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Diminished auditory sensory gating during active auditory verbal hallucinations

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ABSTRACT

Auditory sensory gating, assessed in a paired-click paradigm, indicates the extent to which incoming stimuli are filtered, or "gated", in auditory cortex. Gating is typically computed as the ratio of the peak amplitude of the event related potential (ERP) to a second click (S2) divided by the peak amplitude of the ERP to a first click (S1). Higher gating ratios are purportedly indicative of incomplete suppression of S2 and considered to represent sensory processing dysfunction. In schizophrenia, hallucination severity is positively correlated with gating ratios, and it was hypothesized that a failure of sensory control processes early in auditory sensation (gating) may represent a larger system failure within the auditory data stream; resulting in auditory verbal hallucinations (AVH).

EEG data were collected while patients ($N = 12$) with treatment-resistant AVH pressed a button to indicate the beginning (AVH-on) and end (AVH-off) of each AVH during a paired click protocol. For each participant, separate gating ratios were computed for the P50, N100, and P200 components for each of the AVH-off and AVH-on states. AVH trait severity was assessed using the Psychotic Symptoms Rating Scales AVH Total score (PSYRATS).

The results of a mixed model ANOVA revealed an overall effect for AVH state, such that gating ratios were significantly higher during the AVH-on state than during AVH-off for all three components. PSYRATS score was significantly and negatively correlated with N100 gating ratio only in the AVH-off state.

These findings link onset of AVH with a failure of an empirically-defined auditory inhibition system, auditory sensory gating, and pave the way for a sensory gating model of AVH.

1. Introduction

Auditory verbal hallucinations (AVH) involve the perception of speech in the absence of external auditory stimulation. AVH often contain derogatory and threatening content, thereby increasing patient anxiety and possibly encouraging social withdrawal (Delespaul et al., 2002). While often benign, AVH have also been reported in non-clinical populations; yet the consequences and content of AVH in patients with schizophrenia tend to be more negative and severe. Many authors have linked the etiology of schizophrenia AVH to auditory processing abnormalities. For example, the efference-copy model of AVH developed by Ford et al. (2001, 2007, 2012), suggests that AVH arise from an impaired ability to correctly label auditory verbal processing as either internally self-generated, or as externally generated. For example, Ford et al. (2001) showed that a pattern of larger N100 response to externally-generated speech sounds relative to the N100 response to their own recorded speech sounds found in healthy controls was not observed in patients with schizophrenia. Similarly, other research has suggested that the auditory system of patients with schizophrenia may preferentially respond to emotionally salient or voice-like sounds, as indicated by increased reported detection of speech sounds in noise (Vercammen et al., 2008). Patients with more severe schizotypy have also been shown to report a stronger perception of emotionally salient voice sounds in noise (Galdos et al., 2011). In a parallel line of research, Woodruff et al. (1997) showed that BOLD signal response in language-processing areas of the brain in patients reporting hallucinations were reduced in

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response to speech sounds; they hypothesized that this result was due to competition between hallucinations and the external stimuli for temporal cortical processing sites.

One means of directly measuring auditory perceptual abnormality is by measurement of auditory sensory gating. When assessed in terms of a paired-click paradigm, sensory gating is one means of measuring modulation of incoming auditory information as early as 50 ms into cortical processing. The paired-click paradigm involves presentation of two clicks in rapid succession. In the auditory event-related potential (AERP), a large reduction of the response to the second stimulus (S2) relative to that of the first (S1) is interpreted as effective suppression of redundant stimulus information, and a reduction of 67% (S2/S1 = 1/3) or more is common in healthy neurotypical control subjects (Cromwell et al., 2008). Smaller reduction, or lack of reduced relative AERP amplitude to S2 is typical of patients with schizophrenia (Patterson et al., 2008). Two recent studies have directly tested the hypothesis that sensory gating, as a measure of schizophrenia abnormality of auditory perceptual processing, is related to AVH. Using the PANSS Item *P*3, a general measure of hallucination frequency and severity across sensory modalities, Faugère et al. (2016) demonstrated higher AVH scores (item *P*3) in a group of schizophrenia patients with greater P50 sensory gating impairment relative to that of a group without P50 sensory gating impairment. Smith et al. (2013) demonstrated a positive correlation between the extent of P50 sensory gating deficit and the severity of AVH, assessed with the psychotic symptom rating scales (PSYRATS).

Sensory gating ratios are stable across time and are extremely reliable in healthy neurotypical subjects (Rentzsch et al., 2008; Fuerst et al., 2007). In patients with schizophrenia, gating ratios can be far more variable (Smith et al., 1994), but the sources of that variability are unknown. The present study was designed to test whether auditory sensory gating is a state characteristic that varies as does AVH state (AVH-on versus AVH-off), or whether it may be better considered as a trait marker for AVH. Using a button-press protocol to have patients indicate when AVH-related voices started and stopped, distinct periods of AVH-on and AVH-off were identified. It was predicted that if sensory gating is sensitive to state characteristics within the auditory processing system, sensory gating ratios would evince greater impairment during AVH-on than during AVH-off.

2. Experimental/materials and methods

2.1. Participants

Participants were recruited through referral by other researchers, from the University of New Mexico Health Sciences Center and other community clinics, and through ads posted on bulletin boards throughout the Albuquerque metropolitan area. All data were collected only after review and approval of the study by the University of New Mexico Health Sciences Center Human Subjects Protections Office (HRPO). All participants provided written informed consent and were informed that they could leave the study at any time without penalty. Inclusion criteria required age range was 18–60 years old, and diagnoses of schizophrenia or schizoaffective disorder, which was confirmed with SCID-CV. All participants had a history of frequent AVH documented in the medical record, and AVH frequency of at least two AVH per hour mixed with non-AVH periods, as determined by a hallucination "diary" which was filled out across the week preceding scanning. Exclusionary criteria were history of head injury with more than 5 min of unconsciousness, diagnosis of neurological disorder or disease, and current alcohol or other substance dependence. All participants underwent urine analysis and Breathalyzer to exclude acute drug or alcohol intoxication during data collection. All scans were acquired at the Mind Research Network (MRN) neuroimaging facility in Albuquerque, NM. Magnetoencephalography (MEG) data were simultaneously collected with EEG data for future analysis and structural MRI data were collected for signal localization. As these data were collected as part of a larger study, prior to enrollment, prospective participants' head size was measured to assure they would fit within the MEG helmet and metal screening information was collected to assure that they were safe and comfortable within the MRI environment prior to study enrollment.

2.2. Data collection procedures.

Twelve participants met all study criteria and completed the EEG scanning protocol. Of those, ten participants were administered the Positive and Negative Schizophrenia Syndromes Scale (PANSS; Kay et al., 1989) and the Psychotic Symptoms Rating Scales (PSYRATS; Haddock et al., 1999) on the day of scanning to assess the frequency and severity of their AVH. In the days prior to scanning, all participants were administered a structured button-press training course in which they were trained to reliably recognize the onset and off-set of AVH and to press appropriate buttons to indicate the beginning (AVH-on) and end (AVH-off) of each AVH. Practice on button-press procedures was administered again immediately prior to scanning for review. To assure adherence to AVH-reporting procedures, participants were continuously monitored by study personal during scanning to assure that the sequencing of button presses were appropriate to the AVH-on and AVH-off pattern. Additionally, during data analysis, epochs occurring during periods in which there were multiple consecutive button presses with the same hand were considered artifactual and those data were removed from further analysis.

Participants were seated in a comfortable reclining chair in which head motion was minimized by the use of pillows and foam cushions around the head, neck, and if necessary, the lower back and under the knees. Participants were equipped with gloves fitted with buttons for right and left index fingers, indicating AVH-on with a single right-hand button press (and immediate release) and AVH-off with a single left-hand button press. All EEG data were collected in a single session. EEG data were collected with eyes open, and participants were instructed to gaze at a continuous fixation point (small black cross) projected on the center of a white projection screen placed 36 in. from their face. EEG scans were conducted in a magnetically shielded and acoustically insulated room (Vacuumschmelze GmbH & Co. KG).

Click stimuli were created with Audacity® software, were 3 milliseconds (ms) in duration, square-wave pulses with spectral power across the 8–22,000 Hz range. Stimuli were delivered using Presentation® software into the participant's ear canal using Etymotic earphones. Foam ear inserts were affixed within both ears and hearing thresholds for click stimuli were determined for each ear, for each subject. Click intensity was set to 30 dB above the participant's hearing threshold within the Presentation software. The Presentation software was tested independently using a sound meter to ensure that software dB settings were calibrated. Click pairs were then presented binaurally to the participant with a 500 ms inter-stimulus interval and variable inter-trial-intervals that varied pseudo-randomly by 1 s intervals between 8 and 12 s.

EEG data were collected using a 10–20 electrode array, but latency and amplitude measurements were computed on the basis of data derived from electrode Cz referenced to left earlobe. Maximum impedance of 10 kΩ was allowed for all electrodes. EEG data were digitized at 1200 Hz during data collection and down-sampled to 300 Hz offline prior to analysis. Eye motion was monitored within independent bipolar vertical electrooculogram (VEOG) and horizontal electrooculogram (HEOG). Epochs in which raw EEG or EOG amplitude >100 μV were discarded as artifacts and a minimum of 150 trials of artifact-free trials were collected for all participants. EEG highpass (0.1 Hz) and lowpass (330 Hz) filters were set to minimal system allowable levels during data collection.

After scanning, participants were administered a post-scan interview to review their experiences during scanning, including level of

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