Haloperidol counteracts the ketamine-induced disruption of processing negativity, but not that of the P300 amplitude

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Abstract

Antagonists of the N-methyl-D-aspartate (NMDA) receptors such as ketamine, induce abnormalities in healthy subjects similar to those found in schizophrenia. However, recent evidence, suggests that most of the currently known NMDA antagonists have a broader receptor profile than originally thought. Besides exerting an antagonistic effect on NMDA receptors, they have agonistic effects on dopamine D₂ receptors. Can haloperidol (D₂ antagonist) counteract the disruptive effects of ketamine on psychophysiological parameters of human attention? In a randomized, double-blind, placebo-controlled experiment 18 healthy male volunteers received placebo/placebo, placebo/ketamine (0.3 mg/kg i.v.) and haloperidol (2 mg)/ketamine (0.3 mg/kg i.v.) on three separate test days, after which they were tested in an auditory selective-attention paradigm. Haloperidol/ketamine reduced task performance compared to placebo/placebo, while the task performance in these two treatments did not differ from placebo/ketamine. Furthermore, placebo/ketamine reduced processing negativity compared to both placebo/placebo and haloperidol/ketamine treatments. However, both placebo/ketamine and haloperidol/ketamine reduced P300 amplitude compared to placebo/placebo, while P300 amplitude did not differ between placebo/ketamine and haloperidol/ketamine treatments. The combined effects of haloperidol and ketamine reduced task performance, suggesting that this is dependent on dopaminergic D₂ activity, probably in the prefrontal cortex. In addition, ketamine reduced both P300 amplitude and processing negativity. In contrast to the P300 amplitude, the disruptive effects of ketamine on processing negativity could be prevented by pretreatment with haloperidol. The current results suggest that ketamine reduced P300 amplitude by its antagonistic effect on glutamatergic activity, while it reduced processing negativity by its agonistic effect on dopaminergic D₂ activity.

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Introduction

Since Kraepelin (1913) it is known that patients with schizophrenia exhibit diverse cognitive deficits. These deficits vary from disturbances in information processing to changes in attentional resources, such as an inability to focus attention (Green, 1997). Antagonists of the N-methyl-D-aspartate (NMDA) receptors such as ketamine, induce abnormalities in healthy subjects similar to those found in schizophrenia (Adler et al. 1999; Luby et al. 1959), and exacerbate psychotic symptoms in schizophrenia patients (Lahti et al. 1995; Malhotra et al. 1997). In several early studies using positron emission tomography (PET) ketamine was found to increase

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dopaminergic activity in the striatum (Breier et al. 1998; Smith et al. 1998; Vollenweider et al. 2000). Until recently, it was believed that an (often complex) indirect mechanism was responsible for this increase in dopaminergic activity. Nowadays, however, evidence is accumulating that NMDA antagonists such as ketamine, dizocilpine (MK-801) and phencyclidine (PCP) are also direct agonists of dopaminergic D₄ (Kapur & Seeman, 2002; Seeman & Guan, 2008) and serotonergic receptors (Kapur & Seeman, 2002). In a previous study we found that ketamine reduced psychophysiological parameters of human selective attention (Oranje et al. 2000), similarly to what is usually found in schizophrenia. In the present study, it was investigated whether ketamine could have induced these deficits by its effect on the dopaminergic D₄ receptors.

Processing negativity is a negative deflection in the event-related potential (ERP) appearing above the (pre)frontal areas of the brain, whenever healthy subjects are asked to selectively attend to stimuli defined by certain features, while ignoring others (e.g. male/female voice, left/right ear) (Naätänen, 1990). Patients with schizophrenia show reduced processing negativity, either with (Baribeau-Braun et al. 1983) or without (Michie et al. 1990; Ward et al. 1991) medication compared to healthy subjects. In a previous study we found that ketamine reduced processing negativity of healthy volunteers (Oranje et al. 2000). To our knowledge there are no other studies describing the effect of NMDA antagonists on processing negativity.

A P300 amplitude is elicited by infrequent stimuli (deviants) appearing in a sequence of frequent stimuli (standards). Maximum P300 amplitude is commonly found when the subject is requested to respond to these deviant stimuli, e.g. by pressing a button. Roth & Cannon (1972) found a reduced P300 amplitude in patients with schizophrenia, when compared to healthy controls, a result which has been replicated in many studies since (e.g. Baribeau-Braun et al. 1983; Boutros et al. 1997; Bramon et al. 2004; Javitt et al. 1995; Michie et al. 1990). Besides our previous study only one other publication reports on the effects of ketamine on P300 amplitude, and in both studies ketamine was found to reduce P300 (P3b) amplitude (Oranje et al. 2000; Watson et al. 2008).

Processing negativity and P300 amplitude represent two different levels of attention. Processing negativity was first described by Hillyard et al. (1973). Given the early latency of the phenomenon, they suggested that the underlying attentional process is a tonically maintained set favouring one ear over the other, rather than an active process of discrimination or recognition of each individual stimulus separately. In contrast, P300 amplitude is assumed to reflect aspects of further (conscious) processing of an attended stimulus (for a review on both processing negativity and P300 amplitude see Naätänen, 1990). To our knowledge, there is currently no available literature describing a relationship between these two psychophysiological parameters of attention.

The present study was designed to replicate and further extend an earlier study performed in our laboratory, in which we found a ketamine-induced reduction of processing negativity and P300 amplitude in healthy volunteers (Oranje et al. 2000). To investigate whether ketamine induced these schizophrenia-like anomalies by its agonistic effect on dopaminergic D₄ receptors, healthy volunteers were pretreated with haloperidol (D₂ receptor antagonist) in the present study before they were treated with ketamine, after which they were tested in a selective attention paradigm. The hypothesis was that if ketamine had disrupted processing negativity and P300 amplitude in the previous study by its effect on D₂ receptors, then pretreatment with haloperidol would prevent these disruptions. Plasma prolactin and homovanillic acid (HVA) were assessed, to monitor the effects of haloperidol in the central nervous system.

Methods

Subjects

Healthy male volunteers were recruited through university newspaper advertisements. Only physically healthy subjects without personal or family history in first-degree relatives of psychiatric illness were included. The study was approved by the Human Ethics Board of the University Medical Center Utrecht, with respect to the statements for human research from Helsinki (Amendment of South Africa from 1996). After receiving written and oral information, written informed consent was obtained from all subjects before enrolment in the study. Subsequently, the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al. 1992) and the Schedule for Affective Disorders and Schizophrenia – Lifetime version (SADS-L; Endicott & Spitzer, 1978) were assessed, to ascertain absence of psychiatric illnesses. Furthermore, subjects received a full physical examination including an electrocardiogram and routine laboratory tests (complete blood count, urine analysis and a urine toxicology screen for drug use). Finally, volunteers were screened for hearing deficits by using an audiometer at 500, 1000 and 6000 Hz. Volunteers who could not detect tones at 20 dB were excluded. Eighteen...
subjects proceeded to the active phase of the study. Subjects had a mean age of 23.1 yr (S.D. = 2.98 yr) and a mean weight of 75.8 kg (S.D. = 8.24 kg).

Experimental design

In a randomized, double-blind, placebo-controlled cross-over experiment subjects received either ketamine (placebo/ketamine treatment), haloperidol followed by ketamine (haloperidol/ketamine treatment) or placebo (placebo/placebo treatment) on three separate occasions, a minimum of 1 wk apart. Two placebos were used: one for ketamine and one for haloperidol. Psychophysiological (see below), endocrine (prolactin and cortisol), ketamine plasma levels, physiological (blood pressure and heart rate), biochemical (HVA) and behavioural measures were collected over a 4.5-h period during each session. In addition, three psychometric tests were assessed: the Brief Psychiatric Rating Scale (BPRS), the Profile of Mood Scale (POMS) and the Visual Analog mood Scale (VAS).

Subjects arrived at the research ward of the Department of Psychiatry, University Hospital Utrecht at 08:15 hours, having fasted since 23:00 hours the preceding day. Two in-dwelling venous catheters were inserted into the antecubital vein of each arm. Each catheter was prevented from blood clotting by infusion of 1 ml heparin (100 U/ml) after each blood sample. At 08:45 hours an opaque capsule containing either 2 mg haloperidol (on a haloperidol/ketamine test day) or placebo was administered (orally). At 10:00 hours, infusion with either ketamine or placebo (Ringer’s solution) was started through one of the intravenous catheters using an IVAC 711 automatic infusion pump. Ketamine was infused in the following amounts and time-frames: 0.3 mg/kg during the loading phase (first 40 min), 0.0495 mg/kg during the next 10 min, and 0.213 mg/kg for the sustaining phase (last 85 min). The purpose of the sustaining phase was to achieve a pseudo-steady-state concentration (see also van Berckel et al. 1998). At 10:45 hours the subjects were brought to a soundproof, electrically shielded experimental cabin, where they were seated in a dentist’s chair. To prevent data contamination with movement of head or neck a vacuum cushion was attached to the top of the chair, to restrain the subject’s head. At 11:00 hours the psychophysiological tests commenced.

During each test session three tasks were presented: a prepulse inhibition of the startle reflex (PPI) paradigm, a P50 suppression paradigm and an auditory selective-attention paradigm. The results regarding PPI, P50 suppression and the psychometric tests have been presented elsewhere (Oranje et al. 2002). The order of the tasks was balanced across subjects. Blood samples, immediately followed by the physiological assessments, were collected at 0, 60, 90, 120, 150, 175, 210 and 270 min after administration of the capsule with haloperidol or placebo. The blood samples were collected in 10-ml plastic tubes containing EDTA. They were centrifuged (10 min at 3000 rev/min at 4 °C) and stored at −80 °C until the time of the assays.

Signal recording

Electroencephalogram (EEG) recordings were made with an electrocap (tin electrodes) from 31 scalp locations (10–20 system). However, only data from the electrodes relevant for the present study were analysed, i.e. where the maximum activity for the ERPs measured was to be expected: the midline electrodes Fz (for processing negativity) and Pz [for P300 (P3b) amplitude]. The left mastoid was used as a reference. Horizontal electro-occulogram (EOG) recordings were made from tin electrodes placed to the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes placed infra-orbitally and supra-orbitally to the left eye. The right eye was used for electromyography (EMG) measurement of the orbiculus oculi. For all signal recordings a ground electrode was attached to the middle of the forehead. Impedance was kept <5 kΩ. EEG and EOG signals were recorded with a time constant set to 5 s, EMG signals with a time constant set to 50 ms. Sampling started as soon as an experimental block started, and lasted until the end of it (continuous recording). All signals were digitized online by a computer, at a rate of 4 kHz.

Task

The selective attention task (see also Jonkman et al. 1997) consisted of 300 stimuli presented in such a way that stimuli randomly appeared in either the right or the left ear. Two types of stimuli were presented: standard tones (80%) and deviant tones (20%). The stimulus type (standard or deviant) was defined by tone frequency (either 1000 Hz or 1100 Hz) and was balanced across subjects. The duration of a stimulus (95 dB) was 50 ms, the interstimulus intervals (ISIs) were randomized between 750 ms and 1000 ms. The stimuli were evenly presented to the left or right ear (attended deviants were never presented immediately following each other). The subject was instructed to push a button as fast as possible on detection of the deviant tone in a previously designated ear. The order of ear designation was balanced randomly across the
subjects. After this initial task the subjects were presented the next auditory selective-attention task in which they had to monitor the other ear for deviant stimuli. During the task, the subjects had to maintain their gaze at a fixation cross in the middle of the computer screen. Task performance was measured by means of the percentages hits, false alarms and mean reaction time to hits. A response was considered a hit when it was given within a window of 200–1000 ms after stimulus presentation.

**Signal analysis**

EEG and EOG data of the selective attention task were analysed using Neuroscan software (Neuroscan, USA). First, all signals were baseline-corrected and filtered offline (30 Hz, 24 dB/octet digital low-pass). Second, the EEG was corrected for vertical EOG artifacts by subtracting vertical EOG from EEG epochs by a regression method in the time domain (Kenemans et al. 1991). Last, all EEG epochs containing artifacts (saturation of the A/D converter or amplitudes greater than −100 or 100 μV) were removed from the database. Processing negativity was expressed as the ERPs to the attended stimuli, subtracted with the ERPs to the unattended stimuli within each channel (i.e. for left and right ear separately). The data for processing negativity was pooled over left and right ears. One subject was excluded for processing negativity analysis for not showing processing negativity in the placebo session (amplitude > 0). The P300 amplitude was scored as the maximum amplitude between 300 ms and 600 ms, the processing negativity as the largest negativity between 150 ms and 350 ms.

**Ketamine and HVA plasma levels**

At the end of the experimental phase of the study, both the ketamine and plasma HVA assessments were carried out in a single assay by a technician blind to the sequence of treatment, at the end of the experimental phase of the study. The plasma level of prolactin was assessed by means of microparticle enzyme immunoassay (MEIA) technology: in the sampling centre, reactants and sample for one assay are transferred to a reaction vessel. The reaction vessel is transferred to the processing centre where reagents and sample are incubated to allow them to reach reaction temperature. The reagents and sample are combined, and the reaction mixture is transferred to an inert glass-fibre matrix. An alkaline phosphatase-labelled conjugate is added to the glass-fibre matrix prior to the addition of 4-methylumbelliferyl phosphate (MUP). The conjugate catalyses the hydrolysis of MUP to methylumbelliferone (MU). Measurement of the fluorescent MU as it is generated on the matrix is proportional to the concentration of the analyte in the test sample.

**Statistical analysis**

P300 amplitudes were analysed by means of planned comparisons using repeated-measures MANOVA (within-subject design). The three within factors were: ‘treatment’ (placebo/placebo, placebo/ketamine or haloperidol/ketamine), ‘attention’ (stimulus in attended channel or unattended channel) and ‘stimulus type’ (standard or deviant). If significant differences between treatments were revealed, further analysis was performed using repeated-measures MANOVA with within-factors ‘treatment’ (a combination of two), ‘attention’ and ‘stimulus type’. Similarly, repeated-measures MANOVA with within-factor ‘treatment’ was used to analyse the data regarding the processing negativity. Further analysis was done using paired-sample Student’s t tests, whenever significant differences were revealed.

Repeated-measures MANOVA with within-factors ‘treatment’ and ‘performance’ (hits or false alarms) was used to analyse the performance data. If significant differences between treatments were revealed, paired-sample Student’s t tests were used for further analysis.

Biochemical (ketamine and HVA) and endocrine (prolactin) parameters were analysed by MANOVA with repeated measures (within-factors ‘time’ and ‘treatment’).

**Results**

**Endocrinology**

Baseline (t = 0) plasma levels of prolactin did not differ across the three treatments. The MANOVA revealed
significant main effects of treatment $[F(2, 30) = 25.86, p < 0.001]$ and time $[F(7, 105) = 13.09, p < 0.001]$ as well as a treatment × time interaction $[F(14, 210) = 11.22, p < 0.001]$. Further analysis using Student’s $t$ tests revealed a significant increase in prolactin level from 120 min after administration of haloperidol to the end of the test day in the haloperidol/ketamine treatment. No further effects of treatment were found (Fig. 1).

Biochemical measures

To examine whether the plasma ketamine levels were comparable for both ketamine treatments a MANOVA was performed with within-factors time and treatment (placebo/ketamine and haloperidol/ketamine): no significant effects of treatment were found $[F(1, 16) = 0.003, p = 0.958]$. A rapid increase in plasma ketamine concentration, which reached a pseudo-steady-state concentration [between 116 ng/ml (S.D. = 4.6) and 122 ng/ml (S.D. = 5.5)] after 150 min, was found in the placebo/ketamine and haloperidol/ketamine treatments, respectively. One hour after cessation of the infusion period the plasma level of ketamine declined to 75 ng/ml in both treatments (Fig. 2).

No effect of treatment was found on HVA plasma level: neither baseline ($t = 0$) plasma level nor plasma levels at later stages differed between the placebo/placebo, placebo/ketamine or haloperidol/ketamine treatments (Fig. 3).

Performance

Group means are presented in Table 1. A significant treatment × performance interaction (number of hits and false alarms) was found $[F(2, 34) = 3.30, p < 0.05]$. Further testing with paired-sample Student’s $t$ tests revealed a significantly reduced number of hits for the haloperidol/ketamine treatment when compared to placebo/placebo ($t = 3.02, p < 0.01$), but not with placebo/ketamine. No effect of treatment was found on reaction time.

ERP data

Grand-average ERPs and processing negativity for the three different treatments are presented in Figs 4 and 5. The mean amplitudes of P300 and processing negativity are presented in Table 2.

P300

A treatment main effect $[F(2, 16) = 9.10, p < 0.005]$, an attention main effect $[F(1, 17) = 64.48, p < 0.001]$,
a stimulus type main effect \( F(1, 17) = 54.38, p < 0.001 \), a treatment \( \times \) stimulus type interaction effect \( F(2, 16) = 4.33, p < 0.05 \) and an attention \( \times \) stimulus type interaction effect \( F(1, 17) = 99.12, p < 0.001 \) were found. Further analysis of the treatment effects in the combination placebo/placebo and placebo/ketamine revealed a treatment main effect \( F(1, 17) = 12.61, p < 0.005 \) and a treatment \( \times \) stimulus interaction \( F(1, 17) = 9.19, p < 0.01 \), indicating a reduced P300 amplitude in the ketamine/placebo treatment, which was more pronounced for deviant than for standard stimuli, irrespective of attention.

Similarly, the combination placebo/placebo and haloperidol/ketamine revealed a treatment main effect \( F(1, 17) = 12.16, p < 0.005 \) and a treatment \( \times \) attention \( \times \) stimulus type second-order interaction \( F(1, 17) = 4.93, p < 0.05 \), indicating a reduced P300 amplitude in the haloperidol/ketamine treatment, which was more pronounced for deviant than for standard stimuli, and for non-attended than for attended stimuli. No significant differences in P300 amplitude were found between placebo/ketamine and haloperidol/ketamine treatments.

Processing negativity

Processing negativity \( F(1, 16) = 206.79, p < 0.001 \) was found, irrespective of treatment (expressed as a difference from zero), indicating enhanced processing activity of stimuli in the attended channel. In addition, a treatment main effect was found for processing negativity \( F(2, 32) = 3.70, p < 0.05 \). Further analysis of this treatment main effect revealed significantly reduced processing negativity in the placebo/ketamine treatment when compared to both the placebo/placebo \( t = 3.43, p < 0.005 \) and haloperidol/ketamine \( t = 2.25, p < 0.05 \) treatments. No significant difference was found between the placebo/placebo and haloperidol/ketamine treatments.

Behaviour, mood and other responses

In essence, subjects reported the same phenomena in behaviour, mood and other psychological responses as described in our previous study (van Berckel et al. 1998). All subjects could distinguish between the three test days, but they remained awake and cooperative. Ketamine induced several side-effects, in general starting between 10 min and a maximum of 75 min
after start of the infusion. At the end of the loading dose, all subjects reported mild analgesia in fingertips and lips, vision problems, coordination difficulties and vertigo. The vision problems were best described as difficulties in the speed and accuracy of focusing. Several subjects reported changes in their perception of the room, like ‘the ceiling appears lower’ and ‘the walls are further apart’. One subject reported having the feeling that he was sitting in a roller-coaster, going up and down (thoroughly enjoying the sensation!), while another subject reached such a loss of impulse control that he started singing loudly. Coordination difficulties consisted of problems in writing and walking. Subjects reported problems with keeping their balance and adjusting their steps to the height of the doorsteps; in writing there were problems with finding the right line. In general, subjects compared the sensation of ketamine with being drunk, although they all remarked that the feeling was not quite the same. In contrast to the first study, none of the subjects complained of nausea, and all subjects were able to complete the study. All effects rapidly disappeared after discontinuation of ketamine infusion.

Discussion

To our knowledge, this is the first human study in which both the effects of ketamine alone (placebo/ketamine) and the effects of pretreatment with haloperidol and subsequent administration of ketamine (haloperidol/ketamine) on psychophysiological processes of attention in healthy volunteers were investigated. Placebo/ketamine reduced both processing negativity and P300 amplitude, while having no effect on task performance. In contrast to the P300 amplitude, the disruptive effect of ketamine on processing negativity could be prevented by pretreatment with haloperidol. In addition, reduced task performance was found in the haloperidol/ketamine treatment. No significant differences were found in task performance between the placebo/placebo and placebo/ketamine treatments (i.e. the reaction times and number of hits and false alarms were the same in both treatments), which is consistent with the results of our first study on the effects of ketamine on human selective attention (Oranje et al. 2000). However, the combination of pretreatment with haloperidol and subsequent ketamine administration resulted in a significantly decreased number of hits, which suggests that haloperidol is responsible for this effect. In similar dichotic monitoring tasks a reduction of dopaminergic activity by administration of droperidol (an anaesthetic, with high affinity for dopamine receptors) to

Table 2. Mean P300 amplitudes for lead Pz in µV per channel and stimulus type, and processing negativity amplitude for lead Fz in µV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Attended Standards</th>
<th>Attended Deviants</th>
<th>Non-attended Standards</th>
<th>Non-attended Deviants</th>
<th>Processing negativity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/placebo</td>
<td>3.41 (0.38)</td>
<td>11.23 (1.05)</td>
<td>3.37 (0.42)</td>
<td>5.78 (0.48)</td>
<td>−3.95 (0.34)</td>
</tr>
<tr>
<td>Placebo/ketamine</td>
<td>2.57 (0.20)**</td>
<td>9.99 (0.87)**</td>
<td>2.80 (0.40)**</td>
<td>3.68 (0.47)****</td>
<td>−3.30 (0.27)*</td>
</tr>
<tr>
<td>Haloperidol/ketamine</td>
<td>2.33 (0.28)*</td>
<td>10.57 (1.08)*</td>
<td>2.75 (0.25)*</td>
<td>3.40 (0.45)***</td>
<td>−3.98 (0.27)</td>
</tr>
</tbody>
</table>

Values in parentheses are S.E.M.

Significantly reduced P300 amplitude compared to the placebo/placebo treatment: ** p < 0.01, * p < 0.05.

*Significantly reduced processing negativity amplitude compared to both the placebo/placebo (p < 0.005) and haloperidol/ketamine (p < 0.05) treatments.
healthy volunteers resulted in a significantly lower number of hits (Clark et al. 1987; Shelley et al. 1997), which seems to confirm our assumption that haloperidol is responsible for the decreased task performance in the present study. Haloperidol reduces metabolism in the frontal cortex (Holcomb et al. 1996; Wolkin et al. 1996), the cerebrum (Wolkin et al. 1996) and throughout the entire central nervous system (Bartlett et al. 1998). Furthermore, haloperidol reduced the binding of [11C]clozapine in striatum and frontal cortex in a PET study, indicating competition for D2 dopamine-binding sites not only in the striatum, but in the frontal cortical areas as well (Lundberg et al. 1989). In a recent review, it was suggested that dopaminergic activity in the prefrontal cortex (PFC) is of crucial importance in executive functions and working memory (Seamans & Yang, 2004). In summary, the effect of haloperidol on task performance as found in the present study is probably caused by reduced dopaminergic activity in the PFC, although it is unclear why ketamine’s agonistic effect on dopamine receptors did not prevent this from happening.

Increased P300 amplitude was found following deviant stimuli when compared to standard stimuli and following attended stimuli when compared to unattended stimuli, irrespective of treatment. These results are consistent with studies in which similar selective attention paradigms were used (e.g. Baribeau-Braun et al. 1983; Oranje et al. 2000; Ward et al. 1991). Both placebo/ketamine and the combination haloperidol/ketamine reduced P300 amplitude, especially in the case of deviant stimuli. Furthermore, haloperidol/ketamine reduced P300 for non-attended stimuli more than for the attended stimuli. The result that placebo/ketamine significantly reduced P300 amplitude in the present study, confirms both the results of our previous study (Oranje et al. 2000) and those of Watson et al. (2008). The absence of significant differences between the placebo/ketamine and haloperidol/ketamine treatments, suggests that the reduced P300 amplitude as found in the placebo/ketamine treatment is not the result of a ketamine-induced rise in dopaminergic D2 activity, but probably of ketamine’s effect on glutamatergic activity. The concept that P300 amplitude is not modulated by dopaminergic activity is consistent with earlier results from our laboratory, in which neither an effect of bromocriptine (selective D2 agonist) nor of l-dopa (precursor of dopamine) was found on P300 amplitude of healthy volunteers (Oranje et al. 2006). In addition, Luthringer et al. (1999) found no effects of apomorphine (D1 and D2 agonist) on P300 topography in healthy male volunteers. Furthermore, Coburn et al. (1998) found decreased amplitude and increased latency of P300 ERP in unmedicated patients with schizophrenia compared to healthy controls. Following a 6-wk treatment period with remoxipride or haloperidol (both D2 antagonists) they found a normalized P300 latency but a still decreased P300 amplitude. In addition, Oishi et al. (1996) found no effects of a dose of 50 mg (i.v.) on P300 amplitude in patients with Parkinson’s disease. Indeed, Frodl-Bauch et al. (1999) came to a similar conclusion in their review on the neurochemical substrates of P300, in which they suggested that the glutamatergic system plays an important role in the electrogensis of P300 amplitude, while the dopaminergic system plays only a minor role. (See also Javitt et al. 2008 for a review on biomarkers in schizophrenia.)

Processing negativity was found irrespective of treatment, indicating enhanced processing activity to stimuli in the attended channel. In the placebo/ketamine treatment, processing negativity amplitude was significantly reduced when compared to both the placebo/placebo and haloperidol/ketamine treatments. This is consistent with our previous study (Oranje et al. 2000) in which ketamine reduced processing negativity compared to placebo in healthy volunteers. No differences in processing negativity amplitude were found between placebo/placebo and haloperidol/ketamine. This seems to provide support for the concept that ketamine reduces processing negativity by means of its agonistic effect on dopaminergic D2 receptors (Kapur & Seeman, 2002; Seeman & Guan, 2008). This would imply that, in contrast to P300 amplitude, dopaminergic D2 activity is involved in processing negativity. Indeed, administration of droperidol led to a near significant drop in processing negativity in the study of Shelley et al. (1997). In another study haloperidol was found to decrease middle latency (300–500 ms) processing negativity only, without affecting early (100–300 ms) or late (500–700 ms) latency processing negativity at Fz (Kahkonen et al. 2001). However, it remains unclear why we found neither an effect of l-dopa nor of bromocriptine on processing negativity in healthy volunteers in an earlier study (Oranje et al. 2006).

There are some limitations to this study. The goal of this study was to investigate whether haloperidol would reduce the disruptive effects of ketamine on human selective attention, not to study the effects of this antipsychotic by itself. Therefore, and to reduce eventual test effects and strain on the subjects, it was decided to omit the haloperidol/placebo condition. Thus, only data on the effect of ketamine alone, and the combined effect of haloperidol and ketamine are
available, which limits the conclusions that can be drawn. For this reason, it is unclear whether the effects of haloperidol and ketamine simply add up, or show a more complex interaction with each other. A further limitation might be the small sample size. However, the current results confirm those of our previous study on the effects of ketamine on processing negativity and P300 amplitude. Furthermore, the amplitudes of processing negativity are identical to the first decimal in the placebo/placebo and haloperidol/ketamine treatments, which is a further indication that these results were not affected by a small sample size. However, the results on P300 amplitude, might change with a bigger sample size and therefore need to be considered with the necessary caution.

To summarize, the combined effects of haloperidol and ketamine reduced task performance in healthy subjects. Since ketamine alone did not disrupt task performance, this effect seems solely attributable to the effect of haloperidol, probably by reducing prefrontal dopaminergic activity. Furthermore, ketamine induced reductions in both P300 amplitude and processing negativity in healthy subjects. In contrast to P300 amplitude, the disruptive effects of ketamine on processing negativity could be prevented by pretreatment with haloperidol. The current results suggest that ketamine reduced P300 amplitude by its antagonistic effect on glutamatergic activity, while it reduced processing negativity by its agonistic effect on dopaminergic D2 activity.

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None.

Statement of Interest

None.

References


