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

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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 ≤ 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.

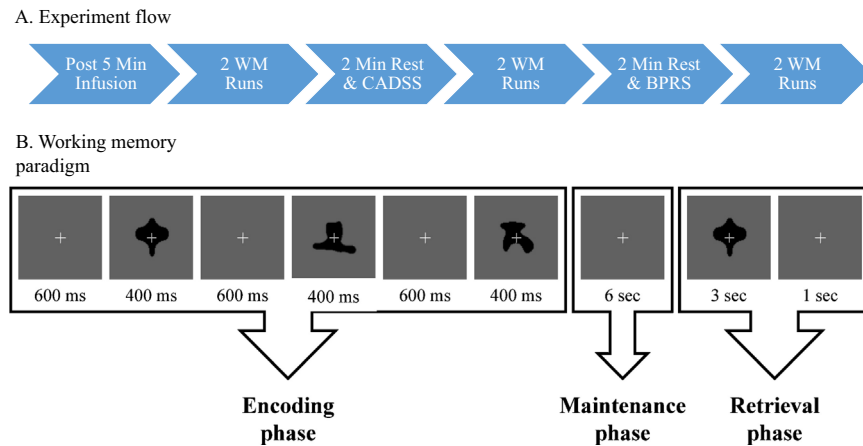
Experiment Design and WM Task

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 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, Gräefelfing, 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 ± 250 μ V and ± 150 μ 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 $91.8\% \pm 10.1$

(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.

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 (0.6×0.6 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

Table 1. Participant Demographics

	Ketamine		Placebo		<i>p</i> 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 $123.0 \text{ ms} \pm 2.9$ for the ketamine group and $119.9 \text{ ms} \pm 3.0$ 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 $116.4 \text{ ms} \pm 3.0$ and $112.1 \text{ ms} \pm 3.0$ 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^a

	Ketamine		Placebo		Statistic	Partial Eta ²
	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.

^aP100 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 Q15 ed potential P100 and a significant load-dependent Q15 ease 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

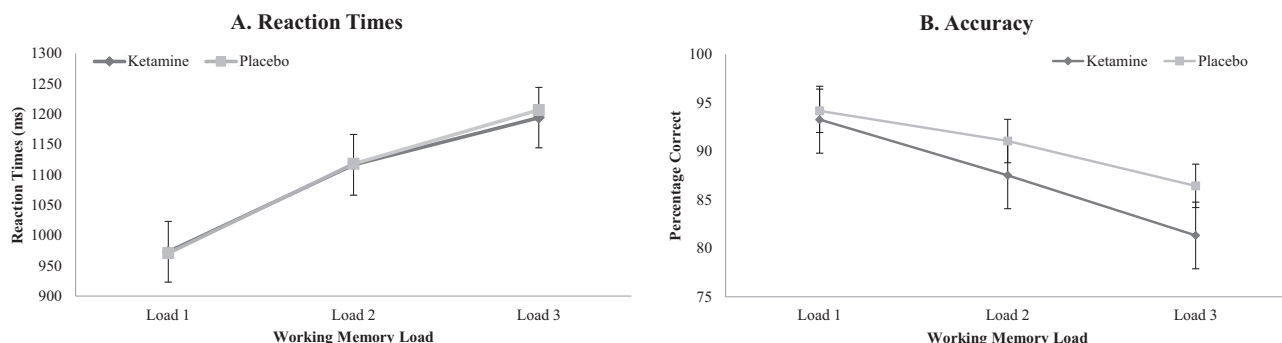


Figure 2. Mean reaction times (A) and accuracy (B) (percentage correct answers) in response to working memory (WM) loads 1, 2, or 3 in the ketamine (black line) and placebo groups (gray lines). There was no significant difference between the groups in terms of reaction times (A), although ketamine was 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-phosphonvalerate) 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).

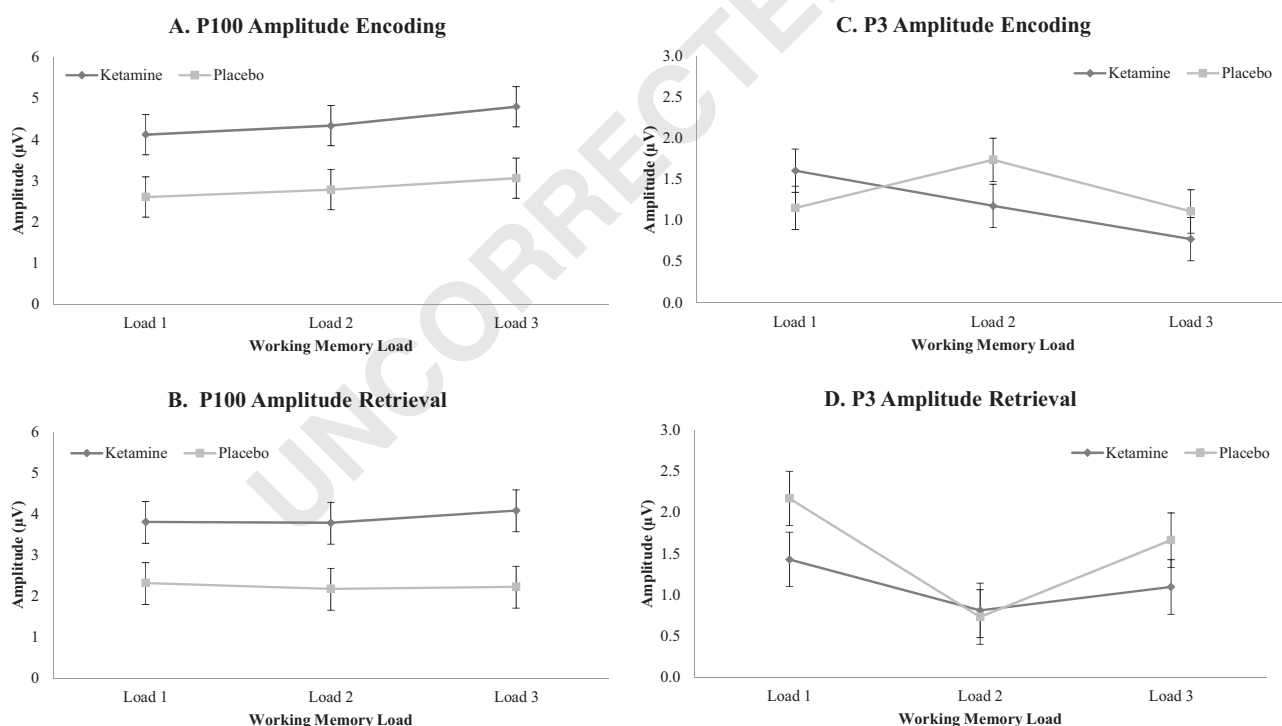


Figure 3. P100 and P300 event-related potential amplitudes. The P100 peak amplitude at the left central occipital electrode (O1) during encoding (A) and retrieval (B); P300 mean amplitude at the central parietal electrode (Pz) during encoding (C) and retrieval (D) in response to working memory (WM) load 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.

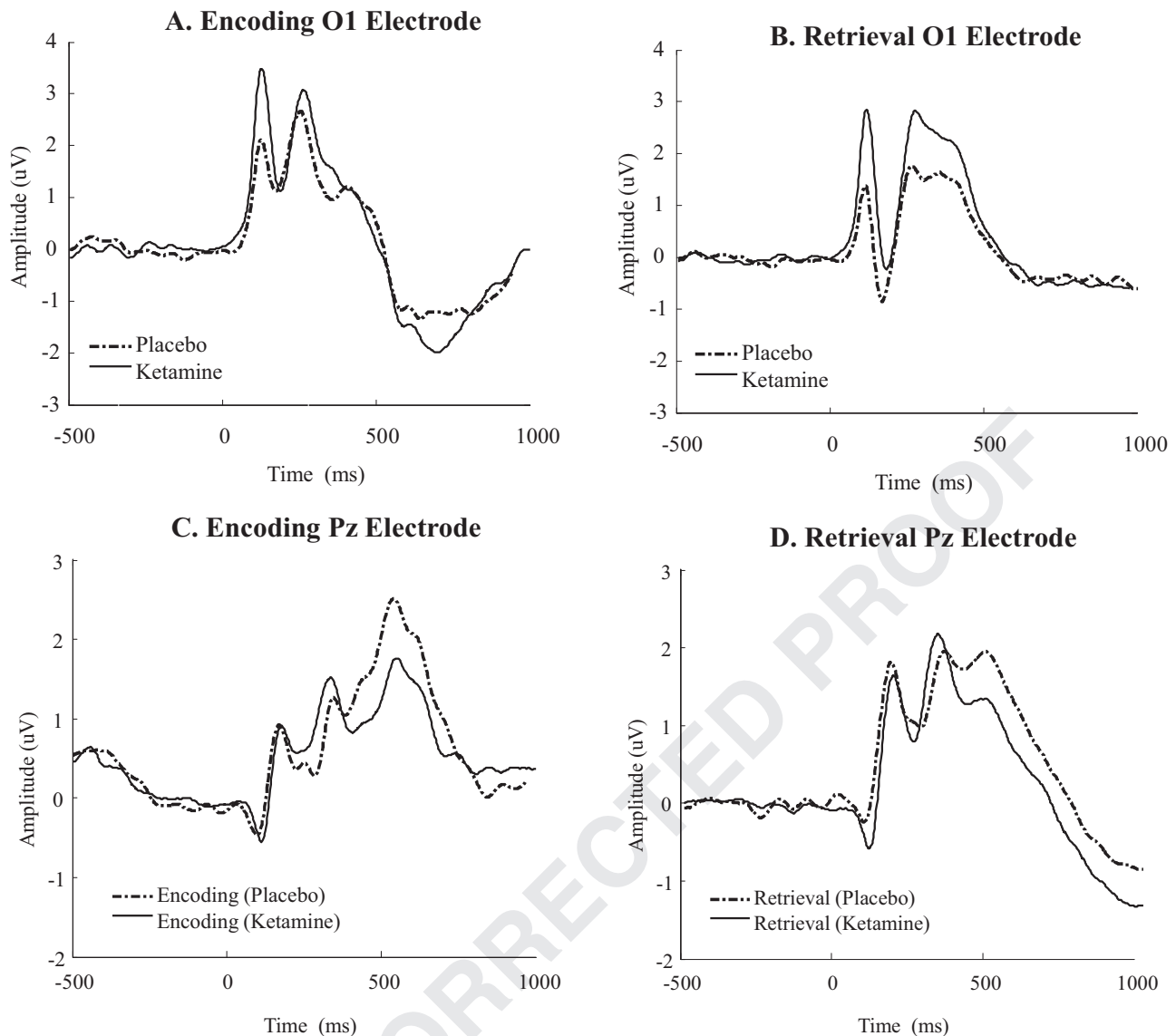


Figure 4. (A–D) Event-related potentials (ERPs) during working memory encoding (A, C) and retrieval (B, D) for ketamine (black line) and placebo (dashed line) groups are shown at a left occipital (O1) and central parietal (Pz) electrode. The P100 ERP can be seen at electrode O1, and the P300 ERP can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

- Heinrichs RW (2005): The primacy of cognition in schizophrenia. *Am Psychol* 60:229–242.
- Green MF (2006): Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry* 67:e12.
- Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, et al. (2000): Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: The New York High-Risk Project. *Am J Psychiatry* 157:1416–1422.
- Albus M, Hubmann W, Scherer J, Dreikorn B, Hecht S, Sobizack N, et al. (2002): A prospective 2-year follow-up study of neurocognitive functioning in patients with first-episode schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 252:262–267.

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5. Hofer A, Baumgartner S, Bodner T, Edlinger M, Hummer M, Kemmler G, *et al.* (2005): Patient outcomes in schizophrenia II: The impact of cognition. *Eur Psychiatry* 20:395–402.
6. Milev P, Ho BC, Arndt S, Andreasen NC (2005): Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry* 162:495–506.
7. Lawlor-Savage L, Goghari VM (2014): Working memory training in schizophrenia and healthy populations. *Behav Sci* 4:301–319.
8. Yeap S, Kelly SP, Sehatpour P, Magno E, Garavan H, Thakore JH, *et al.* (2008): Visual sensory processing deficits in schizophrenia and their relationship to disease state. *Eur Arch Psychiatry Clin Neurosci* 258:305–316.
9. Butler PD, Martinez A, Foxe JJ, Kim D, Zemon V, Silipo G, *et al.* (2007): Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain* 130:417–430.
10. Koychev I, McMullen K, Lees J, Dadhiwala R, Grayson L, Perry C, *et al.* (2012): A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-center double-blind placebo-controlled study. *Eur Neuropsychopharmacol* 22:469–481.
11. Yeap S, Kelly SP, Thakore JH, Foxe JJ (2008): Visual sensory processing deficits in first-episode patients with schizophrenia. *Schizophr Res* 102:340–343.
12. Yeap S, Kelly SP, Sehatpour P, Magno E, Javitt DC, Garavan H, *et al.* (2006): Early visual sensory deficits as endophenotypes for schizophrenia: High-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry* 63:1180–1188.
13. Koychev I, El-Deredy W, Haenschel C, Deakin JF (2010): Visual information processing deficits as biomarkers of vulnerability to schizophrenia: An event-related potential study in schizotypy. *Neuropsychologia* 48:2205–2214.
14. Foxe JJ, Simpson GV (2002): Flow of activation from V1 to frontal cortex in humans. A framework for defining “early” visual processing. *Exp Brain Res* 142:139–150.
15. Fukuda K, Vogel EK (2009): Human variation in overriding attentional capture. *J Neurosci* 29:8726–8733.
16. Barcelo F, Suwazono S, Knight RT (2000): Prefrontal modulation of visual processing in humans. *Nat Neurosci* 3:399–403.
17. Zanto TP, Rubens MT, Thangavel A, Gazzaley A (2011): Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. *Nat Neurosci* 14:656–661.
18. Jeon YW, Polich J (2003): Meta-analysis of P300 and schizophrenia: Patients, paradigms, and practical implications. *Psychophysiology* 40: 684–701.
19. Lee SY, Namkoong K, Cho HH, Song DH, An SK (2010): Reduced visual P300 amplitudes in individuals at ultra-high risk for psychosis and first-episode schizophrenia. *Neurosci Lett* 486:156–160.
20. Qiu YQ, Tang YX, Chan RC, Sun XY, He J (2014): P300 aberration in first-episode schizophrenia patients: A meta-analysis. *PLoS One* 9: e97794.
21. Polich J (2007): Updating P300: An integrative theory of P3a and P3b. *Clin Neurophysiol* 118:2128–2148.
22. Bledowski C, Prvulovic D, Hoehstetter K, Scherg M, Wibrall M, Goebel R, *et al.* (2004): Localizing P300 generators in visual target and distractor processing: A combined event-related potential and functional magnetic resonance imaging study. *J Neurosci* 24: 9353–9360.
23. Bledowski C, Cohen Kadosh K, Wibrall M, Rahm B, Bittner RA, Hoehstetter K, *et al.* (2006): Mental chronometry of working memory retrieval: A combined functional magnetic resonance imaging and event-related potentials approach. *J Neurosci* 26:821–829.
24. Kok A (2001): On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology* 38:557–577.
25. Donchin E, Coles MGH (1988): Is the P300 component a manifestation of context updating. *Behav Brain Sci*, 11, 357–374.
26. Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S (2004): Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophr Res* 70:315–329.
27. Rorty WT, Cannon EH (1972): Some features of the auditory evoked response in schizophrenics. *Arch Gen Psychiatry* 27:466–471.
28. Kim MS, Kang SS, Youn T, Kang DH, Kim JJ, Kwon JS (2003): Neuropsychological correlates of P300 abnormalities in patients with schizophrenia and obsessive-compulsive disorder. *Psychiatry Res* 123:109–123.
29. Nieman DH, Koelman JH, Linszen DH, Bour LJ, Dingemans PM, Ongerboer de Visser BW (2002): Clinical and neuropsychological correlates of the P300 in schizophrenia. *Schizophr Res* 55:105–113.
30. Adler CM, Goldberg TE, Malhotra AK, Pickar D, Breier A (1998): Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. *Biol Psychiatry* 43:811–816.
31. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, *et al.* (1994): Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51: 199–214.
32. Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, *et al.* (1996): NMDA receptor function and human cognition: The effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 14:301–307.
33. Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004): Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* 29: 208–218.
34. Umbrecht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC (2000): Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: Implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry* 57: 1139–1147.
35. Javitt DC (1996): Glutamate receptors and schizophrenia: Opportunities and caveats. *Mol Psychiatry* 1:16–17.
36. Moghaddam B, Javitt D (2012): From revolution to evolution: The glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 37:4–15.
37. Krystal JH, D’Souza DC, Mathalon D, Perry E, Belger A, Hoffman R (2003): NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: Toward a paradigm shift in medication development. *Psychopharmacology* 169:215–233.
38. Levin ED, Bettgeowda C, Weaver T, Christopher NC (1998): Nicotinedizocipine interactions and working and reference memory performance of rats in the radial-arm maze. *Pharmacol Biochem Behav* 61: 335–340.
39. Morris RG, Anderson E, Lynch GS, Baudry M (1986): Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature* 319:774–776.
40. Riedel G, Platt B, Micheau J (2003): Glutamate receptor function in learning and memory. *Behav Brain Res* 140:1–47.
41. Fox K, Sato H, Daw N (1990): The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *J Neurophysiol* 64: 1413–1428.
42. Kwon YH, Nelson SB, Toth LJ, Sur M (1992): Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol* 68:182–196.
43. Driesen NR, McCarthy G, Bhagwagar Z, Bloch MH, Calhoun VD, D’Souza DC, *et al.* (2013): The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. *Neuropsychopharmacology* 38:2613–2622.
44. Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA, *et al.* (2013): NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. *Neuron* 77:736–749.
45. van Loon AM, Fahrenfort JJ, van der Velde B, Lirk PB, Vulink NC, Hollmann MW, *et al.* (2016): NMDA receptor antagonist ketamine distorts object recognition by reducing feedback to early visual cortex. *Cereb Cortex* 26:1986–1996.
46. Self MW, Kooijmans RN, Super H, Lamme VA, Roelfsema PR (2012): Different glutamate receptors convey feedforward and recurrent processing in macaque V1. *Proc Natl Acad Sci U S A* 109: 11031–11036.

47. Knott VJ, Millar AM, McIntosh JF, Shah DK, Fisher DJ, Blais CM, *et al.* (2011): Separate and combined effects of low dose ketamine and nicotine on behavioural and neural correlates of sustained attention. *Biol Psychol* 88:83–93.
48. Oranje B, Gispén-de Wied CC, Westenberg HG, Kemner C, Verbaten MN, Kahn RS (2009): Haloperidol counteracts the ketamine-induced disruption of processing negativity, but not that of the P300 amplitude. *Int J Neuropsychopharmacol* 12:823–832.
49. Oranje B, van Berckel BN, Kemner C, van Ree JM, Kahn RS, Verbaten MN (2000): The effects of a sub-anaesthetic dose of ketamine on human selective attention. *Neuropsychopharmacology* 22:293–302.
50. Gunduz-Bruce H, Reinhart RM, Roach BJ, Gueorguieva R, Oliver S, D'Souza DC, *et al.* (2012): Glutamatergic modulation of auditory information processing in the human brain. *Biol Psychiatry* 71: 969–977.
51. Musso F, Brinkmeyer J, Ecker D, London MK, Thieme G, Warbrick T, *et al.* (2011): Ketamine effects on brain function—simultaneous fMRI/EEG during a visual oddball task. *Neuroimage* 58:508–525.
52. Watson TD, Petrakis IL, Edgecombe J, Perrino A, Krystal JH, Mathalon DH (2009): Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission. *Int J Neuropsychopharmacol* 12:357–370.
53. Ahn KH, Youn T, Cho SS, Ha TH, Ha KS, Kim MS, *et al.* (2003): N-methyl-D-aspartate receptor in working memory impairments in schizophrenia: Event-related potential study of late stage of working memory process. *Prog Neuropsychopharmacol Biol Psychiatry* 27: 993–999.
54. Raine A (1991): The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 17:555–564.
55. Koychev I, McMullen K, Lees J, Dadhiwala R, Grayson L, Perry C, *et al.* (2012): A validation of cognitive biomarkers for the early identification of cognitive enhancing agents in schizotypy: A three-center double-blind placebo-controlled study. *Eur Neuropsychopharmacol* 22:469–481.
56. Nelson HE (1982): National Adult Reading Test (NART): For the Assessment of Premorbid Intelligence in Patients with Dementia: Test Manual. Windsor, UK: NFER-Nelson.
57. De Simoni S, Schwarz AJ, O'Daly OG, Marquand AF, Brittain C, Gonzales C, *et al.* (2013): Test-retest reliability of the BOLD pharmacological MRI response to ketamine in healthy volunteers. *Neuroimage* 64:75–90.
58. Absalom AR, Lee M, Menon DK, Sharar SR, De Smet T, Halliday J, *et al.* (2007): Predictive performance of the Domino, Hijazi, and Clements models during low-dose target-controlled ketamine infusions in healthy volunteers. *Br J Anaesth* 98:615–623.
59. Haenschel C, Bittner RA, Haertling F, Rotarska-Jagiela A, Maurer K, Singer W, *et al.* (2007): Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: A study with event-related potentials and functional magnetic resonance imaging. *Arch Gen Psychiatry* 64:1229–1240.
60. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, *et al.* (1998): Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress* 11:125–136.
61. Overall JE, Gorham DR (1962): The brief psychiatric rating scale. *Psychol Rep* 10:799–812.
62. Krystal JH, Abi-Saab W, Perry E, D'Souza DC, Liu N, Gueorguieva R, *et al.* (2005): Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. *Psychopharmacology* 179:303–309.
63. Lalor EC, Yeap S, Reilly RB, Pearlmutter BA, Foxe JJ (2008): Dissecting the cellular contributions to early visual sensory processing deficits in schizophrenia using the VESPA evoked response. *Schizophr Res* 98:256–264.
64. Moghaddam B, Adams B, Verma A, Daly D (1997): Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 17:2921–2927.
65. Moran RJ, Jones MW, Blockeel AJ, Adams RA, Stephan KE, Friston KJ (2015): Losing control under ketamine: Suppressed cortico-hippocampal drive following acute ketamine in rats. *Neuropsychopharmacology* 40:268–277.
66. Anticevic A, Cole MW, Repovs G, Savic A, Driesen NR, Yang G, *et al.* (2013): Connectivity, pharmacology, and computation: Toward a mechanistic understanding of neural system dysfunction in schizophrenia. *Front Psychiatry* 4:169.
67. Meuwese JD, van Loon AM, Scholte HS, Lirk PB, Vulink NC, Hollmann MW, *et al.* (2013): NMDA receptor antagonist ketamine impairs feature integration in visual perception. *PLoS One* 8:e79326.
68. Kurylo DD, Gazes Y (2008): Effects of ketamine on perceptual grouping in rats. *Physiol Behav* 95:152–156.
69. Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA (2001): Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* 25:455–467.
70. Luck SJ, Hillyard SA, Mouloua M, Woldorff MG, Clark VP, Hawkins HL (1994): Effects of spatial cuing on luminance detectability: Psychophysical and electrophysiological evidence for early selection. *J Exp Psychol Hum Percept Perform* 20:887–904.
71. Corlett PR, Honey GD, Krystal JH, Fletcher PC (2011): Glutamatergic model psychoses: Prediction error, learning, and inference. *Neuropsychopharmacology* 36:294–315.
72. Breier A, Malhotra AK, Pinals DA, Weisenfeld NI, Pickar D (1997): Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *Am J Psychiatry* 154: 805–811.
73. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J (1997): Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol* 7: 25–38.
74. Holcomb HH, Lahti AC, Medoff DR, Weiler M, Tamminga CA (2001): Sequential regional cerebral blood flow brain scans using PET with H₂ (15)O demonstrate ketamine actions in CNS dynamically. *Neuropsychopharmacology* 25:165–172.
75. Anticevic A, Gancsos M, Murray JD, Repovs G, Driesen NR, Ennis DJ, *et al.* (2012): NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. *Proc Natl Acad Sci U S A* 109:16720–16725.
76. Anticevic A, Repovs G, Shulman GL, Barch DM (2010): When less is more: TPJ and default network deactivation during encoding predicts working memory performance. *Neuroimage* 49:2638–2648.
77. Bittner RA, Linden DE, Roebroek A, Hartling F, Rotarska-Jagiela A, Maurer K, *et al.* (2015): The when and where of working memory dysfunction in early-onset schizophrenia—a functional magnetic resonance imaging study. *Cereb Cortex* 25:2494–2506.
78. Anticevic A, Corlett PR, Cole MW, Savic A, Gancsos M, Tang Y, *et al.* (2015): N-methyl-D-aspartate receptor antagonist effects on prefrontal cortical connectivity better model early than chronic schizophrenia. *Biol Psychiatry* 77:569–580.
79. Deakin JF, Lees J, McKie S, Hallak JE, Williams SR, Dursun SM (2008): Glutamate and the neural basis of the subjective effects of ketamine: A pharmacological-magnetic resonance imaging study. *Arch Gen Psychiatry* 65:154–164.
80. Hong LE, Summerfelt A, Buchanan RW, O'Donnell P, Thaker GK, Weiler MA, *et al.* (2010): Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine. *Neuropsychopharmacology* 35:632–640.
81. Ehrlichman RS, Gandal MJ, Maxwell CR, Lazarewicz MT, Finkel LH, Contreras D, *et al.* (2009): N-methyl-D-aspartic acid receptor antagonist-induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia. *Neuroscience* 158:705–712.
82. Langsjö JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, *et al.* (2003): Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* 99:614–623.

83. Langsjo JW, Maksimow A, Salmi E, Kaisti K, Aalto S, Oikonen V, *et al.* (2005): S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology* 103:258–268.
84. Noh HJ, Bae YM, Park SH, Kim JG, Kim B, Kim YS, *et al.* (2009): The vasodilatory effect of ketamine is independent of the N-methyl-D-aspartate receptor: Lack of functional N-methyl-D-aspartate receptors in rat mesenteric artery smooth muscle. *Eur J Anaesthesiol* 26:676–682.
85. Marsman A, van den Heuvel MP, Klomp DW, Kahn RS, Luitjen PR, Hulshoff Pol HE (2013): Glutamate in schizophrenia: A focused review and meta-analysis of (1)H-MRS studies. *Schizophr Bull* 39: 120–129.
86. Mathalon DH, Ahn KH, Perry EB Jr, Cho HS, Roach BJ, Blais RK, *et al.* (2014): Effects of nicotine on the neurophysiological and behavioral effects of ketamine in humans. *Front Psychiatry* 5:3.

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