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Authors

Kort, Naomi S
Ford, Judith M
Roach, Brian J
et al.

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Role of N-Methyl D-aspartate Receptors in Action-based Predictive Coding Deficits in Schizophrenia

Naomi S. Kort[1], **Judith M. Ford**[1,2], **Brian J. Roach**[3], **Handan Gunduz-Bruce**[4,5], **John H. Krystal**[4,5], **Judith Jaeger**[6], **Robert M. G. Reinhart**[7], and **Daniel H. Mathalon**[1,2]

[1] University of California, San Francisco, San Francisco, CA, United States

[2] San Francisco Veterans Affairs Medical Center, San Francisco, CA, United States

[3] Northern California Institute for Research and Education, San Francisco, CA, United States

[4] Yale University School of Medicine, New Haven, CT, United States

Corresponding author: Daniel H. Mathalon, Daniel.Mathalon@ucsf.edu, telephone: (415) 221-4810 x23860, fax: (415) 750-6622, Brain Imaging and EEG Laboratory, SFVAMC 116-D; Building 8, 4150 Clement St., San Francisco, California 94121.

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Patents and Inventions

1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #:5,447,948.September 5, 1995

2) Vladimir, Coric, Krystal, John H, Sanacora, Gerard – Glutamate Modulating Agents in the Treatment of Mental Disorders US Patent No. 8,778,979 B2 Patent Issue Date: July 15, 2014.

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4) Arias A, Petrakis I, Krystal JH. – Composition and methods to treat addiction. Provisional Use Patent Application no. 61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research.

[5] Veterans Affairs Connecticut Healthcare System, West Haven, CT, United States

[6] Albert Einstein College of Medicine and CognitionMetrics, LLC (employee of AstraZeneca at the time the work was done).

[7] Boston University, Boston, MA, United States (employee of Yale University School of Medicine at the time the work was done).

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. In order 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 to the effects of schizophrenia.

Methods—In two separate studies, the N1 component of the event-related potential (ERP) 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 cross-over study, 31 healthy volunteers completed two randomly ordered test days, a saline day and a ketamine day. ERPs during the Talk/Listen task were obtained pre-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 controls 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

schizophrenia; predictive coding; ketamine; *N*-methyl-D-aspartate glutamate receptor; speech motor control; electroencephalography

1. Introduction

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), non-human 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 to 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 over-learned, and the resulting sounds are highly predictable, making vocalization ideal for studying predictive coding in impaired populations where learning, attention, and motivation may be compromised.

Starting with Feinberg (30), and later Frith (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). While 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 post-mortem (68, 69) studies. Given that sub-anesthetic 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 vs. 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. Based on 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 to 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. 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 healthy comparison participants in the schizophrenia study, we directly compared the effect sizes produced by ketamine and by schizophrenia.

2. Methods

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 vs. saline infusion study was conducted on the Bio-Studies Unit at the VA Connecticut Healthcare System (VACHS) in West Haven, CT, and the study received approval from the Institutional Review Boards (IRB) of the VACHS and Yale University School of Medicine in New Haven, CT. The schizophrenia vs. healthy comparison study was conducted at both the VACHS/Yale and at the San Francisco Veterans Affairs Medical Center (SFVAMC)/University of California, San Francisco (UCSF). The study received IRB approval from all institutions. For both studies, participants provided written informed consent.

2.1 Ketamine vs. 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 one week prior to 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 prior to each test day.

Thirty-three participants completed both test days. While 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.

2.1.1. Methods: Ketamine vs. Saline Infusion Study—Across two days separated by on average 12.65 days (11.92 SD), healthy volunteers received ketamine and saline in a double-blind, randomized crossover design. Participants received 3 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 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 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 IV ketamine (or saline) bolus (“Infusion”; Time 2, T2).

2.1.1.1. Behavioral Measures: Ketamine vs. Saline Infusion Study: 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).

2.2. Schizophrenia vs. Healthy Comparison Participants Study

Participants were 34 patients with schizophrenia or schizoaffective disorder (SZ) and 33 healthy comparison participants (HC). All met DSM-IV criteria for schizophrenia or schizoaffective disorder (see Table 1) based either 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 (see Table 1) for at least two weeks prior to study entry.

HC were recruited by advertisements and word-of-mouth. Exclusion criteria for HC included a past or current DSM-IV major Axis I psychiatric disorder based on a SCID (non-patient version) interview, or having a first-degree relative with a psychotic disorder. HC

were matched as a group to the SZ group for age, gender, 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.

2.2.1. Clinical Ratings—A trained research assistant, psychiatrist, or clinical psychologist rated SZ symptom severity during semi-structured interviews using the Positive and Negative Syndrome Scale (PANSS) (97), and the Scales for the Assessment of Negative Symptoms and Positive Symptoms (SANS and SAPS) (98, 99). Time between symptom interviews and ERP testing ranged between 0 to 14 days (mean= 2.1 days, SD= 5 days).

2.3. Common Methods

For a full description of the Talk/Listen EEG paradigm, including technical details associated with its instrumentation and 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 1-2 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 dB meter.

2.3.1. Data Acquisition and Pre-processing—EEG data were acquired (0.05-200Hz band pass filter, 1000Hz 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-oculogram; VEOG, HEOG). Continuous EEG data were 1Hz high-pass filtered and separated into 3s epochs time-locked to onset of the speech sound, with 1500ms before and after speech onset. The 100ms baseline preceding speech onset was subtracted from each EEG epoch after correction for eye movements and blinks using VEOG and HEOG in a regression-based algorithm (100) in BrainVision Analyzer 2 (BrainProducts, Germany). Single trial EEG epochs were then exported for additional processing in Matlab (Mathworks, Inc).

Canonical correlation analysis (CCA) was used as a blind source separation technique to remove broadband or electromyographic noise from single trial EEG data, generating de-noised EEG epochs. Our approach is similar to the CCA method described by others (101, 102), with some important differences (see supplementary methods). Once a complete set of de-noised 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 (>±3 SD from mean) employing 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 100ms preceding speech onset and were averaged separately for Talk and Listen conditions, generating ERP waveforms separately for each participant and test session.

2.3.2. ERP Analysis—Prior to identification of the N1 component, participant-specific ERP waveforms were 30Hz low-pass filtered and averaged across all conditions (i.e., Talk and Listen for Schizophrenia vs. Healthy Comparison Participants 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.

2.3.3. Statistical Analysis: Ketamine vs. Saline Infusion Study—N1 peak amplitudes were analyzed using a 5-way mixed model analysis of variance (ANOVA) with four within-subject factors including Time (T1: Pre-infusion vs. T2: Infusion), Anterior-Posterior Electrode Site (AP; 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 relationship 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 3 symptom domains (Table 3), our significance level was .05/3.

2.3.4. Statistical Analysis: Schizophrenia vs. Healthy Comparison Participants Study—N1 peak amplitudes were analyzed using a 3-way mixed model ANOVA with between-subjects factor of Group (SZ vs. HC), and within-subjects factors of AP and Talk/Listen.

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

2.3.5. 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 SZ were converted to z-scores by subtracting the mean N1 peak amplitude from HC and dividing by 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 healthy participants, expressing abnormalities relative to the saline test day, with the SZ z-scores, expressing abnormalities relative to the HC.

3. Results

3.1. Ketamine vs. Saline Infusion Study

3.1.1. Ketamine did not significantly affect task performance—To determine if 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. Though ketamine slowed speech rate (mean vocalizations/minute: preketamine = 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 (see Table 3). Pre-Ketamine Infusion vs. 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 symptom ratings were virtually identical without ketamine infusion, the psychotomimetic effects of ketamine were similarly evident when compared to the Pre-Saline and Saline Infusion.

3.1.2. 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 to Listen, and this suppression is attenuated during ketamine infusion. Results from the mixed model ANOVA (see 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 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 non-significantly 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 relationship did not meet our Bonferroni corrected significance level of $p=.017$. N1 suppression was not related to BPRS Total ($p=.27$) or BPRS Positive ($p=.14$).

3.2. Schizophrenia vs. Healthy Comparison Participants Study

3.2.1. Groups did not differ in task performance—There was no difference in the rate of vocalizations produced by HC participants (mean = 32.3 vocalizations per minute) and SZ patients (mean = 32.7 vocalizations per minute) ($p=.81$).

3.2.2. Schizophrenia patients showed less N1 suppression than healthy comparison participants—Grand average ERP waveforms for SZ and HC showed N1 amplitude suppression during talking compared to passive listening, with greater suppression evident in the HC (see Figure 2). Results from the repeated measures ANOVA in Table 5 showed a significant Talk/Listen by Group (SZ vs. HC) interaction, indicating that the Talk/Listen N1 effect was significantly greater in HC than SZ. Nonetheless, both groups showed significant N1 suppression in the Talk condition compared to the Listen condition. In addition, N1 in the Talk condition was significantly larger for SZ than for HC, whereas N1 during the Listen condition did not significantly differ between the groups.

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

3.3. Influence of ketamine on N1 compared to schizophrenia

Ketamine and SZ N1 amplitude z-scores, expressing deviations from N1 amplitudes observed during the Saline infusion and in HC, respectively, were used to directly compare the effects of ketamine and schizophrenia (see 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 ($t_{63}=-.337$, $p=.737$).

4. 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.

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 over-learned 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 relationships. 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 in both the NMDAR subunit composition and in specific NMDAR related post-synaptic proteins have been reported (68, 69). Positive genetic associations with schizophrenia have been reported for both the NR1 and NR2B 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 non-human primates (73, 74). In addition, low-dose ketamine has been shown to disrupt prediction error responses during causal learning, and these aberrant responses trended towards 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 not due 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 current 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 for 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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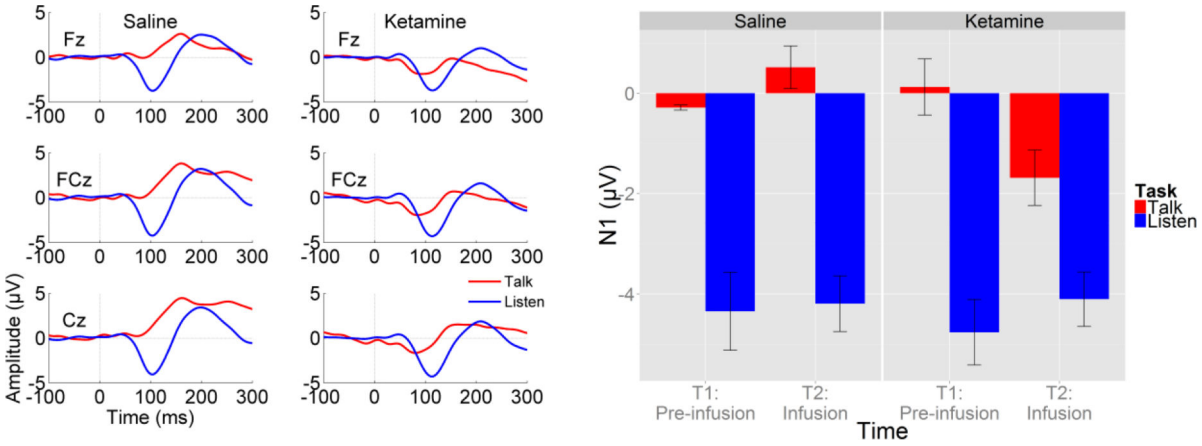

Figure 1. Event-related potential (ERP) results for Talk and Listen for the saline and ketamine infusion days

A. Grand-average ERP waveforms for Talk (red) and Listen (blue) conditions during saline infusion (left) and during ketamine infusion (right). N1 during Talk is suppressed compared to N1 during Listen for the Time 2 saline infusion assessment (Left), as well as for the Time 1 pre-infusion assessments on both saline and ketamine test days (waveforms not shown). N1 suppression during Talk relative to Listen is reduced during the Time 2 ketamine infusion assessment (Right).

B. Mean N1 peak amplitudes (averaged over electrodes Fz, FCz, and Cz) on the saline day and ketamine day at Time 1 (T1: Pre-infusion) and at Time 2 (T2: Infusion). Error bars represent standard errors.

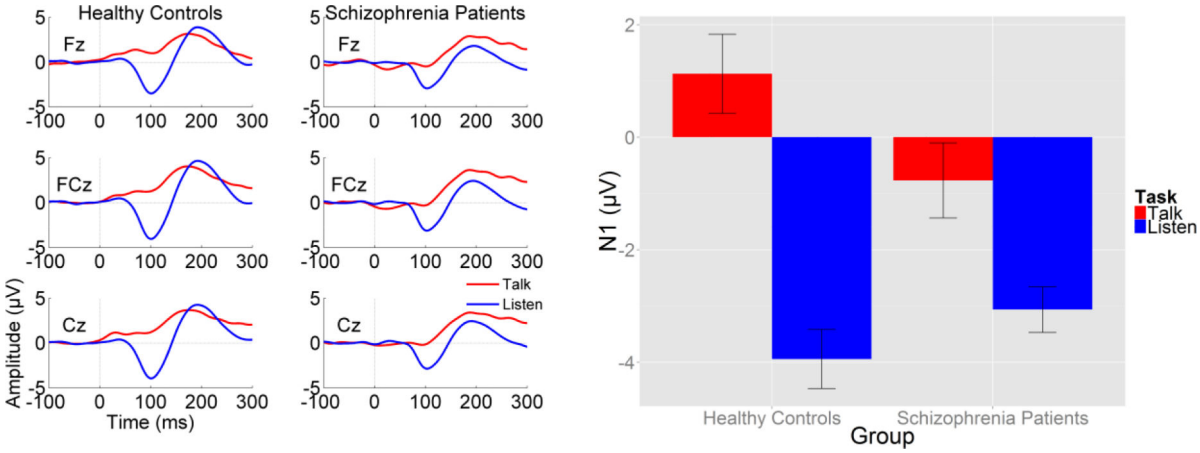

Figure 2. Event-related potential (ERP) results for Talk and Listen for healthy comparison participants and schizophrenia patients

A. Grand-average ERP waveforms for Talk (red) and Listen (blue) conditions for healthy comparison participants (left) and schizophrenia patients (right). N1 during Talk is suppressed compared to 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 standard errors.

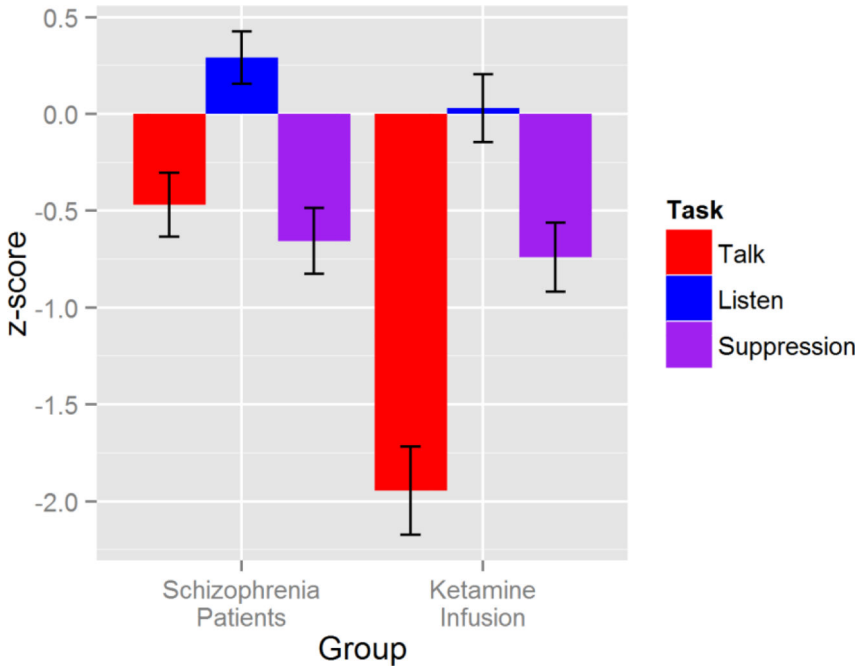

Figure 3.

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.

Table 1

Group Demographic Data

	Healthy Comparison Participants (n=33)	Schizophrenia Patients (n=34)[a]	Ketamine Study Participants (N=31)
Age (years) M (SD)	34.21 (8.99)	34.68 (9.79)	27.0 (4.3)
Handedness[∞]	32 Right/ 1 Left	30 Right/ 3 Left/ 1 Ambidextrous	31 Right
Gender	25 Male/ 8 Female	26 Male/ 8 Female	19 Male/ 12 Female
Education (years) M (SD)[*]	16.1 (2.6)	13.15 (1.48)	15.6 (1.9)
SES[≠] M (SD)[*]	29.9 (11.5)	46.6 (12.0)	31.5 (8.9)
Caretaker SES[≠] M (SD)	31.8 (13.6)	37.5 (17.1)	29.5 (12.5)
Chlorpromazine equivalents (mg) M (SD)		548.0 (532.9)	
PANSS – Positive Symptoms, M (SD)		16.8 (6.9)	
PANSS – Negative Symptoms, M (SD)		11.8 (4.7)	
PANSS – General Symptoms, M (SD)		27.9 (7.3)	
Antipsychotic Medication Type		27 second generation, 4 first generation, 2 both, 1 none	

Note. M = mean, SD = standard deviation. PANSS = Positive and Negative Syndrome Scale (132). DSM-IV = Diagnostic and Statistical Manual IV of the American Psychiatric Association.

[*] $p<0.001$ for test of difference between schizophrenia patients and healthy comparison participants.

[≠] SES = Socioeconomic status based on Hollingshead Scale (1961) (135); higher scores correspond to lower SES.

[∞] Based on a quantitative handedness scale (136).

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

Table 2

Study Procedures

Time (minutes)	Procedure
−115	IV lines and EEG leads placed; BPRS, CADSS symptom ratings; VS; Urine toxicology screen.
−20	Check EEG impedances.
−15	EEG task instructions; Pre-infusion (T1) Talk-Listen ERP paradigm.
−5	VS
0	Ketamine (0.23 mg/kg) or saline 1 min IV bolus delivered.
+1	VS; Ketamine (0.58 mg/kg/hour) or saline IV infusion starts.
+5	VS
+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	VS and blood samples; eye-tracking task[a].
+70	Other ERP tasks[a].
+80	Terminate infusion; VS; retrospective BPRS, CADSS symptom ratings.
+100	VS
+120	VS; safety ratings (mental status exam, field test).

Note. IV = Intravenous; CADSS = Clinician Administered Dissociative Symptoms Scale (93); VS = Vital signs; BPRS = Brief Psychiatric Rating Scale (94).

[a]Not analyzed in the current report.

Table 3

Measures of psychotomimetic effects of ketamine.

Measure	Pre-Saline Infusion mean (SD)	Saline Infusion mean (SD)	Pre-Ketamine Infusion mean (SD)	Ketamine Infusion mean (SD)
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)

Note. SD=Standard deviation. BPRS=Brief Psychiatric Rating Scale. CADSS=Clinician Administered Dissociative Symptom Scale.

Table 4

ANOVA of N1 amplitude during ketamine vs. saline experiment *

Effect	df	F	p-value	Partial Eta Squared
Ketamine/Saline	1,30	3.11	0.088	0.094
Talk/Listen	1,30	100.33	<.0001	0.77
AP (Anterior-Posterior: Fz, FCz, Cz)	2,60	2.59	0.11	0.079
Time (Time 1 vs. Time 2)	1,30	0.06	0.80	0.002
Talk/Listen * Ketamine/Saline	1,30	3.06	0.09	0.093
Ketamine/Saline * AP	2,60	0.62	0.47	0.02
Talk/Listen * AP	2,60	13.69	<.0001	0.313
AP: Talk Fz=FCz>Cz	2,60	4.40	0.04	0.13
AP: Listen Fz<FCz=Cz	2,60	23.81	<.0001	0.44
Talk/Listen * Ketamine/Saline * AP	2,60	0.07	0.85	0.002
Ketamine/Saline * Time	1,30	5.26	0.03	0.149
Talk/Listen * Time	1,30	7.26	0.01	0.195
Talk/Listen * Ketamine/Saline * Time	1,30	15.90	<.0001	0.346
Talk/Listen*Ketamine/Saline: Time 1	1,30	2.58	0.12	0.079
Talk/Listen*Ketamine/Saline: Time 2	1,30	13.52	0.001	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	0.001	0.307
Ketamine/Saline: Listen	1,30	0.07	0.80	0.002
Talk/Listen*Time: Ketamine	1,30	17.73	<.0001	0.371
Time:Talk	1,30	11.38	0.002	0.275
Time:Listen	1,30	2.87	0.10	0.087
Talk/Listen*Time: Saline	1,30	2.23	0.15	0.069
Ketamine/Saline × Time: Talk	1,30	15.88	<.001	0.35
Ketamine/Saline: T1	1,30	0.67	0.42	0.02
Ketamine/Saline: T2	1,30	13.27	<.001	0.31
Ketamine/Saline × Time:Listen	1,30	0.88	0.36	0.03
AP * Time	2,60	6.18	0.01	0.171
Ketamine/Saline * AP * Time	2,60	0.33	0.64	0.011
Talk/Listen * AP * Time	2,60	0.18	0.73	0.006
Talk/Listen * Ketamine/Saline * AP * Time	2,60	0.45	0.55	0.015

* Bold font indicates interactions with Talk/Listen that are parsed with follow-up tests.

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	0.435	0.009
Talk/Listen	1,65	50.851	**<.0001**	0.439
Talk/Listen * Group (HC vs. SZ)	1,65	7.214	**0.009**	0.100
Talk/Listen for HC	1,32	47.435	**<.0001**	0.597
Talk/Listen for SZ	1,33	10.038	**0.003**	0.233
Talk: Group (SZ>HC)	1,65	3.835	**0.054**	0.056
Listen: Group (HC>SZ)	1,95	1.765	0.189	0.026
AP (Anterior-Posterior: Fz, FCz, Cz)	2,130	1.857	0.175	0.028
AP * Group	2,130	1.589	0.214	0.024
Talk/Listen * AP	2,130	6.701	**0.004**	0.093
AP: Talk (n.s.)	2,130	2.91	.077	.043
AP: Listen Fz<FCz>Cz; Fz=Cz	2,130	8.70	.002	.118
Condition * AP * Group	2,130	0.604	0.509	0.009