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Clinical high risk and first episode schizophrenia: Auditory event-related potentials

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ABSTRACT

The clinical high risk (CHR) period is a phase denoting a risk for overt psychosis during which subacute symptoms often appear, and cognitive functions may deteriorate. To compare biological indices during this phase with those during first episode schizophrenia, we cross-sectionally examined sex- and age-matched clinical high risk (CHR, $n=21$), first episode schizophrenia patients (FESZ, $n=20$) and matched healthy controls (HC, $n=25$) on oddball and novelty paradigms and assessed the N100, P200, P3a and P3b as indices of perceptual, attentional and working memory processes. To our knowledge, this is the only such comparison using all of these event-related potentials (ERPs) in two paradigms. We hypothesized that the ERPs would differentiate between the three groups and allow prediction of a diagnostic group. The majority of ERPs were significantly affected in CHR and FESZ compared with controls, with similar effect sizes. Nonetheless, in logistic regression, only the P3a and N100 distinguished CHR and FESZ from healthy controls, suggesting that ERPs not associated with an overt task might be more sensitive to prediction of group membership.

1. Introduction

The clinical high risk (CHR) period is a clinical syndrome denoting a risk for overt psychosis characterized by subthreshold symptoms during which cognitive functions may deteriorate (Yung and McGorry, 1996; Rossler et al., 2011; Giuliano et al., 2012). Conversion to psychosis after CHR diagnosis is in the range of 9–36% between 6 and 36 months (Miller et al., 2002) (Yung et al., 2003; Cannon et al., 2008; Fusar-Poli et al., 2011). Diagnostic criteria such as the COPS (Criteria of Prodromal Syndromes) (Miller et al., 1999) are valuable; however, diagnostic and predictive biological tools are needed to complement them to guide targeted interventions as CHR individuals who progress to psychosis need to be identified and treated (Keshavan et al., 2003). Additionally, CHR individuals who do not progress to psychosis might be vulnerable to other mental conditions (Rossler et al., 2011) and are shown to retain a lower level of functioning than healthy controls with persistent disability at least at 2.5 years after a diagnosis of psychosis risk syndrome (Addington et al., 2011). Event-related brain potentials (ERPs) reflect distinct sensory and cognitive processes, and might offer neurocognitive indices of brain function during the clinical high risk state.

Among ERP components, the P300, or P3b, with typical parietal scalp distribution, is thought to reflect a mechanism involved in the updating of contextual representations in working memory (Donchin, 1981;

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Polich, 2007). A relative decrease in the amplitude of the P300 component is one of the most replicated findings in schizophrenia in comparison with healthy controls (Jeon and Polich, 2003). Decreased amplitudes have been shown in chronic schizophrenia patients (e.g., Pfefferbaum et al., 1984; McCarley et al., 1991; Ford, 1999; Jeon and Polich, 2003; Javitt et al., 2008), in symptomatically unaffected relatives (Price et al., 2006), in patients recently hospitalized for their first psychotic episode (Salisbury et al., 1998; McCarley et al., 2002), and in individuals at high risk for developing schizophrenia (Bramon et al., 2008; Frommann et al., 2008; van Tricht et al., 2010; Fusar-Poli et al., 2011).

A distinct ERP component, the more fronto-centrally scalp distributed novelty P3 or P3a, which arises ~300 ms after stimulus onset, is also affected in schizophrenia and is thought to represent a mechanism involved in the rapid orienting of attention to events that are unexpected and contextually deviant (Squires et al., 1975; Ranganath and Rainer, 2003; Polich, 2007). Amplitude decrease has been shown in chronic schizophrenia patients (Devrim-Ucok et al., 2006; Mathalon et al., 2010) and in clinical high risk (Jahshan et al., 2012; Mondragon-Maya et al., 2013). In recent onset subjects, amplitude deficits (Valkonen-Korhonen et al., 2003b; Hermens et al., 2010; Kaur et al., 2011; Jahshan et al., 2012), but also a lack of them, have been reported (Frodl et al., 2001b; Devrim-Ucok et al., 2006; Atkinson et al., 2012).

High heritability of P3b amplitude has been shown in schizophrenia twin and sibling studies (Bramon et al., 2005; Hall et al., 2007; Groom et al., 2008; Bestelmeyer et al., 2009), and the data suggest that P3b might be an endophenotype of an executive control process. The frontal portion of P300, related to novel P300, has also been found to be decreased in unaffected siblings of patients with schizophrenia (Turetsky et al., 2009; Turetsky et al., 2000). A longitudinal study, aimed at tracking changes in P3b and P3a amplitude in schizophrenia patients, suggests auditory P3b and P3a as trait markers of schizophrenia (Mathalon et al., 2000).

According to Polich (2007), "it is reasonable to infer that stimulus evaluation engages focal attention (P3a) to facilitate context maintenance (P3b), which is associated with memory operations," indicating that assessing the two processes in the same subjects might be the essential step in dissecting and defining the extent of contribution of the two processes to clinical diagnosis. Only a few studies have investigated both the P3b and the P3a components in the same subjects (Kirihara et al., 2009; Mathalon et al., 2010), and to the best of our knowledge not in clinical high risk or recent onset individuals. The aim of the present investigation was thus to assess the P3a and the P3b, in addition to the mid-latency N100 and P200 components, in clinical high risk (HR) subjects, in first episode schizophrenia (FESZ) subjects and in age-matched healthy controls (HC) cross-sectionally, where all subjects including CHR, FESZ and HC were assessed on auditory classical and novelty oddball tasks. Both tasks were administered during the same visit, reducing the possibility of variations in the subject physical and/or mental status (Ford, 1999). Thus, the ERP components were used in a preliminary logistic model to assess their ability to predict group membership.

We note that since complex deviants elicited both a P3a and a P3b (del Re et al., 2014), the P3b to complex deviants will be refered to as P3bn to distinguish it from the P3b elicited by target sounds.

2. Methods

2.1. Participants

Participants comprised 21 CHR (8 females), 20 FESZ (6 females), and 25 HC (13 females), recruited via the Boston Center for Intervention Development and Applied Research (www.bostoncidar.org). HC were recruited from the general community via Internet advertisements. CHR and FESZ were recruited from outpatient clinics affiliated with Harvard Medical School, or through referrals from clinicians. The study was approved by the local IRB committees at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, Brigham and Women's Hospital, and the Veterans' Affairs Boston Healthcare System (Brockton campus). All study participants, or legal guardians for those under 18 years of age, gave written informed consent and received payment for participation.

Inclusion criteria for all subjects were as follows: no mental retardation (IQ < 70), right-handedness, no history of electroconvulsive shock treatment (ECT) ever for HC and within the past 5 years for FESZ, no history of neurological illness, no alcohol/drug dependence in the last 5 years, and no abuse in the past month. The HC participants were drawn from the same geographic bases as the FESZ patients, with comparable age, gender, race and ethnicity, handedness, and parental socioeconomic status (see Table 1). No HC subject met criteria for any current major DSM-IV-TR Axis I disorders or had a history of psychosis, major depression (recurrent), bipolar disorder, obsessive–compulsive disorder, posttraumatic stress disorder, or developmental disorders. HC subjects were also excluded if they had a history of psychiatric hospitalizations, prodromal symptoms, schizotypal or other Cluster A personality disorders, first degree relatives with psychosis, or any current or past use of antipsychotics.

Exclusion criteria for all subjects were sensory-motor handicaps; neurological disorders; medical illnesses that significantly impair neurocognitive function; education less than 5th grade if under 18 years of age and less than 9th grade if over 18 years of age, not fluent in English; DSM-IV substance abuse in the past month; DSM-IV substance dependence, excluding nicotine, in the past 3 months; current suicidality; or study participation by another family member.

In the CHR group, prodromal phase COPS (Criteria of Prodromal Symptoms) criteria were assessed using the Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 1999), and the presence of personality disorders was determined using the Diagnostic Interview of Personality Disorders (DIPD)

Table 1
Socio-demographic and clinical information.

	HC ($n=25$)	CHR ($n=21$)	FESZ ($n=20$)	
Mean age (S.D.)	21.9 (2.4)	20.6 (3.7)	22.4 (4.9)	N.S.
Gender (male/female)	12/13	13/8	14/6	N.S.
Pre-morbid IQ (oral reading)	117.7 (14.9)	115.4 (12.9)	114.9 (14.9)	N.S.
Current IQ	121.4 (14.5)	121.4 (11.0)	106.3 (15.9)	$p<0.01$
Education (years)	14.6 (2.0)	12.9 (2.8)	13.5 (2.6)	N.S.
PSES	1.7 (1.0)	1.9 (0.9)	2.2 (0.95)	N.S.
GAF	84.7 (7.5)	49.2 (9.8)	51.7 (13.1)	$p<0.01$
Time between Ist admission-EEG (years)	N.A.	N.A.	1.36 (0.6)	N.A.
SOPS total	N.A.	26 (8.9)	N.A.	N.A.
SOPS positive	N.A.	11.8 (5.1)	N.A.	N.A.
SOPS negative	N.A.	14.2 (7.7)	N.A.	N.A.
BPRS total	N.A.	N.A.	96.0 (12.6)	N.A.
BPRS positive	N.A.	N.A.	6.9 (3.3)	N.A.
BPRS negative	N.A.	N.A.	6.1 (2.9)	N.A.
Medicated/unmedicated	N.A.	7/14	18/2	$p<0.01$
CPZ equivalents	N.A.	68.6 (51.0)	334.4 (350.4)	$p<0.01$
Targets	35.8 (1.7)	36.6 (1.9)	37.6 (1.9)	N.S.

Values are mean (S.D.); HC, Healthy controls; CHR, Clinical high risk individuals; FESZ, First episode schizophrenia patients; CPZ, Chlorpromazine; PSES, Parental Socioeconomic Status; N.A., not applicable; N.S., not significant, $p>0.05$. CPZ equivalents were calculated for subjects on medication (CHR, $n=7$; FESZ, $n=18$) (according to Stoll (2009) and Woods (2003)); Targets, number of targets counted across the classic and novelty oddball tasks.