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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

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Contributors

E.C. del Re collected EEG data, analyzed the data, and wrote the manuscript. K.M. Spencer designed the study, contributed to data analysis, and edited the manuscript. N. Oribe collected EEG data and was involved with data analysis. L.J. Seidman and R. Mesholam-Gately collected clinical data and edited the manuscript. T. Petryshen, M. Shenton, and J. Goldstein edited the manuscript. R.W. McCarley designed the study, contributed to data analysis, and edited the manuscript. M. Niznikiewicz was involved with EEG data analysis and contributed to manuscript editing. All authors approved the final manuscript

Conflict of interest

All authors declare that they do not have conflicts of interest.

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.

Keywords

N100; P200; P3a; P3b

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; 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., 2007; 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) (Zanarini et al., 1987). The 10 items from the Bonn Scale for the Assessment of Basic Symptoms (BSABS) identified as having high predictive validity for the development of psychosis (Klosterkotter et al., 2001) and together termed Cognitive-Perceptive Basic Symptoms (COPER) (Schultze-Lutter F, 2007b) were also used. These symptoms are implemented in the Schizophrenia Proneness Instrument, Adult Version (SPI-A) (Schultze-Lutter, 2007a). No CHR subject had converted to schizophrenia within the 1-year follow-up used by the study. The following additional diagnoses existed in the CHR group: major depressive disorder (1); major depressive disorder and posttraumatic stress disorder (1); major depressive disorder and phobia (3); major depressive disorder and generalized anxiety (1); bipolar disorder II and anxiety disorder (2), bipolar disorder II and posttraumatic stress disorder (1); dysthymic disorder and anxiety (1); attention deficit-hyperactivity disorder (1); conduct disorder (1); and generalized anxiety (5).

FESZ patients met DSM-IV-TR criteria for either schizophrenia, schizoaffective disorder or schizophreniform disorder. FESZ diagnoses were based on interviews with the Structured Clinical Interview for DSM-IV-TR (SCID), Research Version (First, 2002) and information from medical records. FESZ clinical symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and with the Scale for Asssessment of Positive (SAPS) and Negative (SANS) symptoms (Andreasen 1984, 1983). For FESZ the average

time between first hospitalization and the electroencephalographic (EEG) session was 1.36 ± 0.63 years (range 0.5-2.34 years). Three FESZ patients had additional diagnoses as follows: posttraumatic stress disorder (1); major depressive disorder (1); and specific phobia (1).

All participants were evaluated with the Global Assessment of Functioning scale (GAF) (Jones et al., 1995).

Handedness was assessed using the Annett Handedness Questionnaire (Annett, 1970). Subjects' education years and parents' socioeconomic status (PSES), assessed with the Hollingshead two-factor index (Hollingshead, 1965; Hollingshead, 1975), determined the social status of the study sample. Premorbid IQ was assessed using the reading scale of the Wide Range Achievement Test-4 (WRAT-4) (Wilkinson and Robertson, 2006) and current IQ was assessed using the vocabulary and block design T-score of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Seven CHR and 18 FESZ subjects were medicated at the time of testing. Medications were as follows: for CHR subjects, aripripazole 2, risperidone 2, quetiapine 1, olanzapine 1, aripripazole + olanzepine 1; for FESZ subjects, aripripazole 3, quetiapine 2, olanzepine 1, risperidone 2, paliperidone 1, clozapine 1; fluphenazine decanoate +fluphenazine HCl 1; fluphenazine HCl + ziprasidone 1; quetiapine + aripripazole 1; quetiapine + olanzepine 1; risperidone + aripripazole 1; risperidone + ziprasidone 1; risperidone + aripripazole + risperidone 1. Medication dosage was estimated using chlorpromazine (CPZ) equivalents (Table 1).

All demographic and clinical data are summarized in Table 1.

2.2. Stimuli and tasks

Subjects performed a classic two-stimulus oddball task and a three-stimulus novelty oddball task, each 4 min in duration. In the classic oddball, stimuli were tones (82 ms in duration, 75 dB SPL), with 20% (36) infrequent target tones (1.5 kHz) and 80% (144) frequent standard tones (1 kHz) presented with a stimulus onset asynchrony of 976 ms (onset-to-onset). The subjects' task was to silently count the targets. In the novelty oddball task, infrequent non-target complex deviants were also included. Complex deviants consisted of complex environmental stimuli (300-320 ms in duration, 75 dB SPL) such as dog barking ot door slamming. Six environmental sounds were presented six times each during the task. Novel auditory oddball sequences consisted of 20% (36) target (1.5 kHz), 20% (36) novel, and 60% (108) standard tones (1 kHz).

2.3. EEG recording and processing

The EEG was recorded with a Biosemi Active-Two system using sintered Ag/Ag-Cl electrodes in an electrode cap at 71 standard scalp sites, as described elsewhere (Oribe et al., 2013). The EEG data were processed using BrainVision Analyzer 2.0. The bipolar vertical electro-oculogram (EOG) was derived from electrode Fp1 and an electrode below the left eye. The horizontal EOG was derived from electrodes on the left and right outer canthi. The continuous EEG recordings were segmented from -100 to 900 ms relative to stimulus onset and re-referenced to the algebraic average of the left and right mastoids. Ocular artifact correction was performed using an earlier described method (Gratton et al., 1983). Epochs with artifacts exceeding ± 100 μV with a maximal allowed difference of 200 μV were

excluded. Average ERPs were computed from the artifact-free epochs and baseline-corrected with a pre-stimulus baseline of -100 to 0 ms following digital filtering (0-16 Hz).

2.4. ERP analyses

The P3a was measured at frontal (electrodes F1/Fz/F2) and central (C1/Cz/C2) regions; the P3b, elicited by targets in the oddball paradigm, and the P3bn, elicited by complex environmental sounds in the novelty paradigm, were measured at central and parietal (electrodes P1/Pz/P2) regions. The P3a and P3bn in the novelty waveform were analyzed as previously described (del Re et al., 2014). The N100 and the P200, measured in response to standard stimuli, were assessed at frontal (F1/Fz/F2) and central (C1/Cz/C2) regions. The latency ranges for selecting ERP component peaks in individual subject data were determined by visual inspection of the grand average ERPs. All electrodes of interest were inspected to ensure that the same component was being selected at each site. In the classic oddball data, the P3b peak was selected as the most positive point between 250 and 400 ms (Fig. 1). In the case of a bimodal peak, the later parietal maximum peak was manually selected. In the novelty oddball data, the P3a/b waveform was biphasic (Fig. 2). The P3a and P3bn peaks were selected as the most positive peaks between 215-285 ms and 315-390 ms, respectively. In both tasks, the N100 peak was selected as the most negative point between 80 and 150 ms, and the P200 peak was selected as the most positive point between 150 and 300 ms.

The number of epochs included in an average by paradigm and group did not differ significantly. Details are presented in Supplementary Table 3.

2.5. Statistical analyses

All statistical analyses were performed with SPSS v. 22 except effect sizes, which were calculated with G*Power 3.1, 2009 (Faul et al., 2007). Accuracy was assessed using the number of counted targets and tested in an analysis of variance (ANOVA) with Group (HC/CHR/FESZ) as the between-subjects factor and Task (classic/novelty oddball) as the within-subjects factor. ERP peak amplitude and latency were analyzed using multivariate analysis of variance (MANOVA) models. For P3a the model included Group as a between-subjects factor and Region as a within-subjects factor (frontal: F1/2,Fz; central: C1/2,Cz). For P3b and P3bn, the model included Group as a between-subjects factor and Region as a within-subjects factor (central: C1/2,Cz; parietal P1/2, Pz). N100 and P200 were analysed with Group as a between-subjects factor and Task (classic and novel) and Region (frontal/central) as within-subject factors. Where significant group differences were found in the MANOVA, effect sizes are reported as Cohen's *f* for three-group comparisons and as Cohen's *d* for two-group comparisons. Tukey's test was applied for post hoc comparisons of groups. Correlations between ERP and clinical/demographic measures were computed using Spearman's rho and were Bonferroni-corrected, i.e., the *p* value was corrected for the number of variables included in the correlation analysis. The Chi-square test was used to compare categorical data. The impact of ERPs and demographic variables on diagnostic group was assessed with logistic regression.

3. Results

3.1. Subject group characteristics and task performance

The groups did not differ by age (F[2,63] = 1.33, p = 0.272), years of education (F[2,63] = 2.7, p = 0.08), or premorbid IQ (F[2,61] = 0.228, p = 0.798). There were significant differences in current IQ (F[2,61] = 6.7, p < 0.01), which did not differ between CHR and HC (t[42] = 0.4113, p = 0.68), but was lower in FESZ compared with HC (t[41] = -3.2, p < 0.01) and CHR (t[37] = 3.4, p < 0.01). The GAF score differed among the groups (F[2,61] = 7.7, p < 0.01), with equivalent scores in CHR and FESZ (t[39] = 0.68 p = 0.49), which were both lower than in HC (CHR vs. HC: t[42] = −13.5, p < 0.001; FESZ vs. HC: t[41] = −10.33, p < 0.001). PSES did not differ among groups (F[2,63] = 1.8, p = 0.179). The proportion of males and females did not differ between groups (χ^2[2] = 2.33; p = 0.33). CPZ-equivalent medication dosages were lower in medicated CHR than FESZ (t[18.6] = 3.1, p < 0.01 with t calculated for unequal variances). There were no significant differences in accuracy among the groups (F[2,63] = 0.33), p = 0.72). These data are summarized in Table 1.

3.2. Classic oddball task: P3b

The P3b elicited by target stimuli in the classic oddball task had a central-parietal scalp distribution (see Fig. 1), and no significant Group × Region interaction (F[1,63]=2.43; p=0.096) was found. There was an effect of Group on P3b amplitude (F[2,63] = 5.9, p < 0.01, f = 0.36). Tukey's test post-hoc comparisons indicated that P3b amplitude was equivalent in CHR and FESZ (p =0.782) and reduced in each group compared with HC (CHR vs. HC, p<0.05; FESZ vs. HC, p < 0.01). P3b latency did not differ between groups (F[2,63] = 2.8, p = 0.068) (see Supplementary Table 1).

3.3. Novelty oddball task: P3a, P3bn and P3b

Complex environmental auditory stimuli elicited a biphasic late positive waveform (Fig. 1). The P3a peak had a central distribution, while the P3bn peak had a central-parietal distribution. For the P3a there was no significant interaction of Region × Group, but there was an effect of Group on peak amplitude (F[2,63] = 8.3, p < 0.01, f = 0.51). Tukey's post-hoc comparisons found that P3a amplitudes in CHR and FESZ did not differ (p = 0.812), but were reduced compared with HC (CHR vs. HC, p < 0.01; FESZ vs. HC, p < 0.05). P3a latency did not differ between groups (F[2,63] = 0.15, p = 0.859). There was also a Group effect on P3bn amplitude (F[2,63] = 8.9, p < 0.01, f = 0.5). P3bn amplitudes, in CHR and FESZ, according to Tukey's tests, did not differ (p = 0.9), and were reduced compared with HC (CHR vs. HC, p < 0.01; FESZ vs. HC, p < 0.01). P3bn latency did not differ between groups (F[2,63] = 2.7, p = 0.073).

The analysis of P3b amplitude elicited by targets in the novelty oddball task did not show a significant effect of Group (F[2,63]=2.43; p=0.1). The analysis of P3b latency elicited by targets in the novelty oddball task demonstrated a main effect of Group (F[2,63]=3.5; p<0.05). Tukey's post hoc analysis showed longer latency in CHR compared with FESZ (p<0.05), but equivalent latencies between CHR and HC (p=0.14) and between FESZ and HC (p=0.7).

To investigate further the effect of three- versus two-stimulus paradigms on the amplitude of targets, the P3b elicited by targets in the oddball paradigms at the Pz electrode was correlated with the P3b elicited by targets in the novelty oddball task, also measured at the Pz electrode. Spearman's analysis demonstrated a positive correlation between the two measures. In the control group, the rho was 0.47, $p<0.05$; in the CHR group, the rho was 0.71, $p<0.01$; while in FESZ, the rho was 0.5, $p<0.05$.

3.4. N100 and P200

The N100 and P200 evoked by standard stimuli in the classic and novelty oddball tasks are presented in Fig. 2. For N100 amplitude there was an effect of Group ($F[2,63] = 5.8$, $p<0.01$, $f = 0.43$). Post hoc Tukey's tests showed that N100 amplitudes did not differ between CHR and FESZ ($p =0.93$) and were reduced compared with HC (CHR vs. HC, $p < 0.05$; FESZ vs. HC, $p < 0.01$). The effect of Task was not significant ($F[1,63] = 0.13$, $p=0.72$), nor was the Task × Group interaction ($F[2,63] = 2.9$, $p = 0.061$). N100 latency did not differ between groups ($F[2,63] = 0.78$, $p = 0.464$), but was significantly shorter ($F[1,63] = 7.1$, $p < 0.05$) in the classic oddball (121.9 ± 14.6 ms) than in the novelty oddball task (126.7 ± 14.8 ms).

For P200 amplitude there was an effect of Group ($F[2,63] = 4.57$, $p < 0.05$, $f = 0.38$). P200 amplitude was lower in CHR compared with HC ($p < 0.05$) and FESZ ($p <0.05$) but was not significantly different in FESZ compared twith HC (p=0.9). The effect of Task was significant, with P200 amplitude being greater in the classic oddball than the novelty oddball task ($F[1,63] = 19.7$, $p < 0.01$, $f = 0.56$). For P200 latency, there were no significant effects of Group ($F[2,63] = 2.2$; p = n.s.) or Task ($F[1,63] = 2.2$, $p = 0.14$), and the Group × Task interaction was not significant ($F[2,63] = 0.28$, $p = 0.75$).

3.5. Effect of medication in FESZ and CHR

There were no significant correlations between CPZ-equivalent medication dosages and ERP latency or amplitude in medicated FESZ or CHR. In addition, effects of medication were evaluated in CHR subjects by comparing unmedicated (14/21) and medicated (7/21) CHR subgroups on clinical, demographic, and ERP measures. No differences were found (Supplementary Table 2 and Fig. 3).

3.6. Logistic regression analysis

The impact of ERPs and demographic variables on diagnostic group membership was assessed by direct logistic regression. The independent variables were entered simultaneously, and included the classic oddball P3b at Pz, novelty oddball P3a at Fz, novelty oddball P3b at Pz, and N100 and P200 amplitudes averaged at frontal and central electrodes across tasks, in addition to age, years of education and current IQ. The dependent variable was diagnosis.

Model 1 compared CHR and FESZ. The significant model ($\chi^2[8, n=39] = 26.9$, $p = 0.001$; Hosmer and Lemeshow Goodness of Fit $p > 0.05$) explained between 49.8% (Cox and Snell R^2) and 66.6% (Nagelkerke R^2) of the variance with 84.6% of the cases correctly classified. Current IQ ($B = 0.151$, $p < 0.05$) and P200 amplitude (B−1.48, $p < 0.05$) uniquely

contributed to the model, indicating that higher IQ and lower P200 amplitude distinguished CHR from FESZ (Table 2A).

The CHR and HC groups and the FESZ and HC groups were compared separately, with the same model. The significant model comparing CHR with controls (Table 2B; $\chi^2[8, n=46] = 31.6$, $p < 0.001$; Hosmer and Lemeshow Goodness of Fit $p > 0.05$) explained between 49.6% (Cox and Snell R^2) and 66.4 % (Nagelkerke R^2) of the variance with 87.0% of the cases correctly classified. N100 ($B = -0.8$, $p < 0.05$) and P3a amplitudes ($B = 0.41$, $p < 0.01$) uniquely contributed to the model's predictive ability, indicating that decreased N100 and P3a amplitude increased the probability of a subject belonging to the CHR group. Regression of variables to compare FESZ and HC (Table 2C) also produced a significant model ($\chi^2[8, n=43] = 32.7$, $p < 0.001$; Hosmer and Lemeshow Goodness of Fit $p > 0.05$), explaining between 53.2% (Cox and Snell R^2) and 71.6% (Nagelkerke R^2 square) of the variance with 83.7% of the cases correctly classified. Lower current IQ (B=0.18, p<0.05), lower amplitude of P3a (B=0.61, p<0.05) and decreased N100 amplitude (B=-01.22, p<0.05) predicted FESZ status.

3.7. Relationships between ERP variables and clinical scales

Correlations between the ERP measures entered into the regression models and BPRS total, positive and negative scale scores; SANS total and SAPS total scores; and SOPS total, positive, and negative scale scores; the GAF scale was also explored. None of the probability values survived Bonferroni correction. Nonetheless, an inverse correlation between P3b amplitude at Pz and the SAPS psychotic index (rho=−0.57, p<0.01) and the BPRS total positive score (rho=−0.44, p=0.05) was detected at trend level. An additional trend level inverse correlation was found between P3b at Pz and the BPRS total score for anxiety symptoms (rho=-0.53, p<0.05).

4. Discussion

Although the groups did not differ behaviorally, electrophysiological evidence of “deficits of both attention and memory” was observed in CHR and FESZ compared with age-matched controls. Similarity of effect sizes, an index of the magnitude of abnormalities, suggests that deficits in brain mechanisms that underlie P3a and P3b exist at both the CHR stage and at the onset of psychosis.

The data are in line with the findings of P3b deficits in individuals at risk of psychosis (van der Stelt et al., 2004; Frommann et al., 2008; Fusar-Poli et al., 2011) and first episode patients (Salisbury et al., 1998; McCarley et al., 2002), and indicate reduced P3a amplitude in both CHR and first episode individuals. P3a deficits in the schizophrenia spectrum have not been consistently reported. For example, two recent cross-sectional studies have shown comparable and significantly reduced P3a amplitude in prodromal and recent onset patients with respect to controls (Jahshan et al., 2012; Mondragon-Maya et al., 2013). In contrast, Atkinson et al. (Atkinson et al., 2012) have reported reduced P3a amplitude in prodromal but not first episode patients, and Devrim-Ucok et al. (2006) reported normal P3a amplitude in first episode patients.

In chronic schizophrenia patients, in addition to P3a deficits (Grillon et al., 1990; Devrim-Ucok et al., 2006; Mathalon et al., 2010), unchanged or even increased P3a amplitudes have been reported (Grillon et al., 1990; Schall et al., 1999; Frodl et al., 2001a). Differences in paradigms might partly explain differences in outcome. Most recent studies have assessed P3a in a passive two-stimulus paradigm, while older studies, and our own, have used an active novelty paradigm, where novel stimuli are imbedded in an oddball paradigm. Although the P3a components elicited in both types of paradigms are most probably variants of the same ERP, the morphology of P3a components is strongly influenced by attention and task demands (Polich, 2007).

Our data on N100 measured to standard stimuli indicate comparable effect sizes of amplitude decreases in both CHR and FESZ relative to HC. The data confirm findings of reduced N100 amplitude in FESZ (Salisbury et al., 2010; Foxe et al., 2011) and indicate similar deficits in CHR individuals. Although no N100 group differences to standard stimuli in an oddball paradigm in at-risk individuals were reported in other studies (Bramon et al., 2008; van Tricht et al., 2010), gating studies have shown S1 and S1-S2 N100 deficits in prodromes but not in at-risk individuals (Brockhaus-Dumke et al., 2008). Longitudinally, a Time × Group interaction for N100 and P200 has been reported with deepening deficits in high risk individuals transitioning to psychosis (van Tricht et al., 2010; van Tricht et al., 2011; van Tricht et al., 2012). Several studies have shown that N100 abnormalities are present in unaffected relatives/twins of schizophrenia patients (Blackwood et al., 1991; Frangou et al., 1997; Ahveninen et al., 2006; Anokhin et al., 2006; Foxe et al., 2011), and magnetic resonance imaging (MRI) studies of gray matter have shown reduction of superior temporal gyrus at illness onset (Shenton et al., 1992; McCarley et al., 1999; Shenton et al., 2001) in young of schizophrenia patients (Rajarethinam et al., 2004) and in clinical high risk individuals whether they later develop schizophrenia or not (Borgwardt et al., 2007; Takahashi et al., 2010; Mechelli et al., 2011).

We note that in another study with similar subject samples, the N100 evoked by standard stimuli in a visual oddball task was decreased in FESZ but not in CHR (Oribe et al., 2013). Comparison of those findings with the present findings suggests that early auditory processing might be more affected than early visual processing in CHR individuals.

An attempt to distinguish CHR and FESZ using a logistic regression model generated a prediction model confirming results of the MANOVA, where.the amplitude of the P200 was an independent predictor of CHR versus FESZ status. The same model aimed at distinguishing CHR from HC or FESZ from HC in separate analyses demonstrated that the N100 and the P3a distinguished both CHR and FESZ from HC. Combined EEG-functional MRI studies indicate the P3a to be a part of the salience network involving the anterior cingulate and the insula (Crottaz-Herbette and Menon, 2006), regions repeatedly found to be affected in schizophrenia, and in a variety of other disorders such as mania, depression and anxiety (Devinsky et al., 1995; Hatton et al., 2012). As the N100 in Näätänen's model (Näätänen, 1990) is also considered an important aspect of for the redirection of attention to salient stimuli, our data indicate that mechanisms that are supported by the salience network might be indicative of CHR and FESZ states. Considering that the present study investigated cross-sectional data, and considering that there were no conversions to overt psychosis

among those at clinical high risk at the 1-year time point, it might be hypothesized that the P3a and the N100 are indexing brain processing characteristics shared by CHR and FESZ and marked by functional disability (Cornblatt et al., 2003; Addington et al., 2011).

Recent studies of non-converting individuals in fact indicate that CHR might be prone to a variety of mental disorders (Rossler et al., 2011; Carrion et al., 2013). Accordingly, Rosburg and collegues (Rosburg et al., 2008) demonstrated that "A reduced N100 amplitude is found in first degree relatives of schizophrenia patients, but the risk of developing schizophrenia is not reflected in the N100 amplitude reduction." All in all, N100 amplitude deficits seem to reflect underlying abnormalities of brain functioning that do not necessarily overlap with developing schizophrenia.

The P3a and P3b have been shown to be trait markers of schizophrenia (Mathalon et al., 2000). Nonetheless, we propose that because P3a and P3b abnormalities are also present in CHR and show a lack of specificity (Ford, 1999), P3a and P3b might indicate trait marker status of a core deficit that is common to, but not specific to, schizophrenia.

The GAF was equivalent in CHR and FESZ and significant lower compared with controls, indicating that impaired functioning as measured on the GAF scale, might represent a common thread between both CHR and FESZ that may be mediated by neurocognitive impairments indexed with ERPs.

Although we cannot exclude the effects of medication on our results as the majority of FESZ in this study were medicated, none of the ERP amplitude or latency findings in FESZ correlated with chlorpromazine-equivalent dosage. In addition, comparison of ERPs in medication-naïve and medicated CHR individuals demonstrated a lack of ERP differences (Fig. 3). Although Turetsky (2009) reported reduced P3a amplitude with increased CPZ-equivalent dosage in chronic schizophrenia patients, other reports indicate that medication might have a very minor effect on P3a (Valkonen-Korhonen et al., 2003a; Mondragon-Maya et al., 2013) and N100 (Foxe et al., 2011).

In summary, if we keep in mind the limited sample size, this study indicates that deficits of memory and attention in CHR, as indexed by ERPs in classical and novelty oddball tasks, are as profound as those of first episode schizophrenia patients, suggesting that these two groups are characterized by similar deficits of middle and late latency ERPs, irrespective of whether CHR and FESZ diagnoses represent a continuum or two different conditions. In addition, in regression analysis, the N100 and P3a amplitudes were the most sensitive ERP measures in discriminating between healthy and afflicted individuals. We suggest that these specific ERPs might be indices of a core disability independent of psychosis that distinguishes healthy controls from individuals at clinical high risk and individuals by schizophrenia of recent onset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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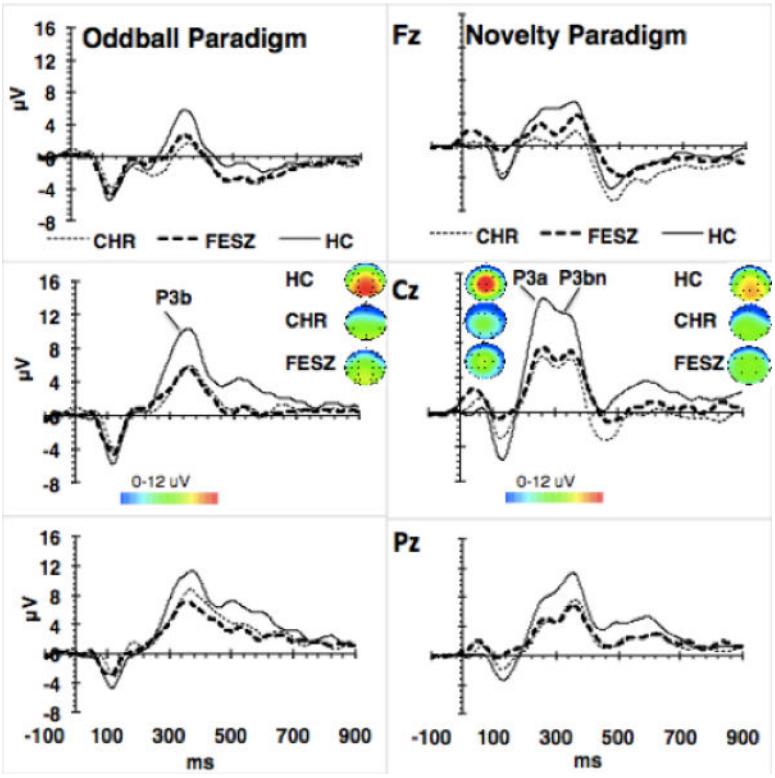

Fig. 1.

P3a/b. Grand average ERPs to targets in the oddball task, and complex environmental sounds in the novelty oddball paradigm. HC, healthy controls; CHR, clinical high risk; FESZ, first episode schizophrenia patients. Topographical maps indicate scalp distribution of P3a/b in the 3 groups. P3b and P3bn were measured between 315 and 390 ms; P3a between 215 and 285 ms. P3b and P3bn amplitudes measured at Cz and Pz were not different in CHR and FESZ, and both were significantly lower than in HC; P3a amplitude measured at Fz and Cz was also not different in CHR and FESZ but significantly lower than in HC.

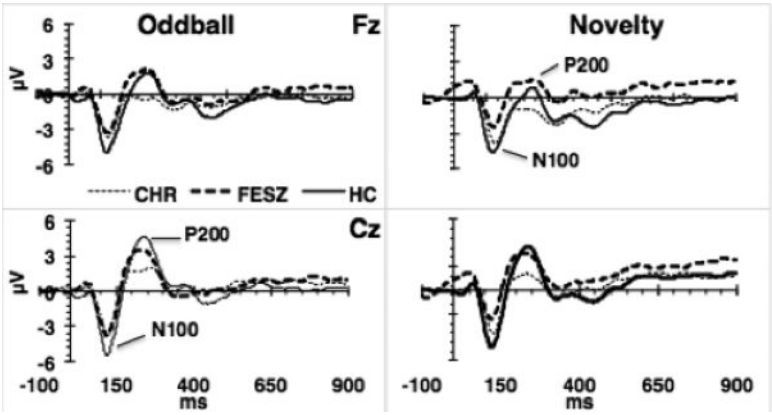

Fig. 2.

N100-P200. Grand average ERPs of standards in the oddball and novelty paradigms. P200 amplitude was significantly lower in CHR compared with both FESZ and HC, whereas P200 amplitude of these two latter groups did not differ. N100 amplitude was decreased and not significantly different across tasks in CHR and FESZ compared with HC.

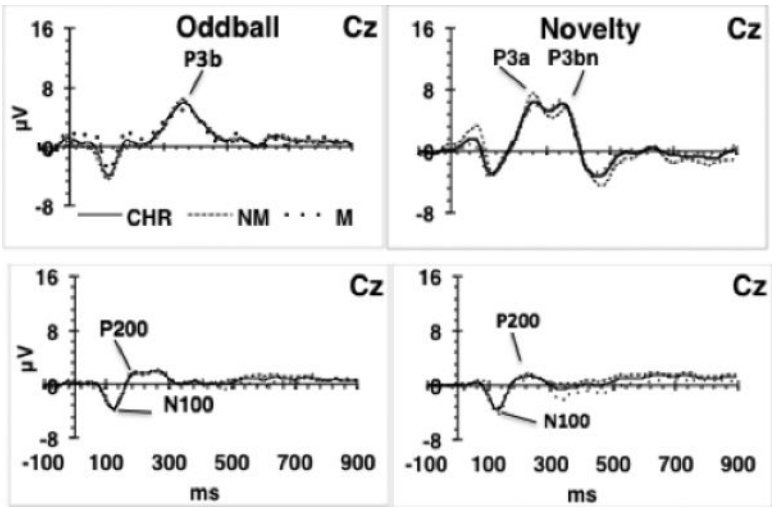

Fig. 3.

Medicated and unmedicated CHR subjects' grand averages. Comparison of grand average ERPs in medicated (M) vs. not medicated (NM) CHR subjects. CHR, medicated + not medicated; NM, not medicated, *n*=14; M, medicated, *n*=7. No significant differences were found between M and NM for any of the ERPs assessed.

Table 1

Socio-demographic and clinical information.

	HC (*n*=25)	CHR (*n*=21)	FESZ (*n*=20)	
Mean age (SD)	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 (SD); 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.

Table 2 A, B and C

Regression models

A. CHR vs. FESZ	B	S.E.	Sig.	95% C.I.	Exp (*B*)
IQ	0.151	0.071	0.034	1.012	1.338
Age	0.171	0.275	0.535	0.692	2.036
Education (years)	−0.505	0.451	0.263	0.249	1.461
Target P3b	0.188	0.135	0.164	0.926	1.571
Novel P3b	0.150	0.142	0.289	0.880	1.535
Novel P3a	0.026	0.144	0.854	0.775	1.361
N100	−0.034	0.374	0.927	0.464	2.010
P200	−1.481	0.676	0.028	0.060	0.855
Constant	−13.78	7.532	0.067		
B. CHR vs. Controls					
IQ	0.028	0.044	0.524	0.943	1.122
Age	−0.319	0.297	0.282	0.406	1.300
Education (years)	0.786	0.419	0.061	0.965	4.992
Target P3b	0.028	0.096	0.769	0.853	1.240
Novel P3b	−0.006	0.118	0.958	0.789	1.252
Novel P3a	0.411	0.157	0.009	1.108	2.052
N100	−0.800	0.347	0.021	0.228	0.886
P200	0.252	0.252	0.317	0.785	2.109
Constant	−14.27	7.611	0.061		
C. FESZ vs. Controls					
IQ	0.181	0.084	0.031	1.017	1.412
Age	−0.115	0.231	0.617	0.567	1.400
Education (years)	0.133	0.403	0.742	0.518	2.518
Target P3b	0.034	0.140	0.808	0.786	1.363
Novel P3b	0.065	0.160	0.685	0.780	1.459
Novel P3a	0.608	0.243	0.012	1.142	2.955
N100	−1.216	0.578	0.035	0.095	0.921
P200	−0.280	0.333	0.400	0.393	1.452
Constant	−29.678	12.705	0.019		

A. The indicated ERPs and demographic variables were investigated for their ability to predict high risk vs. first episode schizophrenia status; **B.** high risk vs. control or **C.** first episode vs. control status.