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ORIGINAL INVESTIGATION

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Impairment of specific episodic memory processes by sub-psychotic doses of ketamine: the effects of levels of processing at encoding and of the subsequent retrieval task

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Abstract *Rationale:* The precise nature of the impact of the *N*-methyl-D-aspartate antagonist, ketamine, upon human episodic memory, has yet to be elucidated fully. *Objectives:* This study sought to assess the effects of ketamine on the sub-processes facilitating memory encoding and retrieval. *Methods:* We evaluated the effects of the drug on a series of memory performance measures depending upon whether it was administered at the encoding or retrieval stage and on the nature of the encoding task used. Twelve healthy volunteers participated in a double-blind, placebo-controlled, randomized, within-subjects study. Intravenous infusions of placebo, 50 ng/ml ketamine or 100 ng/ml ketamine were administered. We investigated the effects of ketamine on three key aspects of episodic memory: encoding vs retrieval processes, source memory, and depth of processing. Data were analysed using both multinomial modelling and standard measures of item discrimination and response bias. *Results:* Deleterious effects of ketamine on episodic memory were primarily attributable to its effects on encoding, rather than retrieval processes. Recognition memory was impaired for items encoded at an intermediate level of processing, but preserved for shallowly and deeply encoded items. Increased source guessing bias was also observed when encoding took place under ketamine. *Conclusions:* The effects of ketamine upon episodic memory seem, therefore, to predominate at encoding. Furthermore, our results are also consistent with a specific impairment of encoding processes that result in subsequent recollective, as opposed to familiarity-based, retrieval. The observed effects are compatible with memory deficits seen in schizophrenia and thus provide some support for the ketamine model of the disease.

Keywords Memory · Ketamine · Encoding · Retrieval · Source memory

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Introduction

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that produces a range of psychotic and cognitive phenomena thought to mimic schizophrenia. At the cognitive level, episodic memory impairment has been observed consistently (Ghoneim et al. 1985; Harris et al. 1975; Hetem et al. 2000; Krystal et al. 1994; Malhotra et al. 1996; Newcomer et al. 1999; Radant et al. 1998), in line with the suggestion that memory deficits may be a central feature of schizophrenia (Aleman et al. 1999; Calev et al. 1983; Gold et al. 1992; Heinrichs and Zakzanis 1998; McKenna et al. 1990). More recently, Morgan et al. (2004) produced evidence that both working and episodic memory deficits under ketamine are relatively specific, occurring in the face of preserved attentional and executive perfor-

mance. The purpose of the current study was to investigate the specific cognitive processes that may underlie the disruption of episodic memory associated with ketamine administration.

Encoding and retrieval of information require different, though overlapping, brain systems (Fletcher and Henson 2001), suggesting that there may be different effects of ketamine on memory performance depending upon when the drug is administered. Whereas most studies have explored effects when ketamine is present at both stages (Ghoneim et al. 1985; Harris et al. 1975; Krystal et al. 1994; Malhotra et al. 1996; Newcomer et al. 1999; Radant et al. 1998), Oye et al. (1992) and Hetem et al. (2000) reported a disruption of episodic memory when ketamine was administered before, but not after, encoding. This suggests a selective disruption of encoding processes, but does not rule out the possibility that memory impairment results only when both encoding *and* retrieval systems are affected since, in both cases, the retrieval stage occurred during ketamine exposure. In the current study, subjects encoded items *prior* to ketamine infusion, and retrieval of these items was then tested *during* drug administration; a second list was then encoded *during* drug treatment, which was concluded *prior* to retrieval.

According to the dual-process model (Jacoby 1991, Yonelinas 1994), successful recognition of previously encountered stimuli may occur following rich recollection of contextual detail associated with the encoding of the stimulus or, in the absence of such information, may occur on the basis of a sense of familiarity only. These have been conceptualised as functionally distinct processes, mediated by dissociable neural systems (Cansino et al. 2002; Dobbins et al. 2002; Henson et al. 1999; Rugg et al. 1999). In order to investigate whether ketamine may have distinct effects on these processes, we implemented two experimental manipulations. Firstly, the 'depth of processing' that occurs when subjects encode information influences their ability to subsequently retrieve the information from memory (Craik and Lockhart 1972). This effect is disrupted in patients with schizophrenia (Brebion et al. 1997; Heckers et al. 1998), indicating a failure of the recollective processes that confer the mnemonic advantage associated with deep encoding, compared to weaker, familiarity-based recognition associated with shallow encoding. We therefore varied the depth of processing that subjects would use during encoding by using three levels of processing ('shallow', 'intermediate' and 'deep'). Second, the depth manipulation also served as the basis for a subsequent source memory judgement at retrieval. Dysfunctional source monitoring is a central mechanism underlying the theoretical model of schizophrenic symptoms proposed by Frith (1992) and Frith and Done (1988) and is consistent with a number of studies reporting impairment of source memory in schizophrenia (Brebion et al. 1999, 2000, 2002; Danion et al. 1999, Keefe et al. 1999, 2002; Moritz et al. 2003; Morrison and Haddock 1997; Stirling et al. 1997; Vinogradov et al. 1997). This recollection-familiarity distinction was explored by Hetem et al. (2000) who observed that ketamine administration at encoding reduced the number of 'remember' (recollection) and 'know' responses in a subsequent recognition memory test. However, the recognition test did not include new items ('lures') making it difficult to differentiate memory effects from a drug-induced change in response bias.

In summary, our study had two goals. First, we wished to characterise, with greater specificity, the impact of low-dose ketamine on episodic memory processes. Second, we wished to relate our findings to the use of ketamine as a model for impaired memory in schizophrenia. On the basis of previous studies involving patients with schizophrenia, we predicted that memory deficits would predominate when ketamine was administered at encoding. Furthermore, in schizophrenia, evidence suggests that tasks engaging recollective processes might prove especially vulnerable. Hence, we used tasks emphasising the contribution of such processes to determine whether recollection-based memory might prove especially vulnerable to the effects of ketamine.

Methods

Subjects

Thirteen right-handed healthy volunteers (6 men) were tested with their informed consent. The study was approved by the Addenbrooke's NHS Trust research ethics committee. No subject had a history of drug abuse in the last 12 months, of psychiatric disorders or of serious medical illness. All subjects were non-smokers. Subjects had a mean age of 32.6 years (range 18–64), mean National Adult Reading Test (NART) IQ of 97.54 (±27.79) (Nelson 1982)) and were within 10% of ideal body mass index. Data from one subject were excluded as evidence of dyslexia became apparent during testing. Data from the intermediate level of drug administration (see below) were lost from one subject due to evidence of extravasation of the infusion. However, this subject's data were retained for analyses comparing placebo and higher drug level conditions.

Note that data from these subjects were also obtained for a series of other working memory and attentional tasks; these are published elsewhere (Honey et al. 2003)

Procedure

The study was a double-blind, placebo-controlled, randomised, within-subjects design. Subjects attended on three occasions receiving a different infusion on each (saline, 50 ng/ml plasma ketamine, and 100 ng/ml plasma ketamine). Visits were 48 h apart and order of infusion was counterbalanced across subjects. Target plasma levels were chosen to avoid marked psychotic and dissociative side effects of the drug.

Bilateral intravenous catheters were inserted into subjects' forearms, one for ketamine infusion, the other for serial blood sampling for plasma ketamine levels. Racemic ketamine (1 mg/ml solution) was administered by bolus and continuous infusion using a computerised pump (Graseby

3500, Graseby Medical Ltd., UK). The pump was programmed (Anaetech Ltd., UK) to infuse ketamine continuously at varying doses to achieve constant estimated target plasma concentrations of 50 or 100 ng/ml, using pharmacokinetic parameters of a three-compartment model (Domino et al. 1982). At the conclusion of testing (approximately 2 h later) target plasma levels were reduced such that estimated plasma ketamine levels 90 min after behaviour testing would be approximately 28 ng/ml in both dosing groups (see below).

Subjective rating scales and clinical assessments

During the infusion, patients were interviewed clinically using an abbreviated form of the *Present State Examination, 9th Edition* (Wing et al. 1974) designed to focus on symptoms relevant to likely effects of ketamine, and abbreviated to limit the duration of drug exposure.

Episodic memory tasks

Seven hundred and twenty words were selected from the MRC psycholinguistic database (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm), and divided into six sets (used for two lists on each of the three visits) matched for frequency of occurrence in written English (Francis and Kucera 1982). Neutral words were chosen that were approximately balanced on active/passive odd/even syllables dimensions. Words were counterbalanced across foil and targets and across tasks and drug dosage. In this way, we removed systematic item- or list-specific effects from the data. Words were presented on a computer screen, using DMDX (Forster and Forster, http://www.u.arizona.edu/~jforster/dmdx/official.htm). The three manipulations of interest were made as follows:

1. Effects of ketamine on encoding and retrieval
   During each visit, subjects were presented with two lists, each consisting of 90 words, constituting two separate study phases. The first study set (list 1) was presented before drug infusion (see Fig. 1). Recognition of these items was then tested approximately 60 min after drug administration was initiated. A second study set (list 2) was presented to subjects for encoding whilst steady-state infusion was maintained. The estimated plasma ketamine level was then allowed to decline and retrieval was tested 90 min later.
2. Depth of processing manipulation
   Each of the 90-item lists comprised 30 items for each of three study tasks, corresponding to subjective binary judgements of pleasantness (pleasant/unpleasant), action (active/passive), or number of syllables (even/odd). Each item was preceded by an instruction ('Pleasant?', 'Active?", or 'Syllables?') to specify the decision required. Subjects indicated a yes/no response via a keyboard. Items were presented in a randomised order for 3.5 s, with an inter-stimulus interval (ISI) of 2 s. Henceforth, we shall refer to these tasks operationally according to the level of subsequent recognition memory that they produced: Depth 1, Depth 2 and Depth 3 for the syllables, active/passive and pleasant/unpleasant judgements, respectively.
3. Source monitoring
   The depth of processing manipulation also formed the basis for a subsequent source decision at test. To facilitate subsequent source judgement, the position of an item's presentation on screen was consistently related to the judgement required: Depth 2 items were presented at the top of the screen, Depth 1 items in the centre, and Depth 3 items at the bottom of the screen. Before the study phase, subjects were informed that a subsequent test of item detection and source discrimination would occur.

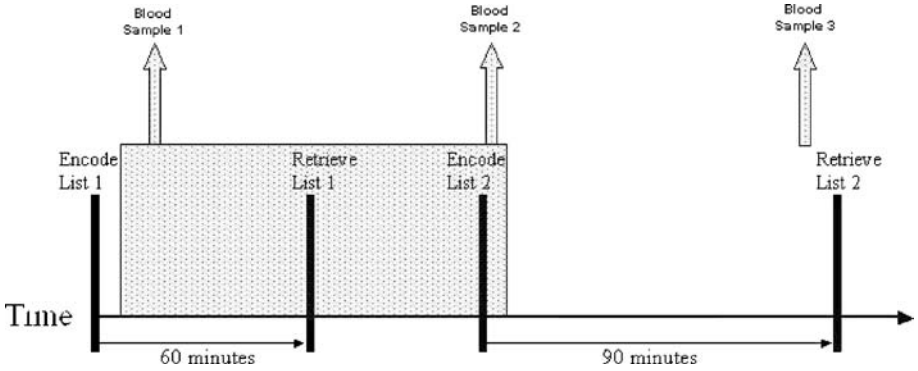

Fig. 1 Experimental design. Ketamine was administered subsequent to encoding of *List 1* items, which were retrieved during drug exposure, thereby identifying effects of the drug on retrieval processes; *List 2* was encoded during drug exposure, with memory for these items test after elimination of the drug towards baseline level, thereby identifying the effects of ketamine on encoding processes. Peripheral venous blood samples were drawn on three occasions: at approximately 15 min (15.6±4.9 min) after initiation of drug infusion, at the completion of all on-drug assessments, and finally at the end of off-drug testing (approximately 90 min post-encoding list 2 (90.9± 3.3 min). In total, subjects were maintained on ketamine for approximately 2 h (117.5±10.4 min). Blood samples were placed on ice, plasma obtained by centrifugation, and plasma samples stored at −20°C. Ketamine plasma levels were measured by gas chromatography–mass spectrometry (Kharasch and Labroo 1992)

During the test phase, subjects made a recognition and then a source response to each presented word. Sixty of the studied words (20 items from each level of processing) and 30 foils (unseen words) were presented on a computer screen for 4.5 s (ISI=2 s). Subjects responded by saying whether the item was old and, if so, the encoding task that they had performed on it.

Statistical analysis

Data analysis aimed to differentiate between key features of the recognition and source memory tasks, taking into account the frequently competing effects of item detection, source memory and guessing biases (Batchelder and Riefer 1990; Bayen et al. 1996). In order to obtain separate and independent parameter estimates for these critical features, the data were analysed using a two-high threshold multinomial model (Batchelder and Riefer 1990) for three sources (see Fig. 2) via maximum likelihood estimation for item detection, source discrimination and response bias. Multinomial models have previously been successfully applied to source memory data across a range of cognitive paradigms and pathological conditions involving memory deficits (Batchelder et al. 1997; Keefe et al. 2002; Simons et al. 2002).

The multinomial model was implemented using GPT software (X. Hu, http://irvin.psyc.memphis.edu/xhuoffice/gpt/index.htm), and the comparison of individual parameter estimates across treatments was performed using spreadsheet-based algorithms (Dodson et al. 1998). For each of the four possible sources (Depth 1, Depth 2, Depth 3 and New) there were five possible responses ('Depth 1', 'Depth 2', 'Depth 3', 'new' and 'don't know'). Response frequencies were recorded for each of these 20 cells under each of the three treatment conditions, and a model was constructed to account for item recognition and source monitoring, with independent assessment of guessing bias (see Fig. 2). The model was applied separately to response frequencies for both lists 1 and 2 and under each of the three treatment conditions. Mean parameter estimates and standard deviations were based on 100 simulations using data

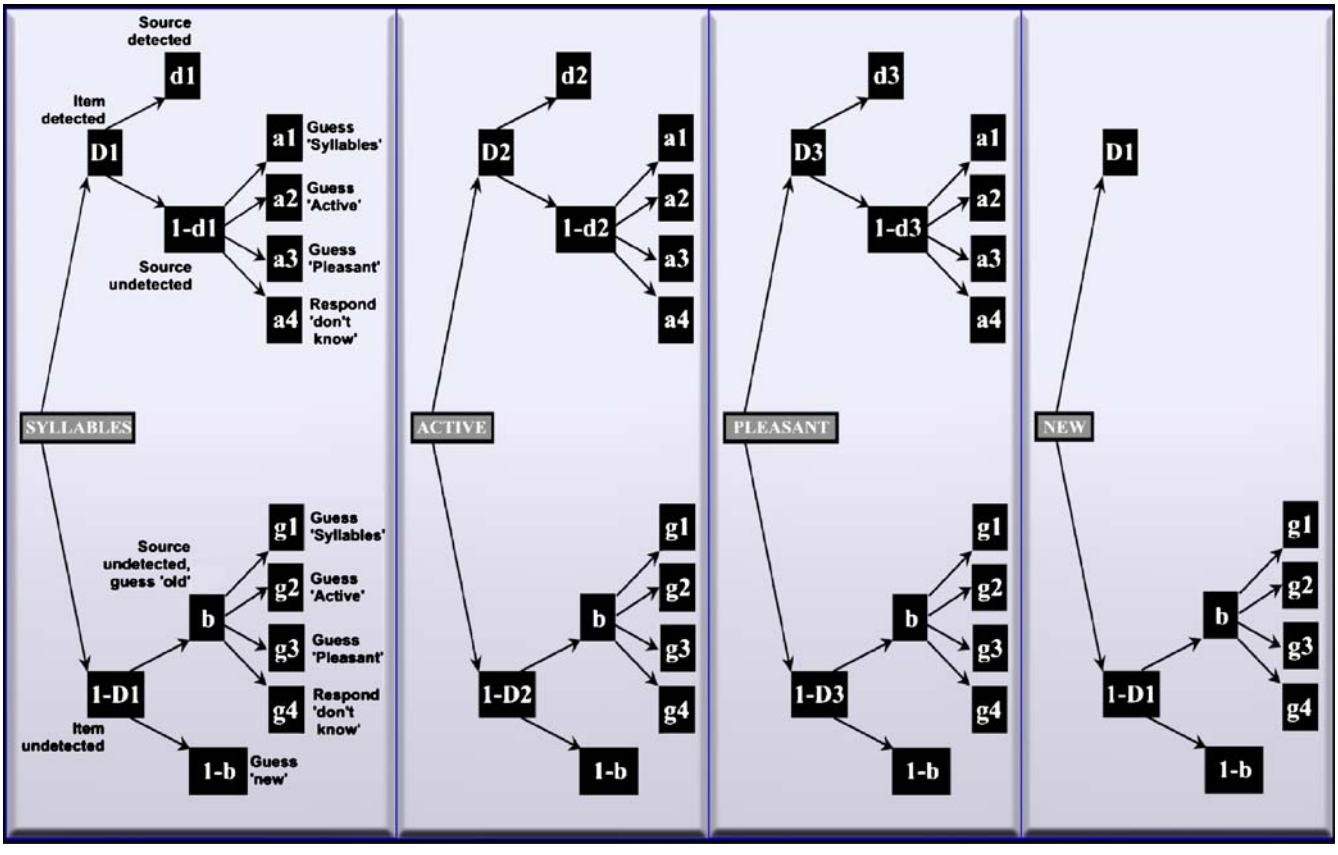

Fig. 2 Multinomial model for three sources. Model estimation provided separate parameter estimates for correct detection of items encoded under Depth 2 and Depth 3 conditions (parameters D_2 and D_3). We assumed that correct detection for Depth 1 encoded items would be similar to that for new items (this was empirically supported by significantly reduced model fit indices for models incorporating separate parameter estimates for detection of new and shallow items), and so were modelled as a combined parameter, D_1. Correct source discrimination was modelled by parameters d_1, d_2 and d_3 for Depth 1, Depth 2 and Depth 3 items, respectively. Guessing parameters for source memory were also separately modelled and allowed to vary according to the level of processing during the study phase: parameters a_1–a_3 represented response biases for each source when the item was correctly detected, but source information was undetected; parameters g_1–g_3 represented guessing responses when both the item and source were undetected. Guessing bias for item detection was represented by parameter b. The 'don't know' response was modelled by parameters a_4 and g_4

resampling techniques. Goodness of fit was tested using the log-likelihood statistic, G^2 (Riefer and Batchelder 1988).

For completeness, the data were also analysed using standard response measures derived from signal detection theory (SDT): the discrimination accuracy index, P_r, and the response bias index, B_r (see Table 4).

Results

Plasma levels

Observed ketamine plasma levels are presented in Table 1. At time point 2, plasma levels were in accordance with those predicted by the model (low dose=55.0 ng/ml; high dose=105.7 ng/ml). However, plasma levels at time point 1 were substantially lower than those predicted by the model (low-dose mean=31.98 ng/ml; high dose mean=61.48). At time point 3, plasma levels were in accordance with the target level of 28 ng/ml for the low-dose condition (mean=24.29); however, the mean ketamine plasma level was above the target level in the high-dose condition (mean=37.59). The implications of this variability on memory testing are addressed below.

Subjective ratings and clinical assessments

The ratings from the PSE-9 are presented in Table 2 and in a previous paper (Honey et al. 2003). The main subjective symptoms were tiredness, inefficient thinking and poor concentration. Whereas three subjects scored on the section for ideas of reference, these phenomena were subtle, fleeting and accompanied by full insight. No subjects experienced hallucinations. Only three subjects showed any more than questionable evidence of thought disorder using the Thought, Language and Communication Disorder (TLC) scale, which was barely evident in all cases: two subjects were rated as having mild poverty of content of speech at a dose of 100 ng/ml. One subject showed circumstantiality while receiving placebo, which increased when ketamine was administered; at a dose of 100 ng/ml, derailment was also evident in this subject. Scores on PSE were not measurably predictive of cognitive performance.

Table 1 Ketamine plasma levels

Target dose (ng/ml)	Time point	Mean (SD)	Range
50	1	31.98 (12.5)	20.0–58.0
	2	55.0 (10.5)	52.6–74.9
	3	24.29 (3.6)	20.5–30.4
100	1	61.48 (25.1)	29.6–104.4
	2	105.7 (21.4)	93.0–154.8
	3	37.59 (7.6)	25.0–47.5

Mean and standard deviations (ng/ml) for plasma levels of ketamine at 15 min post-infusion (time point 1), 100 min post-infusion (time point 2), and 90 min post-testing (time point 3) for the 50-ng/ml ketamine and 100-ng/ml dose conditions. Data from one subject at the low-dose condition was excluded because of extravascular infusion during this session

Table 2 Subjective ratings and clinical assessments

PSE-9 subscale	Placebo	Ketamine	
		50 ng/ml	100 ng/ml
Tiredness	2	3	6
Nervous tension	–	–	2
Autonomic anxiety	–	1	–
Subjectively inefficient thinking	2	6	11
Poor concentration	2	6	11
Depressed mood	1	–	1
Expansive mood	2	3	9
Subjective ideomotor pressure	1	1	3
Derealisation	–	–	–
Depersonalisation	–	–	–
Delusional mood	–	–	–
Heightened perception	–	1	3
Dulled perception	–	–	–
Changed perception	–	–	2
Changed perception time, déjà vu	–	–	–
Auditory hallucinations	–	–	–
Visual hallucinations	–	–	–
Olfactory hallucinations	–	–	–
Ideas/delusions of reference/ misinterpretation	–	–	3

Number of participants exhibiting symptoms on the PSE-9 subscales for the placebo, 50-ng/ml ketamine and 100-ng/ml ketamine conditions

Episodic memory

Depth of processing effects on item detection and guessing strategies under placebo

Raw frequencies for response parameters for both lists 1 and 2 under placebo are presented in Table 5. Recognition memory was greatest for Depth 3, intermediate for Depth 2 and lowest for Depth 1. This pattern was consistent for lists 1 and 2 and was observed with both multinomial modelling (see Fig. 3a) and the SDT measure of recognition discrimination (see Fig. 3b and Tables 4, 5): depth of processing produced a significant effect on subsequent recognition and source memory [$F(1,11)=103$, $p<0.001$].

Source memory was also highest for Depth 3 items but lowest for Depth 2 items; Depth 1 items tended to fall between these. The pattern observed for source memory across levels of processing using multinomial modelling (see Fig. 3a) was replicated using SDT measures: a task by depth interaction was observed for the P_r index [$F(1,11)=15.3$, $p<0.01$] (see Fig. 3b).

Multinomial modelling allowed us to estimate subjects' guessing biases for each of the sources, both when the item was detected (parameters a_1–a_3) and when undetected (parameters g_1–g_3). A double dissociation between depth and guess-

Table 3 Multinomial model parameter estimates, confidence intervals and model fit statistics under each of the drug treatment conditions

		List 1 (retrieval)		List 2 (encoding)	
		Placebo	Ketamine 100 ng/ml	Placebo	100 ng/ml
D_1	Depth 1, item detection	0.29 [.27, .31]	**0.35*** [.33, .37]	0.33 [.31, .35]	0.3 [.28, .32]
D_2	Depth 2, item detection	0.71 [.69, .73]	0.74 [.72, .76]	0.62 [.6, .64]	**0.53** [.51, .55]
D_3	Depth 3, item detection	0.81 [.79, .83]	0.77 [.75, .79]	0.78 [.76, .8]	0.77 [.75, .79]
d_1	Depth 1, source discrimination	0.76 [.71, .81]	**0.63** [.58, .68]	0.58 [.52, .64]	0.59 [.52, .66]
d_2	Depth 2, source discrimination	0.32 [.24, .4]	**0.56*** [.52, .6]	0.44 [.39, .49]	0.5 [.45, .55]
d_3	Depth 3, source discrimination	0.71 [.68, .74]	0.71 [.69, .73]	0.67 [.63, .71]	0.64 [.6, .68]
b	Guess bias, item undetected	0.19 [.18, .2]	**0.14*** [.13, .15]	0.28 [.26, .3]	0.29 [.27, .31]
a_1	Guess depth 1, item detected	0.12 [.1, .14]	0.16 [.14, .18]	0.17 [.15, .19]	0.22 [.18, .26]
a_2	Guess depth 2, item detected	0.49 [.44, .54]	**0.31*** [.27, .35]	0.36 [.31, .41]	0.29 [.25, 33]
a_3	Guess depth 3, item detected	0.24 [.2, .28]	0.2 [.17, .23]	0.26 [.22, .3]	0.28 [.24, .32]
a_4	'Don't know' source, item detected	0.15	0.33	0.21	0.21
g_1	Guess depth 1, item undetected	0.47 [.42, .52]	0.55 [.5, .6]	0.38 [.35, .41]	**0.5** [.46, .54]
g_2	Guess depth 2, item undetected	0.16 [.14, .18]	**0.08*** [.06, .1]	0.15 [.13, .17]	0.14 [.12, .16]
g_3	Guess depth 3, item undetected	0.17 [.14, .2]	0.21 [.17, .25]	0.23 [.2, .26]	0.21 [.19, .23]
g_4	'Don't know' source, item undetected	0.2	0.16	0.24	0.15
	G^2 (3)	3.48	6.02	4.66	6.41
	P value	0.323	0.111	0.198	0.093

List 1 represents the effect on drug on retrieval; list 2 the effect of drug on encoding. Figures in bold indicate parameters for which confidence intervals were non-overlapping between placebo and either the high-dose condition, or both low- and high-dose conditions. Items shown with an asterisk indicate that confidence intervals for the 50-ng/ml ketamine condition also did not overlap with the placebo condition

ing bias was observed. Following correct item detection but failed source discrimination, subjects' guessing bias for source judgements was stronger for the more deeply encoded items, Depth 2 and Depth 3 (parameters a_2 and a_3) compared to Depth 1 items (a_1) (see Table 3 and Fig. 4); indeed this was strongest for the Depth 2 items (a_2). The opposite pattern was observed when subjects failed to detect the item as old: increased bias towards the shallowly encoded Depth 1 items (parameter g_1) was evident compared to the Depth 2 and Depth 3 items (g_2 and g_3). This pattern was observed for both list 1 and list 2.

Effects of ketamine

Encoding Recognition of items following Depth 2 encoding (parameter D_2) was reduced under the higher dose of ketamine (see Fig. 5a). An increase in parameter g_1 (bias to

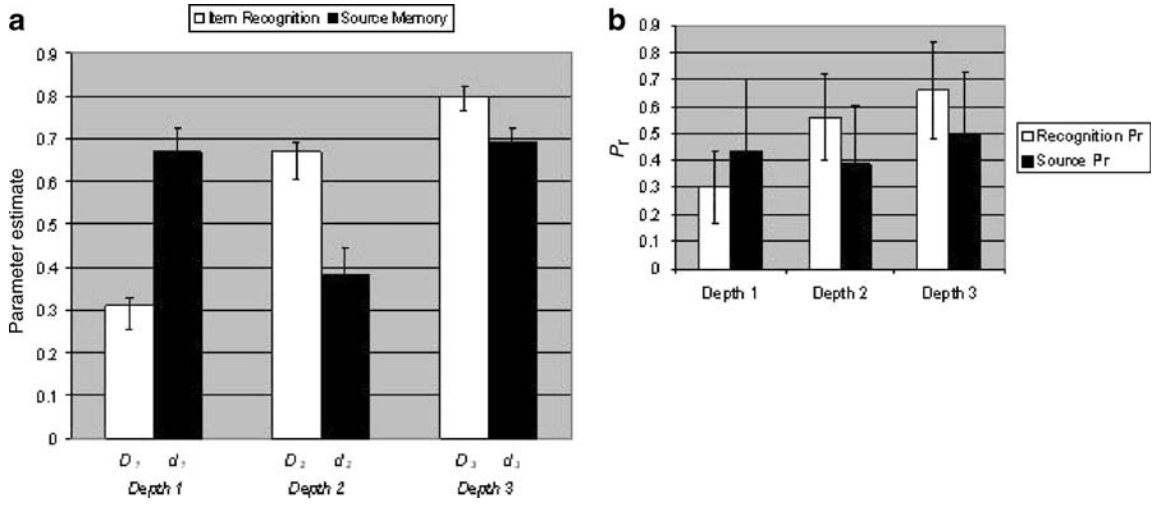

Fig. 3 Effects of depth of processing on recognition and source memory on placebo. **a** Multinomial parameters (with 95% confidence intervals) for item recognition (*light columns*) across three levels of processing (parameters D_1–D_3) and source memory (*dark columns*; parameters d_1–d_3) averaged across placebo conditions for list 1 and list 2. **b** Discrimination scores, P_r (with standard deviations) for source and recognition tasks, averaged from the placebo conditions for list 1 and list 2. Both the multinomial parameters and the discrimination index, indicate that item discrimination increases linearly with depth of processing; source discrimination is strongest for the deeply encoded Depth 3 items, but weakest for Depth 2 items

Table 4 Discrimination accuracy (P_r) and response bias (B_r) for item detection and source memory for source 1 (active/passive), source 2 (even/odd number of syllables) and source 3 (pleasant/unpleasant) items under each of the drug conditions

			List 1 (retrieval)		List 2 (encoding)	
			Placebo	Ketamine 100 ng/ml	Placebo	Ketamine 100 ng/ml
Item detection	P_r	1	0.27 (.14)	0.34 (.16)	0.33 (.18)	0.29 (.18)
		2	0.6 (.18)	0.66 (.16)	0.52 (.19)	0.45 (.19)
		3	0.68 (.2)	0.68 (.19)	0.64 (.2)	0.6 (.19)
	B_r	1	0.21 (.18)	0.15 (.17)	0.28 (.19)	0.29 (.2)
		2	0.36 (.23)	0.28 (.24)	0.4 (.23)	0.35 (.2)
		3	0.43 (.2)	0.3 (.2)	0.52 (.23)	0.46 (.21)
Source memory	P_r	1	0.51 (.3)	0.46 (.2)	0.36 (.26)	0.32 (.3)
		2	0.4 (.3)	0.55 (.2)	0.38 (.19)	0.36 (.3)
		3	0.54 (.3)	0.58 (.23)	0.46 (.24)	0.44 (.2)
	B_r	1	0.21 (.18)	0.31 (.29)	0.31 (.14)	0.41 (.25)
		2	0.36 (.23)	0.25 (.19)	0.27 (.17)	0.28 (.19)
		3	0.44 (.2)	0.4 (.25)	0.45 (.23)	0.42 (.27)

List 1 represents the effect on drug on retrieval; list 2, the effect of drug on encoding. The discrimination index, P_r, is calculated by a simple subtraction of the proportion of new items falsely identified as having been studied (proportion of 'false alarms', P_{FA}) from the number of old items correctly identified as studied (proportion of 'hits', P_{HIT}), i.e. $P_r=P_{HIT}-P_{FA}$. The bias index, B_r, which provides an indirect measure of the 'liberality' of subjects' responses (Corwin 1994)was calculated as follows: $B_r=P_{FA}/(1-P_r)$. We acknowledge that this analysis does not model explicitly a number of critical features of source memory that may be susceptible to the effects of ketamine. Nevertheless we believe that this analysis may be complementary to the main analysis

guess 'depth 1' when the item and source was undetected) was also observed under ketamine (see Fig. 5). Between-treatment differences in these parameter estimates were tested by fitting the model under the constraint that the parameter estimate for the ketamine-treated conditions were equal to the placebo condition, and comparing this to the model fit when both conditions were allowed to take different values between conditions. The D_2 parameter for the ketamine 100 ng/ml treatment was significantly different from placebo [$G^2(1)=4.206$, $p=0.04$] and ketamine 50 ng/ml [$G^2(1)=4.8$, $p=0.029$; 11 subjects only]. The g_1 parameter under ketamine 100 ng/ml treatment was also signifi-

Table 5 Item source response frequencies for depth 1 (even/odd number of syllables), depth 2 (active/passive), depth 3 (pleasant/unpleasant) and new item under placebo and 100 ng/ml ketamine

Item	Response	List 1 (retrieval)		List 2 (encoding)	
		Placebo	Ketamine 100 ng/ml	Placebo	Ketamine 100 ng/ml
(Depth 1) (number of Syllables)	Depth 1	**70**	**69**	**69**	**72**
	Depth 2	16	7	20	13
	Depth 3	6	10	14	14
	Don't know	9	19	22	20
	New	139	135	115	119
(Depth 2) (active/passive)	Depth 1	18	19	21	29
	Depth 2	**112**	**124**	**100**	**88**
	Depth 3	31	18	31	27
	Don't know	20	25	22	16
	New	55	54	66	80
(Depth 3) (Pleasant/Unpleasant)	Depth 1	28	21	24	23
	Depth 2	14	11	19	23
	Depth 3	**154**	**144**	**145**	**138**
	Don't know	10	16	15	14
	New	36	48	37	39
New	Depth 1	7	3	10	11
	Depth 2	23	18	26	37
	Depth 3	10	7	18	17
	Don't know	10	4	14	8
	New	**310**	**328**	**294**	**290**

List 1 represents the effect on drug on retrieval; list 2, the effect of drug on encoding. Figures in bold indicate correct responses

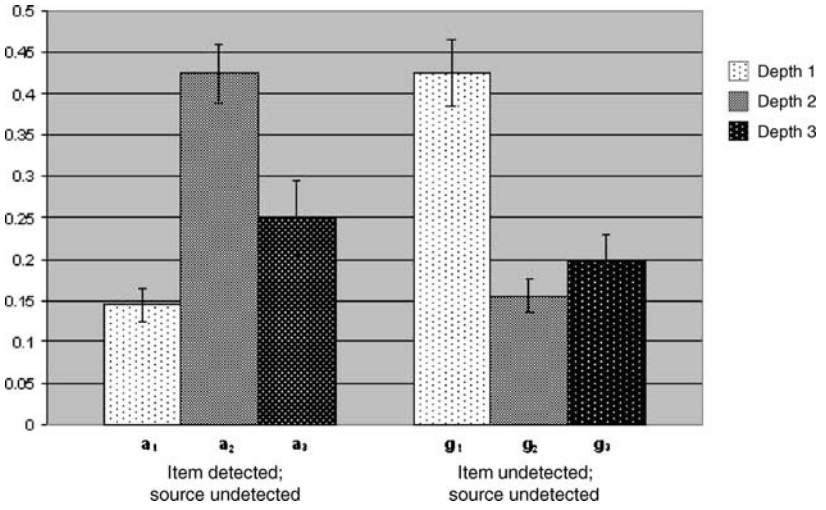

Fig. 4 Multinomial modelling of guessing biases for source memory. Parameters averaged across list 1 and list 2. Parameters a_1–a_3 indicate guessing biases for source when the item was detected: responses are increased for the deeper conditions, and preferentially towards Depth 2 items, for which source memory was consistently low; parameters g_1–g_3 represent guessing biases for source when the item was undetected. Responses are biased towards the shallowly encoded Depth 1 items, perhaps reflecting the 'it had to be you' metacognitive strategy (see text for discussion)

cantly different from placebo [$G^2(1)=4.577$, $p=0.032$], but not the ketamine 50 ng/ml condition [$G^2(1)=1.389$, $p=0.24$; 11 subjects only].

These effects were echoed by those seen in the SDT analysis: the greatest reduction in P_r at the higher ketamine dose was seen for Depth 2 items, consistent with the effect observed for the multinomial parameter D_2. Furthermore, the bias index, B_r, was significantly increased under ketamine for the Depth 1 items [$F(1,11)=12.7$, $p<0.01$] (see Fig. 5b), consistent with the increased guessing bias (parameter g_1) for Depth 1 items under ketamine observed using multinomial modelling.

To address the issue of whether the variability in ketamine plasma levels observed at 90 min after drug treatment may have affected the parameter estimates for list 2, we conducted a mean split of the sample at ketamine 100 ng/ml to form a 'high residual' group (mean ketamine plasma level=43.95±2.98 mg/ml; $n=6$) and 'low residual' group (mean ketamine plasma level=31.23±4.73; $n=6$). The multinomial model was then fitted to each of the subsamples. The model provided an adequate fit to the data for both groups [high residual group: $G^2(1)=6.089$, $p=0.107$; low residual group: $G^2(1)=7.385$, $p=0.061$]. In order to compare the parameter estimates for D_1 and g_2 across the

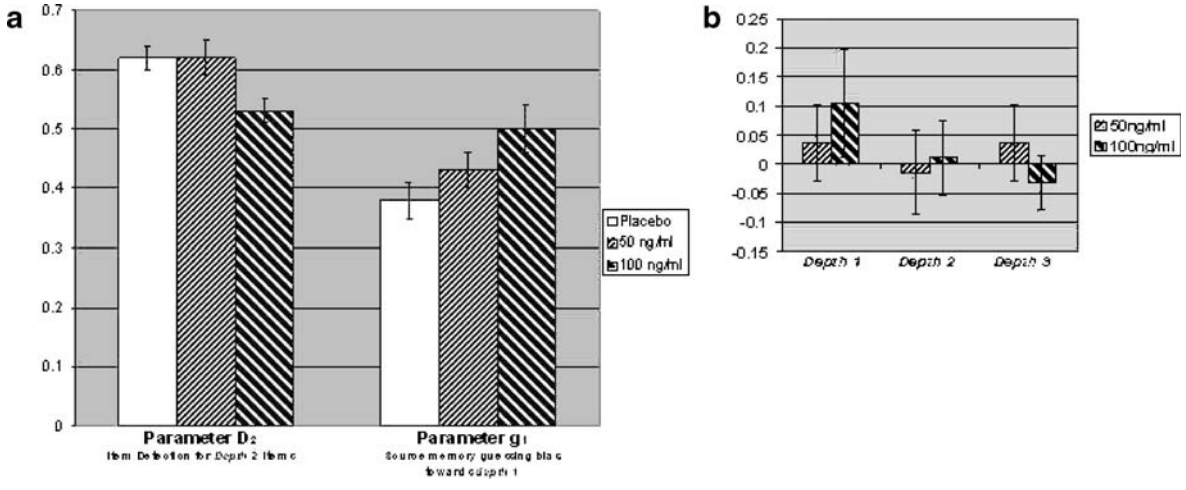

Fig. 5 **a** Changes in multinomial parameter estimates for D_2 and g_1 across treatment groups (with 95% confidence intervals). The reduction in parameter D_2 at the higher dose of ketamine indicates a significant reduction in item detection for Depth 2 items; the increase in parameter g_1 indicates the increased tendency under ketamine treatment to guess source judgements, biased towards the shallowly encoded, Depth 1 source. **b** Changes in response biases for the three levels of encoding under ketamine treatment, indexed by the liberality bias, B_r (with standard deviations). A significant increase in response liberality is seen under ketamine treatment for the Depth 1 items

subsamples, the model fit for the 'high residual' group was compared to the fit under the constraint that the parameter estimate was equal to the low residual group. The comparison of the model fits for the D_1 parameter indicated that the two subsamples were not significantly different on this parameter [$G^2(1)=0.602$, $p=0.438$]; however, there was a significant difference between the subsamples on parameter g_2 [$G^2(1)=15.892$, $p=0.004$].

Retrieval For the recognition task, comparison of the multinomial model fit between placebo and ketamine showed a significant reduction in guessing undetected items as 'old' under ketamine [parameter *b:* $G^2(1)=5.825$, $p=0.016$]. Using the SDT model, a trend towards a reduction in the bias index, B_r, for recognition [$F(1,11)=3.4$, $p=0.09$] was seen (this reduced liberality is in keeping with the reduced guessing bias indicated by the multinomial approach). Interestingly, the proportion of items deemed correctly as old that were subsequently given a 'don't know' response for the source judgement task was significantly greater with the administration of ketamine at retrieval compared to when it was given at encoding [$F(1,11)=5.8$, $p<0.05$] (Table 5). Similarly the multinomial parameter, a_4, was increased under ketamine for list 1. These observations are consistent with the interpretation that guessing tendencies were reduced when ketamine was administered at retrieval.

Source memory was also affected by ketamine at retrieval: Depth 2 items were associated with increased source memory under ketamine treatment [parameter d_2: $G^2(1)=7.955$, $p=0.0048$] and a reduced guessing bias towards Depth 2 when the item was detected as old but source was undetected [parameter a_2: $G^2(1)=6.357$, $p=0.012$]. This was supported by a significant Drug × Depth interaction in the P_r index for source memory [$F(1,11)=6.5$, $p<0.05$]. Non-overlapping confidence intervals were also observed for parameters D_1, d_1 and g_2 (see Table 3); however, formal comparison of the groups using nested models showed that the difference between groups was non-significant ($p>0.05$).

Summary of findings

The deleterious effects of ketamine on episodic memory were observed when the drug was administered at encoding. There was a subsequently reduced recognition of Depth 2 items and an increased guessing bias towards Depth 1 when making a source memory judgement. When ketamine was administered at retrieval, reduced guessing biases were observed for both item detection and source memory, and indeed there was some improvement in recognition of Depth 2 items.

Discussion

A number of existing studies have shown that episodic memory is impaired by the administration of ketamine. Our study design has allowed us to investigate more precisely the nature of this disruption and thereby further inform our understanding of the impairment in schizophrenia. The specificity of our findings concurs with recent observations made by Morgan et al. (2004), who showed that the effects of ketamine are relatively specific to memory processes, with deficits including a source memory impairment. Our experimental design enabled a dissociation of effects of the drug on encoding and retrieval processes, on its differential effects upon material encoded under three different task conditions, and the extent to which it produces impairment in recognition and source memory. We have shown that a deleterious effect occurs primarily when the drug is administered at encoding. Indeed, in some respects, performance seems to improve when ketamine is given at retrieval. Second, the disruption is expressed both in recognition memory and in source memory. Third, the depth of encoding may be important to whether the ketamine-related deficit at retrieval will be seen: thus, item detection was significantly impaired only when words were encoded under Depth 2 conditions. Below, we consider each of these effects in turn.

Encoding vs retrieval effects of ketamine

Episodic memory deficits were observed when items were encoded during ketamine exposure but not when the infusion was administered at the retrieval phase only. These data therefore suggest that impaired encoding processes may underlie the disruption of episodic memory after ketamine treatment. Of course, we must acknowledge that ketamine administered at encoding resulted in measurable levels of ketamine when retrieval was tested 90 min later. However, since administration of ketamine solely at retrieval produced no deficit, we believe that the deleterious effect is specific to encoding. Further evidence in favour of this view is that subjects with high residual plasma levels did not show a greater deficit than those with low residual levels. Thus, we add to the growing evidence that ketamine disrupts the encoding of new information into episodic memory. However, we must be cautious in asserting this specificity: as with previous work, residual ketamine was present under retrieval conditions (even 90 min after the infusion had stopped). Furthermore, we must acknowledge the possibility that ketamine levels may have been lower during retrieval (60 min after the start of drug infusion) than at encoding (90 min). Although existing models would suggest that any such effect would be minimal, we must nevertheless acknowledge the possibility. One further possibility is that the encoding effects of ketamine resulted from an exacerbation of participants' tiredness after prolonged periods of cognitive testing. However, subjects did not report any difficulties in this respect and the apparent task specificity of the drug effect is difficult to equate with such a general explanation.

Caveats aside, ketamine produces a model of memory impairment that is compatible with that seen in schizophrenic patients (Brebion et al. 1997; Chan et al. 2000; Gold et al. 1992; McClain 1983). However, we acknowledge other work suggesting a retrieval-specific deficit in

schizophrenia (Calev 1984a,b). Variable patterns of memory impairment are associated with a range of symptom profiles (Tamlyn et al. 1992), and it will therefore be important in future studies to identify the symptoms of the illness that correspond to the specific cognitive deficits observed after ketamine treatment.

The effects of ketamine observed on retrieval—an improvement in certain performance measures—are intriguing but unexpected. We treat them with caution in view of this. A decrease in response liberality was apparent, indicated by reduced guessing biases. Reduced guessing and an increased tendency towards 'don't know' responses represent an appropriate strategy when an increasingly cautious approach is adopted. This apparent caution may arise from subjects' awareness that they were under the influence of the drug and thus less confident in their performance. Another possibility is that the presence of ketamine at retrieval somehow facilitates memory for the encoded items. The finding, though, was unexpected and not one upon which we feel confident to speculate at present. Whatever the explanation for the effects at retrieval, they provide compelling evidence that the deleterious effects of ketamine can be attributed to a disruption of encoding processes.

Depth of processing and ketamine

The disruption of episodic memory observed in this study after ketamine treatment was associated with the Depth 2 items, whereas item recognition for more shallowly encoded items (Depth 1) and more deeply encoded items (Depth 3) were not observably affected by ketamine. Before discussing the implications of our significant findings, caution is appropriate: the use of multinomial modelling does not permit a direct test for a drug by depth interaction. Consequently, while we are justified in interpreting our significant findings, we must be cautious with respect to non-significant effects. The apparent specificity of our findings is an observation that must therefore be treated with caution.

The most plausible interpretation of this specific effect invokes an established model of recognition memory, in which item detection is based on either *recollection*: the recall of rich contextual detail associated with the item, or *familiarity* (Jacoby 1991; Yonelinas 1994). We suggest that ketamine produces an impairment in encoding processes that enable later recollection. Depth 1 items, which produce the shallowest level of encoding and a subsequent recognition based primarily upon familiarity, would thereby prove relatively invulnerable to the drug's effect. For the Depth 3 task, the strength of encoding produced by the *pleasant/unpleasant* judgement may produce a protective effect rendering words less vulnerable to disruption. Under placebo, recognition of Depth 2 items was weaker than Depth 3, indicating a reduced depth of processing at encoding, and therefore potentially increased vulnerability to drug modulation. The disruption of encoding of Depth 2 items most closely approximates that engaged in previous studies (Ghoneim et al. 1985; Harris et al. 1975; Krystal et al. 1994; Malhotra et al. 1996; Newcomer et al. 1999; Radant et al. 1998), for which the level of processing at encoding was not experimentally manipulated, and was therefore unlikely to be consistently subjected to an efficient deep encoding strategy (as for Depth 3 items), but would likely have been more deeply encoded than when attention is directed to a phonological strategy (as for Depth 1 items). Perhaps ketamine reduces the degree of semantic processing accompanying performance of the Depth 2 task, resulting in a reduction of the accompanying episodic encoding and consequently impaired subsequent memory. This is consistent with previous observations of ketamine-induced changes in tasks that engage semantic processing (Adler et al. 1998).

A previous study has evaluated the interaction of ketamine with levels of processing (Morgan et al. 2004): they explored performance on a cued recall task following deep (living vs non-living) and shallow (number of vowels) encoding tasks. Although not significant, there was a strong trend towards impairment of word stem cued recall following both encoding tasks under ketamine. The use of a different level of retrieval cueing, however, makes the results of our study difficult to compare directly with those of Morgan et al. (2004).

Source memory and depth of encoding

Under placebo conditions, although recognition scores were reduced for Depth 1 compared to Depth 2 items, the reverse was seen for source memory scores. This most likely reflects the use of metacognitive strategies, wherein an item that conveys a sense of familiarity but does not produce a recollective experience (as would be the case for the shallow encoding produced by the Depth 1 task) could be attributed to the appropriate source on this basis. This is akin to the 'it had to be you effect' (Johnson and Raye 1981) consistently observed in source memory tasks. It explains why, paradoxically, the most shallowly encoded items may have some advantage when it comes to the source decision. When ketamine was administered at encoding, the guessing bias, g_1 (a tendency to guess that items had been encoded under Depth 1 conditions) was increased (see Fig. 5a). This suggests that a greater proportion of words were recognised on the basis of familiarity rather than recollection leading to a greater tendency to use the guessing strategy described above. A note of caution should be raised, however. We did not find an impairment in Depth 2 source memory following encoding under ketamine. This would be predicted on the basis of our interpretation since a reduction in recollection-based recognition should lead to a relative reduction in source memory. Whereas we did observe a trend towards a decrease in source guessing bias (a_2; see Table 3), no strong evidence was found of a disruption in source memory for Depth 2 items. This perhaps reflects an insensitivity of our model to presumably subtle effects. Perhaps a remember–know paradigm would have been more sensitive to the effects that we are postulating. This is not to say that source memory was not disrupted since we observed a significant change in the guessing bias, indicating that ad-

ministration of ketamine at encoding does influence subsequent source memory function.

We suggest, therefore, that our results indicate an impairment in subsequent recollective processes when ketamine is administered at the encoding stage and that this impairment is most prominent when an encoding task is used that would normally engender recollective processes but is insufficiently deep to protect this mechanism. This finding must be viewed in conjunction with that of Hetem et al. (2000) that ketamine produced indistinguishable effects on subsequent 'remember' and 'know' responses, suggesting that it embarrasses recollection and familiarity to equal degrees. However, a crucial difference between our test phase and that of Hetem et al. is that we included new items ('lures'). This makes the two sets of findings difficult to compare. With respect to the validity of ketamine as a model for schizophrenia, we note that our findings are consistent with a number of studies showing that patients with schizophrenia demonstrate impaired episodic memory requiring recollection of information, resulting in increased dependence on familiarity (Brebion et al. 2002; Danion et al. 1999; Keefe et al. 2002; Moritz et al. 2003; Morrison and Haddock 1997; Vinogradov et al. 1997).

Of course, both the encoding and retrieval tasks require a degree of vigilance and we must consider the possibility that some of our deficits might arise from general problems with this rather than specific episodic memory encoding processes. We do not believe this to be so for three reasons. First, the retrieval task, which took several minutes longer than the encoding task was not impaired when performed under ketamine. Second, there was no evidence for a serial position effect, i.e. items towards the end of the encoding list were no more likely to be forgotten than items at the beginning. Third, subjects underwent a series of tests at the same time (for reasons of space, these are reported elsewhere; Honey et al. 2003). A number of these tasks made profound and sustained demands upon their vigilance and attention (e.g. a spatial working memory task and the Tower of London task) but did not show deficits at these doses of the drug. We therefore suggest that we have identified a highly specific effect of the drug, rather than a non-specific deficit in vigilance.

Ketamine as a model for schizophrenia?

This study does not provide an explanation for memory deficits in schizophrenia. Its primary goal was to explore more fully the nature of the drug's impact upon episodic memory. In doing so, we have highlighted two phenomena that would certainly be compatible with findings in people with schizophrenia (a stronger effect at encoding and a deficit that may predominate in association with recollective rather than familiarity-based memory). There are, of course, many respects in which acute administration of ketamine differs sharply from the illness itself and these impose limitations in comparability. Furthermore, in attempting to disentangle encoding and retrieval effects, we have produced a further divergence between the model and the illness. Nonetheless, we believe that the study has achieved its primary aims. Ultimately, a model will be useful insofar as it develops predictive and explanatory power. The current study must be considered preludial in that it forms part of an increasing body of work assessing the face validity of the model.

In addition, one must acknowledge also the areas in which our findings do not tally with those observed in schizophrenia. For example, source accuracy was not measurably impaired as a consequence of ketamine, a finding that is at odds with observations in people with schizophrenia (Brebion et al. 1999, 2000, 2002; Danion et al. 1999; Keefe et al. 1999, 2002; Moritz et al. 2003; Morrison and Haddock 1997; Stirling et al. 1997; Vinogradov et al. 1997). One possible explanation for this may be a limitation is sensitivity as noted above. Moreover, our task design optimised source performance by associating each of the sources with a different level of processing, making source judgements relatively robust to drug effects.

In conclusion, this study has demonstrated that ketamine is associated with a disruption of episodic memory encoding: an impairment that mimics that seen in schizophrenia. Our findings provide support for the involvement of glutamatergic pathophysiological mechanisms in schizophrenia and demonstrate that ketamine provides an appropriate model of an important part of the cognitive dysfunction associated with the illness.

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