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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). Haenschel *et al.* (14) reported that P100 amplitude predicted performance during a 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 (15,16). 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 (17) and after a reversible experimental lesion induced by transcranial magnetic stimulation (18).

Several studies have reported that patients with schizophrenia have reduced amplitude of the P300 ERP component (19–21). P300 potentials are typically evoked by infrequent target stimuli that differ in quality or duration from more frequent stimuli (22,23), but they are also elicited by WM tasks during both encoding and retrieval (24,25). P300 has been conceptualized as a neurophysiological correlate of WM update in response to changes in the environment (26). Patients with schizophrenia show a reduction in P300

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(21,27,28), which has been shown to correlate with the level of cognitive impairment (29,30).

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 (31–35) has been key to the development of the NMDA-deficiency theory of schizophrenia (36–38). The importance of glutamate to cognition was demonstrated by preclinical 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 (39–41). 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 (42,43) and prefrontal (44,45) 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 (46) and primates (47).

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 (48–51). Visual experiments have focused exclusively on later ERP components, reporting an attenuation of the P300 component (52–54).

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) (55). Individuals scoring $\leq$42 [cutoff for high schizotypy based on a previous study in the same population (10)] 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

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 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 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 (14) 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