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Auditory event-related potential of subjects with suspected pre-psychotic state and first-episode psychosis

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ABSTRACT

Background: Recent schizophrenia research exploring the complicated pathogenesis of schizophrenia has focused on the subjects with at-risk mental states in order to exclude the influence of confounding factors. This study explores 3 sets of auditory-related event potentials in subjects with different risk levels of psychosis.
Methods: Subjects were recruited from the SOPRES study in Taiwan. P50 and N100 using an auditory paired-click paradigm and duration MMN were assessed on 32 first-episode psychosis (FEP), 30 ultra-high risk (UHR), 37 E-BARS (early/broad at-risk mental states) participants and 56 controls.
Results: MMN was correlated with neither P50 nor N100, whereas many parameters of the latter two were inter-correlated with each other. Compared to healthy controls, MMNs were significantly lower in all 3 clinical groups (E-BARS, UHR and FEP). A gradient of sensory-gating deficits, manifested by increased P50 ratios (S2/S1) and decreased N100 differences, across different levels of clinical severity was suggested by a linear trend. For the UHR subjects, P50 gating ratio, N100 gating ratio, N100 difference, and N100 S2 amplitude might be potential indicators to discriminate converters from non-converters.
Conclusions: By including subjects with E-BARS, our results provide new insight regarding pre-attentive auditory event-related potential in subjects across different risk levels of psychotic disorders. Impaired deviance detection shown by MMNs already exists in people at a pre-psychotic state regardless of clinical severity, while sensory-gating deficits shown by P50/N100 varies depending on the risk levels in prodromal period. Further longitudinal research exploring the relationship between ERPs and subjects with a suspected pre-psychotic state is needed.

1. Introduction

Schizophrenia is a disorder of the brain that involves several levels of deficits (Braff and Light, 2004; Rissling and Light, 2010b). Most neurobiological studies of schizophrenia have been conducted in chronic patients; however, the long duration of illness per se could be a confounder, making the interpretation of neurobiological findings rather difficult (Mathalon et al., 2000; Premkumar et al., 2008; Tanskanen et al., 2010). Also, the long-term use of antipsychotics has profound effects on brain neurochemistry and possibly brain morphology (Breier, 2004). A promising approach to explore the complicated pathogenesis of schizophrenia without being confounded by these factors is to monitor the progression of subjects from a pre-psychotic state to a full-blown psychotic episode (Cornblatt et al., 2003; Keshavan et al., 2011).

In the past decade, researchers worldwide have conducted prospective studies in this regard, but the majority of them focused on the ultra-high risk or late-prodromal state (Breier, 2004; Olsen and Rosenbaum, 2006), while little is known about what happened prior to ultra-high risk state. Keshvan et al. proposed the concept of early/broad at-risk mental states (E-BARS) to suggest needs to explore individuals at an earlier stage and broader range of at-risk mental states (Keshavan et al., 2011). In Taiwan, a study on the psychopathological progress of the pre-psychotic state (the SOPRES study) was initiated in 2006. In addition to including ultra-high risk subjects who demonstrated a significantly higher probability of transition to a full-blown psychotic episode, the SOPRES study also recruited subjects at marginal-risk (subjects presenting with non-specific cognitive and affective symptoms did not

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yet meet any diagnostic category), intermediate risk (subjects with schizotypal-like and some negative symptoms), and first-episode psychosis (Liu et al., 2010; Liu et al., 2011). Thus the SOPRES data allows us to explore individuals putatively at pre-psychotic state while not reaching the severity of ultra-high risk criteria.

Auditory event-related potentials (ERP), including P50, N100, and mismatch negativity (MMN), have been utilized to study normal versus defective information processing in schizophrenia (Adler et al., 1982; Nagamoto et al., 1991; Clementz et al., 1997; Michie, 2001; Keshavan et al., 2008). Sensory-gating methods using paired-click paradigm (Nagamoto et al., 1989; Nagamoto et al., 1991) had provided strong relationship between genes and the pathophysiological aspect of the illness (Freedman et al., 1997). They have also been identified as candidate endophenotypes of schizophrenia in order to reveal possible schizophrenia genes (Turetsky et al., 2007; 2008; Javitt et al., 2008; Rissling and Light, 2010a). Several studies have investigated the relationship of auditory ERP components in high-risk subjects. For example, P300 amplitude reduction has been correlated with an increased vulnerability to psychosis (Bramon et al., 2008; Frommann et al., 2008; Ozgurdal et al., 2008; van Tricht et al., 2010). MMN amplitudes of prodromal subjects were found to be at an intermediate stage between those of the control and schizophrenia subjects, although the difference did not reach statistical significance (Brockhaus-Dumke et al., 2005). P50 and N100 were found with marginal differences between healthy control subjects and high-risk groups in P50 ratio (S2/S1) and N100 difference (S1-S2), while no significant differences in any parameter between converters and non-converters (i.e. at-risk subjects versus truly prodromal patients) (Brockhaus-Dumke et al., 2008).

As compared with other studies that recorded ERPs solely in ultra-high risk subjects or drug-naïve genetically high-risk probands, this study concurrently investigated the auditory ERPs of subjects at different levels of clinical severity, from normal controls to an early/broad at-risk mental state, ultra-high risk state, and first-episode psychosis. Also an addition to previous studies on UHR subjects, we examined the intercorrelation between P50, N100, and MMN, explored the features of P50, N100, and MMN among these clinical subgroups, and compared the baseline ERP findings between the converters and non-converters of our ultra-high risk subjects.

2. Methods

2.1. Participants

Subjects were participants in the SOPRES study who agreed to receive electrophysiological assessments. The rationale and methodology for the SOPRES study have been described elsewhere (Liu et al., 2010; Liu et al., 2011). Briefly, individuals presenting with "non-specific Cognitive deficits, Affective symptoms, Social Isolation, and School failure" (CASIS) (Cornblatt et al., 2003) or having newly developed psychotic-like symptoms were referred for assessment. The SOPRES study was approved by the National Taiwan University Hospital (NTUH) Institute Review Board. All subjects and/or their parents provided signed written informed consent before their participation in this study.

Originally, the levels of clinical severity were categorized into four groups by employing the Thought/Perception Diagnostic Interview Schedule (TP-DIS) (Liu et al., 2011). The group of first-episode psychosis (FEP) included participants with schizophrenia, schizophreniform disorder, brief psychotic disorder, or schizoaffective disorder meeting the DSM-IV criteria in the preceding one year. The ultra-high risk group (UHR) included participants with attenuated psychotic symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) (McGorry et al., 2003). The intermediate-risk group (IRG) included participants who presented with odd thinking, feelings, speech, or perceptual experiences, which were not as severe as in the UHR group but met the criteria of schizotypal disorder according to the 10th edition of the International Classification of Diseases (ICD-10) without the duration requirement of two years. The marginal-risk group (MRG) included participants with CASIS symptoms (Cornblatt et al., 2003) without meeting either the threshold for the IRG or other diagnostic category. A group of age- and gender-matched healthy volunteers were also recruited. Of note, in our SOPRES 2-year follow-up, only one third of patients from the UHR group have converted into full-blown psychosis while none of the IRG and MRG subjects converted, and in our preliminary analysis, either from eyeballing the scatter plots or statistically tested, there is no significant distinction between these 2 groups in terms of the results of our interests, thus we combined these two groups to be an analogue of the recently proposed "early/broad at-risk mental states" (E-BARS) in later analyses.

Subjects with an IQ below 70, aged younger than 16 years, with a history of traumatic brain injury, a history of central nervous system illness, a prior psychotic episode lasting for more than one year, or current use of psychoactive stimulants were excluded. The pre-psychotic subjects who developed first-episode psychosis during the 2-year follow-up were defined as converters. In this study all converters came from the UHR group, while none of the E-BARS subjects converted to FEP.

2.2. Experimental procedures

Audiometry testing was used to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1000, and 6000 Hz presented to either ear. A standard protocol for auditory P50 and MMN paradigm was followed (Lijffijt et al., 2009; Light et al., 2010; Shan et al., 2010). The participants had not smoked for at least 1 h before sessions (Adler et al., 1992; Olincy and Martin, 2005), and were asked to lie down in the supine position in a comfortable recliner in a sound attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a fixation point (P50 and N100 session) or a cartoon running with no sound on the video monitor (MMN session).

The EEG signals were recorded with a Quik-Cap (Compumedics Neuroscan, El Paso, TX, USA) from 32 scalp locations (10–20 system). The auditory stimuli were generated by a Neuroscan STIM system, and data were recorded on a Neuroscan ACQUIRE system (Compumedics Neuroscan, El Paso, TX, USA). Stimuli were digitized at a rate of 1 kHz and an on-line band-pass filter at 0.5–100 Hz, without 60-Hz notch filter applied. Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes were located above and below the left eye and at the outer canthi of both eyes to monitor blinks and eye movements. Electrode impedances were kept below 5 kΩ prior to recording.

Auditory ERPs were presented to the subjects binaurally via foam insert earphones in two consecutive sessions, i.e. the session of paired-click paradigm for P50/N100 followed by the duration MMN session. On-line averaging was used to monitor the number of trials free from gross artifacts (defined as activities exceeding ±100 μV in the −100–500 ms time window following stimuli). Regarding the pair-click P50/N100 paradigm, paired auditory clicks (1 ms, 85 dB) were presented every 8–12 s through the whole test session (average: 10 s), with a 500-msec inter-stimulus interval (Clementz et al., 1998; de Wilde et al., 2007). The paired-click P50/N100 session was terminated when a minimum of 120 artifact-free trials had been obtained, which took about 30 min. For the duration MMN paradigm, pure tone stimuli (1 kHz, 85 dB SPL, 5 ms rise/fall, Hanning window) were generated by the Neuroscan STIM system. The auditory stimuli consisted of standard stimuli (90%, 50-msec duration) and deviant stimuli (10%, 100-msec duration) delivered in a pseudo-random order with the constraint that deviant stimuli could not be repeated back-to-back. The cartoon soundtrack was turned off and replaced by the experimental auditory stimuli which were presented at a fixed 500-msec