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Developmental trajectory of mismatch negativity and visual event-related potentials in healthy controls: Implications for neurodevelopmental vs. neurodegenerative models of schizophrenia

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ABSTRACT

Sensory processing deficits are core features of schizophrenia, reflected in impaired generation of event-related potential (ERP) measures such as auditory mismatch negativity (MMN) and visual P1. To understand the potential time course of development of deficits in schizophrenia, we obtained MMN to unattended duration, intensity and frequency deviants, and visual P1 to attended LSF stimuli, in 43 healthy individuals ages 6 to 25 years (mean 17), and compared results to data from 30 adult schizophrenia patients (mean age 38). We analyzed "time-domain" measures of amplitude and latency, and event-related spectral perturbation (ERSP, "time-frequency") to evaluate underlying neurophysiological mechanisms.

Duration and intensity MMN amplitudes increased from childhood to late adolescence, while frequency MMN reached maximum amplitude during early development. As reported previously, in ERSP analyses, MMN activity corresponded primarily to theta-band (4–7 Hz) activity, while responses to standards occurred primarily in alpha (8–12 Hz) across age groups. Both deviant-induced theta and standard-induced alpha activity declined significantly with age for all deviant types. Likewise, visual P1 also showed an amplitude decline over development, reflecting a reduction in both evoked power and ITC.

While MMN "difference" waveform ERP data suggest failure of maturation in schizophrenia, MMN ERSP analyses instead support a neurodegenerative process, as these isolate responses to deviants and standards, showing large low-frequency evoked power for both in children. Neurodegenerative processes are also supported by large visual P1 amplitudes and large low-frequency evoked power in children, in contrast with adult schizophrenia. Sensory processing deficits in schizophrenia may be related to accelerated synaptic pruning.

1. Introduction

Deficits in sensory processing are core characteristics of schizophrenia (rev. in Javitt, 2015). These deficits may be assessed objectively using event-related potentials (ERP) such as auditory mismatch negativity (MMN) and visual P1, which index neurophysiological processing within auditory and visual sensory cortices, respectively. Deficits in both MMN and visual P1 have been extensively replicated in schizophrenia (e.g. Friedman et al., 2012). The present study evaluates MMN and visual P1 in a cohort of normally developing children and adolescents in order to permit interpretation of ERP abnormalities in schizophrenia within a neurodevelopmental framework.

We have previously shown that higher cognitive abilities as reflected in attention/vigilance or composite scores on the MATRICS consensus cognitive battery (MCCB) increase dramatically from late childhood to adulthood, whereas sensory measures such as face (FER) or auditory (AER) emotion recognition tend to develop earlier and then plateau (Corcoran et al., 2015). Theories of schizophrenia pathogenesis based upon higher order cognitive assessment might suggest a "developmental arrest" during late adolescence, with schizophrenia patients retaining the cognitive abilities, in general, of 12–16 year olds (Fuller et al., 2002). However, studies of sensory systems might provide complementary information and assist in identifying both early neurodevelopmental and later neurodegenerative processes.

MMN is typically assessed within the context of an auditory "oddball" paradigm, in which less frequent deviant stimuli interrupt a series of repetitive standard stimuli (Friedman et al., 2012). Deviants typically differ from standards in duration, intensity or frequency, though can

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vary in any domain, such as spatial location or phonological features (Kantrowitz et al., 2015). The most common analysis of auditory oddball data is in the time-domain, in which the mismatch negativity (MMN) event-related potential (ERP) is calculated as the difference waveform in frontocentral and other regions between averaged responses to deviants (larger in amplitude) and standards (smaller in amplitude).

Reduction in auditory MMN ERP amplitude is among the most replicated biomarkers of schizophrenia (Javitt, 2015), and it is an early core characteristic of schizophrenia, evident even in prodromal stages of illness (Bodatsch et al., 2011; Higuchi et al., 2013; Kayser et al., 2014; Perez et al., 2014; Shaikh et al., 2012; van Tricht et al., 2015). Auditory MMN may further deteriorate after illness onset in initially high functioning subjects (Devrim-Ucok et al., 2008; Kaur et al., 2013; Salisbury et al., 2007), although others show stable deficits following onset (Koshiyama et al., 2017; Light and Braff, 2005).

It has been reported that over normal development, auditory MMN tends to increase gradually from childhood through adolescence, specifically for deviants of higher frequency (Bishop et al., 2011; Cooray et al., 2016; Mahajan and McArthur, 2015), suggesting its reduction in schizophrenia may represent a failure of maturation in line with that observed for higher cognitive functions (Corcoran et al., 2015; Fuller et al., 2002; Hood et al., 1989). Nevertheless, literature on normal MMN development during the at-risk period for development of schizophrenia (early teens-late twenties) is sparse - especially for non-tonal deviants such as duration or intensity - limiting the degree to which the MMN literature in schizophrenia can be assessed within a developmental framework.

Deficits in visual processing are also evident in schizophrenia, specifically impairment in magnocellular-based processing of low spatial frequency (LSF) stimuli, indexed by the visual P1 ERP, a bilateral positivity at 100–120 ms over dorsal occipital scalp (Javitt, 2015). Visual P1 amplitude reduction is a replicated finding in schizophrenia (Javitt, 2015) that appears stable after illness onset (Oribe et al., 2015). Cross-sectional behavioral studies show abnormal visual processing in clinical high-risk samples (Kimhy et al., 2007; Mittal et al., 2015), that may significantly predict conversion to schizophrenia (Corcoran et al., 2015). As visual P1 amplitudes significantly decrease over normal development (Batty and Taylor, 2006; Hileman et al., 2011; MacNamara et al., 2016; Meaux et al., 2014), the small visual P1 amplitude observed in schizophrenia may be due to either early maturational or later neurodegenerative processes (Friedman et al., 2012).

In addition to conventional time-domain analysis of the ERP data, we also conducted time-frequency analyses (event-related spectral perturbation, ERSP), which provide additional data regarding underlying neurophysiological mechanisms (Javitt, 2015; Lee et al., 2017). Auditory stimuli normally evoke power in the low-frequency range, with deviants evoking theta (4–7 Hz) and standards primarily evoking alpha (7–12 Hz) power; individuals with schizophrenia have reduction in low-frequency evoked power (and intertrial coherence) to both standards and deviants (Lee et al., 2017).

As opposed to MMN amplitude measured in the time-domain, evoked theta to MMN deviants is high in children and decreases over development (Bishop et al., 2011; Ehlers et al., 2014), potentially reflecting normal developmental pruning and refinement of sensory maps. To the extent that this is true, reductions in MMN theta amplitude may serve as an index of the accelerated pruning that may contribute to development of neurocognitive impairments in schizophrenia (Feinberg, 1990). We have also recently observed that deficits in visual P1 are associated with theta-band dysfunction (Martinez et al., 2015). The developmental trajectory of visual-evoked low-frequency responses, however, remains to be determined.

To gain insight into the potential time course over which auditory and visual processing deficits develop in schizophrenia, we administered a passive auditory oddball paradigm, with attended visual stimuli (Friedman et al., 2012) to young people ages 6 to 25 in the NKI-Rockland community-ascertained cohort (Nooner et al., 2012). This paradigm was previously administered to schizophrenia patients, finding reductions in auditory MMN and visual P1 (Friedman et al., 2012), and significant reduction in low-frequency evoked power for both auditory MMN deviants and standards (Lee et al., 2017). Therefore, we can contextualize these findings of abnormal auditory and visual processing in schizophrenia in respect to their normal developmental trajectory, using the same paradigm. For auditory processing, we expected to replicate increases in auditory MMN ERP in the context of decreases in low-frequency evoked power over development (Bishop et al., 2011; Ehlers et al., 2014; MacNamara et al., 2016). Likewise, we expected a decrease in visual P1 over development (MacNamara et al., 2016), and hypothesized large low-frequency evoked power in children, similar to that previously seen for auditory stimuli (Bishop et al., 2011). Together, these findings would evaluate the utility of MMN and other sensory ERP for investigation of neurodevelopmental vs. neurodegenerative processes in schizophrenia.

2. Methods

2.1. Participants

Subjects were 43 young people ascertained from the NKI-Rockland community-ascertained cohort (Nooner et al., 2012), ranging in age from 6 to 25, mean (SD) age = 17.4 (5.5) years, 58% male. Also, EEG data for the same auditory oddball paradigm were available from thirty adults with schizophrenia mean (SD) age = 38.0 (10.7) years, previously studied within the Schizophrenia Research Division at the Nathan Kline Institute (Friedman et al., 2012; Lee et al., 2017). Written informed consent was obtained from adults, and for parents of minors, who themselves provided written assent. Exclusion criteria for all participants included organic brain disorders, mental retardation, past drug or alcohol dependence, current drug or alcohol abuse, and hearing/vision impairments. The study was approved by the Institutional Review Boards of Nathan Kline Institute and Columbia University.

2.2. Procedure

The paradigm is as described previously (Friedman et al., 2012): a series of tones were presented at random with stimulus onset asynchrony (SOA) of 500–505 ms. Standards occurred with a sequential probability of 70%, and were harmonic tones of three superimposed sinusoids of 500, 1000 and 15,000 Hz, that were 100 ms in duration, 85 dB and with a 5 ms rise and fall. Each of the three deviants had a sequential probability of 10%. The frequency deviant was 10% lower in pitch; the duration deviant was 50 ms longer in duration; and the intensity deviant was 10 dB lower in loudness.

During auditory stimulus presentation, participants attended to a sequence of visual stimuli, which consisted of 39% HSF (5 Hz) and 39% LSF (1 Hz) horizontal gratings, viewed at 114 cm, with a stimulus field subtended 6.1–4.6° of visual angle. Stimuli were presented centrally against a 50% gray background isoluminant with mean luminance of the sinewave gratings, with SOA 875 ± 25 ms.

There was no stimulus overlap, and auditory and visual stimuli were presented in 250 s blocks, with eight blocks per participant.

2.3. Data acquisition

Continuous EEG data, with digital timing tags, were acquired using a 64-channel ANT with standard reference and ground procedures. Sample rate was 512 Hz. Eyeblinks were removed using independent component analysis (ICA) in EEGLAB (<10%). Using BESA, data were epoched (−500 to 1000 ms) with baseline (−500 to 0) correction, and then high-pass filtered (0.30 Hz, 6 db/oct, forward). Epochs with activity exceeding ±120 μV were rejected, resulting in 68% of 250 trials retained. Interpolation of channels occurred at <10%. Epochs were averaged offline for each stimulus type for each participant.

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