaminergic function in chronic recreational ketamine users. Am J Psychiatry 162:2352–2359

Nelson CL, Burk JA, Bruno JP, Martin S (2002) Effects of acute and repeated systemic administration of ketamine on prefrontal acetylcholine release and sustained attention performance in rats. Psychopharmacology 161:168–179

Newcomer JW, Krystal JH (2001) NMDA receptor regulation of memory and behaviour in humans. Hippocampus 11:529–542

Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW (1999) Ketamine-Induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 20:106–118

Ohno M, Yamamoto T, Watanabe S (1994) Intrahippocampal administration of a glycine site antagonist impairs working memory performance of rats. Eur J Pharmacol 253:183–187

Olney J, Labruyere J, Price MT (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 244:1360–1362

Olney J, Labruyere J, Wang G, Wozniak D, Price MT, Sesma M (1991) NMDA antagonist neurotoxicity: mechanism and prevention. Science 254:1515–1518

Oranje B, van Berckel BNM, Kemmer C, van Ree JM, Kahn RS, Verbaten MN (2000) The effects of a sub-anaesthetic dose of ketamine on human selective attention. Neuropsychopharmacology 22:293–302

Oye I, Paulsen O, Maurset A (1992) Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260:1209–1213

Parwani A, Weiler MA, Blaxton TA, Warfel D, Hardin M, Frey K, Lahti AC (2005) The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology (Berl) 183:265–274

Paulus MP, Hozcak NE, Zauscher BE, Frank L, Brown GG, Schuckit MA (2002) Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. Neuropsychopharmacology 26:53–63

Petrides M, Alivisatos B, Evans AC, Meyer E (1993) Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci U S A 90:873–877

Petrakis I, Limoncelli D, Gueorguieva R, Jaltow P, Boutros NN, Trevisan L, Gelernter J, Krystal JH (2004) Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. Am J Psychiatry 1776–1782

Renstall J, Tully AM, Ward PJ, Kidd AG (1988) Total intravenous anesthesia for military surgery. A technique using ketamine, midazolam and vecuronium. Anaesthesia 43:46–49

Rossell SL, David AS (2006) Are semantic processing deficits in schizophrenia an access or a storage problem? Schizophr Res 82:121–134

Rossell SL, Bullmore ET, Williams SC, David AS (2001) Brain activation during automatic and controlled processing of semantic relations: a priming experiment using lexical-decision. Neuropsychologia 39:1167–1176

Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA (2005) Selective cognitive impairments associated with NMDA receptor blockade in humans. Neuropsychopharmacology 30:633–639

Rusted JM, Eaton-Williams P, Warburton DM (1991) A comparison of the effects of scopolamine and diazepam on working memory. Psychopharmacology (Berl) 105:442–445

Sams-Dodd F (1995) Automation of the social interaction task by a video-tracking system: behavioral effects of repeated phencyclidine treatment. J Neurosci Methods 59:157–167

Sams-Dodd F (1996) Phencycldine-induced stereotyped behavior and social isolation in rats. Behav Pharmacol 7:3–23

Saykin AJ, Gur RC, Gur RE, Mozeley PD, Mozeley LH, Resnick SM, Kester DB, Stafiniak P (1991) Neuropsychological function in schizophrenia: selective impairment in memory and learning. Arch Gen Psychiatry 48:618–624

Schacter DL (1999) The seven sins of memory. Insights from psychology and cognitive neuroscience. Am Psychol 54:182–203

Shallice T (1982) Specific impairments of planning. Philos Trans R Soc Lond B 298:199–209

Siegel RK (1978) Phencyclidine and ketamine intoxication: a study of recreational users. In: Peterson RC, Stillman R (eds) Phencyclidine abuse: an appraisal, National Institute on Drug Abuse research monograph. NIDA, Rockville, MD, pp 119–140

Slamecka NA, Graf P (1978) The generation effect: delineation of a phenomenon. Journal of Experimental Psychology: Human Learning and Memory 4:592–604

Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkun SA, Simokowitz P, Hurley A, Cooper T, Volkow ND, Cancro R (1998) Glutamate modulation of dopamine measured in vivo with position emission tomography (PET) and 11C raclopride in normal human subjects. Neuropsychopharmacology 18:18–25

Steinpreis RE, Sokolowski JD, Papanikolau A, Salamone JD (1994) The effects of haloperidol and clozapine on PCP-and amphetamine-induced suppression of social behaviour in the rat. Pharmacol Biochem Behav 47:579–585

Stone JM, Erlandsson K, Arstad E, Bressan RA, Squassante L, Teneggi V, Ell PJ, Pilowsky LS (2006) Ketamine displaces the novel NMDA receptor SPET probe [(123)I]CNS-1261 in humans in vivo. Nucl Med Biol 33:239–243

Tamlyn D, McKenna PJ, Mortimer AM, Lund CE, Hammond S, Baddeley AD (1992) Memory impairment in schizophrenia: its extent, affiliations and neuropsychological character. Psychol Med 22:101–115

Tucker MR, Hann JR, Phillips CL (1984) Subanesthetic doses of ketamine, diazepam, and nitrous oxide for adult outpatient sedation. J Oral Maxillofac Surg 42:668–672

Tulving E (1972) Episodic and semantic memory. In: Tulving E, Donaldson W (eds) Organization of memory. Academic Press, New York, pp 381–403

Tulving E (1985) How many memory systems are there? American Psychologist 40:398

Tulving E (1998) Neurocognitive processes of human memory. In: von Euler C, Lundbreg I, Llinas R (eds) Basic mechanisms in cognition and language. Elsevier, Amsterdam, pp 261–281

Tulving E, Markowitsch HJ (1998) Episodic and declarative memory: role of the hippocampus. Hippocampus 8:198–204

Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC (2000) Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. Arch Gen Psychiatry 57:1139–1147

Verma A, Moghaddam B (1997) NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: modulation by dopamine. J Neurosci 16:373–379

Ware LA (1979) Neuropsychological functioning in users and nonusers of phencyclidine. Dissertation abstracts 5126B. South Illinois University, Carbondale

Weingartner HJ, Rawlings R, George DT, Eckardt M (1998) Triazolam-induced changes in alcoholic thought processes. Psychopharmacology (Berl) 138:311–317

White PF, Way WL, Trevor AJ (1982) Ketamine—its pharmacology and therapeutic uses. Anesthesiology 23:645–653

Wu JC, Buchsbaum MS, Bunney BS (1991) Positron emission tomography study of phencyclidine users as a possible drug model of schizophrenia. Jpn J Psychopharmacol 11:47–48

Zsigmond EK, Domino EF (1980) Clinical pharmacology and current uses of ketamine. In: Aldrite J, Stanley T (eds) Trends in intravenous anesthesia. Yearbook Medical Publishers, Chicago, IL, pp 283–328