



Contributions of early cortical processing and reading ability to functional status in individuals at clinical high risk for psychosis



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ABSTRACT

Background: There is a growing recognition that individuals at clinical high risk need intervention for functional impairments, along with emerging psychosis, as the majority of clinical high risk (CHR) individuals show persistent deficits in social and role functioning regardless of transition to psychosis. Recent studies have demonstrated reduced reading ability as a potential cause of functional disability in schizophrenia, related to underlying deficits in generation of mismatch negativity (MMN). The present study extends these findings to subjects at CHR.

Methods: The sample consisted of 34 CHR individuals and 33 healthy comparison subjects (CNTLs) from the Recognition and Prevention (RAP) Program at the Zucker Hillside Hospital in New York. At baseline, reading measures were collected, along with MMN to pitch, duration, and intensity deviants, and measures of neurocognition, and social and role (academic/work) functioning.

Results: CHR subjects showed impairments in reading ability, neurocognition, and MMN generation, relative to CNTLs. Lower-amplitude MMN responses were correlated with worse reading ability, slower processing speed, and poorer social and role functioning. However, when entered into a simultaneous regression, only reduced responses to deviance in sound duration and volume predicted poor social and role functioning, respectively.

Conclusions: Deficits in reading ability exist even prior to illness onset in schizophrenia and may represent a decline in performance from prior abilities. As in schizophrenia, deficits are related to impaired MMN generation, suggesting specific contributions of sensory-level impairment to neurocognitive processes related to social and role function.

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1. Introduction

Schizophrenia is a severe mental disorder associated with significant disruptions in functioning. Impairments in social and occupational functioning reduce independence, limit educational attainment, and decrease quality of life (Green, 2006; Harvey et al., 2012), placing a substantial burden on patients, family members, friends and wider society (Knapp et al., 2004; Awad and Voruganti, 2008). Given that functional impairments in schizophrenia are rooted early in development, pre-illness social problems and school difficulties can provide a pivotal pathway to understanding the determinants of long-term disability. Recent research in schizophrenia has, therefore, focused on the detection of individuals at clinical high-risk (CHR) for developing the illness, with

the ultimate goal of permitting focused intervention to prevent both conversion to psychosis and functional disability.

In established schizophrenia, several factors including neurocognition, negative symptoms, and social cognition are strongly connected to everyday functioning. In addition, over recent years there has been increasing appreciation of the importance of impaired sensory processing. For example, amplitudes of the auditory mismatch negativity (MMN) are strongly associated with work, community, and independent functioning both in patients with schizophrenia (Light and Braff, 2005a, b; Kawakubo and Kasai, 2006; Wynn et al., 2010; Kim et al., 2014; Lee et al., 2014) and first-episode psychosis (Friedman et al., 2012). The MMN is an auditory event-related potential (ERP) that reflects deviance-detection within the primary auditory cortex (Wible et al., 2001; Light and Näätänen, 2013). MMN amplitude reductions in schizophrenia were first demonstrated over 20 years ago (Shelley et al., 1991; Javitt et al., 1993) and were tied to impaired neurotransmission at N-methyl-D-aspartate (NMDA) receptors (Javitt et al., 1996; Umbricht et al., 2000; Javitt,

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2009). Since then, impairments have been replicated multiple times, with patients showing deficits of approximately 1 standard deviation (SD) across a range of deviant types (Umbricht and Krljes, 2005; Todd et al., 2008). Deficits in reading ability have also been increasingly documented over recent years (Revheim et al., 2006; Martinez et al., 2012; Whitford et al., 2013). In a recent study in patients with schizophrenia, reading ability deficits were related with impaired MMN generation (Revheim et al., 2014), suggesting that deficits in early auditory processing may cascade up to produce impairments in higher-order abilities that are in turn linked to functioning in the environment.

To date, studies of sensory function in individuals at CHR have focused primarily on MMN from the vantage of transition to schizophrenia. Such studies have demonstrated consistent reductions of MMN in CHR individuals, albeit of smaller magnitude (typically 0.6–0.8 SDs vs. controls) than those observed in schizophrenia (Bodatsch et al., 2011; Atkinson et al., 2012; Jahshan et al., 2012; Shaikh et al., 2012; Higuchi et al., 2013; Perez et al., 2014; Solis-Vivanco et al., 2014). In addition, reductions in MMN amplitudes significantly predict conversion to psychosis among CHR individuals (Bodatsch et al., 2011; Atkinson et al., 2012; Shaikh et al., 2012; Higuchi et al., 2013; Perez et al., 2014). However, a relationship between MMN and functioning in this vulnerable population has remained relatively unexplored.

Given that the antecedents of functional disability associated with schizophrenia are present years prior to the onset of the illness, adolescents and young adults at CHR may provide a timely window for investigating the contributions of early cortical processing to social and role functioning. Although prior MMN studies in CHR individuals have focused primarily on predictions of conversion to psychosis, the present study focuses as well on early sensory contributions to social and role functioning within the CHR population. In recent studies (Carrión et al., 2011; Olvet et al., 2013; Meyer et al., 2014), we have demonstrated significant social and role (i.e., work/academic) functioning impairments in individuals meeting CHR criteria. Furthermore, patients showed neurocognitive impairments that were highly predictive of impaired social and role functioning. Moreover, initial CHR classification is associated with persistent and long-standing functional difficulties independent of emerging psychotic symptoms (Carrión et al., 2013), suggesting that functional impairments may be viewed as an important component of the CHR state irrespective of ultimate conversion status. The present study was designed to replicate and extend these investigations by utilizing a neurophysiological biomarker of early auditory cortical function, along with standard neuropsychological measures, to further examine pathways to impaired functioning in CHR individuals. In addition, given recent reports of impaired reading ability in schizophrenia, the present study includes measures of reading ability. Passage reading is a skill that comes into play in a wide set of circumstances and is critical for academic success (Herbers et al., 2012). Passage reading, in contrast to reading single words, requires the manipulation of visual symbols into smaller speech sounds and depends on the detection of rapidly changing auditory stimuli. Although reading deficits have recently been reported in a limited sample of CHR subjects (Revheim et al., 2014), their relationship with underlying sensory impairments and functioning remains to be determined.

2. Methods and materials

2.1. Participants

Thirty-four subjects (age range, 12–22) met clinical high-risk, positive (CHR+) criteria based on the presence of one or more moderate, moderately severe, or severe (scores of 3, 4, or 5) Scale of Prodromal Symptoms rated (scale of 0–6) attenuated positive symptoms (SOPS, Miller et al., 1999, 2002, 2003). Referrals to the RAP Program were made by affiliated outpatient and inpatient psychiatry departments, local mental health providers, school psychologists or counselors, or were self-referred.

Thirty-three healthy comparison subjects (CNTLs) were also enrolled and recruited through announcements in local newspapers and within the medical center during the same time period as the patients. Inclusion criteria were a baseline age between 12–25 years. Exclusion criteria for all participants included: (1) Schizophrenia-spectrum diagnosis (Orvaschel and Puig-Antich, 1994); (2) non-English speaking; (3) history of neurological disorder; (4) IQ < 70; (5) healthy controls with a first-degree relative with a diagnosed Axis I psychotic disorder were also excluded.

This cross-sectional report includes a subsample of CHR+ participants enrolled in the larger second phase of the Recognition and Prevention (RAP) Program (2006–2012, total N = 139), an NIMH funded (2000–2012) longitudinal investigation. This subsample was recruited from all CHR+ subjects that consecutively entered the RAP Program from 2010–2012 who were willing to participate in the ERP protocol. Written informed consent (≥ 18 years-old) or assent (<18) with consent from parents was obtained. The research protocol was approved by the Institutional Review Board at the North Shore-LIJ Health System.

2.2. Measures

Prodromal symptoms were assessed by the Structured Interview for Prodromal Syndromes (SIPS) and the companion SOPS (Miller et al., 1999, 2002, 2003). Social and role functioning was assessed using the GF:Social and GF:Role scales (Cornblatt et al., 2007). The GF:Social scale assesses peer relationships, peer conflict, age-appropriate intimate relationships, and involvement with family members. The GF:Role scale rates performance and amount of support needed in one's specific role (i.e., school, work).

Reading ability was assessed with the Gray Oral Reading Test (GORT-4, Wiederholt and Bryant, 2001), Comprehensive Test of Phonological Processing (CTOPP, Wagner et al., 1999) and Wide Range Achievement Test-3 (WRAT-3, Wilkinson, 1993). The GORT-4 Overall Reading Quotient (ORQ, $M = 100$, $SD = 15$) measured overall reading ability and subscale scores ($M = 10$, $SD = 3$) measure rate (time taken to read a story), accuracy (correct pronunciation), fluency (rate + accuracy), and comprehension (accuracy on multiple-choice questions). The CTOPP Phonological Awareness Composite Score (PACS) and Alternate PACS (APACS) measured phonological processing abilities (Revheim et al., 2006). The WRAT-3 Reading subtest measured single-word reading skills. The MATRICS Consensus Cognitive Battery (MCCB, Green and Nuechterlein, 2004; Green et al., 2004) assessed neurocognitive performance in six domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, and reasoning/problem solving. Estimated full-scale IQ scores were derived from the vocabulary and block design subscales of the WISC-III (Wechsler, 1991) for subjects <16 years old and WAIS-R (Wechsler, 1981) for subjects >16 years old.

2.3. Auditory stimuli presentation

Stimulus parameters were based on a previous report (Friedman et al., 2012). Sound stimuli were presented binaurally through foam insert headphones (ER-1, Etymotic, Illinois, USA) in a fixed order at stimulus onset asynchronies of 500–505 ms using stimulus delivery software (Presentation, Neurobehavioral Systems, California, USA). Sound stimuli were a standard harmonic tone ($p = .67$, 85 dB, 100 ms duration, 5 ms rise and fall time, overlapping 500, 1000, and 1500 Hz sinusoids). Deviant tones ($p = .11$ for each) included a frequency (three superimposed sinusoids at 450, 900 and 1650 Hz), intensity (75 dB), and duration deviant (150 ms). Stimuli occurred in a fixed order (2 standards, 1 deviant). Deviant stimuli were also presented in a fixed order (duration, intensity, and frequency). Auditory stimuli were presented simultaneously with a visual distractor task in which subjects were asked to attend to a sequence of visual stimuli presented at central fixation and respond to a designated target stimulus that

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