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The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers

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The cognitive and subjective effects of sub-anaesthetic doses of ketamine on healthy volunteers were examined. Twelve healthy volunteers received 25 mg ketamine, 10 mg ketamine and saline placebo, i.m. in a double-blind, Latin square design. A cognitive, perceptual and self-report test battery was administered over 45 min. The order of tests was rotated to control for timing effects. Ketamine (25 mg) significantly affected verbal learning and memory, parallel visual search, some measures of psychomotor performance, measures of arousal, subjective mood ratings and visual perception. Measures of attention and frontal lobe functioning were relatively unaffected. Thus, low doses of ketamine had selective, dose-related effects on memory, perceptual and psychomotor functions. The disruption of memory and perceptual processes may help to explain the unique subjective state induced by ketamine.

Key words: ketamine; memory; perception; psychomotor performance

Introduction

Investigations into the phenomenological and neuropsychological effects of the *N*-methyl-D-aspartate (NMDA) receptor antagonists in healthy volunteers began >30 years ago, soon after the introduction of these compounds into general medical use (Luby *et al.*, 1959; Davies and Beech, 1960; Bakker and Amini, 1961). Studies in the psychiatric and anaesthetic fields were also carried out (e.g. Domino, Chodoff and Corssen, 1965; Corssen and Domino, 1966). This research examined both of the available NMDA antagonists, phencyclidine (PCP) and ketamine, both of which were regarded as psychotomimetic. PCP, which has a 10-fold higher potency and receptor affinity than ketamine (Javitt and Zukin, 1991) is, however, no longer in general use.

Interest in this area has been rekindled recently. Javitt and Zukin (1991) restated the view that NMDA receptor antagonists provide a pharmacological model of schizophrenia, basing their argument on the effects observed during emergence from anaesthesia, in healthy volunteer experiments, in drug abuse and in people with schizophrenia. Further experimental evidence from ketamine studies has also begun to be reported (e.g. Foster *et al.*, 1991; Øye, Paulsen and Maurset, 1992; Krystal *et al.*, 1994a, b).

Ketamine is a dissociative anaesthetic. When used at anaesthetic doses (1–4 mg/kg i.v., 4–10 mg/kg i.m.), it produces a state of light hypnosis, profound analgesia, with relatively preserved laryngeal reflexes and muscular tone, increased cardiovascular output and little respiratory depression (e.g. Corssen and Domino, 1966). Its pharmacokinetics are well understood (Grant, Nimmo and Clements, 1981). It is highly soluble, with one main active metabolite and a rapid redistribution and metabolism. Peak plasma level following i.m. ketamine occurs after a mean of 22(±4) min and can occur within 5 min of an i.m. dose (Grant, Nimmo and Clements, 1981). Ketamine passes rapidly through the blood–brain barrier and then is redistributed rapidly to less well-perfused tissues. The redistribution half-life is ~10 min (Haas and Harper, 1992).

The pharmacodynamics of its activity are less well understood. The two optical isomers *R* and *S* ketamine have different affinities for the NMDA receptor; the *S* form is more potent, and the *R* form has more sigma receptor affinity (Domino, 1992). Neurophysiologically, the NMDA receptor is involved in glutamate neurotransmission, with both direct activity and involvement in the mechanism of long-term potentiation, the proposed mechanism underlying memory (Ledoux, 1992).

Previous studies of the effects of PCP and ketamine have employed a variety of dose schedules and routes of administration, and a wide range of psychomotor, cognitive and subjective measures. Despite the methodological variation, these compounds have consistently reported effects on most of the measures employed.

Measures of arousal and general psychomotor speed are clearly affected by NMDA antagonists. For example, Davies and Beech (1960) reported a reduction in critical flicker fusion threshold (CFFT) and psychomotor slowing on a finger tapping task following 0.1 mg/kg PCP. NMDA antagonists have been reported to affect frontal lobe function and several different aspects of memory function. Bakker and Amini (1961) reported significant increases in Stroop interference and

errors, and a significant slowing on Raven's Progressive Matrices following 10 mg of oral PCP. PCP also produced significant detrimental effects on verbal paired associate learning and digit span (Bakker and Amini, 1961), whilst ketamine has been reported to impair the recall and recognition of word list materials (Ghoneim, Hinrichs and Mewalt, 1985; Øye, Paulsen and Maurset, 1992).

In the perceptual area, Davies and Beech (1960) reported a PCP-related decline in the spiral after-effect. Gregory (1986) reported that whilst his own colour vision, acuity, stereopsis, visual and auditory recognition remained relatively normal following an i.v. infusion of 50 μg ketamine/kg/min, he experienced marked synaesthesia, movement-like instability and distortions of perceived patterns and pictures. Øye, Paulse and Maurset (1992) reported a range of dose-related subjective changes in somatosensory, auditory and visual perceptions.

The subjective effects of PCP and ketamine have been examined in separate studies. Hansen *et al.* (1988), who investigated the effects of 25–200 mg i.m. ketamine doses, obtained clear descriptions of changes in body perception, floating and out of body experiences, insights into self, visions and synaesthesia, timelessness and extreme feelings of empathy. Similar disturbances of body image, time perception, visual illusions and hallucinations, perceptual field narrowing and changes in salience, floating feelings and out of body dreams were also all described by subjects during the experiments reported by Davies and Beech (1960) and Bakker and Amini (1961). In contrast, Øye, Paulsen and Maurset (1992) obtained very modest ketamine effects on subjective ratings made with visual analogue scales, except for alert/drowsy ratings, which became significantly more drowsy.

Since the present study was initiated, Krystal *et al.* (1994a) have also reported significant effects of 0.5 mg/kg ketamine on the delayed recall of three-word lists, and impairments on the Wisconsin Card Sorting test, verbal fluency and a continuous performance (vigilance) task. These most recent results contribute to the overall impression obtained from the literature that most measurable aspects of cognitive function are affected by NMDA blockade. However, as different measures have been examined under different dose conditions, using various methodologies, it is unclear whether NMDA antagonists necessarily and/or specifically affect all areas of psychomotor and cognitive function. For example, the hypothesis that ketamine has psychotomimetic effects might predict particular impairment to frontal and temporal lobe functions (e.g. Shallice, Burgess and Frith, 1991). Thus, the objectives of the present study were to determine whether ketamine has globally or selectively impairing effects on cognitive function, and to relate the objectively measured effects to subjectively reported experience.

This study was designed to sample ketamine effects on a wide range of psychomotor and cognitive functions following the i.m. administration of two relatively low doses to the unpaid health professional subjects. The test battery combined many of the measures that had been examined separately in previous studies (verbal memory, Stroop interference, visual perception, reaction time, CFFT, continuous attention and subjective rating scales) with some additional tests (e.g. parallel and serial visual search) that had not been examined previously following ketamine or PCP. The battery was intended to assess psychomotor and cognitive functions operating at multiple levels; ranging from very early, pre-attentive parallel visual search processes to the high level attentional control processes that are required to complete the Stroop and trailmaking tasks.

A very low fixed dose regime was chosen on the grounds that, whilst high doses might cause global non-specific impairments, low doses would be more likely to induce specific deficits. The potentially adverse effects of high doses were also considered likely to cause practical, experimental and compliance problems.

Method

Ethical approval and indemnity were obtained from local Health Authority Research Ethics Committees. Subjects were recruited from the mental health and postgraduate psychology professions. Fourteen healthy subjects (10 male and four female, aged between 25 and 43 years) entered the study, although two subjects withdrew after the first drug session.

Subjects were tested individually, in a comfortable room, in the presence of a doctor. Two drug-free test days provided practice with the test materials and procedures. On the three subsequent test days, subjects received an i.m. injection of saline (placebo), 10 mg ketamine or 25 mg ketamine made up to 1 ml of solution. Test sessions were separated by at least 1 week. The subjects and two experimenters were blind to the dose; the third experimenter administered the injections and acted as medical supervisor (L. G.). Pulse rate and blood pressure were recorded immediately before, and 10 min after the injection. The subject rested for 10 min following the injection. The test session lasted 45 min.

Two of the 14 volunteers (one male and one female) experienced adverse reactions (nausea, vomiting and an unpleasant dissociative experience) following their first ketamine dose and withdrew from the study.

Dose orders were determined according to a Latin square and the orders randomly assigned to the subjects. In order to control for timing effects, the cognitive tests were divided into three sets (A, B and C) and the order of test set administration was rotated across subjects. A test order was assigned in rotation to each subject as they entered the study. Four subjects always proceeded in the order ABC (group ABC), four in the order BAC (group BAC) and four in the order CAB (group CAB). Test order was unrelated to the subject's dose order; two of the four subjects in each test order group shared a common dose order. The shared dose order varied across the three test order groups. Tests were completed in a fixed order within each set, as described below, and each set took ~15 min to complete.

The test battery

Test set A

Set A comprised assessments of parallel and serial visual search processes, vigilance and psychomotor speed. The three tests were selected from the Automated Psychological Tests program v3.0a (Tiplady, 1992a) and controlled by a BBC Master microcomputer.

The visual search task required the detection of a target stimulus embedded in an array of distractor stimuli. All stimuli were alphabetic letter shapes presented at random orientations (i.e. rotated to any angle). Target stimuli were L-shaped, distractors were X-shaped in the first phase of the task and T-shaped in the second phase. Subjects viewed each array and pressed one of two keys to indicate, as quickly as possible, whether the array contained a target or not. The 100 trials were divided equally between 'L in X' and 'L in T' trials. Array size increased progressively within each of the two phases of the task, from 2^2 to 5^2. Each set contained equal numbers of the four array size trials (2^2, 3^2, 4^2 and 5^2). Approximately 60% of the arrays contained a target stimulus.

The initial 'L in X' phase of the task was designed to elicit a parallel 'pop-out' type of search. Search times are effectively independent of stimulus array size and are assumed to reflect the operation of a fast, pre-attentive parallel search mechanism (Krose and Julesz, 1990). The 'L in T' phase, where the distractors and targets are visually similar, was intended to elicit a more serial, voluntarily controlled type of search, in which array size is the primary determinant of search time.

The continuous attention task (CAT, Tiplady, 1992b) is a non-verbal development of the continuous performance task (CPT), requiring the detection of consecutive identical random block patterns within a continuous stream of patterns that are each presented for 100 ms. Continuous attention performance was represented by the index of errors (I_E) measure derived by Pigache (1976). Given the relatively easy discriminations involved in the CAT, this was more appropriate than signal detection measures of performance.

Four-choice reaction time (4CRT) responses were made using a keypad containing four coloured buttons that corresponded to a visual display. Two types of 4CRT trial block were alternated within the test session. Half of the trial blocks involved random response sequences; the other half involved easily learned, fixed sequences.

Test set B

This paper and pencil test set comprised an associative verbal memory test (Watson *et al.*, 1994) and two tests of frontal lobe function; the Stroop task (Stroop, 1935) and trailmaking (Reitan, 1958). The face–name–occupation associate memory test assessed memory for the first name, surname and occupation that had been associated with each of four photographs of unfamiliar faces. Recall was cued by the photographs. Although visual recognition of the faces is necessary for the task to be completed successfully, the task is specifically sensitive to, and is primarily a measure of, verbal recall capacity. The stimulus set was re-presented until all the verbal items could be recalled, up to a maximum of three presentations. A different parallel version of the test was used on each test day.

The trailmaking control task (A) measured the time taken to draw a trail that joined the letters A–T in alphabetic order. The second task (B) measured the time taken to join an alternating sequence of letters and numbers (1–A–2–B–3–C, etc.). The Stroop test comprised a colour naming control task and a conventional Stroop word–colour interference task. The Stroop stimuli were presented on cards; subjects were asked to name the colours of successive stimuli, proceeding down each of four columns in turn. The psychomotor and executive control components of the Stroop and trailmaking tasks were examined independently by subtracting the control task completion times from the Stroop colour–word naming time and the trailmaking (B) time in each case. The resulting measures reflect the additional requirement to sustain attention on the print colour whilst ignoring the more salient but incongruent colour names in the Stroop task, and to shift between numeric and alphabetic sequences in the trailmaking task.

Test set C

This set comprised assessments of visual perception, time estimation, tactile perception, CFFT and subjective self-assessment of arousal, mood and time perception.

Changes in visual perception were assessed by projecting a series of images onto a large screen. Under normal conditions, these images elicit the illusory perception of either movement, colour change or altered object size. For example, in the Zollner illusion, which comprises a series of long parallel 'herringbone' patterns that alternately point in opposite directions, the herringbone 'spines' typically appear to be converging rather than parallel. Subjects were asked to comment on what they perceived and on any changes in their perception of the images compared with other test days.

Subjects were asked to estimate 30 s of elapsed time with and without distraction. On the first occasion, the subject was asked to undertake their estimation of 30 s whilst the experimenter continued with the next task. The subject had to interrupt the experimenter to give their estimate. On the second occasion, the time estimation task was carried out without any parallel activity or talking. Tactile perception was also assessed in two tasks. In the first, the subject attempted to identify a series of six alphanumeric characters traced by the experimenter onto the subject's left palm. Performance was measured by the number of letters correctly identified on first presentation. In the second task, the subject identified a set of four common objects using touch alone.

Critical flicker fusion, which is known to be highly sensitive to sedative drug effects and may be taken as an index of CNS activity (e.g. Sherwood and Kerr, 1993), was assessed using the Leeds Psychomotor Tester. The mean of three flicker-to-fusion and three fusion-to-flicker thresholds was determined for each test session. Subjective mood was assessed using visual analogue scales (Bond and Lader, 1976). The following dimensions were rated: alert–drowsy, calm–excited, muzzy–clearheaded, tense–relaxed, attentive–dreamy and interested–bored. A further scale represented the speed at which time was passing.

Results

The data were examined in one-way repeated measures ANOVA that assessed ketamine dose-related (placebo, 10 mg and 25 mg ketamine) differences. *Post-hoc* means contrasts were used to assess the significance of the dose-related differences.

Visual search time values from trials on which a target was detected were averaged for analysis. An initial ANOVA

confirmed that the 'L in X' and 'L in T' search tasks had produced different search time patterns; Fig. 1 shows that stimulus array size had a larger effect on the 'L in T' search times than on the 'L in X' search times. A two-way (search type × array size) repeated measures ANOVA on mean correct target search time yielded a significant search type × array size interaction [$F(3,33)=22.7$, $p<0.0001$], as well as significant search type ('L in T' versus 'L in X') [$F(1,33)=142.3$, $p<0.0001$] and array size [$F(3,33)=53.1$, $p<0.0001$] main effects.

Response time data from the 'L in X' visual search task and 'L in T' visual search task were also analysed separately. A two-way repeated measures ANOVA assessed the effects of dose (placebo, 10 mg and 25 mg ketamine) and array size (2 × 2, 3 × 3, 4 × 4 and 5 × 5) on mean reaction time. ANOVA revealed a significant dose effect on 'L in X' search time [$F(2,66)=2.4$, $p=0.05$] and array size effect [$F(3,66)=17.0$, $p=0.0001$]. The dose × array size interaction also approached significance [$F(6,66)=1.9$, $p=0.10$]. Figure 1 illustrates the effects of both dose and array size. Means comparisons indicate that the only significant dose difference was between 10 mg ketamine and 25 mg ketamine. ANOVA revealed a significant effect of array size on 'L in T' search time [$F(3,66)=42.7$, $p=0.0001$] but no effect of ketamine dose.

There was no evidence of a ketamine effect on tactile object recognition or on object naming. All subjects recognized and correctly named all items from the three sets of common objects by touch alone.

The visual search and remaining cognitive and psychomotor test results are summarized in Table 1. Table 2 shows the results of means comparisons contrasts performed on measures significantly affected by dose.

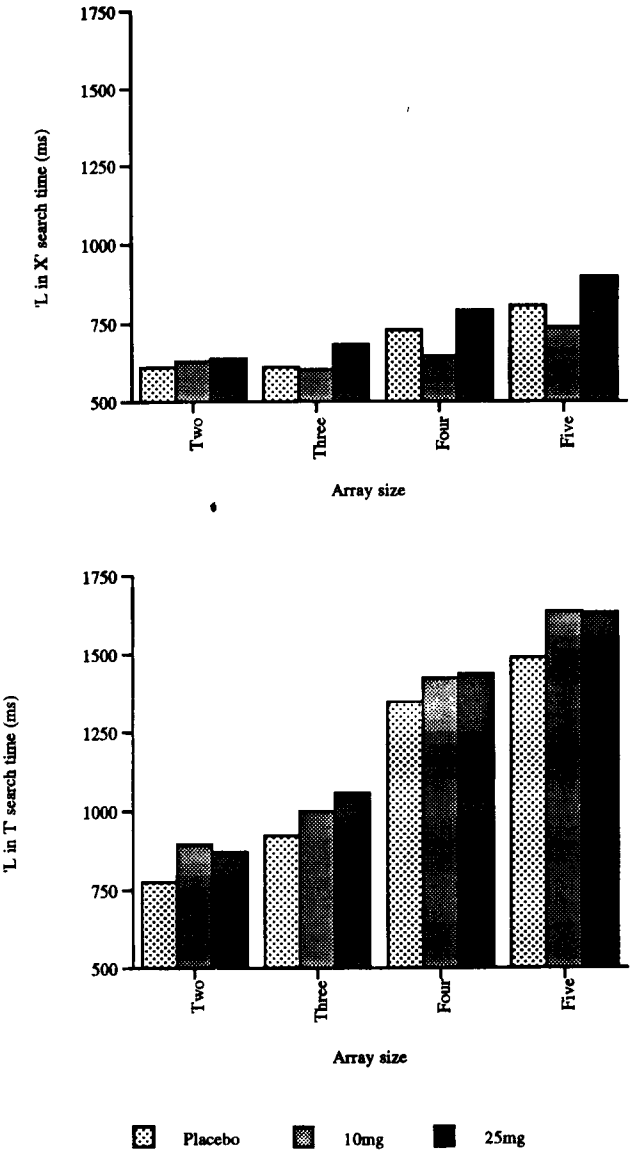

Figure 1 Ketamine dose and array size effects on 'L in X' and 'L in T' visual search time

Subjective effects of ketamine

When asked if they felt the effects of a drug, all subjects were able to discriminate the 25 mg dose from placebo, although only five could discriminate the 10 mg dose. In contrast, however, only three visual analogue rating scales showed significant or near significant dose effects. Subjects reported feeling more excited/less calm following the 25 mg than with either the 10 mg or placebo ($p=0.06$). They also felt more muzzy/less clearheaded following both the 10 and 25 mg doses ($p=0.04$). The clearest change in subjective rating was a dose-related increase in feeling dreamy/less attentive ($p=0.0001$).

There was a wide variation in the strength and form of the subjective experience, although the following themes emerged clearly from descriptions given during, and written after, the sessions. The most consistent report of change in external perception was the prominence of distant sounds, 'sounds such as fans, scratches, biros, were far more audible'. Some noted that the 'computer tasks blurred, shimmering and moving' with an 'optical (eyeball) instability, making the world move'. Consistent with this, there was a ketamine-related increase in the illusory perception of movement present in a number of the perceptual stimuli, such as the McKay's rays. The predominant perceptual effect was that images became less stable; shimmering and movement were both reported frequently. In contrast, subjects were invariably able to make normal size constancy judgements and were susceptible in the normal way to the illusion images they were shown.

There were consistent reports of feelings of disconnection and removal from the external world: 'everything's out there somewhere, not to grips with the world'. After 25 mg of ketamine, all subjects reported changes in feelings of self-perception and identity. This was described as a physical disconnection from, and distortion of, normal body sensations. For example, 'one step behind myself, a very big person in a small room'. A few subjects reported a corresponding distortion of their internal reality. For example 'an intense feeling of despair that I was nothing, that nothing mattered and that my current state would go on forever'.

Subjects who experienced the most dramatic effects of ketamine, described a distorted sense of time: '30 minutes seemed to go by in about 5 minutes'. However, there was also a

Table 1 The effects of ketamine dose on cognitive and psychomotor performance measures

	Placebo		10 mg ketamine		25 mg ketamine		
	Mean	SD	Mean	SD	Mean	SD	Significance
Visual search RT:							
'L in X'	689.4 ms	163.0	654.2 ms	145.6	752.2 ms	228.6	$p=0.05$
'L in T'	1132.3 ms	187.4	1237.9 ms	432.3	1249.5 ms	436.8	NS
4-Choice RT:							
random	361.8 ms	62.9	378.4 ms	54.7	378.8 ms	88.1	NS
fixed	272.3 ms	73.9	289.2 ms	69.0	252.4 ms	53.5	NS ($p=0.15$)
Continuous attention:							
error index (I_E)	0.15	0.08	0.14	0.08	0.2	0.15	NS
Memory score	42.8	3.3	43.2	3.2	39.6	4.7	$p=0.006$
Trailmaking:							
(control) A	8.9 s	2.6	9.1 s	5.2	11.6 s	5.5	$p=0.03$
(set shifting) B	11.1 s	3.1	12.3 s	3.2	15.3 s	8.4	$p=0.04$
A − B	2.2 s	2.5	3.2 s	3.2	3.7 s	4.9	NS
Stroop:							
colour-naming control	47.2 s	9.2	49.7 s	10.5	52.8 s	10.7	$p=0.02$
colour–word naming	66.7 s	12.6	71.7 s	15.8	73.9 s	18.6	NS ($p=0.07$)
interference − control	19.5 s	9.0	22.0 s	9.3	21.1 s	14.6	NS
Tactile letter perception (no. correct)	5	0.7	4.25	1.1	4	1.5	NS ($p=0.08$)
Time estimation:							
estimate I	33.3 s	9.8	33.3 s	11.2	39.8 s	18.4	NS
estimate II	36.9 s	7.2	32.6 s	10.4	36.7 s	12.1	NS
CFFT	24.3	2.3	23.9	2.3	23.1	2.0	NS

Table 2 *Post-hoc* mean comparisons for significant ketamine dose effects

	Placebo versus 10 mg ketamine	Placebo versus 25 mg ketamine	10 mg versus 25 mg ketamine
Visual search	NS	NS	$p=0.017$
Trailmaking (control)	NS	$p=0.02$	$p=0.03$
Stroop (control)	NS	$p=0.007$	NS ($p=0.10$)
Memory	NS	$p=0.007$	$p=0.003$

sense in which time was not passing at all: 'there was only the present and some sort of sense that it would go on'. Emotionally the experience was generally pleasant, 'a certain euphoric effect', 'like drunkenness, two gin and tonics', and the attitude towards testing changed, e.g. 'happier to make mistakes'. Most felt a sense of openness and empathy: 'I felt somewhat disinhibited, wanting to tell people about past life events'; 'I felt that people could see right through into me'. Some subjects noted that they could also feel threatened and vulnerable by this, and would have been uncomfortable with strangers. Some of the subjects noted how childhood memories seemed to come easily or spontaneously to mind. A number of people tried to describe a newness or difference in everyday objects or actions, with a change in their sense of familiarity 'the floor feels so different, you can never understand how new and different the floor is'.

Although a small number of subjects experienced unpleasant and unusual reactions (e.g. 'I feel like I'm being washed down the plug hole starting at the toes'), that included extreme anxiety (e.g. 'feeling that I was going to die'), at no point did any of the experimenters consider that any of the subjects, including the two who withdrew, displayed fully formed psychotic phenomena.

Discussion

Ketamine significantly affected parallel visual search time, immediate verbal memory, trailmaking (A and B) time, colour naming time and three subjective mood measures in data obtained from 12 subjects. There were marginally significant dose-related trends towards impairment in Stroop colour–word naming time and tactile letter perception, and non-significant dose-related trends towards impairment in 'L in T' visual search time, random 4CRT, continuous attention, CFFT and Stroop and trailmaking interference.

Two ketamine-related trends towards improvement were also observed. Fixed sequence 4CRTs were faster following 25 mg ketamine than following either placebo or 10 mg ketamine [$F(2,22)=2.1$, $p=0.15$]. This pattern was quite distinct from that obtained for the random sequences, where responses following both active doses were slowed. The 25 mg dose apparently enhanced the capacity to use the predictability of the fixed sequences and produced responses that were faster than under placebo conditions. In contrast, 10 mg ketamine was also associated with 'L in X' visual search times that were 40 ms faster than the placebo-related search times and significantly faster (100 ms) than the 25 mg-related times.

The 'L in T' search times, which increased steeply as array size increased, showed no significant ketamine effect, although they were consistently longer following both 10 and 25 mg ketamine. However, whilst 25 mg ketamine also slowed 'L in X' detection and produced a larger array size effect compared with placebo (more serial), the 10 mg ketamine dose increased 'L in X' detection speed and produced a smaller array size effect, reflecting a more parallel search (see Fig. 1).

The results of previous research indicate a link between dopamine depletion and longer, more serial visual search. Medicated schizophrenic patients and Parkinson's disease patients (who are assumed to have a net dopamine deficiency) have also shown selective disturbances to parallel visual search processes, which became more serial (Hess, Lieb and Schüttler, 1990; Troscianko and Calvert, 1993). Thus, as the capacity for parallel visual search appears to be dopamine-mediated, the 10 mg effect observed here may have been caused by the indirect dopamine agonist activity that is attributed to ketamine (Church and Lodge, 1990). In the present study, 10 mg ketamine apparently increased the tendency for the contrasting targets to 'pop-out' and so perhaps reduced the already small number of visual fixations required to detect the target. This may reflect a separate dopamine-mediated ketamine effect that was masked by the more toxic effects of the higher dose. Such differential dose effects have been reported previously; for example ketamine is known to have an anticonvulsant effect at low doses but a proconvulsant effect at high doses (Church, 1990). Differential dose effects on cognitive function are also known; whilst high dose i.v. lignocaine significantly impaired digit–symbol substitution performance, low dose lignocaine produced a significant improvement (Armstrong *et al.*, 1991).

The effect of 25 mg ketamine on name–face–occupation memory performance was the most robust effect obtained in the study. It provides strong evidence for a ketamine-related immediate memory impairment, which may have bearing on the subjective experiences associated with ketamine and the performance of other types of cognitive task. In other studies, ketamine has affected the delayed but not immediate verbal recall of three-item word lists (Krystal *et al.*, 1994a), immediate and delayed verbal recall (Ghoneim, Hinrichs and Mewalt, 1985) as well as short-term memory (Bakker and Amini, 1961). Although the processing stage at which memory is disrupted by ketamine remains to be specified (cf. Ghoneim, Hinrichs and Mewalt, 1985; Øye and Maurset, 1992), the present results add to the considerable evidence that ketamine (and related compounds) significantly reduce the ability to recall recently presented material.

As described above, ketamine, and the 25 mg dose in particular, produced clear psychomotor retardation. Although the Stroop interference and trailmaking (B) tasks took longer to complete following ketamine, neither Stroop interference time nor trailmaking (B) time showed a significant dose effect after the corresponding colour naming and trailmaking (A) times had been subtracted. We may therefore conclude that ketamine had a considerably greater effect upon memory, perception and psychomotor speed than upon the executive control functions measured by Stroop and trailmaking interference. The absence of a significant dose effect on the CAT adds further weight to this argument.

The present results do not accord entirely with the results of a similar study reported by Krystal *et al.* (1994a), who recently reported significant ketamine effects on tasks considered to be sensitive to frontal lobe dysfunction; vigilance (CPT), verbal fluency and the Wisconsin Card Sorting task. However, the ketamine effects on these tasks might also have been caused by impairments to memory and non-executive psychomotor functions. In particular, the perseverative errors that are typical of poor performance on the Wisconsin and verbal fluency tasks might easily be caused by poor memory function rather than by poor executive control. This possibility would not have been raised by Krystal *et al.* (1994a) as they did not obtain an immediate memory deficit following ketamine. However, the absence of an immediate recall effect in their study may, in turn, be due to the very small number of words used in their memory test (three), rather than to the absence of an underlying deficit.

There was perfect subjective discrimination of the 25 mg dose, and evidence for a significant transient change in visual, auditory, tactile and self-perception. In contrast to this, only three subjective rating scales showed significant change, indicating that the ketamine-induced state could not be expressed easily in terms of these rating scales. Preston and Bigelow (1991) have also noted that discrimination of psychoactive compounds does not necessarily rely on clearly reported subjective effects.

The most consistent subjective self-report obtained here was one of the difficulty in describing the ketamine state, which yielded individual interpretations of the subjects' sense of unreality. The experience typically involved a sense of novelty and unfamiliarity; for example 'the floor feels so different, you can never understand how new and different the floor is'. In contrast, subjects reported remarkably consistent changes in visual perception (most particularly, shimmering and illusory movement), which were very similar to the personal observations reported by Gregory (1986).

The objective results include significant ketamine effects on memory, visual perception and psychomotor function as well as several non-significant but converging trends towards impairment on a range of other psychomotor and attentional measures. The overall profile suggests that psychomotor and attentional performance was partially compromised by ketamine and by 25 mg in particular, but to a much lesser extent than were memory and perception. The disruption of memory and perceptual processes, seen in conjunction with relatively preserved executive control functions, may partly explain the unique subjective state induced by ketamine. The amnesic and perceptual changes observed here may reflect a breakdown of very short-term memory and perceptual processes that provide the basis for normal, integrated perceptual experience (Kahneman, Treisman and Gibbs, 1992). Further examination of ketamine effects on perceptual and cognitive functions that may directly underlie our experience of reality is required.

Conclusion

Low doses of ketamine were shown to have selective effects on memory, visual search and psychomotor performance, with relative sparing of frontal lobe and attentional functions. Subjects' reported experiences may reflect the breakdown of perceptual and memory processes that provide the basis for an integrated perceptual experience of the world.

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