Glutamatergic Modulation of Auditory Information Processing in the Human Brain

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Background: Auditory mismatch negativity (MMN) and P300 event-related potentials (ERPs) are reduced in schizophrenia patients and healthy volunteers administered the *N*-methyl-D-aspartate glutamate receptor antagonist, ketamine. In rodents, *N*-acetylcysteine (NAC), a stimulator of the cystine-glutamate exchanger, attenuates the cognitive and behavioral effects of *N*-methyl-D-aspartate receptor antagonists. On the basis of these findings, we tested whether NAC would reduce ketamine effects on behavior, MMN, and P300 in healthy humans.

Methods: This randomized, double-blind, placebo-controlled study consisted of 2 test days during which subjects ($n = 16$) were administered oral NAC (3000 mg in divided doses) or matching placebo 165 min before the infusion of saline and then ketamine (as a bolus of .23 mg/kg over 1 min followed by .58 mg/kg for 30 min, and then .29 mg/kg for 40 min) in a fixed order. Behavioral and ERP data including auditory MMN and P300 were collected during each test day.

Results: Ketamine produced psychotic-like positive symptoms, reductions in working memory and sustained attention performance, and amplitude reductions for the frequency- and intensity-deviant MMNs and P300. NAC pretreatment did not reduce the behavioral or ERP effects of ketamine. In addition, NAC reduced frequency-deviant MMN amplitude and increased target and novelty P3 amplitudes. The decrements in frequency-deviant MMN amplitude produced by ketamine and NAC were not additive.

Conclusions: NAC did not attenuate the effects of ketamine in humans, in contrast to previous studies in animals. NAC merits further investigation as a cognitive enhancing agent due to its ability to increase the P300 amplitude.

Key Words: Glutamate, ketamine, MMN, *N*-acetylcysteine, NMDA, P300

The noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate (Glu) receptor antagonist ketamine produces cognitive and behavioral effects that bear resemblance to the features of schizophrenia (1–3). Several event-related potentials (ERPs) that are reduced in schizophrenia, including mismatch negativity (MMN) (4,5) and P300 (6–11), seem sensitive to the effects of ketamine (12–15).

Event-related potentials provide a quantitative assessment of neural activity. Mismatch negativity is a negative voltage deflection in the auditory ERP that peaks approximately 100–150 msec after any discriminable deviant sound occurring during a series of repeated standard sounds (16). The MMN is automatically elicited by deviant sounds, even when attention is directed away from the auditory channel.

The P300 is a positive voltage deflection that peaks approximately 300 msec after the presentation of an infrequent target, novel, or otherwise salient stimulus. The P300 amplitude is thought to reflect attentional resource allocation (17,18), phasic attentional shifts (19), working memory updating of stimulus context (20,21), or stimulus salience (22,23). Its latency is thought to reflect processing speed or efficiency during stimulus evaluation (24). P3b is the P300 elicited by infrequent task-relevant target stimuli and reflects top-down allocation of attentional resources with a parietal scalp maximum. P3a is the P300 elicited by infrequent task-irrelevant deviant stimuli, which are either novel or otherwise salient (25–27). It reflects "bottom-up" orienting of attentional resources with a frontocentral scalp maximum (28).

Because ketamine induces symptoms and cognitive and electrophysiological abnormalities that are similar to those observed in schizophrenia, agents that attenuate the effects of ketamine in humans are of interest for drug development (29). Drugs enhancing the activity of the cystine-Glu exchanger have been proposed as an exemplar of this approach (30). The cystine-Glu exchanger is expressed primarily in glial cells but also in neurons (31,32) where it exchanges intracellular Glu for extracellular cystine (Figure 1). This nonvesicular release of Glu into the extracellular space stimulates the presynaptic metabotropic Glu receptors (mGluR2/3) (33,34) that function as autoreceptors and inhibit Glu release (35,36).

Baker *et al.* (30) reported that stimulation of the cystine-Glu exchanger by *N*-acetylcysteine (NAC) attenuated the behavioral and cognitive effects of phencyclidine, a potent noncompetitive NMDA receptor antagonist. NAC delivers cysteine that is oxidized to cystine in the extracellular space. The supply of cystine to the cells is a rate-limiting step for the synthesis of glutathione, a major antioxidant. Given reduced glutathione concentrations in the cerebrospinal fluid and prefrontal cortex in schizophrenia (37), stimulation of the cystine-Glu exchanger by NAC might be beneficial in this disorder (38). In a clinical trial, NAC augmentation reduced symptoms (30), and another study reported increase in MMN amplitude (39) in schizophrenia patients.

Our goal was to determine whether NAC pretreatment would attenuate the effects of ketamine on behavior, cognitive function, and ERPs in healthy humans. We predicted that ketamine would increase positive and negative symptoms, reduce working memory and sustained attention performance, and decrease MMN and P300. We also predicted, on the basis of the aforementioned pre-

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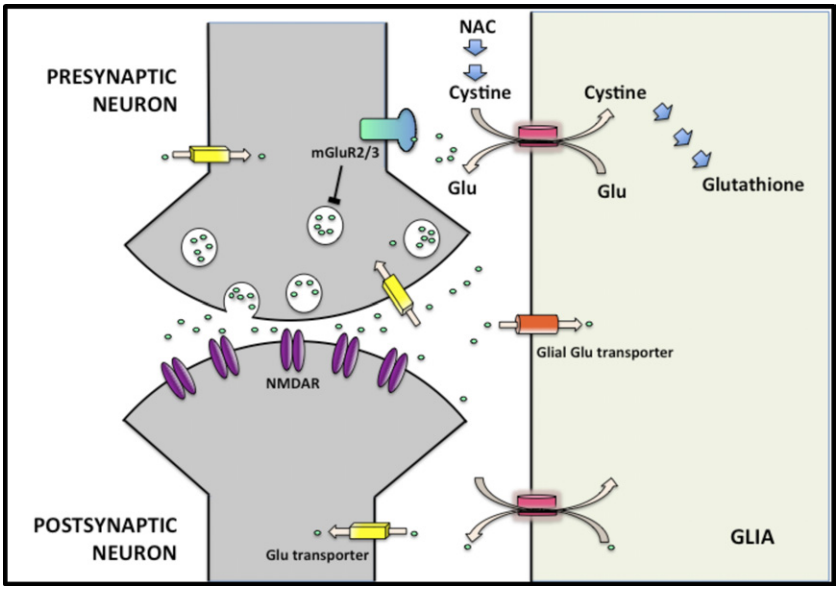

Figure 1. The interaction between the glial cystine–glutamate (Glu) exchanger and presynaptic mGluR2/3. *N*-acetylcysteine (NAC) activates the exchanger by supplying cystine, which leads to increased Glu in the extracellular space. This stimulates the mGluR2/3 and reduces synaptic release of Glu (Baker *et al.* [30]). In addition, by enhancing cystine uptake, NAC promotes the synthesis of glutathione, which is a major antioxidant (Himi *et al.* [75]). Note that the cystine-Glu exchanger is also expressed on cortical neurons, although subcellular localization of the exchanger has not been well-characterized (Burdo *et al.* [31]). Blue arrows, chemical reaction/effect; line with bar, inhibition; pink arrows, transport. NMDAR, *N*-methyl-D-aspartate receptor. Reprinted from (57), with permission from Elsevier, copyright 2009.

clinical findings, that NAC pretreatment would attenuate the effects of ketamine.

Methods and Materials

Subjects

The study was approved by the institutional review boards of Yale Medical School and the Veterans Administration Connecticut Healthcare System. Healthy volunteers were recruited by advertisements. All subjects gave written informed consent. They had no personal or family history of psychiatric or substance abuse disorders as determined by Structured Clinical Interview for DSM-IV, Non-Patient Edition. Additionally, a family member or friend was contacted to verify the information about the participant. Subjects were instructed to abstain from psychoactive substance use for the duration of the study, including 1 week before and after. A majority of the subjects were nonsmokers (14 of 16). The 2 smokers (1–2 cigarettes/day) did not smoke on the test days and showed no signs of withdrawal. Urine toxicology and pregnancy tests were performed on each study day. Women were studied during the follicular phase of their menstrual cycle (40,41).

Study Design

This was a double-blind, placebo-controlled study, consisting of 2 test days, where subjects were randomized to active NAC on one day and placebo NAC on the other test day. Due to the potent effects of ketamine, blinding of ketamine was not possible. The test days were at least 3 days apart (median: 7 days; 3 minimum, 65 maximum). The NAC and placebo capsules were administered orally in divided doses: 2000 mg followed by 1000 mg 2 hours later. Each morning, 165 min after NAC or placebo administration, subjects received a 1-min bolus of normal saline, followed by a 70-min-long saline infusion during which behavioral, cognitive, and ERP data were collected. The order of tests were fixed and included the following: spatial working memory (SWM), rapid visual processing (RVP), P300, MMN, Positive and Negative Syndrome Scale (42–44) general and positive and negative subscales, the Clinical Administered Dissociative States Scale (CADSS) (45), and a Visual Analog Scale of mood states (VAS). The modified PANSS (general) was administered at baseline and end of the test day (exit interview). Ketamine was administered intravenously as a bolus of .23 mg/kg over 1 min followed by .58 mg/kg for 30 min (SPM and RVP), and then .29 mg/kg for 40 min (P300 and MMN). The PANSS subscales, CADSS, and VAS were collected immediately after ketamine infusion.

Cognitive Measures

Cognitive performance was assessed with SWM and RVP tasks administered with a computerized cognitive assessment battery (46). Working memory and attention have been consistently shown to be impaired in schizophrenia (47,48) and in healthy volunteers administered ketamine (43). The SWM is a test of SWM and strategy performance. The RVP is a test of visual sustained attention with a small working memory component. Details on these tests are available in Supplement 1.

ERP Tasks

Subjects were seated in comfortable chairs in front of a liquid crystal display video screen in an acoustically shielded, dimly lit testing chamber. They were monitored by video and could interact with the research assistant. The responses of the subjects were continuously monitored on a screen outside the chamber for drowsiness and task performance. Electroencephalographic data were recorded with Neuroscan Synamps amplifiers with a 1000-Hz sampling rate and a bandpass filter of .05–100 Hz. For further information, please see Supplement 1.

The MMN paradigm, which was adapted from Näätänen *et al.* (49) comprised three runs, each including frequent (50 % probability) standard tones and three types of infrequent deviant tones (16.7% probability for each type) presented every 500 msec. Details of the MMN paradigm are available in Supplement 1.

The auditory oddball (P300) paradigm included three runs, each containing a pseudo-random sequence of 150 stimuli comprising 120 standards (80%), 15 targets (10%), and 15 novels (10%) presented with a stimulus onset asynchrony of 1250 msec. For more information on the P300 paradigm, please see Supplement 1. The ERP data and signal processing methods are also detailed in Supplement 1.

Physiological Measures/Adverse Events

Blood pressure and heart rate were monitored at regular intervals. Adverse events were monitored before and after each test

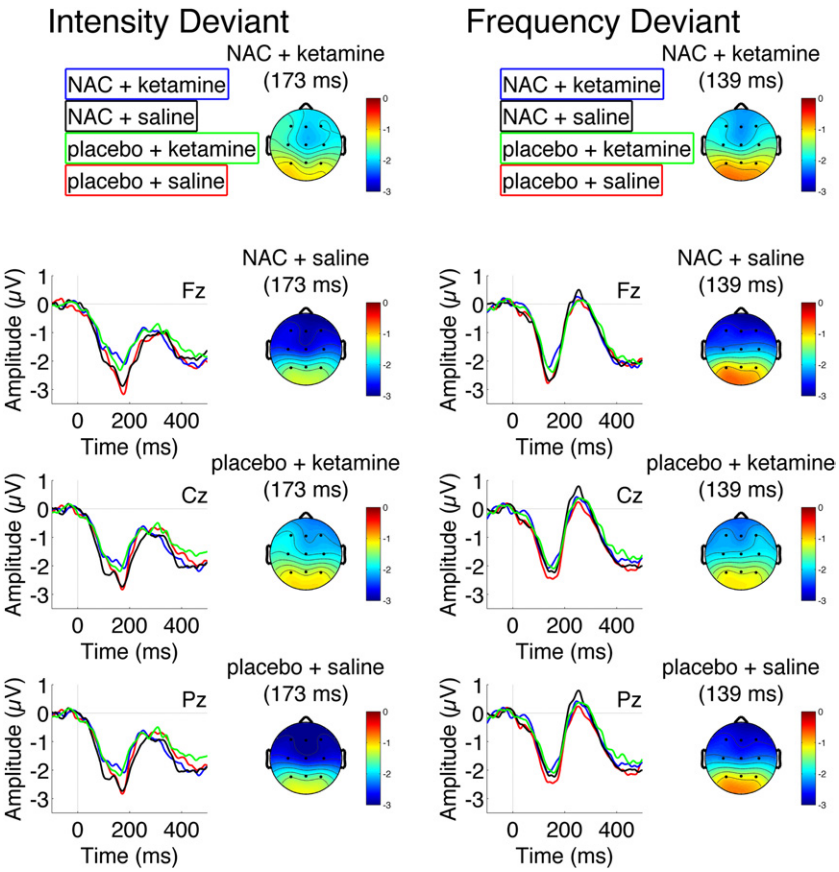

Figure 2. Grand average difference wave event-related potentials for Intensity (left) and Frequency (right) deviants are plotted from electrodes Fz, Cz, and Pz to show interactive effects of *N*-acetylcysteine (NAC) and ketamine on auditory mismatch negativity amplitude. Time is shown in milliseconds on the x-axis and amplitude in microVolts on the y-axis. Scalp topographic maps of mismatch negativity amplitude are shown for the negative peak chosen from the grand average across all conditions at electrode Cz for Intensity (173 msec) and Frequency (139 msec) deviants.

session. Ketamine levels were collected 10 min into each infusion. Long-term safety assessments were completed at 1 week and 3 and 6 months after study completion.

Statistical Analysis

All variables were examined for normality with normal probability plots and Kolmogorov-Smirnov test statistics. Because of the skewed distributions of the SWM task performance and other behavioral data, nonparametric analyses were performed (50). The raw behavioral data were first converted into ranks and then were entered into a mixed model with NAC (active vs. placebo) and time (baseline, saline, ketamine, and exit) as within-subject factors and subject as the clustering factor. The variance-covariance structure was unconstrained. Of main interest in all analyses was the NAC (NAC vs. placebo) × ketamine (saline vs. ketamine) interaction. Contrasts were used to parse any significant interactions or main effects. The overall alpha level for each scale (PANSS, CADSS, VAS) was fixed at $p = .05$. We used Bonferroni corrections for testing subscales (e.g., PANSS positive and negative symptom subscales). Because this is an entirely within-subject design, we have not controlled for between-subject factors (such as education and gender). All other outcome measures conformed to normality, so they were analyzed without the use of any transformations, with linear mixed models with NAC (active vs. placebo) and ketamine (saline vs. ketamine) as within-subject factors, subject as a random effect and an unstructured variance-covariance matrix for condition within subject. The same post hoc testing procedure as described in the preceding text was used to parse any observed significant interactions and main effects. Bonferroni correction for six RVP measures was applied. Order effects were considered, but they were dropped from the models because they were not significant. Alternative correlation structures were also considered but dismissed because they did not fit the data as well according to Schwartz Bayesian Criterion.

ERP Data Analysis

The ERP data from the MMN and P300 paradigms were normally distributed. For the MMN data, a mixed model was fitted to examine the effects of NAC, ketamine, and their interaction on MMN amplitude. The fixed factors were NAC (NAC vs. placebo), ketamine (ketamine vs. saline), stimulus type (intensity, frequency, duration) and electrode (Fz, Cz, Pz). For the P300 paradigm, a separate mixed model was fitted to examine the effects of NAC, ketamine, and their interaction on P300 amplitude to targets and novels. The fixed factors were NAC (active vs. placebo), ketamine (ketamine vs. saline), stimulus type (target vs. novel), and electrode (Fz, Cz, Pz). In both models, all possible interactions among the fixed factors were considered, and backward elimination procedure was used to drop nonsignificant effects under the constraint that at each step the model had to be hierarchically well-formulated. Because the NAC × ketamine interaction was of utmost interest, it was always kept in the models regardless of significance. Both models included a random effect for subject, a NAC × ketamine within-subjects effect, and a structured variance-covariance matrix across electrodes and stimulus types. The best-fitting variance-covariance structure was selected on the basis of Schwartz Bayesian Criterion. To explain significant interactions in the model, post hoc contrasts were performed.

Results

The subjects were healthy volunteers with a mean age of 27 ± 5.6 years, 13 men and 3 women, all right-handed, with mean edu-

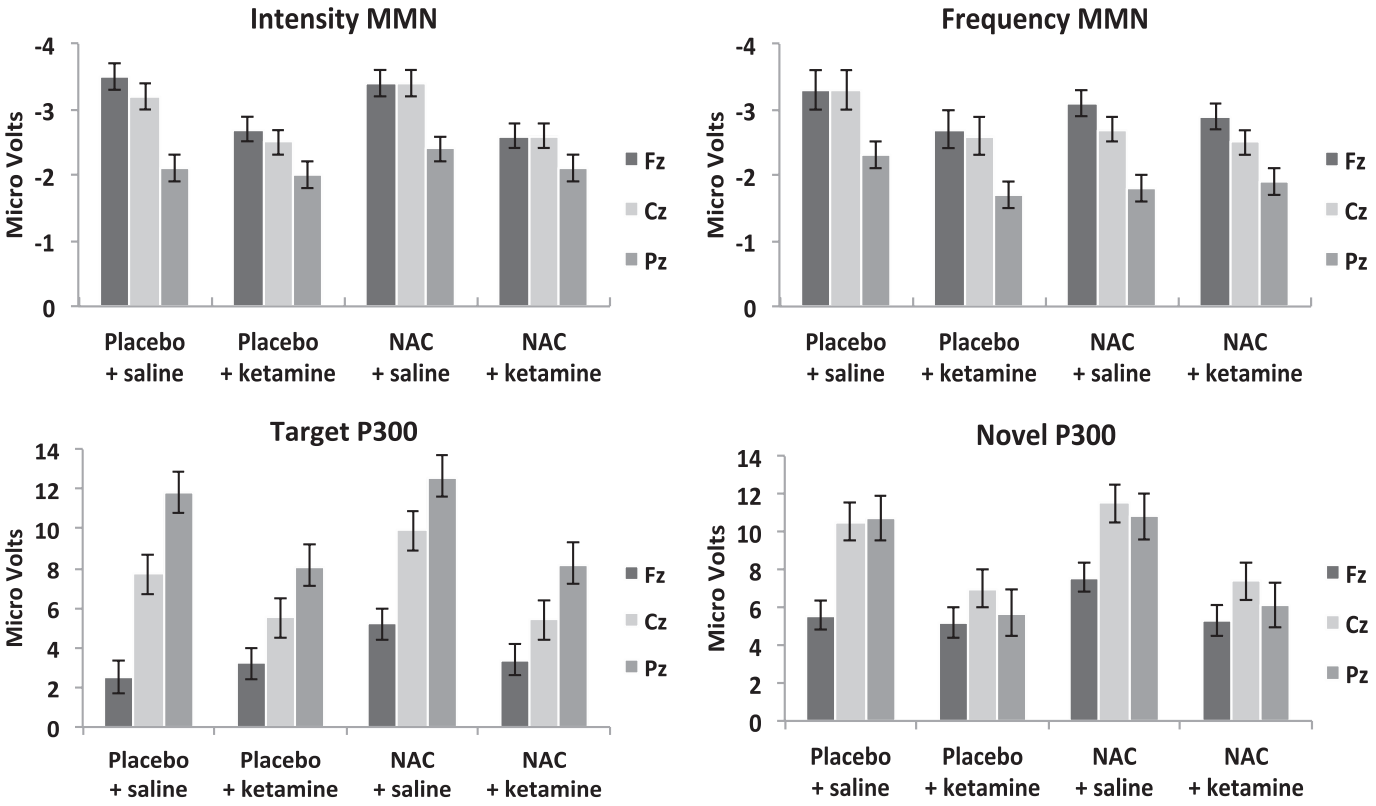

Figure 3. Interactive effects *N*-acetylcysteine (NAC) and ketamine on mismatch negativity (MMN) amplitude (intensity and frequency deviants) and auditory P300 (target and novel stimuli) shown as least square means and standard errors across conditions.

cation of 16.8 ± 2.2 years and estimated IQ of 118.9 ± 12.1 as measured by the National Adult Reading Test (NART). Fourteen of the subjects were Caucasian, one was Native-American, and one was Hispanic. A total of 43 subjects consented; 21 of them never initiated the study due to ineligibility or scheduling conflicts, and 6 subjects dropped out. Sixteen subjects completed the study procedures. There were no serious adverse events. Four subjects reported mild nausea after the ketamine bolus but were no longer nauseated by the time data collection was initiated. Plasma ketamine levels did not differ significantly between the active (mean 75.7 ± 32 ng/mL) and placebo NAC (mean 66.4 ± 23.8 ng/mL) days [$F(1,12) = 3.33$, $p = .10$]. Ketamine led to significant increases in blood pressure and heart rate (all $p < .001$). The effect of ketamine on the vital sign changes did not differ significantly between the placebo and active NAC test days (all $p > .5$).

Behavioral Results

Ketamine increased PANSS positive symptom scores [analysis of variance type statistic (ATS)(2.1) = 119.6, $p < .0001$] but did not affect PANSS negative symptoms [ATS(1) = 1.1, $p = .31$]. NAC did not produce positive or negative symptoms and did not modulate ketamine effects on PANSS positive symptoms [NAC × time: ATS(2.1) = .90, $p = .41$]. For PANSS negative symptoms, there was a significant NAC × time interaction [ATS(1) = 6.58, $p = .01$], where PANSS negative symptoms were higher at exit than at baseline on the NAC day [ATS(1) = 4.15, $p = .04$], but the difference between baseline and exit values did not survive correction for multiple testing.

Analysis of CADSS clinician-rated items revealed that ketamine increased dissociative symptoms [Time ATS(1.4) = 180.1, $p < .0001$], with significant post hoc comparisons of ketamine with other conditions (all $p < .0001$); however, there were no differences in these increases due to NAC [NAC × time, ATS(1.0) = .13, $p = .73$]. The CADSS self-rated items showed a similar pattern of results with only a significant time effect [ATS(1.6) = 159.0, $p < .0001$], indicating higher scores during ketamine than during saline, baseline, and postketamine assessments (all p values $< .0001$). The CADSS self-rated scores during saline were also significantly higher than during baseline and exit (both p values = .002), but there were no differences in these increases due to NAC [NAC × time, ATS(1.5) = .52, $p = .54$].

For VAS anxiety scores, only a significant time effect was observed [ATS(2.0) = 9.8, $p < .0001$]. The VAS anxiety scores at postketamine were significantly lower than VAS anxiety scores during baseline, saline, and ketamine assessments (all p values $< .0001$). There were no significant differences due to NAC [NAC × time, ATS(2.2) = .23, $p = .82$]. The VAS euphoria scores showed only a significant time effect [ATS(2.2) = 35.8, $p < .0001$] where higher scores were found during ketamine infusion than during baseline, saline, and postketamine assessments (all p values $< .0001$). There were no significant differences due to NAC [NAC × time, ATS(2.6) = .88, $p = .43$].

Cognitive Tests

For SWM "between searches error" (eight boxes, defined as occasions upon which the subject revisits a box in which a token has previously been found), a significant ketamine effect was observed [ATS(1) = 3.8, $p = .05$], which did not survive correction for multiple tests. The SWM between searches error scores during ketamine were higher than during saline. The NAC × ketamine interaction was not significant [ATS(1) = 2.6, $p = .11$]. The SWM "within search error" (eight boxes, defined as the number of errors made within a search [i.e., repeated responses to a box previously opened and shown

Table 1. Medication Effects on Mean Peak Amplitudes of P300 and MMN Difference Waves at Midline Electrodes

	Placebo+Saline	Placebo+Ketamine	NAC+Saline	NAC+Ketamine
P300				
Targets				
Fz	2.5 ± .8	3.2 ± .8	5.2 ± .8	3.4 ± .8
Cz	7.7 ± 1.0	5.5 ± 1.0	9.9 ± 1.0	5.4 ± 1.0
Pz	11.8 ± 1.1	8.1 ± 1.1	12.6 ± 1.1	8.2 ± 1.1
Novels				
Fz	5.6 ± .8	5.2 ± .8	7.6 ± .8	5.3 ± .8
Cz	10.5 ± 1.0	7.0 ± 1.0	11.5 ± 1.0	7.4 ± 1.0
Pz	10.7 ± 1.2	5.7 ± 1.2	10.8 ± 1.2	6.1 ± 1.2
MMN				
Intensity				
Fz	−3.5 ± .2	−2.7 ± .2	−3.4 ± .2	−2.6 ± .2
Cz	−3.2 ± .2	−2.5 ± .2	−3.4 ± .2	−2.6 ± .2
Pz	−2.1 ± .2	−2.0 ± .2	−2.4 ± .2	−2.1 ± .2
Frequency				
Fz	−3.3 ± .3	−2.7 ± .3	−3.1 ± .2	−2.9 ± .2
Cz	−3.3 ± .3	−2.6 ± .3	−2.7 ± .2	−2.5 ± .2
Pz	−2.3 ± .2	−1.7 ± .2	−1.8 ± .2	−1.9 ± .2
Duration				
Fz	−3.2 ± .3	−3.1 ± .3	−3.2 ± .3	−2.8 ± .3
Cz	−3.1 ± .3	−3.1 ± .3	−3.3 ± .3	−2.8 ± .3
Pz	−2.4 ± .2	−2.3 ± .2	−2.4 ± .2	−2.1 ± .2

Medication effects on mean peak amplitudes (least squares means and standard errors) of P300 (target and novel), and MMN difference waves (intensity, frequency, and duration deviants) at midline electrodes (Fz, Cz, and Pz).

MMN, mismatch negativity; NAC, *N*-acetylcysteine.

to be empty]) showed a significant ketamine effect [ATS(1) = 11.7, p = .0006]. The SWM within search error scores during ketamine were higher than SWM within search error scores during saline. The NAC × ketamine interaction was not significant [ATS(1) = .15, p = .70].

The RVP A′ (a signal detection measure of sensitivity to errors) showed a significant ketamine effect [F(1,41) = 12.1, p = .001], where A′ was significantly lower (worse performance) on ketamine than on saline. The NAC × ketamine interaction was not significant [F(1,41) = 1.4, p = .25]. For the probability of "Hit," a significant ketamine effect was observed as well [F(1,41) = 13.0, p = .0008], where the probability of hit was significantly lower on ketamine than on saline. The NAC × ketamine interaction was not significant [F(1,41) = 1.7, p = .20]. Similarly, for RVP number of correct rejections, a significant ketamine effect was observed [F(1,41) = 4.9, p = .04] but failed correction for multiple tests. The RVP correct rejections during ketamine were decreased, compared with during saline. The NAC × ketamine interaction was not significant [F(1,41) = .3, p = .58].

ERP Results

MMN. We found no drug effects on the number of epochs for MMN deviants (all p values > .15). There was a significant NAC × ketamine × stimulus type interaction effect on MMN amplitude [F(2,494) = 5.91, p = .003]. Post hoc tests revealed significant NAC × ketamine interactions for the frequency [F(3,494) = 4.28, p = .005] and intensity [F(3,494) = 5.44, p = .001] but not the duration [F(3,494) = 1.1, p = .3] deviants (Figures 2 and 3, Table 1). Ketamine alone reduced MMN amplitude for the intensity deviant [F(1,494) = 7.3, p = .007]. The effect of ketamine on the intensity deviant remained significant [F(1,494) = 8.82, p = .003], despite pretreatment with NAC. Both NAC alone [F(1,494) = 5.43, p = .02] and ketamine alone [F(1,494) = 11, p = .001] reduced MMN amplitude for the frequency deviant. For the frequency deviant, the effect of NAC and ketamine given together was no different from the effect of NAC alone [F(1,494) = .26, p = .6] or that of ketamine alone [F(1,494) = .23, p = .6].

The Auditory Oddball (P300) Paradigm

Correct Responses and Reaction Times. There were no drug effects on the number of epochs for the P300 paradigm (statistics not performed due to limited variability). For percent correct responses to targets, there were no significant effects of ketamine [ATS(1) = 2.3, p = .13], NAC [ATS(1) = .02, p = .9], or NAC × ketamine interaction [ATS(1) = .02, p = .9]. For target reaction times, the findings were similar; there were no significant effects of ketamine [ATS(1) = 2.1, p = .15], NAC [ATS(1) = .15, p = .7], or NAC × ketamine interaction [ATS(1) = .14, p = .7].

P300. In the overall model, there was a significant ketamine effect [F(1,313) = 27.6, p < .0001], indicating that P300 amplitudes were smaller on ketamine than on saline (Table 1, Figures 3 and 4). This ketamine effect significantly depended on electrode (ketamine × electrode interaction [F(2,313) = 9.94, p < .001]), with the effect evident at Cz [F(1,313) = 23.4, p < .0001] and Pz [F(1,313) = 27.3, p < .0001] but not Fz [F(1,313) = 2.76, p = .1]. However, the ketamine effect did not significantly interact with the stimulus type [F(1,310) = .70, p = .40]. Similarly, the ketamine × electrode interaction did not significantly depend on stimulus type [F(2,310) = .31, p = .73], indicating that ketamine produced similar reductions in the amplitudes of both target P3a and novelty P3b at central and parietal sites (Figure 4). Although there was no main effect of NAC [F(1,313) = 1.83, p = .18], there was a significant NAC × ketamine interaction [F(1,313) = 5.58, p = .02] (Figures 3 and 4). Post hoc tests showed that NAC alone, relative to placebo, significantly increased P300 amplitudes [F(1,313) = 5.29, p = .02], an effect that did not significantly depend on stimulus type [F(1,300) = .46, p = .50], electrode [F(2,300) = .54, p = .58], or their interaction [F(2,300) = .45, p = .64], However, NAC pretreatment, relative to placebo, did not significantly modulate P300 amplitude during ketamine administration [F(1,313) = .01, p = .9]. Thus, despite the enhancing effect of NAC on P300, it did not prevent or attenuate the reduction of P300 amplitude of ketamine. Other significant effects included a stimulus

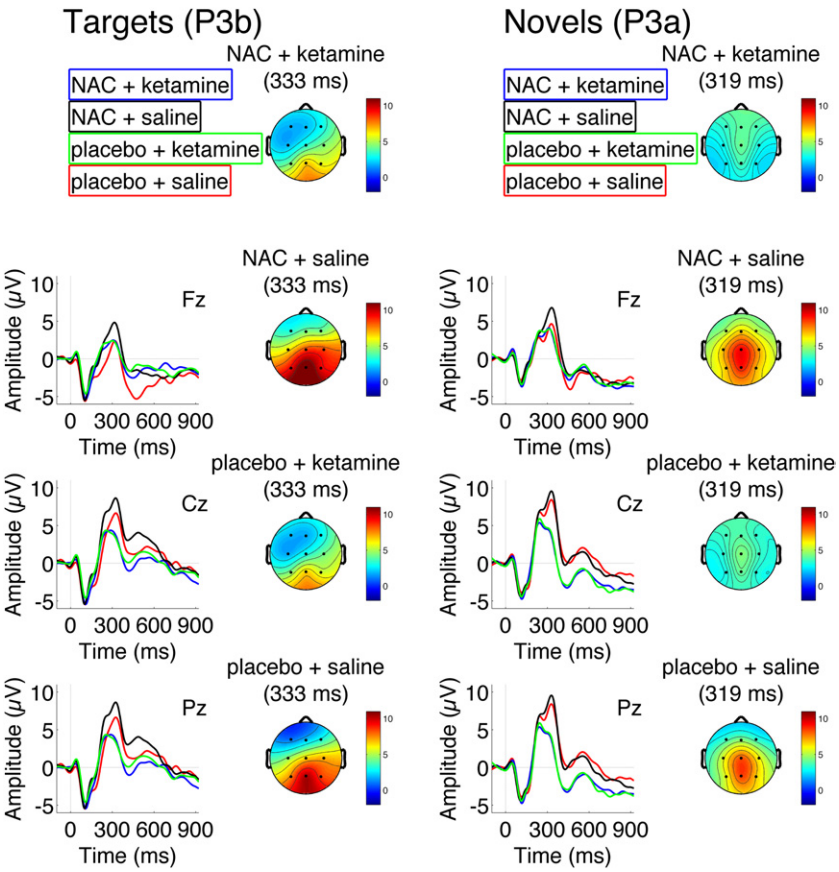

Figure 4. Grand average event-related potentials for Targets (left) and Novels (right) are plotted from electrodes Fz, Cz, and Pz to show interactive effects of *N*-acetylcysteine (NAC) and ketamine on auditory P300 amplitude. Time is shown in milliseconds on the x-axis and amplitude in microVolts on the y-axis. Scalp topographic maps of P300 amplitude are shown for the positive peak chosen from the grand average across all conditions at electrode Pz for Targets (333 msec) and Cz for Novels (319 msec).

type × electrode interaction [$F(2,313) = 57.72$, $p < .0001$] (Figures 3 and 4), confirming the expected parietal distribution of the target P3b and the more centro-frontal distribution of the novelty P3a. There were significant differences between target and novel stimuli values for all electrodes (all p values $< .001$), where novel stimuli values were higher than targets for Fz and Cz and lower for Pz.

Discussion

As hypothesized, ketamine produced significant increase in PANSS positive symptoms, reduction in working memory and sustained attention performance, and MMN and P300 amplitudes. The reduction of MMN by ketamine was only evident for frequency and intensity deviants, sparing the duration deviant. This underscores that the MMNs elicited by different deviant types are not uniform in their underlying generators (51–53). Notably, the duration deviant MMN has been shown to have the greatest sensitivity to the schizophrenia effect (5,54). Ketamine produced similar reductions of both the target P3b and novelty P3a, suggesting that it impacted the generators and/or neurophysiological mechanisms common to both of these P300 sub-components.

The NAC alone did not have significant effects on behavioral or cognitive performance, but it reduced frequency-deviant MMN amplitude and significantly increased P300 amplitude. However, unlike the findings in rodents, NAC pretreatment did not attenuate the behavioral/cognitive and ERP effects of ketamine in healthy volunteers.

Neurochemical mechanisms activated by acute systemic ketamine administration have been reviewed elsewhere (55–57). Although in vitro ketamine has affinity not only for NMDA but several other receptors including dopamine (58), selective D_2 agonist bromocriptine, dopamine precursor L-dopa (59), and D_1 and D_2 agonist apomorphine did not affect P300 amplitude in healthy volunteers (60). Pretreatment with the D_2 antagonist haloperidol did not affect the effect of ketamine on P300 (61), consistent with these findings. Acute depletion of precursors of dopamine and 5-hydroxytryptamine alone or in combination did not modulate MMN (62). Similarly, haloperidol failed to block perceptual changes induced by ketamine (63). These findings do not implicate the dopaminergic system as a primary modulator of the effect of ketamine on ERP or behavioral indices but are in keeping with a disinhibited prefrontal network activity resulting from NMDA receptor antagonism (12–15,64).

Our findings suggest that, in humans, stimulation of the mGluR2/3 receptors by NAC does not enhance the NMDA receptor function impaired by ketamine. The dissociation between the animal and human data might represent differences primarily in the effects of NAC, because the effects of ketamine in humans paralleled those in rodents. It is possible that the distribution of the cystine-Glu exchanger that differs between species and locally in the brain plays a role in this (31,65). Interestingly, NAC supplementation in smaller doses (2000 mg/day vs. 3000 mg/day in our study) was found to improve some symptoms in patients with schizophrenia (66). Although this discrepancy might suggest a limitation of the ketamine model for schizophrenia, other explanations such as the effect of chronic NAC administration (6 months in the clinical trial vs. single-day pretreatment in our study) is difficult to rule out. In another study, 2000-mg/day NAC treatment over 2 months was associated with increase in MMN in a small sample of schizophrenic patients (39); however, their MMN measurements were confounded by N1, and the attention of subjects was not diverted away

from the auditory channel that is typically done while studying MMN. Thus, their findings might have limited relevance to our findings.

Glutamatergic modulation of MMN has been studied in detail with intracortical recordings in primates (64) where phencyclidine decreased MMN to the frequency and intensity deviants in a dose-dependent fashion. Our findings in healthy humans parallel these data showing reduced MMN for the frequency and intensity deviants in response to ketamine. NAC, however, produced a reduction of the frequency deviant MMN amplitude. The divergence of the effects of NAC on pre-attentive processes (MMN) and attention-mediated processes orienting to novelty and detection of targets might be due to the differences in regional distribution/regulation of cellular mechanisms underlying generation of P300 (67–70) and MMN (16,71,72).

That NAC enhanced P300 amplitude in healthy humans suggests that NAC further increases the capacity of normally functioning glutamatergic networks subserving this measure. This might be due to a transient increase in extrasynaptic Glu levels as NAC promotes uptake of cystine into the cells in exchange for Glu, suggesting a role for NAC via an extrasynaptic effect. Supporting this perspective, a recent study found that NAC treatment was associated with a decrease in the binding potential of a tracer with affinity for an allosteric site on mGluR5, which is extrasynaptically expressed (73). This suggestion would further necessitate an inverted U-shape relationship between extrasynaptic Glu levels and P300 amplitude, because ketamine induces potent increases in extrasynaptic Glu levels (74) and leads to reduced P300, shifting from optimal peak Glu levels to excessive levels associated with the descending portion of the inverted-U function. Alternatively, the effect of NAC on P300 might be linked to stimulation of presynaptic autoreceptors leading to decreased Glu release, suggesting a synaptic effect as suggested by Baker *et al.* (30). This possibility more readily fits our observation, because ketamine leads to enhanced Glu release opposite to the effect of NAC, consistent with the divergent effects of these agents on P300. The effect of NAC might also involve additional/alternative mechanisms, including increasing glutathione synthesis within the cells and/or its reducing properties as demonstrated earlier (75). Further preclinical electrophysiological studies are needed to clarify these mechanisms.

With regard to the methods, repeated measure designs as we have employed are sensitive to test effects; however, by randomizing subjects to active and placebo NAC, we have minimized this potential problem, because our primary outcome measure was the effect of NAC pretreatment on ketamine-induced changes. Our P300 paradigm was not traditional, because the standard stimuli were 20-, 30-, or 40-Hz click trains (500 msec) instead of typical higher frequency tones with shorter duration. However, this is unlikely to affect the results, because the same paradigm was used for all drug conditions. Moreover, our results on P300 are consistent with findings by other groups on ketamine with traditional P300 paradigms (12,15,61).

In summary, NMDA antagonism as modeled by systemic ketamine administration in healthy volunteers led to expected changes in behavioral/cognitive measures and reduction in ERP indices of pre-attentive reflections of sensory echoic memory (MMN) and top-down (P3b) and bottom-up (P3a) attentional processes. NAC alone was associated with a reduction in MMN for the frequency deviant and significant increases in P300 amplitude for both target and novel stimuli. Pretreatment with NAC did not affect the changes induced by ketamine. Our finding of interactive effects of NAC and ketamine for the ERP indices but a lack thereof for the behavioral/cognitive measures suggests that electrophysiological indices lay more proximal to the biochemical processes induced by these agents and that further mechanisms play a role in modulating complex behavior. These findings also suggest that improvements in endophenotypes might not readily translate into functional improvement. The beneficial effect of NAC on P300, a measure of target detection, merits further investigation as a potential cognitive enhancing agent.

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ClinicalTrials.gov: N-Acetylcysteine and NMDA Antagonist Interactions, http://clinicaltrials.gov/ct2/show/NCT00611897?term=Gunduz-Bruce&rank=4; NCT00611897.

Supplementary material cited in this article is available online.

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