Archival Report

Role of *N*-Methyl-D-Aspartate Receptors in Action-Based Predictive Coding Deficits in Schizophrenia

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ABSTRACT

BACKGROUND: Recent theoretical models of schizophrenia posit that dysfunction of the neural mechanisms subserving predictive coding contributes to symptoms and cognitive deficits, and this dysfunction is further posited to result from *N*-methyl-D-aspartate glutamate receptor (NMDAR) hypofunction. Previously, by examining auditory cortical responses to self-generated speech sounds, we demonstrated that predictive coding during vocalization is disrupted in schizophrenia. To test the hypothesized contribution of NMDAR hypofunction to this disruption, we examined the effects of the NMDAR antagonist, ketamine, on predictive coding during vocalization in healthy volunteers and compared them with the effects of schizophrenia.

METHODS: In two separate studies, the N1 component of the event-related potential elicited by speech sounds during vocalization (talk) and passive playback (listen) were compared to assess the degree of N1 suppression during vocalization, a putative measure of auditory predictive coding. In the crossover study, 31 healthy volunteers completed two randomly ordered test days, a saline day and a ketamine day. Event-related potentials during the talk/listen task were obtained before infusion and during infusion on both days, and N1 amplitudes were compared across days. In the case-control study, N1 amplitudes from 34 schizophrenia patients and 33 healthy control volunteers were compared.

RESULTS: N1 suppression to self-produced vocalizations was significantly and similarly diminished by ketamine (Cohen's $d = 1.14$) and schizophrenia (Cohen's $d = .85$).

CONCLUSIONS: Disruption of NMDARs causes dysfunction in predictive coding during vocalization in a manner similar to the dysfunction observed in schizophrenia patients, consistent with the theorized contribution of NMDAR hypofunction to predictive coding deficits in schizophrenia.

Keywords: Electroencephalography, Ketamine, *N*-methyl-D-aspartate glutamate receptor, Predictive coding, Schizophrenia, Speech motor control

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Predicting imminent events is a fundamental strategy to efficiently process the overwhelming amount of information from the environment (1,2). While predictions can be based on regularities in the environment, or past learning, all animals are adept at predicting the sensory consequences of their own actions. Examples of action-based predictive coding are ubiquitous across species (3) and have been linked to the concepts of efference copy (4) and corollary discharge (5).

Modulation of auditory cortex during vocalization has been studied across species, including songbirds (6), nonhuman primates (7), and humans (8–20), and is posited to be mediated by predictive coding. In human speech (15,20–24), it is theorized that premotor cortex sends a forward model of the speech motor plan (i.e., efference copy) to auditory cortex where it generates a representation of the predicted auditory feedback (i.e., corollary discharge). This prediction is then compared with the actual auditory feedback, and when they match, the prediction error is minimized and the auditory

cortical response is attenuated (8–13,15,17,18,20,23). In contrast, mismatches between the predicted and perceived auditory feedback result in prediction errors and enhanced auditory cortical responses (12,16–18,20,25–27). Prediction errors can be used to update and make online changes to motor plans, refine future predictions, and maintain vocalization quality (16,17,21,22,28,29). In humans, speaking is overlearned, and the resulting sounds are highly predictable, making vocalization ideal for studying predictive coding in impaired populations in whom learning, attention, and motivation may be compromised.

Starting with Feinberg (30), and later Frith *et al.* (31), it was hypothesized that schizophrenia may involve dysfunction of these mechanisms, giving rise to psychotic symptoms involving misattribution of self-generated thoughts and actions to external sources. Recent models extended these earlier theories within a broader predictive coding framework (32–36), incorporating evidence that schizophrenia involves a more

general dysfunction of the neural mechanisms that allow predictions to be made and verified (25,34,37–39).

Many prior electroencephalographic (EEG) studies found that patients with schizophrenia exhibit reduced suppression of auditory cortical responses, specifically the N1 component of the auditory event-related brain potential (ERP), to self-produced speech sounds (14,23–25,40–42). Although these findings support deficits in cortical modulation of sensory responses to self-generated actions in schizophrenia, a broader range of studies implicate deficits in predictive coding based on recent sensory contextual information (37,43–48). For example, the widely replicated deficit in mismatch negativity (MMN) (46), an ERP component elicited by deviant auditory stimuli in auditory oddball sequences, has been considered to reflect deficient predictive coding of recent contextual information in schizophrenia (33,35,36,43,45,48–52).

Several lines of evidence support the *N*-methyl-D-aspartate glutamate receptor (NMDAR) hypofunction model of schizophrenia (34,53–57), including pharmacological (34,53–56, 58–62), genetic (63–65), neuroimaging (66,67), and postmortem (68,69) studies. Given that subanesthetic doses of NMDAR antagonists, including ketamine, transiently induce schizophrenia-like positive, negative, and cognitive symptoms (53–55,57,62,70–72), NMDAR antagonists provide a pharmacological tool for probing the potential role of NMDAR hypofunction in generating these symptoms in both animal (73–77) and human (53–56,59–62,78–82) studies. Such studies implicate NMDAR function in predictive coding-based learning and remembering the recent stimulus history (2,34,39,52). Specifically, blocking NMDAR function with ketamine impedes prediction error-dependent associative learning (56) and promotes aberrant prediction error signals implicated in the development of delusions (34,39). Moreover, in animal (73–75) and human (59,78,79,81–83) studies, NMDAR antagonists have disrupted MMN (35,36,49,50,52). While these studies implicate NMDAR dysfunction in context-based predictive coding deficits, it is unknown whether NMDAR antagonists disrupt predictions of the sensory consequences of motor actions, as seen in schizophrenia patients during talking (14,23,25,40–42,84) and other motor acts (85–89).

In the present study, we examined the acute effect of ketamine on action-based predictive coding of self-generated speech sounds in healthy volunteers. In a randomized placebo-controlled crossover study design, we compared the effect of intravenous ketamine with saline on the suppression of the speech sound-evoked auditory N1 ERP component elicited during vocalization relative to passive listening. In the talk/listen task, EEG was obtained as participants said the single vowel /a/ and then passively listened to playback of their speech. From previous studies (9–20,38,40,84), we hypothesized that under saline infusion, participants would show robust N1 amplitude suppression to self-produced speech, whereas under ketamine infusion, this suppression would be attenuated. To enable comparison of the effects of ketamine with the effects of schizophrenia, the identical talk/listen task was also administered to a group of chronic schizophrenia patients and age-matched healthy comparison participants (HCs). We hypothesized that schizophrenia would be associated with attenuated suppression of the auditory N1 in response to self-produced speech sounds, replicating our

prior studies (14,23,25,40,42,84). By expressing N1 suppression effect sizes as deviations from either the saline condition in the ketamine study or HCs in the schizophrenia study, we directly compared the effect sizes produced by ketamine and by schizophrenia.

METHODS AND MATERIALS

Data were collected in parallel studies. The talk/listen experimental paradigm, EEG acquisition, and ERP analyses were identical for the two studies and are described below. The ketamine versus saline infusion study was conducted on the Bio-Studies Unit at the Veterans Administration Connecticut Healthcare System (VACHS) in West Haven, CT, and the study received approval from the institutional review boards of the VACHS and Yale University School of Medicine in New Haven, CT. The schizophrenia versus HC study was conducted at both the VACHS/Yale and at the San Francisco Veterans Affairs Medical Center/University of California, San Francisco. The study received institutional review board approval from all institutions. For both studies, participants provided written informed consent.

Ketamine Versus Saline Infusion Study

Participants were recruited via locally posted flyers and newspaper/online advertisements and were paid for their participation. Participants were medically healthy by physical examination, history, electrocardiography, and laboratory testing. They had no history of a DSM-IV Axis I disorder, no major current or recent (<6 weeks) life stressors, and no first-degree relative with a history of psychosis. Screening procedures included the Structured Clinical Interview for DSM-IV (SCID) (90). Participants were instructed to refrain from psychoactive substances from 1 week before through completion of the study. A participant-identified outside informant was interviewed to corroborate information provided by potential participants. Urine toxicology testing at screening ruled out recent illicit substance use and pregnancy. Participants were instructed to fast overnight before each test day.

Thirty-three participants completed both test days. Although there were no serious adverse events, minor adverse events and study discontinuations were reported to the VACHS Human Studies Subcommittee. As with prior Bio-Studies Unit ketamine studies, clinical follow-ups indicated that all adverse events associated with acute ketamine resolved spontaneously without any late-appearing or persistent adverse effects (91). There were no significant differences between study completers and non-completers in age, sex, or education. Two participants were excluded from the final analysis due to poor quality EEG data on both test days. Demographic data are presented in Table 1. There was no overlap between participants in the ketamine study and the schizophrenia study.

Methods. Across 2 days separated by 12.65 ± 11.92 days, healthy volunteers received ketamine and saline in a double-blind, randomized crossover design. Participants received three intravenous infusions of ketamine or saline; 0.23 mg/kg bolus over 1 minute, followed by 0.58 mg/kg/hour for 30 minutes, followed by 0.29 mg/kg/hour for 50 minutes, similar

Table 1. Group Demographic Data

Variable	Healthy Comparison Participants (n = 33)	Schizophrenia Patients (n = 34)[a]	Ketamine Study Participants (n = 31)
Age, Mean (SD), Years	34.21 (8.99)	34.68 (9.79)	27.0 (4.3)
Handedness,[b] n			
Right	32	30	31
Left	1	3	0
Ambidextrous	0	1	0
Sex, n			
Male	25	26	19
Female	8	8	12
Education,[c] Mean (SD), Years	16.1 (2.6)	13.15 (1.48)	15.6 (1.9)
SES,[c,d] Mean (SD)	29.9 (11.5)	46.6 (12.0)	31.5 (8.9)
Caretaker SES,[d] Mean (SD)	31.8 (13.6)	37.5 (17.1)	29.5 (12.5)
Chlorpromazine Equivalents, Mean (SD), mg		548.0 (532.9)	
PANSS Positive Symptoms, Mean (SD)		16.8 (6.9)	
PANSS Negative Symptoms, Mean (SD)		11.8 (4.7)	
PANSS General Symptoms, Mean (SD)		27.9 (7.3)	
Antipsychotic Medication Type, n			
Second generation		27	
First generation		4	
Both		2	
None		1	

PANSS, Positive and Negative Syndrome Scale (97); SES, socioeconomic status.

[a]DSM-IV diagnoses: 29 schizophrenia (4 undifferentiated, 20 paranoid, 4 residual, 1 catatonic); 5 schizoaffective disorder (2 depressive type, 3 bipolar type).

[b]Based on a quantitative handedness scale (95).

[c]$p < .001$ for test of difference between schizophrenia patients and healthy comparison participants.

[d]Based on Hollingshead Scale (1961) (96); higher scores correspond to lower SES.

to many prior studies (60,61,80,82,91,92). This infusion strategy produces stable plasma ketamine levels (61,92), although only the bolus and first infusion rate coincided with the talk/listen paradigm.

Table 2 shows the timing of procedures. Behavioral ratings were obtained at baseline and were repeated periodically after the infusion. EEG data were collected during the talk/listen paradigm administered just before (pre-infusion; time 1, T1) and 10 to 20 minutes after onset of the intravenous ketamine (or saline) bolus (infusion; time 2, T2).

Behavioral Measures. Clinical symptoms induced by ketamine (and saline) were assessed by a trained rater using the Clinician Administered Dissociative Symptoms Scale (CADSS) (93) and a subset of items from the Brief Psychiatric Rating Scale (BPRS; Positive Symptoms: Conceptual Disorganization, Unusual Thought Content, Grandiosity, Suspiciousness, Hallucinatory Behavior; Negative Symptoms: Emotional Withdrawal, Motor Retardation, Blunted Affect) (94).

Schizophrenia Versus HC Study

Participants were 34 patients with schizophrenia or schizoaffective disorder (SZ) and 33 HCs. All met DSM-IV criteria for schizophrenia or schizoaffective disorder (Table 1) either based on a SCID interview (90) conducted by a psychiatrist or psychologist or by consensus of a SCID administered by a trained research assistant and a clinical interview conducted

by a psychiatrist or psychologist. All patients were on stable doses of antipsychotic medication (Table 1) for at least 2 weeks before study entry.

HCs were recruited by advertisements and word of mouth. Exclusion criteria for HCs included a past or current DSM-IV major Axis I psychiatric disorder based on a SCID (nonpatient version) interview or having a first-degree relative with a psychotic disorder. HCs were matched as a group to the SZ group for age, sex, handedness (95), and caretaker socioeconomic status (96).

Participants were excluded for 1) meeting DSM-IV criteria for alcohol or drug abuse within 30 days of study entry or dependence within the past year, 2) significant head injury, 3) neurological disorders, or 4) other medical illnesses compromising the central nervous system.

Clinical Ratings. A trained research assistant, psychiatrist, or clinical psychologist rated SZ symptom severity during semistructured interviews using the Positive and Negative Syndrome Scale (PANSS) (97), and the Scales for the Assessment of Negative Symptoms and Positive Symptoms (98,99). Time between symptom interviews and ERP testing ranged between 0 and 14 days (2.1 ± 5 days).

Common Methods

For a full description of the talk/listen EEG paradigm, including technical details associated with its instrumentation and

Table 2. Study Procedures

Time, Minutes	Procedure
−115	IV lines and EEG leads placed; BPRS, CADSS symptom ratings; vital signs; urine toxicology screen
−20	Check EEG impedances
−15	EEG task instructions; pre-infusion (T1) talk/listen ERP paradigm
−5	Vital signs
0	Ketamine (0.23 mg/kg) or saline 1-min IV bolus delivered
1	Vital signs; ketamine (0.58 mg/kg/hour) or saline IV infusion starts
5	Vital signs
10	Infusion (T2) talk/listen ERP paradigm
20	Other ERP tasks[a]
30	Reduced ketamine (0.29 mg/kg/hour) or saline IV infusion starts
35	Vital signs and blood samples; eye-tracking task[a]
70	Other ERP tasks[a]
80	Terminate infusion; vital signs; retrospective BPRS, CADSS symptom ratings
100	Vital signs
120	Vital signs; safety ratings (mental status examination, field test)

BPRS, Brief Psychiatric Rating Scale (94); CADSS, Clinician Administered Dissociative Symptoms Scale (93); EEG, electroencephalogram; ERP, event-related brain potential; IV, intravenous; T1, time 1; T2, time 2.

[a]Not analyzed in the current report.

vocalization training, see our previously published protocol (24). In brief, the paradigm involves EEG recording during two conditions: talk and listen. In the talk condition, participants vocalized the vowel /a/ into a microphone every 1 to 2 seconds for 3 minutes. These speech sounds were instantaneously fed back to the participant via headphones and were digitally recorded. In the listen condition, participants passively listened to the playback of their recorded speech sounds. Speech recording and playback were achieved using Presentation software (www.neurobs.com). Loudness was the same during talk and listen conditions based on equilibration of headphone audio output measured by a decibel meter.

Data Acquisition and Preprocessing. EEG data were acquired (0.05–200 Hz band-pass filter, 1000 Hz analog-to-digital conversion rate) from 28 scalp sites based on the International 10-20 System, referenced to the TP10 (right mastoid) electrode. Additional electrodes were placed on the inner and outer canthi of both eyes and above and below the right eye to measure eye movements and blinks (vertical and horizontal electro-oculograms). Continuous EEG data were 1-Hz high-pass filtered and separated into 3-second epochs time-locked to onset of the speech sound, with 1500 ms before and after speech onset. The 100-ms baseline preceding speech onset was subtracted from each EEG epoch after correction for eye movements and blinks using vertical and horizontal electro-oculograms in a regression-based algorithm (100) in BrainVision Analyzer 2 (BrainProducts, Gilching, Germany). Single trial EEG epochs were then exported for additional processing in MATLAB (The MathWorks, Inc., Natick, MA).

Canonical correlation analysis was used as a blind source separation technique to remove broadband or electromyographic noise from single-trial EEG data, generating denoised EEG epochs. Our approach is similar to the canonical correlation analysis method described by others (101,102), with some important differences (Supplement). Once a complete set of denoised EEG epochs were generated for a participant, epochs were subjected to selected steps from the Fully Automated Statistical Thresholding for EEG artifact Rejection toolbox (103), as previously done (86). The method searches for statistical outliers ($>\pm3$ SD from mean) using multiple descriptive measures.

Outlier epochs were removed from the set of single-trial epochs, and within an epoch, outlier channels were removed and interpolated. Surviving EEG epochs were baseline corrected again using the 100-ms preceding speech onset and were averaged separately for talk and listen conditions, generating ERP waveforms separately for each participant and test session.

ERP Analysis. Before identification of the N1 component, participant-specific ERP waveforms were 30-Hz low-pass filtered and averaged across all conditions (i.e., talk and listen for SZ vs. HC study; talk and listen from all ketamine vs. saline study sessions) and re-referenced to an average mastoid reference (104). Resulting participant-specific grand average ERP waveforms were used to identify the N1 peak latency separately for Fz, FCz, and Cz, between 60 and 140 ms. The mean peak latency from these three electrodes was calculated, and then the N1 peak amplitude was defined by the microvolt value at this latency for each condition and electrode.

Statistical Analysis: Ketamine Versus Saline Infusion Study. N1 peak amplitudes were analyzed using a five-way mixed model analysis of variance (ANOVA) with four within-subject factors, including time (T1: pre-infusion vs. T2: infusion), anterior-posterior electrode site (Fz, FCz, Cz), ketamine/saline (ketamine vs. saline), and talk/listen (talk vs. listen) and between-subjects factor of infusion order (day 1: ketamine, day 2: saline vs. day 1: saline, day 2: ketamine) to test for possible drug infusion order effects. There was no significant effect of infusion order, nor did infusion order significantly interact with other factors in the model; to simplify the model, it was dropped from further analyses.

Pearson's correlation tests were used to assess the relation between ketamine-related change (T2-T1) in symptoms and change (T2-T1) in N1 suppression (talk-listen, averaged across Fz, FCz, and Cz). Because there were three symptom domains (Table 3), our significance level was .05/3.

Statistical Analysis: SZ Versus HC Study. N1 peak amplitudes were analyzed using a three-way mixed model ANOVA with between-subjects factor of group (SZ vs. HC), and within-subjects factors of anterior-posterior electrode site and talk/listen.

Pearson's correlation tests were used to assess the relation between PANSS positive, negative, total scores, and N1 suppression (talk-listen, averaged across Fz, FCz, and Cz). Because there were three symptom domains, our significance level was .05/3.

Table 3. Measures of Psychotomimetic Effects of Ketamine

Measure	Pre-Saline Infusion	Saline Infusion	Pre-Ketamine Infusion	Ketamine Infusion
BPRS Total	8.03 (0.18)	8.06 (0.25)	8.06 (0.25)	20.52 (5.81)
BPRS Positive	4.03 (0.18)	4.01 (0.18)	4.03 (0.18)	11.06 (3.62)
CADSS	0.03 (0.18)	0.03 (0.18)	0.00 (0.00)	34.10 (16.17)

Values are mean (SD).
BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative Symptom Scale.

Statistical Analysis Comparing Ketamine and Schizophrenia Study Effect Sizes. N1 peak amplitudes from the ketamine infusion test day were converted to z scores by subtracting the mean N1 peak amplitude from the saline day and dividing by the saline day SD. N1 peak amplitudes from SZs were converted to z scores by subtracting the mean N1 peak amplitude from HCs and dividing by the HC group SD. This was done for N1 peak amplitudes from the talk and listen conditions and for the talk-listen suppression effect. Independent samples t tests directly compared the ketamine z scores from the HCs, expressing abnormalities relative to the saline test day, with the SZ z scores, expressing abnormalities relative to the HCs.

RESULTS

Ketamine Versus Saline Infusion Study

Ketamine Did Not Significantly Affect Task Performance. To determine whether ketamine affected the speech rate, the average number of vocalizations in 3 minutes was analyzed in 3-way mixed model ANOVA with ketamine/saline and time as within-subject factors and infusion order as between-subjects factor. Although ketamine slowed speech rate (mean vocalizations/minute: pre-ketamine = 37.5, ketamine = 33.8; pre-saline = 37.9, saline = 37.7), the ketamine/saline × time interaction was not significant (p = .11). No main effects or interactions were significant.

Psychotomimetic effects of ketamine were measured using the BPRS and CADSS (Table 3). Pre-ketamine infusion versus ketamine infusion paired t tests showed a significant increase in symptom ratings, corresponding with ketamine significantly increasing symptoms (BPRS total t = −11.915, p < .001; BPRS positive t = −10.902, p < .001; CADSS t = −11.737, p < .001). Given that symptom ratings were virtually identical without ketamine infusion, the psychotomimetic effects of ketamine were similarly evident compared with the pre-saline and saline infusion.

Ketamine Significantly Reduced N1 Suppression. As can be seen in the grand average ERPs shown in Figure 1, N1 is relatively suppressed during talk compared with listen, and this suppression is attenuated during ketamine infusion. Results from the mixed model ANOVA (Table 4) bear this out, showing a significant talk/listen × ketamine/saline × time interaction. This interaction was parsed several ways. First, a talk/listen × ketamine/saline ANOVA was run separately for T1 and T2. The talk/listen × ketamine/saline interaction was significant at T2 (infusion) but not at T1 (pre-infusion), indicating that the talk-listen N1 difference score was reduced during ketamine infusion relative to saline infusion. Further interrogation showed that despite attenuation of the talk/listen effect by ketamine, there was still a significantly smaller N1 during talk than listen during both ketamine and saline infusions. Moreover, separate tests of the T2 ketamine/saline
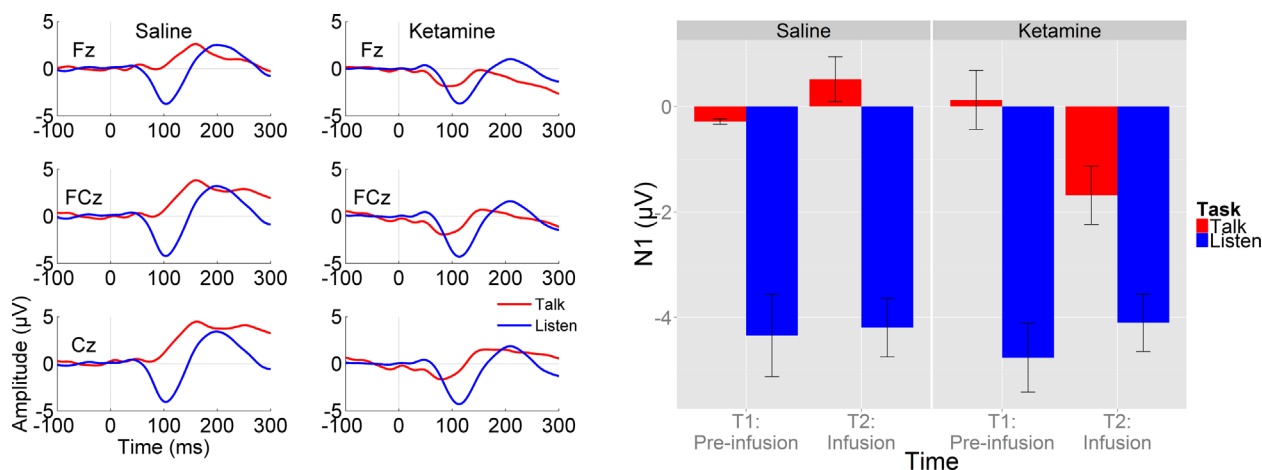

Figure 1. Event-related potential results for talk and listen for the saline and ketamine infusion days. **(A)** Grand-average event-related potential waveforms for talk (red) and listen (blue) conditions during saline infusion (left) and during ketamine infusion (right). N1 during talk is suppressed compared with N1 during listen for the time 2 (T2) saline infusion assessment (left), as well as for the time 1 (T1) pre-infusion assessments on both saline and ketamine test days (waveforms not shown). N1 suppression during talk relative to listen is reduced during the T2 ketamine infusion assessment (right). **(B)** Mean N1 peak amplitudes (averaged over electrodes Fz, FCz, and Cz) on the saline day and ketamine day at T1 (pre-infusion) and at T2 (infusion). Error bars represent SEs.

Table 4. Analysis of Variance of N1 Amplitude During Ketamine Versus Saline Experiment

Effect	df	F	p Value	Partial Eta Squared
Ketamine/Saline	1,30	3.11	.088	0.094
Talk/Listen	1,30	100.33	<.0001	0.77
AP (Fz, FCz, Cz)	2,60	2.59	.11	0.079
Time (T1 vs. T2)	1,30	0.06	.80	0.002
Talk/Listen × Ketamine/Saline	1,30	3.06	.09	0.093
Ketamine/Saline × AP	2,60	0.62	.47	0.02
Talk/Listen × AP[a]	2,60	13.69	<.0001	0.313
AP: talk, Fz = FCz > Cz	2,60	4.40	.04	0.13
AP: listen, Fz < FCz = Cz	2,60	23.81	<.0001	0.44
Talk/Listen × Ketamine/Saline × AP	2,60	0.07	.85	0.002
Ketamine/Saline × Time	1,30	5.26	.03	0.149
Talk/Listen × Time	1,30	7.26	.01	0.195
Talk/Listen × Ketamine/Saline × Time[a]	1,30	15.90	<.0001	0.346
Talk/listen × ketamine/saline: T1	1,30	2.58	.12	0.079
Talk/listen × ketamine/saline: T2	1,30	13.52	.001	0.311
Talk/listen: saline	1,30	71.43	<.0001	0.704
Talk/listen: ketamine	1,30	19.14	<.0001	0.389
Ketamine/saline: talk	1,30	13.27	.001	0.307
Ketamine/saline: listen	1,30	0.07	.80	0.002
Talk/listen × time: ketamine[a]	1,30	17.73	<.0001	0.371
Time: talk	1,30	11.38	.002	0.275
Time: listen	1,30	2.87	.10	0.087
Talk/listen × time: saline	1,30	2.23	.15	0.069
Ketamine/saline × time: talk[a]	1,30	15.88	<.001	0.35
Ketamine/saline: T1	1,30	.67	.42	0.02
Ketamine/saline: T2	1,30	13.27	<.001	0.31
Ketamine/saline × time: listen	1,30	0.88	.36	0.03
AP × Time	2,60	6.18	.01	0.171
Ketamine/Saline × AP × Time	2,60	0.33	.64	0.011
Talk/Listen × AP × Time	2,60	0.18	.73	0.006
Talk/Listen × Ketamine/Saline × AP × Time	2,60	0.45	.55	0.015

AP, anterior-posterior; T1, time 1; T2, time 2.

[a]Interactions with talk/listen that are parsed with follow-up tests.

effect for talk and for listen revealed that ketamine, relative to saline, significantly increased talk N1 but had no significant effect on listen N1.

Second, a talk/listen × time ANOVA was run separately for the ketamine and saline infusion days. There was a significant talk/listen × time effect on the ketamine day, but not on the saline day, indicating that the talk-listen N1 difference score was significantly attenuated during ketamine infusion relative to pre-ketamine baseline. Nonetheless, the talk-listen difference was significant during ketamine infusion and pre-ketamine baseline assessment. Furthermore, relative to the pre-ketamine baseline, ketamine infusion significantly increased talk N1 amplitude and nonsignificantly decreased listen N1 amplitude.

Third, a ketamine/saline × time ANOVA was run separately for talk and listen conditions. For talk, but not for listen, there was a significant ketamine/saline × time interaction. This interaction was driven by an increase in talk N1 amplitude by ketamine relative to T1 pre-ketamine and relative to T2 saline infusion, as previously noted.

People whose N1 suppression was more attenuated by ketamine had more severe dissociative experiences reflected in the total CADSS score ($r = -.36$, $p < .05$), but this relation did not meet our Bonferroni corrected significance level of $p = .017$. N1 suppression was not related to BPRS total ($p = .27$) or BPRS positive ($p = .14$).

SZ Versus HC Study

Groups Did Not Differ in Task Performance. There was no difference in the rate of vocalizations produced by HCs (mean = 32.3 vocalizations per minute) and SZ patients (mean = 32.7 vocalizations per minute) ($p = .81$).

SZ Patients Showed Less N1 Suppression Than HCs. Grand average ERP waveforms for SZs and HCs showed N1 amplitude suppression during talking compared with passive listening, with greater suppression evident in the HCs (Figure 2). Results from the repeated measures ANOVA in Table 5 showed a significant talk/listen × group (SZ vs. HC)
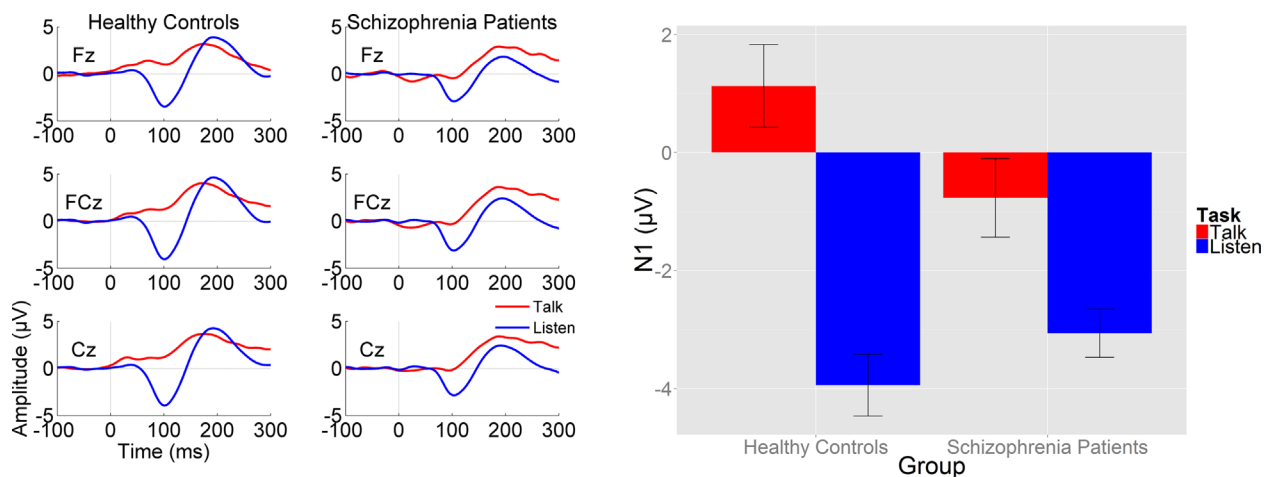
Figure 2. Event-related potential results for talk and listen for healthy comparison participants and schizophrenia patients. **(A)** Grand-average event-related potential waveforms for talk (red) and listen (blue) conditions for healthy comparison participants (left) and schizophrenia patients (right). N1 during talk is suppressed compared with listen in healthy comparison participants. The N1 suppression during talk relative to listen is attenuated in schizophrenia patients. **(B)** Mean N1 peak amplitudes averaged over electrodes Fz, FCz, and Cz for healthy comparison participants (left) and schizophrenia patients (right). Error bars represent SEs.

interaction, indicating that the talk/listen N1 effect was significantly greater in HCs than SZs. Nonetheless, both groups showed significant N1 suppression in the talk condition compared with the listen condition. In addition, N1 in the talk condition was significantly larger for SZs than for HCs, whereas N1 during the listen condition did not significantly differ between the groups.

None of the relations between N1 suppression and PANSS (positive, negative, general) scores were significant.

Influence of Ketamine on N1 Compared With Schizophrenia

Ketamine and SZ N1 amplitude z scores, expressing deviations from N1 amplitudes observed during the saline infusion and in HCs, respectively, were used to directly compare the effects of ketamine and schizophrenia (Figure 3). The effects of ketamine and schizophrenia on N1 amplitudes were significantly different

during talk ($t_{63} = -5.299$, $p < .001$) but not listen ($t_{63} = -1.196$, $p = .236$), nor did they differ for N1 talk/listen suppression effect ($t_{63} = -.337$, $p = .737$).

DISCUSSION

Suppression of the neural response to spoken sounds during vocalization reflects successful predictive coding of the sensory consequences of speaking. In this study, we have shown that transient blockade of NMDARs via infusion of the NMDAR antagonist ketamine disrupts predictive coding during vocalization by decreasing auditory cortical suppression to the spoken, and predicted, speech sound. The disturbance of predictive coding in healthy volunteers under the influence of ketamine mimics that seen in schizophrenia, with both groups showing a similar reduction in cortical suppression during talking relative to listening.

Table 5. Group Analyses of N1 During Talking and Listening Across SZ and HC

Effect	df	F	p Value	Partial Eta Squared
Group	1,65	0.616	.435	0.009
Talk/Listen[a]	1,65	50.851	<.0001	0.439
Talk/Listen × Group (HC vs. SZ)[a]	1,65	7.214	.009	0.100
Talk/listen for HC[a]	1,32	47.435	<.0001	0.597
Talk/listen for SZ[a]	1,33	10.038	.003	0.233
Talk: group (SZ > HC)[a]	1,65	3.835	.054	0.056
Listen: group (HC > SZ)	1,95	1.765	.189	0.026
AP (Fz, FCz, Cz)	2,130	1.857	.175	0.028
AP × Group	2,130	1.589	.214	0.024
Talk/Listen × AP[a]	2,130	6.701	.004	0.093
AP: talk	2,130	2.91	.077	0.043
AP: listen Fz < FCz >Cz; Fz = Cz	2,130	8.70	.002	0.118
Condition × AP × Group	2,130	0.604	.509	0.009

AP, anterior-posterior; HC, healthy comparison participant; SZ, patient with schizophrenia or schizoaffective disorder.
[a]Interactions with talk/listen that are parsed with follow-up tests.
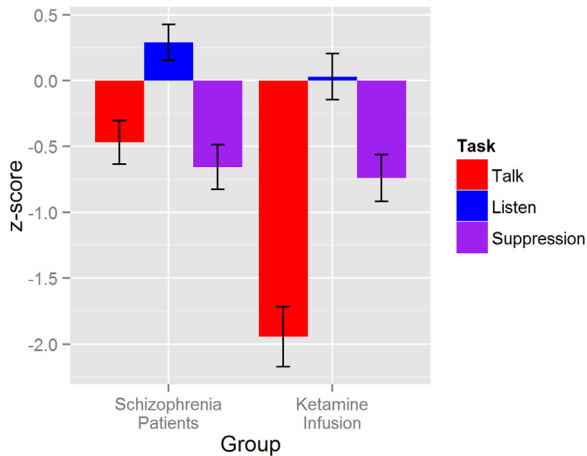
Figure 3. N1 amplitudes of schizophrenia patients *z* scored to the N1 amplitudes of the healthy comparison participants (left), and N1 amplitudes during ketamine infusion *z* scored to the N1 amplitudes during saline infusion (right) for talk (red), listen (blue), and suppression (i.e., talk-listen; purple). The effect of ketamine on N1 amplitudes in healthy participants was similar to the effect of schizophrenia.

These findings have important implications for understanding the pathophysiology of schizophrenia. This study shows, for the first time, that disrupting NMDAR function impedes the predictive coding of the overlearned sensations resulting from motor actions. The suppression of sensory cortical responses to self-generated stimuli provides a mechanism for distinguishing these stimuli from those arising from the environment, an essential part of self-monitoring (105). Disruption of this mechanism could result in the misattribution of self-generated sensations to external sources, which is hypothesized to underlie certain types of psychotic symptoms such as hallucinations and delusions of alien control (30,31); however, our data do not corroborate these symptom relations. We have shown that disruption of NMDARs is sufficient to create a deficit in cortical self-monitoring during vocalization in healthy volunteers that mimics the deficit observed in schizophrenia.

The results of this study add to the increasing evidence implicating NMDAR hypofunction in the pathophysiology of schizophrenia. NMDAR antagonists, including ketamine and phencyclidine, induce schizophrenia-like symptoms (53–55,57,62,70–72). Alterations both in the NMDAR subunit composition and in specific NMDAR-related postsynaptic proteins have been reported (68,69). Positive genetic associations with schizophrenia have been reported for both the NR_1 and the NR_{2B} subunits of the NMDAR (63–65). NMDAR function has been implicated in generating the MMN response to deviant auditory stimuli, a reflection of predictive coding in the auditory system that is based on recent contextual information (35,36,49–52). In particular, MMN deficits similar to those found in schizophrenia have been induced by ketamine in healthy volunteers (59,78,79,81–83), rodents (75,106), and nonhuman primates (73,74). In addition, low-dose ketamine has been shown to disrupt prediction error responses during causal learning, and these aberrant responses trended toward predicting ketamine-induced delusional ideation (56). Moreover, larger baseline prediction error responses during

causal learning as reflected by functional magnetic resonance imaging activation in prefrontal cortex (56), but smaller electrophysiological prediction error signals as reflected by the MMN (107), have been shown to predict severity of positive symptoms under higher doses of ketamine in healthy volunteers.

Action-based predictive coding is a unique case of predictive coding. Unlike context-based predictive coding, the motor-sensory prediction originates from premotor cortex and involves multisensory integration (somatosensory and auditory during speech production). Furthermore, prediction errors can be used in real time to change the motor plan to correct any execution errors. We have shown that disrupting the NMDAR can transiently alter a motor predictive coding mechanism. Ketamine specifically altered the N1 response during self-produced vocalizations but not during passive listening to playback of these vocalizations. Therefore, N1 suppression deficits were due not to changes in sensory perception but to changes in predicting the sensory consequences of talking. These findings support hierarchical models of predictive coding (2,39,108) that posit a role of NMDARs in the representation of the prediction.

The present study has several limitations. First, we used one dose of ketamine, making a dose-response curve function impossible to estimate. Second, predictive coding deficits with ketamine and in schizophrenia were not related to dissociative or psychotic symptoms, counter to expectations. Third, we could not compare context-based (e.g., MMN) and action-based (N1 suppression during talking) predictive coding effects because MMN was not collected in the ketamine study. Fourth, antipsychotic medications influence extracellular glutamate and potentially modulate NMDA receptor subunit composition (109). However, the N1 suppression deficit in schizophrenia is unlikely to be a consequence of antipsychotic medication; it is seen in unmedicated first-degree relatives (42) and individuals at clinical high risk of psychosis (40).

In conclusion, this study demonstrates that transient disruption of NMDARs via administration of ketamine impedes cortical self-monitoring of speech by decreasing cortical suppression (and correspondingly increasing the prediction error signal). Furthermore, we showed that this transient disruption mimics the deficits evident in schizophrenia. This work implicates NMDAR hypofunction as a contributor to action-based predictive coding deficits in schizophrenia, further motivating the development of interventions that target this putative pathophysiological mechanism.

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