Archival Report

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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

SEE COMMENTARY ON PAGE 465

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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 noncompleters 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