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A tale of two sites: Differential impairment of frequency and duration mismatch negativity across a primarily inpatient versus a primarily outpatient site in schizophrenia

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ABSTRACT

Deficits in mismatch negativity (MMN) generation are among the best replicated neurophysiological deficits in schizophrenia, with reduced amplitude reflecting impaired information processing at the level of supratemporal auditory cortex. Differential patterns of MMN dysfunction according to deviant types have been reported across studies, with some research groups showing impairment in duration MMN but not frequency MMN, and other research groups reporting both findings. We evaluate the hypothesis that recruitment setting, reflecting current functional status, might be an important determinant of the pattern of MMN dysfunction. Here, we evaluated patterns of MMN dysfunction, along with tone matching and neuropsychological performance in subjects drawn from 1) a predominant inpatient/residential care setting (Nathan Kline Institute) and 2) a predominant outpatient setting (Columbia University). As predicted, compared to healthy controls, deficits in duration MMN were observed across sites, whereas deficits in frequency MMN/tone matching were confined to the chronic inpatient setting. Within patients, the frequency MMN deficit was highly correlated with impairments in tone matching ability across sites ($r = -0.52$, $p < 0.0001$), as well as impairments in verbal learning ($r = -0.54$, $p < 0.0001$). Responses to standard stimuli in the MMN paradigm were assessed using measures of alpha evoked power and inter-trial coherence (ITC). While deficits in alpha ITC were observed across sites (both $p < 0.05$), deficits in alpha power were observed at the inpatient ($p = 0.001$) but not outpatient ($p = 0.2$) site. Overall, these finding indicate that impairments of frequency MMN generation and response power to standard stimuli could be particularly linked to forms of schizophrenia that are associated with poor functional outcome.

1. Introduction

Schizophrenia is a severe mental disorder associated with generalized impairments in cognitive function. Deficits involve impairments not only in complex functions such as executive function and working memory but also basic sensory function such as auditory or visual processing (rev. in Javitt, 2009; Javitt and Freedman, 2015; Kantrowitz et al., 2015a). Auditory mismatch negativity (MMN) is a neurophysiological biomarker that indexes neural mechanisms underlying cognitive dysfunction in schizophrenia (rev. in Hay et al., 2015; Javitt et al., 2000b; Javitt and Sweet, 2015; Light and Naatanen, 2013; Naatanen et al., 2014). Moreover, MMN deficits correlate highly with level of function in established (Friedman et al., 2012; Light and Naatanen, 2013), first-episode (Salisbury et al., 2016) and prodromal (Carrion et al., 2015; Perez et al., 2014) schizophrenia, suggesting that it indexes core pathophysiological mechanisms.

MMN is generated most frequently by deviant stimuli within an auditory oddball paradigm (Mantysalo and Naatanen, 1987) in which a series of standard stimuli are interrupted infrequently by a physically or conceptually deviant oddball stimuli. Deviants may differ from standards according to multiple characteristics, to date MMN deficits in schizophrenia have been most extensively studied to duration- and frequency (pitch)-deviant stimuli. Furthermore, the relative degree of deficit for duration vs. frequency MMN is the subject of ongoing controversy (Avissar et al., 2017), with some research groups reporting selective deficits in duration MMN (e.g. Todd et al., 2008) and others reporting deficits across MMN types (e.g. Friedman et al., 2012). The basis for the differential findings remains unknown.

Abbreviations: MMN, Mismatch negativity; ITC, Intertrial coherence; ERSP, Event related spectral perturbation; PANSS, Positive and negative symptoms scales; MCCB, The Measurement and Treatment Research to Improve Cognition in Schizophrenia(MATRCS) consensus cognitive battery.

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Schizophrenia patients also show severe deficits in delayed tone matching ability, a process that is known to localize primarily to auditory sensory cortex (Javitt et al., 1997; Strous et al., 1995). However, despite these elevated tone matching thresholds, patients do not show increased susceptibility to either same- (Rabinowicz et al., 2000) or cross-(March et al., 1999) modality distractors, suggesting that top-down modulation of the auditory system remains intact (Javitt and Sweet, 2015).

We have previously shown that tone matching deficits strongly distinguish between patients recruited primarily from a chronic inpatient/residential care setting vs. those drawn from a primarily outpatient setting (Rabinowicz et al., 2000). The present study takes advantage of the recent establishment of a laboratory studying primarily schizophrenia outpatients (Columbia University) to evaluate patterns of MMN deficit relative to those observed in previous studies involving primarily inpatient/residential care patients (Nathan Kline Institute, NKI).

Based upon our prior tone matching findings (Rabinowicz et al., 2000), we hypothesized that frequency MMN deficits would be observed primarily among patients drawn from the inpatient/residential care setting, and would be selectively associated with impaired tone matching ability. Recently, it has been demonstrated that impaired early auditory processing affects psychosocial function in part through effects on verbal learning (Thomas et al., 2017). We thus also hypothesized that similar relationships might be observed across recruitment sites in the present study.

Finally, we have recently observed that schizophrenia patients drawn from a primarily inpatient facility (NKI) show deficits in response to standard as well as deviant stimuli in the auditory paradigm when event-related spectral perturbation (ERSP, "time-frequency") analyses are used to differentiate stimulus-related alpha (8–12 Hz) activity from MMN-related activity that occurs primarily in the theta (4–7 Hz) frequency range (Hong et al., 2012; Javitt et al., 2017; Javitt et al., 2000a; Kaser et al., 2013). Stimulus-related alpha is thought to preferentially reflect thalamocortical activity (Haegens et al., 2015; Potes et al., 2014) and thus may index the earliest stages of the auditory thalamocortical response. By contrast, theta activity may reflect subsequent cortico-cortical synchrony related to deviance detection (Javitt et al., 2017).

In addition, ERSP analyses permit differentiation of activity related to phase-reset of ongoing rhythms, manifest as alterations in intertrial coherence (ITC), with alterations in single-trial power that may ("evoked power") or may not ("induced power") be strongly phase-locked to the eliciting stimulus. ITC and single-trial power may reflect actions of separate thalamocortical systems (Viaene et al., 2011).

Auditory inputs from thalamus to auditory cortex have been divided into non-lemniscal inputs deriving prominently from the thalamic matrix vs. lemniscal inputs deriving from the thalamic core. Non-lemniscal inputs project primarily to superficial cortical layers and provide modulatory inputs that primarily induce phase-reset of ongoing cortical rhythms. By contrast, leminiscal inputs project primarily to layer 4 and mediate driving input to cortex that leads to increases in both single-trial power and ITC (Jones, 2009; Viaene et al., 2011).

Furthermore, non-lemniscal inputs show poor tonotopic organization but strong sensitivity to rhythm and thus may be preferentially involved in generation of MMN to duration deviance. By contrast, leminiscal inputs have strong tonotopic organization and may be preferentially involved in generation of MMN to frequency deviance (rev. in Lee et al., 2017). Based upon these differential projection systems, we have recently proposed that impairments in (non-lemniscal) phase-reset mechanisms may contribute to selective impairments in duration MMN across schizophrenia groups, whereas additional pathology related to core projections may contribute to additional deficits in frequency MMN in lower functioning schizophrenia subjects (Lee et al., 2017).

Here, we tested the hypothesis further by evaluating differential ITC vs. single-trial power deficits in the alpha-band response to standard stimuli in high functioning vs. lower functioning patients with schizophrenia. We hypothesized that patients drawn from the primarily outpatient site (Columbia) would show deficits in alpha ITC to standards, whereas those drawn from the primarily inpatient site (NKI) would show deficits related to both ITC and single-trial power. Furthermore, consistent with our prior observations, we hypothesized that deficits in response to standard stimuli would correlate with impaired MMN generation, suggesting important thalamocortical as well as corticocortical contributions to impaired MMN generation in schizophrenia.

2. Methods

2.1. Participant

A total 167 subjects were studied across the two sites (Table 1). Subjects met DSM-IV criteria for schizophrenia and were of either gender and of age 18–60 yrs. Exclusion criteria included current or past history of substance or alcohol dependence or abuse, and a lifetime history of other psychiatric (Axis I) or neurologic disorders. The structured clinical interview for DSM-IV (SCID) was used to establish diagnosis. The study was approved by the Institutional Review Boards of the respective institutions and written informed consent was obtained from all subjects. Controls were recruited from the staff and surrounding community at each site. Subjects were paid for their participation.

2.2. Procedure

Stimulation procedures were identical to those described previously (Lee et al., 2017). Briefly, auditory stimuli consisted of a sequence of tones presented in random order with a stimulus onset asynchrony of 500–505 ms. Standard stimuli (70% sequential probability) were harmonic tones composed of three superimposed sinusoids (500, 1000, and 1500 Hz) 100-ms in duration, ~85 dB, and with 5-ms rise and fall time. Frequency, duration and intensity deviants (10% probability each) were 10% lower in frequency, 50-ms longer in duration and 10 dB lower in intensity, respectively. At the beginning of each run, the first 15 auditory stimuli were standards. Intensity deviants were excluded from analysis. Simultaneous visual stimuli were presented as distractors. For the visual task, a sequence of schematic animal pictures was presented sequentially on the screen and subjects were instructed to press the button in response to a predesignated target animal. Visual/auditory stimuli were presented in interleaved fashion during 250 s blocks, with brief pauses between blocks.

2.3. Data acquisition

At NKI, continuous EEG data along with digital timing tags were acquired with either a 72- or 168-channel BioSemi® Active II system with standard reference and ground procedures. At Columbia, data were obtained on a 64-channel Brainvision® system with standard reference and ground procedure. All data were transformed to an 81 channel reference free montage prior to analysis using a spherical spline approach implemented in BESA 5.1 (Perrin et al., 1989) and were then epoched from −500 ms to 1000 ms. An independent component analysis (ICA) was performed for artifact removal. In addition, epochs exceeding ±100 μV were rejected.

For ERP analyses, waveforms were averaged by stimulus type and baseline-corrected relative to pre-stimulus baseline. MMN waveforms were determined by subtraction of standard from deviant responses. Standard and MMN responses were assessed at the frontal midline (Fz) electrode relative to mastoids. Frequency and duration MMN were determined within the 110–200 and 180–260 ms ranges, respectively (Supplemental Table 1).

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