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## Effects of Acute Ketamine Infusion on Visual Working Memory: Event-Related Potentials

Q1 Juan Koychev, John Francis William Deakin, Wael El-Deredy, and Corinna Haenschel

### ABSTRACT

**BACKGROUND:** Working memory (WM) deficits are a core feature of schizophrenia. Electrophysiological studies suggest that impaired early visual processing may contribute to impaired WM in the visual domain. Abnormal N-methyl-D-aspartate (NMDA) receptor function has been implicated both in WM and in early visual processing deficits in schizophrenia. We investigated whether ketamine, a noncompetitive NMDA antagonist, would replicate in healthy volunteers the WM performance and early visual processing abnormalities we and others have reported in patients with schizophrenia.

**METHODS:** Forty-four healthy volunteers were randomly assigned to receive intravenous ketamine or placebo. During infusion, the effects of ketamine were recorded using standardized psychiatric scales. Visual evoked potentials (P100 and P300 components) were recorded during performance of a delayed matching to sample task.

**RESULTS:** Ketamine induced mild psychosis-like symptoms and impaired WM performance. It also significantly increased the P100 amplitude, while P300 amplitude decreased in a load-dependent manner. Amplitudes of P100 during retrieval correlated with cognitive performance only in the placebo group.

**CONCLUSIONS:** We confirmed previous studies showing that ketamine reproduces the impairment of WM performance and smaller P300 amplitudes observed in schizophrenia. However, ketamine increased visual P100 amplitude in contrast to our observation of reduced P100 amplitudes in established schizophrenia. The effects of ketamine on WM and P300 are likely to involve impaired NMDA function, as these receptors are implicated in changes of synaptic strength underlying associative learning and memory. Increased P100 amplitude may reflect the secondary disinhibition of cortical glutamate release that occurs after NMDA blockade.

**Keywords:** ERPs, Ketamine, P100, P300, Visual processing, Working memory

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Cognitive deficits, such as working memory (WM) impairment, are cardinal features of schizophrenia (1) that are present before the onset of psychosis and are independent of illness relapse (2–4). These deficits are more accurate predictors of poor social and occupational function than psychotic symptoms (5–7). Much attention has been focused on developing treatments to improve the executive functions of dorsolateral prefrontal cortex, which control and coordinate the many subprocesses necessary for WM (e.g., the ability to hold and manipulate information online). However, more recent electrophysiological evidence suggests that WM impairment in schizophrenia may arise in part from abnormalities in very early perceptual subprocesses.

Several studies report that patients with schizophrenia have reduced amplitude of early visual evoked response potentials (ERPs) as early as 100 ms after stimulus onset—the P100 potential (8–11). This may be a trait marker for vulnerability, as it has been reported in unaffected first-degree relatives (12) and high schizotypal individuals (13). Koychev *et al.* (13) reported that P100 amplitude predicted performance during visual WM task in healthy control subjects but was reduced in patients with early-onset schizophrenia. These P100 effects

in patients were demonstrated to be independent of drug dosage or symptom severity (8). Based on these and other data, it has been suggested that cognitive deficits in schizophrenia could involve abnormal sensory (i.e., bottom-up) processing (9). An alternative view is that P100 reduction reflects abnormal modulation by higher order areas. This view is based on observations that P100 responses to more complex tasks may depend on recurrent feedback from higher cognitive areas (14,15). Direct evidence for prefrontal facilitation of P100 was provided by a study that showed reduced P100 to a bifield visual discrimination task in patients with prefrontal cortex lesions (16) and after a reversible experimental lesion induced by transcranial magnetic stimulation (17).

Several studies have reported that patients with schizophrenia have reduced amplitude of the P300 ERP component (18–20). P300 potentials are typically evoked by infrequent target stimuli that differ in quality or duration from more frequent stimuli (21,22), but they are also elicited by WM tasks during both encoding and retrieval (23,24). P300 has been conceptualized as a neurophysiological correlate of WM update in response to changes in the environment (25). Patients with schizophrenia show a reduction in P300

(20,26,27), which has been shown to correlate with the level of cognitive impairment (28,29).

Changes in early visual processing in schizophrenia inevitably implicate abnormal cortical glutamate function in their pathogenesis. Indeed, the ability of noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine and ketamine to mimic symptoms, cognitive impairments, and electrophysiological changes of schizophrenia in healthy volunteers (30–34) has been key to the development of the NMDA-deficiency theory of schizophrenia (35–37). The importance of glutamate to cognition was demonstrated by pre-clinical work showing that glutamate gated ion channels (NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptors) jointly modulate learning and memory (38–40). Whereas AMPA has been suggested to be involved in the feedforward visual information transfer, NMDA receptor activity has been implicated in longer term changes in excitability that underlie experience-dependent learning and memory by modulating neurons that have already been depolarized by sensory input. The modulatory role of NMDA receptor activity has been investigated within visual (41,42) and prefrontal (43,44) cortices to study visual perception and WM, respectively. In addition, there is evidence that NMDA antagonism enhances AMPA-mediated responses and disrupts modulation of sensory cortex by top-down processes in humans (45) and primates (46).

In summary, ketamine has been shown to disrupt both early perceptual and WM processes in animals and human functional magnetic resonance imaging (fMRI) studies. However, there is surprisingly little known about the influence of ketamine on the neurophysiological changes measured with ERPs in the context of WM processes. Studies so far have focused on auditory oddball paradigms and reported reductions in P300 as well as a marker of automatic WM update, mismatch negativity (47–50). Visual experiments have focused exclusively on later ERP components, reporting an attenuation of the P300 component (51–53).

In this study, we sought to address the gap in knowledge relating to the effects of ketamine on early visual processing and the impact these have on WM. We administered ketamine in a double-blind, placebo-controlled randomized design to a group of healthy volunteers and recorded continuous electroencephalograms (EEGs) while the volunteers performed a visual WM task. We predicted that ketamine would reproduce the early visual and higher cognitive WM deficits reported in schizophrenia. We expected that this would be evident in impaired cognitive performance as well as reduced P100 and P300 ERP amplitudes after ketamine administration. We reasoned that if the WM deficit associated with NMDA dysfunction is due to a disruption of early sensory information, this would be reflected in reduced P100 amplitude. In contrast, if the effects are due to later memory processing, we expected to see a change in the P300 amplitude.

## METHODS AND MATERIALS

### Participants

This study was approved by North West 5 Research Ethics Committee, Haydock Park, United Kingdom (Reference

No. 10/H1010/3). Participants were recruited from a departmental database of volunteers who had completed the Schizotypal Personality Questionnaire (SPQ) (54). Individuals scoring  $\leq 42$  [cutoff for high schizotypy based on a previous study in the same population (55)] were invited to attend at the Manchester Wellcome Trust Clinical Research Facility, where they provided written consent for assessment and for testing. The participants completed the SPQ again and went through a medical and psychiatric history interview and physical examination (including electrocardiogram and body mass index measurement). Participants were selected if they were 18 to 55 years old with no personal or family history of psychotic mental illness and deemed to be healthy on physical assessment with a body mass index between 18 and 30. Exclusion criteria were SPQ score  $> 42$ , pregnancy (positive urine dipstick), any concurrent medication aside from simple analgesia, history of severe allergic reaction to drugs, severe physical or mental illness, current alcohol or substance misuse or dependence, positive urine dipstick for illicit drugs, smoking more than five cigarettes per week, and consumption of more than six caffeinated drinks per day or any caffeinated drink in the 2 hours preceding the appointment. Included participants completed the National Adult Reading Test (56) to determine verbal IQ.

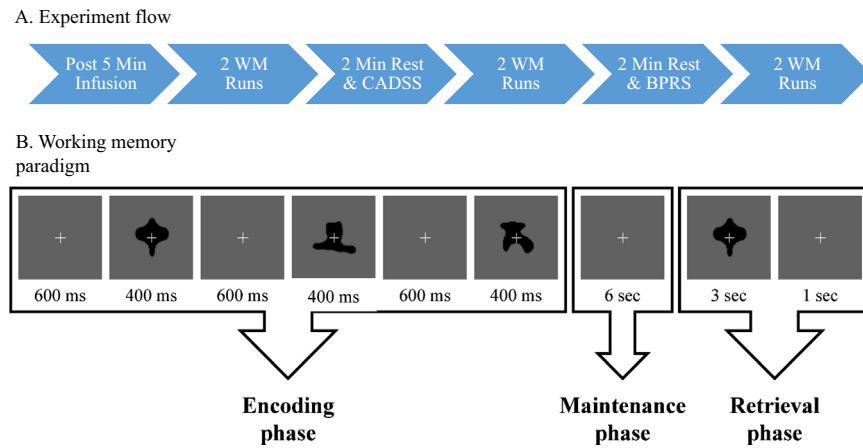
### Experiment Design and WM Task

Forty-four participants met inclusion criteria and were randomly assigned to receive either placebo or ketamine in a double-blind design. Participants were seated in front of a monitor and familiarized themselves with the study task. Infusion with either ketamine or placebo began after a 20-minute EEG resting-state recording. Ketamine was administered at a rate allowing stable plasma concentration of 100 ng/mL (57). We used the Clements 250 infusion model, which was shown to reliably predict ketamine plasma concentrations (i.e., within 2 SD of the observed plasma concentration) (58). To achieve the target plasma levels, the ketamine doses delivered were  $0.16 \text{ mg/kg} \pm 0.0028$  (mean  $\pm$  SD) during the first minute followed by approximately  $0.39 \text{ mg/kg/hour}$  (for 100 ng/mL target plasma concentration). The doses of ketamine were chosen on the basis that they would induce both subjective and cognitive subjective effects. Participants began the EEG task 5 minutes after the start of infusion (Figure 1A).

### WM Task

The experiment consisted of a delayed matching-to-sample WM task with minor modifications from another experiment (59) described in full elsewhere (13). Briefly, participants were instructed to remember one, two, or three abstract forms presented successively in the center of a black screen (Figure 1B). After a delay period, a new or previously presented form appeared on the screen, and the participants pressed a button indicating if they did or did not recognize the form from the sample (keyboard buttons “Y” or “N,” respectively). To our knowledge, none of the participants had been exposed to a similar WM task or been part of studies testing cognition.

Each run lasted 6 minutes and consisted of 30 trials, 10 of each WM load intermixed pseudorandomly. Participants completed three blocks with a block made up of two runs (the runs



6 seconds, a target probe appeared on the screen (presentation time 3 seconds), and the participants had to indicate whether it was part of the initial sample set. The participants pressed “Y” if the target image was part of the encoding sequence and “N” if it was not. An interstimulus interval of 1 second separated the trials.

were separated by a 2-minute resting trace). Blocks were separated by 10-minute breaks. We completed the Clinician Administered Dissociative Symptom Scale (CADSS) (60) during the first break and the Brief Psychiatric Rating Scale (BPRS) (61) during the second break. Physical observations including blood pressure, pulse, and temperature were recorded before testing commenced and after each block. On completion of the final block, the infusion was stopped. Participants were observed and their vital signs were recorded for a minimum of 2 hours before being discharged.

### ERP Data Acquisition, Processing, and Analysis

Continuous EEG recording was obtained using the ActiveTwo BioSemi electrode system (BioSemi, Amsterdam, Netherlands) from 64 active scalp electrodes digitized at 512 Hz with an open passband from DC to 150 Hz. A detailed description of the BioSemi electrode referencing and grounding convention can be found at <http://www.biosemi.com/faq/cms&drl.htm>.

BESA version 5.2 (Brain Electrical Source Analysis, Gräfelfing, Germany) was used to analyze data using an average reference calculated over the scalp electrodes offline. Only trials in which participants responded correctly to the WM task were included in the analysis. Epoch trials were defined as 400-ms prestimulus to 1000-ms poststimulus with a baseline of -100 ms to 0 ms. For the encoding phase, we analyzed the response to the last object to appear within the encoding series (object 1 in load 1, object 2 in load 2, and object 3 in load 3). For the retrieval phase, we analyzed the responses to the target image. All electrode channels were subjected to automatic artifact rejection to correct for blinks and saccades (thresholds for exclusion of vertical and horizontal movements were  $\pm 250 \mu\text{V}$  and  $\pm 150 \mu\text{V}$ , respectively). The continuous data were then examined for outstanding blink artifacts, which were removed manually. The trials that survived artifact correction were filtered with a high-pass filter of 0.3 Hz (6 dB/octave) and a low-pass filter of 30 Hz (24 dB/octave). The mean percentages of retained trials ( $\pm$  SD) for ketamine were  $91.2\% \pm 6.7$  (encoding) and  $91.8\% \pm 10.1$

**Figure 1.** Procedures. **(A)** Experimental flow. All participants completed six runs, grouped into three blocks. A block was made up of two runs interrupted by a 2-minute resting trace. After completion of the first block, participants rested and the Clinician Administered Dissociative Symptom Scale (CADSS) was scored. Following the second block, the Brief Psychiatric Rating Scale (BPRS) was administered during the rest. **(B)** Working memory (WM) paradigm. In the center of a black screen ( $0.6 \times 0.6$  visual angles), 36 nonnatural objects were presented. Participants were instructed to remember one, two, or three subsequently presented images. Each trial began with a screen saying “New trial,” after which the encoding stimuli were presented for 400 ms each. The encoding images were separated by an interstimulus interval of 600 ms, during which a fixation cross appeared on the screen. After a delay (maintenance) period of

(retrieval) and for saline were  $97.8\% \pm 2.7$  (encoding) and  $98.5\% \pm 1.7$  (retrieval).

### Evoked Response Potentials

**P100.** Averaged mean amplitude from five occipital electrodes was used (PO8, O2, O1, PO7, Oz) to analyze P100. P100 was calculated by extracting the mean amplitude of the 20-ms window centered on the mean P100 latency for each individual participant. The latter was established by examining the global field power and manually extracting the latency of the increases in activity corresponding to P100 peak.

**P300.** Based on the grand average, we measured P300 in a time window between 400 and 750 ms. We averaged the mean amplitude of three central parietal electrodes (P1, Pz, P2) for each WM load during encoding and retrieval.

### Statistics

Repeated measures analysis of variance (ANOVA) with within-subject factors of WM load (loads 1, 2, and 3) and a between-subject factor of drug (ketamine and saline groups) was used to analyze reaction time (RT), percentage correct responses (accuracy), P100 amplitude, P100 latency, and P300 amplitude. This was done for encoding and retrieval stimuli separately. For the P300 models, we tested the hypothesis that P100 modulates the subsequent P300 signal by running a correlation between P100 and P300. We also ran a mixed-model repeated measures ANOVA with a time-varying (WM load) covariate (P100) including P100 as a covariate separately for encoding and retrieval. Significant drug  $\times$  WM load interactions were followed with linear post hoc analyses. Pearson’s correlations were used to explore the relationship between an individual’s overall cognitive performance (percentage correct responses on WM task across WM load) and the average of their ERP amplitudes (P100 and P300) as well as their clinical scores (CADSS and BPRS). The correlations were performed separately for the ketamine and placebo groups.

**Table 1. Participant Demographics**

	Ketamine		Placebo		p Value
	Mean	SE	Mean	SE	
Age, Years	23.7	1.3	23.4	0.8	.87
Education, Years	15.2	0.7	15.9	0.33	.24
IQ (NART)	114.1	1.0	114.0	1.2	.6
SPQ	3.1	1.1	6.4	1.3	.99

NART, National Adult Reading Test; SPQ, Schizotypal Personality Questionnaire.

**RESULTS**

**Demographics and Questionnaire Data**

The two groups did not differ statistically in terms of age, IQ score, SPQ score, and years of education (Table 1). The ketamine challenge resulted in significantly higher BPRS and CADSS scores compared with the saline-treated group ( $F_{1,42} = 9.026, p < .01$  and  $F_{1,42} = 8.479, p < .01$ , respectively) (Table 2).

**Behavioral Results**

Figure 2 shows the mean RTs and the percentage of correct responses (accuracy) for both groups. With an increase in WM load, accuracy decreased in both groups ( $F_{2,84} = 65.761, p < .001$ ; partial  $\eta^2 = 0.61$ ), and there was no main effect of drug. However, there was a significant drug  $\times$  WM load interaction ( $F_{2,84} = 3.548, p = .04$ ; partial  $\eta^2 = 0.15$ ). This effect was due to performance under ketamine worsening significantly more with increase in WM load compared with placebo (Figure 2). There was also a significant negative correlation between CADSS scores and mean accuracy ( $r = -.578, p < .01$ ) for the ketamine but not the placebo group ( $r = -.065, p = .78$ ). These results were significant against a Bonferroni corrected critical value of 0.0125. RT increased with WM load for both groups ( $F_{2,84} = 128.535, p < .001$ ; partial  $\eta^2 = 0.75$ ), but this was not modified by ketamine.

**ERP Results Encoding Phase**

**P100 Amplitude.** The mean latency and SE of the P100 component in encoding was 123.0 ms  $\pm$  2.9 for the ketamine group and 119.9 ms  $\pm$  3.0 for the placebo group. There was no effect of drug on latency. However, P100 peaked significantly earlier with greater WM loads ( $F_{2,84} = 10.97, p = .001$ ).

The P100 amplitude was significantly greater under ketamine ( $F_{1,42} = 5.884, p = .02$ ; partial  $\eta^2 = 0.12$ ) compared with the placebo group. P100 amplitude also increased with WM load ( $F_{2,84} = 7.481, p = .001$ ; partial  $\eta^2 = 0.15$ ). This was confirmed by a significant linear contrast ( $F_{2,84} = 15.81, p < .01$ ; partial  $\eta^2 = 0.27$ ). There was no interaction of WM load with drug. Ketamine and placebo P100 amplitude did not correlate with either mean percentage correct responses or psychiatric scale scores (BPRS and CADSS).

**P300 Amplitude.** There was no main effect of drug in the P300 model ( $F_{(1,42)} = -0.261, p = .61$ ). This was not modulated by including P100 in a mixed-model repeated measures ANOVA as a time-varying covariate. However, there was a significant interaction between WM load and drug

( $F_{(2,84)} = 4.461, p = .01$ , partial  $\eta^2 = 0.10$ ). This was due to a linear decrease in P300 amplitude in the ketamine group but not the placebo group ( $F_{(2,84)} = 4.461, p = .01$ , partial  $\eta^2 = 0.15$ ). The main effect of WM load was significant ( $F_{2,84} = 4.87, p = .01$ ; partial  $\eta^2 = 0.10$ ) with a significant linear decrease of P300 with WM load ( $F_{1,42} = 9.231, p < .001$ ; partial  $\eta^2 = 0.18$ ).

The P300 amplitude correlated negatively with task accuracy across the three WM loads at trend for statistical significance for the ketamine group ( $r = -.41, p = .06$ ) but not the placebo group. P300 amplitude did not correlate significantly with either psychiatric scale or encoding P100 for either of the two groups.

**ERP Results Retrieval Phase**

**P100 Amplitude.** The P100 peaked at a latency of 116.4 ms  $\pm$  3.0 and 112.1 ms  $\pm$  3.0 for ketamine compared with control, respectively, with no main effect of drug. There was again a trend for the latency to be shorter with higher WM loads ( $F_{2,84} = 2.69, p = .07$ ). In the retrieval condition, ketamine significantly increased P100 amplitude relative to placebo ( $F_{1,42} = 5.620, p = .02$ ; partial  $\eta^2 = 0.12$ ). WM load did not have a significant effect on P100 amplitude, nor did it interact with drug.

P100 amplitude correlated positively with mean WM accuracy over all three loads in the placebo group only ( $r = .48, p = .02$ ). There was no significant correlation between BPRS and CADSS and P100 amplitude for either ketamine or placebo.

**P300 Amplitude.** There was no main effect of drug in the P300 amplitude model, and a mixed-model repeated measures ANOVA with a time-varying covariate confirmed that this model was not modulated by P100. However, the interaction between drug and WM load approached significance ( $F_{2,84} = 2.677, p = .08$ , partial  $\eta^2 = 0.06$ ). This was due to a larger P300 in the placebo group for WM loads 1 and 3 (Figure 3D). WM load exerted a significant main effect ( $F_{2,84} = 15.310, p < .001$ , partial  $\eta^2 = 0.27$ ), which was due to a decrease in P300 amplitude with WM load.

P300 amplitude in the retrieval phase correlated negatively with cognitive performance at trend in the ketamine group only ( $r = -.39, p = .08$ ) (Figure 4). P300 did not correlate with either psychiatric rating scales or retrieval P100 for either of the two groups.

**DISCUSSION**

In this study, we used ERPs to examine the effects of intravenous ketamine challenge on visual WM in healthy

**Table 2. Effects of Ketamine on CADSS, BPRS, RT and Accuracy on WM Task, and P100 and P300 Amplitude<sup>a</sup>**

	Ketamine		Placebo		Statistic	Partial Eta <sup>2</sup>
	Mean	SE	Mean	SE		
Phenomenological Effects						
CADSS	4.18	0.82	1.46	0.39	$F_{1,42} = 9.026, p = .004$	0.18
BPRS	19.9	0.44	18.46	0.23	$F_{1,42} = 8.479, p = .006$	0.17
Reaction Time (ms)						
Level 1 RT	973.0	29.0	970.6	29.0		
Level 2 RT	1116.5	33.3	1118.0	33.3		
Level 3 RT	1194.2	38.4	1206.7	38.4		
Load × Drug					$F_{2,84} = 0.145, p = .87$	0.003
Across Levels	1094.6	31.7	1098.4	31.7	$F_{1,42} = 0.007, p = .93$	< 0.001
WM Task Accuracy (Percentage Correct)						
Level 1	93.26	1.52	94.17	1.52		
Level 2	87.53	2.00	91.06	2.00		
Level 3	81.33	1.86	86.44	1.86		
Load × Drug					$F_{2,84} = 3.548, p = .038$	0.15
Across Levels	87.37	1.66	90.56	1.66	$F_{1,42} = 1.833, p = .2$	0.04
P100 Amplitude Encoding Stimulus (μV)						
Level 1	4.13	0.45	2.61	0.45		
Level 2	4.35	0.49	2.79	0.49		
Level 3	4.81	0.50	3.07	0.50		
Load × Drug					$F_{2,84} = 0.298, p = .74$	0.02
Across Levels	4.43	0.47	2.82	0.47	$F_{1,42} = 5.884, p = .02$	0.12
P100 Amplitude Retrieval Stimulus (μV)						
Level 1	3.81	0.49	2.32	0.49		
Level 2	3.79	0.50	2.18	0.50		
Level 3	4.09	0.52	2.23	0.52		
Load × Drug					$F_{2,84} = 1.035, p = .36$	0.01
Across Levels	3.90	0.49	2.24	0.49	$F_{1,42} = 5.618, p = .02$	0.12
P300 Amplitude Encoding Stimulus (μV)						
Level 1	1.61	0.26	1.16	0.26		
Level 2	1.18	0.30	1.74	0.30		
Level 3	0.77	0.18	1.11	0.18		
Load × Drug					$F_{2,84} = 4.461, p = .01$	0.10
Across Levels	1.19	0.21	1.34	0.21	$F_{1,42} = .261, p = .61$	< 0.01
P300 Amplitude Retrieval Stimulus (μV)						
Level 1	1.43	0.31	2.18	0.31		
Level 2	0.81	0.20	0.73	0.20		
Level 3	1.10	0.33	1.67	0.33		
Load × Drug					$F_{2,84} = 2.675, p = .08$	0.06
Across Levels	1.11	0.25	1.53	0.25	$F_{1,42} = 0.254, p = .25$	0.03

BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative Symptom Scale; RT, reaction time; WM, working memory.

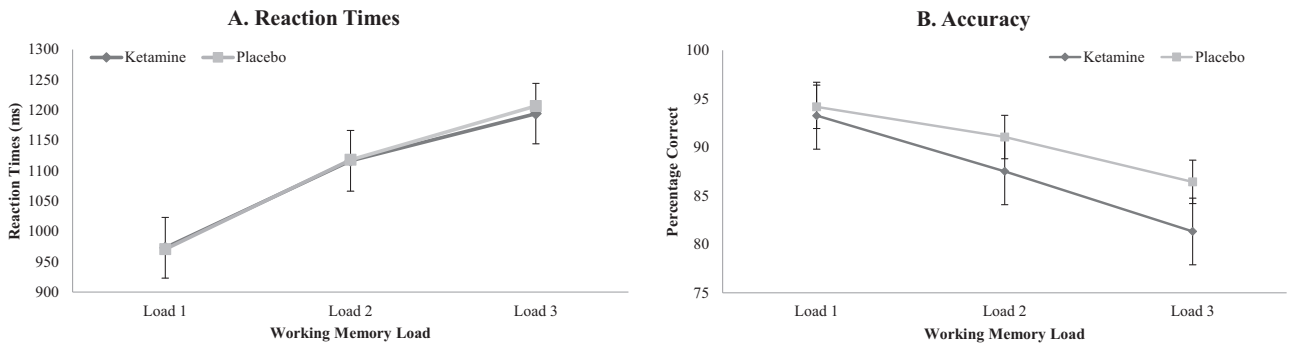
<sup>a</sup>P100 and P300 amplitude encoding and retrieval presented separately.

volunteers. In line with previous literature (31,62), ketamine caused phenomenological experiences similar to psychosis and impaired WM performance. We found that ketamine was associated with a significant augmentation of the early visual Q14 Q15 ed potential P100 and a significant load-dependent decrease in P300 amplitude during encoding. During retrieval, P100 was again significantly higher with ketamine, whereas P300 reduction with WM load differed only at trend level between the conditions. In addition, the amplitudes of P100 during retrieval correlated with cognitive performance in the placebo group with the effect disrupted by ketamine.

Also, P300 under ketamine correlated negatively at trend with cognitive performance in both encoding and retrieval conditions.

**P100 Effect**

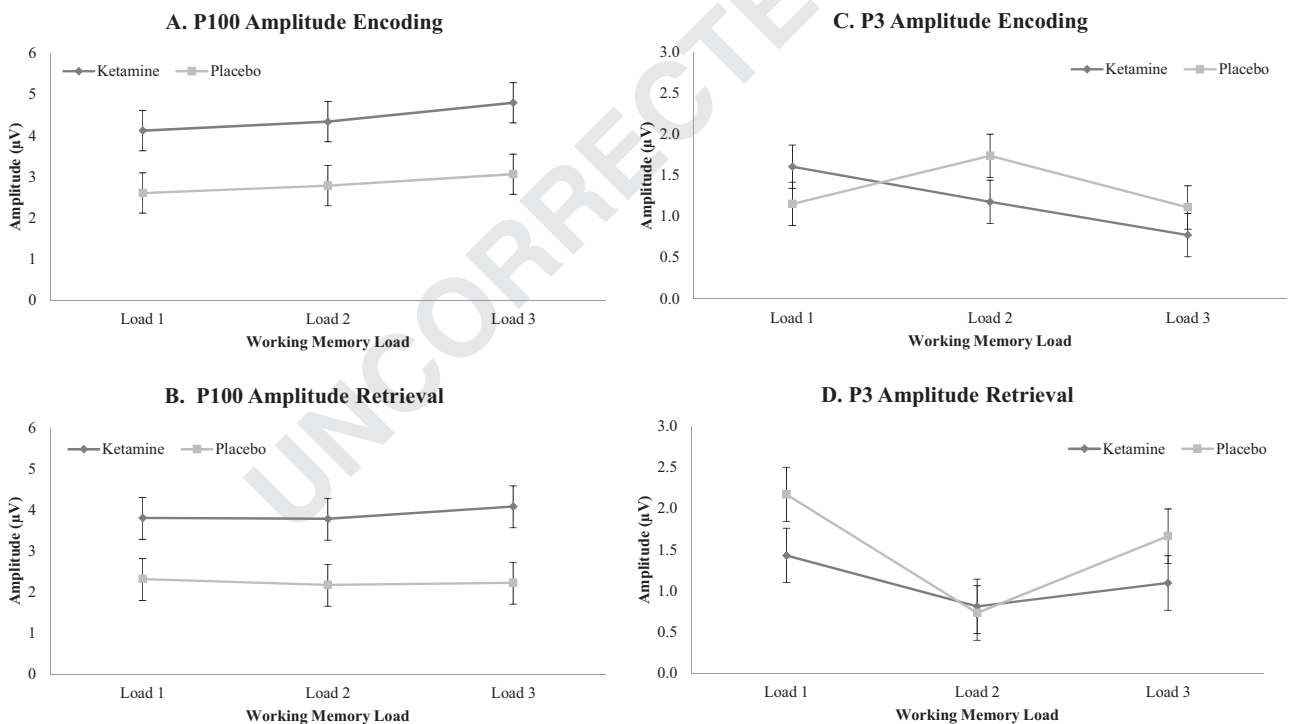
P100 amplitude was greater under ketamine than under placebo, which went against our prediction that the pattern observed in schizophrenia (8,10–12,59,63) would be replicated. There are several potential ways to interpret our unexpected finding. A parsimonious explanation follows from



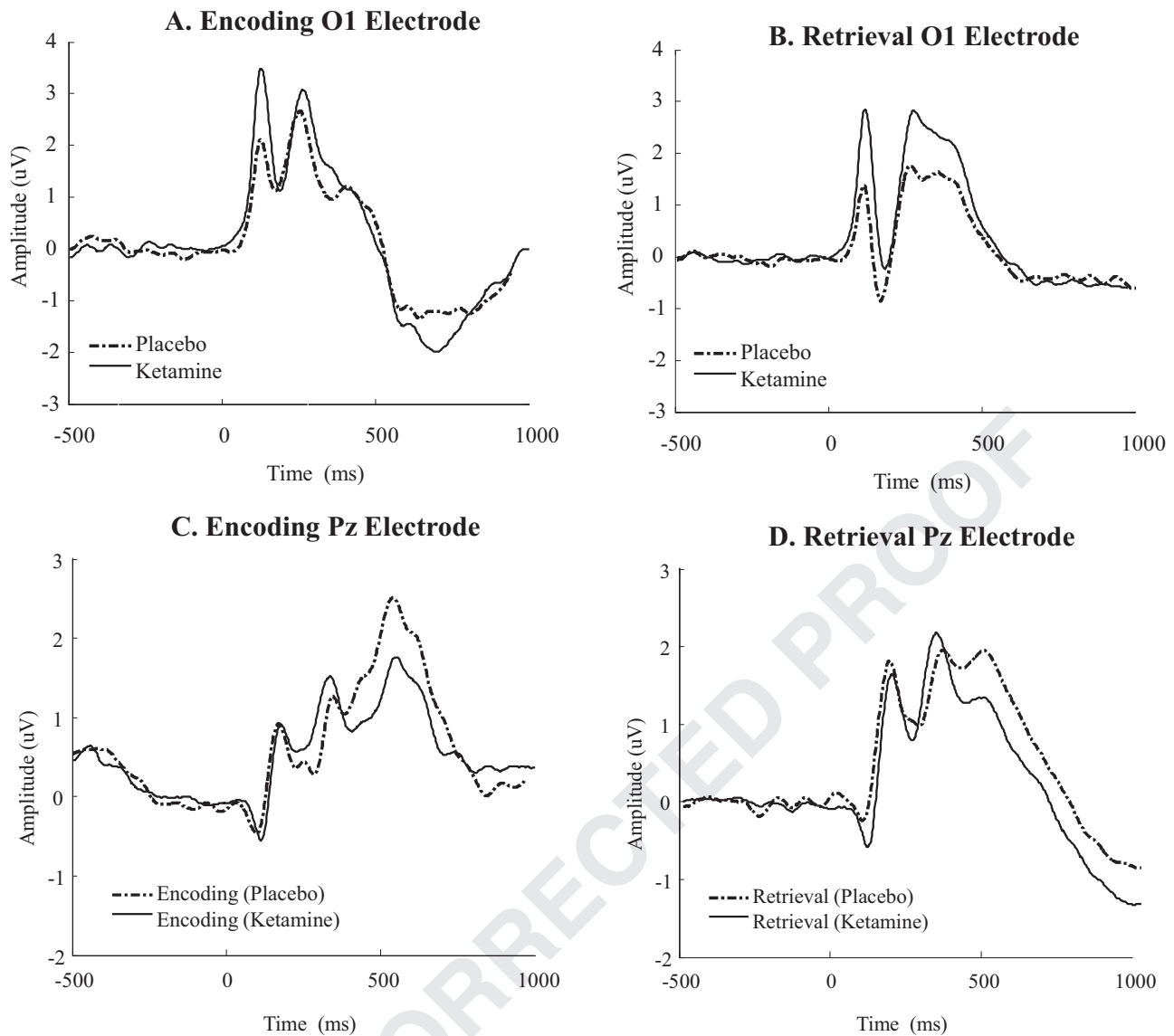
**Figure 2.** Mean reaction times (A) and accuracy (B) (percentage correct answers) in response to working memory (WM) loads 1, 2, or 3 in the ketamine (black line) and placebo groups (gray lines). There was no significant difference between the groups in terms of reaction times (A), although ketamine was associated with a more significant decrease in WM performance with increase in WM load relative to placebo (B). Error bars represent SE.

evidence that in visual cortex, NMDA receptors facilitate modulatory feedback through lateral connections, while AMPA underlies feedforward processes (46). Preclinical research has shown that ketamine-induced NMDA blockade is associated with disinhibition of glutamate release and consequent activation of AMPA receptors (64,65). Furthermore, one parsimonious explanation is that NMDA hypofunction causes a disruption in the excitatory (glutamate) and inhibitory (gamma-aminobutyric acid) balance in the neural circuitry (37,66). Blocking NMDA leads to gamma-aminobutyric acidergic disinhibition and as a consequence to an increase in bottom-up stimulation of AMPA receptors. The dual

glutamatergic effects of ketamine have been proposed as the basis of the ketamine-induced disruption of feature integration reported in humans (67) and animals (68). Similarly, Self *et al.* (46) demonstrated in macaques that NMDA antagonism (using NMDA antagonist 2-amino-5-phosphonovaleate) disrupts recurrent but not feedforward processing in V1. Therefore, the ketamine-induced P100 augmentation shown here could be due to loss of lateral NMDA modulation and a potentiation of feedforward, AMPA-mediated processes. In line with this idea is the observation that under ketamine participants report heightened perceptual experiences (69).



**Figure 3.** P100 and P300 event-related potential amplitudes. The P100 peak amplitude at the left central occipital electrode (O1) during encoding (A) and retrieval (B); P300 mean amplitude at the central parietal electrode (Pz) during encoding (C) and retrieval (D) in response to working memory (WM) load 1, 2, or 3 in ketamine (black line) and placebo (gray line) groups. Whereas P1 amplitude significantly increased under ketamine across WM loads in response to both encoding and retrieval stimuli (A, B), P300 amplitude for both encoding and retrieval was reduced (C, D). Error bars represent SE.



**Figure 4.** (A–D) Event-related potentials (ERPs) during working memory encoding (A, C) and retrieval (B, D) for ketamine (black line) and placebo (dashed line) groups are shown at a left occipital (O1) and central parietal (Pz) electrode. The P100 ERP can be seen at electrode O1, and the P300 ERP can be seen at electrode Pz.

An alternative or perhaps complementary explanation is based on evidence that P100 is under attentional (i.e., top-down) control (70). Within the framework of predictive coding, it has been suggested that ketamine impairs top-down predictions but increases abnormal prediction error responses by stimulating AMPA (64,71). Early positron emission tomography metabolic mapping studies reported that ketamine focally increased prefrontal cortex metabolism (glucose uptake), probably by disinhibiting local glutamate release (72–74). Furthermore, the functional impact of disinhibition has also been shown to alter global connectivity and an inability of the default mode network to disengage during WM performance (75). This has been shown to be associated with impaired WM performance (76). A noisier signal and

disinhibition of long-range facilitatory projections to occipital cortex from prefrontal cortex could thus account for the increased P100 amplitude we observed.

If fronto-occipital disinhibition does occur under ketamine, a critical difference may be present between this state and established schizophrenia. Using the same paradigm, we recently showed reduced functional connectivity between ventrolateral prefrontal cortex and extrastriate visual areas on fMRI in patients with schizophrenia compared with control subjects (77). One possibility is that ketamine models a state of acute NMDA impairment in early psychosis in which frontal disinhibition may occur. In contrast, in chronic psychosis, frontal cortex function is inhibited, potentially as a result of chronic glutamate dysfunction. In direct support of this view, a



more recent fMRI study demonstrated that ketamine in healthy volunteers induced a state of frontal hyperconnectivity. This was similar to what the authors observed in the early, but not chronic, stages of schizophrenia (78).

However, any decisive interpretation of the net effect of ketamine is likely to be an oversimplification. It is not possible to identify with confidence the net effect of ketamine on visual cortical function on the basis of our finding. Using fMRI, we have shown that ketamine causes complex temporal and regional blood oxygen level-dependent changes, including hypoactivation and hyperactivation with the prefrontal and parietal cortices preferentially affected (79). This is in line with EEG studies that have demonstrated increases in high-frequency and decreases in low-frequency neural oscillations in humans (80) and in mice (81). In addition, resting-state positron emission tomography studies have demonstrated that ketamine-induced increase in regional blood flow is counterintuitively associated with reduced oxygen extraction (82,83), possibly related to the direct vascular effect of ketamine (84).

Whatever the exact genesis of the P100 increase under ketamine, the present study suggests that while acute ketamine challenge may recreate a facet of the core pathophysiology in psychosis, it is unlikely to be capturing the changing role of glutamate subsystems in the evolution of the illness. Given the evidence for decreasing frontal glutamate levels with age in patients with schizophrenia (85), further P100 studies specifically targeting patients early in the disease are needed to further test the hypothesis that ketamine recreates states typical for the initial, but not chronic stages, of psychotic illness [see also (78)].

### P300

We found that ketamine was associated with a decrease in P300 amplitude with WM load exertion. This finding is consistent with previous studies in the auditory and visual domains (47–53,86) although we observed a strong effect only in the encoding phase with the retrieval significance reduced to a trend. We also found a trend for correlation between P300 and cognitive performance under ketamine for both encoding and retrieval conditions. A study using EEG space source localization and fMRI showed that ketamine extinguished primarily the parietal locus of the frontoparietal network generating P300 (51). This is in agreement with other studies showing that ketamine preferentially attenuates the parietally generated P300b component, which is understood to be an aspect of top-down allocation of attentional resources (26) and WM update (24). We did not find evidence that P300 was directly modulated by the earlier P100—this is based on the lack of a significant covariate effect of P100 in the P300 analyses. These results argue that ketamine disrupts P300 through direct effects on the parietal cortex processes rather than solely as a consequence of its action on the visual cortex.

### Limitations

An inherent limitation to nearly all ketamine experiment designs is that the extent to which researchers are blinded is limited by the obvious subjective effects of ketamine.

We sought to remedy this by having separate study personnel record and process the EEG data (A. Shepherd and I. Koychev, respectively).

### Conclusions

This is the first study to explore the effects of ketamine on early visual processing in WM in healthy volunteers. We found evidence of a dysfunctional increase in early visual P100 amplitude. This finding contrasts with reduced P100 amplitudes reported in chronic schizophrenia as well as in individuals with familial or personality trait vulnerability. This may suggest that while acute ketamine captures some of the phenomenological features of psychosis, it does not fully replicate the neurochemical basis of cognitive deficits associated with the chronic condition. Visual P100 studies in early psychosis are required to test the hypothesis that hyperglutamatergic states similar to the ones caused by ketamine occur only in the earliest disease stages. The study also replicated cognitive deficits and P300 reduction with ketamine. The current findings provide insight into the critical differences between established psychotic illness and its best validated pharmacological model.

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### ARTICLE INFORMATION

From the Neuroscience and Psychiatry Unit (IK, JFWD) and School of Psychological Sciences (WE-D), University of Manchester, Manchester; Department of Psychiatry (IK), University of Oxford, Warneford Hospital, Oxford; Manchester Mental Health and Social Care Trust (JFWD), Manchester; Department of Psychology (CH), City University, London, United Kingdom; and School of Biomedical Engineering (WE-D), University of Valparaiso, Valparaiso, Chile.

Address correspondence to Ivan Koychev, Neuroscience and Psychiatry Unit, The University of Manchester, G.800, Stopford Building, Oxford Road, Manchester, M13 9PT, United Kingdom; E-mail: ivan.koychev@doctors.org.uk.

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