REDUCED PARIETAL P300 AMPLITUDE IS ASSOCIATED WITH AN INCREASED RISK FOR A FIRST PSYCHOTIC EPISODE

Mirjam J. van Tricht, Dorien H. Nieman, Johannes H.T.M. Koelman, Johan N. van der Meer, Lo J. Bour, Lieuwe de Haan, Don H. Linszen

*Biological Psychiatry, 2010: 68, 642-8*
ABSTRACT

BACKGROUND
P300 abnormalities indicate impaired information processing and are one of the most reliable biological markers of schizophrenia. We sought to investigate whether abnormalities in P300 (P3) or other event-related potentials are also present in subjects at ultra high risk (UHR) for developing psychosis and whether they are helpful in predicting transition to psychosis.

METHODS
N1, N2, N2b, P2, and P3 amplitudes were assessed in 61 UHR subjects, of whom 18 subjects (30%) made a transition to psychosis over a 3-year follow-up period (UHR + T: age 20.4 years) and 43 (70%) did not (UHR + NT: age 19.3 years), and 28 age- and intelligence-matched healthy control subjects (age 20.0 years). Psychopathology was also assessed.

RESULTS
The UHR + T subjects showed smaller parietal P3 amplitudes, compared with control subjects and UHR + NT subjects. Moreover, the N2b was higher in control subjects compared with both UHR groups. We found no differences in N1 or P2 components between the groups, and our UHR subjects did not exhibit bilateral P3 asymmetry. Reduced P3 amplitudes were the best predictor for subsequent psychosis in the UHR group. The P3 amplitude reduction was related to increased social anhedonia and withdrawal and a lower global assessment of social functioning and social personal adjustment.

CONCLUSIONS
The UHR + T subjects showed reduced parietal P3 amplitudes. In addition, a reduced P3 amplitude was the best predictor for subsequent psychosis. If replicated, these findings might contribute to a more accurate prediction of a first psychotic episode. Furthermore, reduced social functioning might be related to information processing deficits in UHR subjects.
INTRODUCTION

Schizophrenia and other psychotic disorders are usually preceded by a prodromal phase, in which a change in premorbid functioning occurs (Nieman et al., 2007; Yung et al., 2003). Many attempts have been made to identify factors in this prodromal phase that predict transition to psychosis. The term Ultra High Risk (UHR) indicates a syndrome that is regarded as a risk factor for subsequent psychosis within the next year (McGorry et al., 2003; Yung et al., 2007). UHR subjects are thought to be at high risk for a first psychotic episode on the basis of one of the following clinical symptoms: 1) genetic risk in combination with reduced functioning; 2) Attenuated Positive Symptoms, and 3) Brief Limited Intermittent Psychotic Symptoms (BLIPS). However, psychosis is not inevitable. Despite an acceptable predictive validity of these UHR criteria (Cannon et al., 2007; Yung et al., 2006; Woods et al., 2009), there are still many false positives. Therefore, a need to identify signs within this group of an impending first psychotic episode still exists. Studies in UHR subjects have already revealed abnormalities on neuroimaging (Job et al., 2003; Pantelis et al., 2007; Takahashi et al., 2009a) and neuropsychological (Brewer et al., 2006; Niendam et al., 2007) examinations before the onset of a first psychotic episode, indicating a pre-existing vulnerability to psychosis.

Event related potentials (ERP) have been frequently used in the search for biological markers of schizophrenia and psychosis (Bramon et al., 2004; Jeon & Polich, 2003; Shin et al., 2009; van der Stelt et al., 2005). The P3 has been proposed to be one of the most reliable biological markers of schizophrenia (Jeon & Polich, 2001; Jeon & Polich, 2003). The P3 is a scalp-recorded late ERP, occurring approximately 300 msec after an attended unusual or task-relevant stimulus. Two subcomponents of the P3 can be distinguished (Squires et al., 1975). The P3a potential, which typically reaches its maximum at frontal electrode positions, is thought to reflect automatic initial processing when a novel or distracting stimulus is detected. This component is followed by a parietal maximal P3b, which is a proportional reflection of subsequent effortful attentional resources, associated with updating task-relevant information in memory (Demiralp et al., 2002; Donchin & Coles, 1988; Kok, 2001). Both P3a and P3b abnormalities have been reported in schizophrenia patients and their relatives (Bramon et al., 2005; Demiralp et al., 2002; Jeon & Polich, 2003; Turetsky et al., 2000), albeit the P3b component has received significantly more attention.

Recent studies have demonstrated smaller P3 amplitudes in UHR subjects (Bramon et al., 2008; Frommann et al., 2008; Ozgürdal et al., 2008; van der Stelt et al., 2005). These studies have consistently reported P3 amplitude reductions at midline scalp sites. In addition, one of these studies reported abnormalities in P3 left–right symmetry in UHR subjects (Frommann et al., 2008). Other studies investigating P3 asymmetry in UHR subjects, however, have not replicated this finding (Bramon et al., 2008; Ozgürdal et al., 2008; van der Stelt et al., 2005).

Abnormalities in N1 (Potts et al., 1998), P2 (O’Donnell et al., 1994; Salisbury et al., 2009), and N2 (Salisbury et al., 1994) components have also been reported in schizophrenia patients, although findings are contradictory (van der Stelt et al., 2004; Winterer et al., 2001). The N1 is presumed to reflect primary and secondary auditory
functions as well as alertness and motivation (Potts et al., 1998), whereas the N2 indexes cognitive processes involved in the categorization of deviant stimuli (O’Donnell et al., 1993). The N2b (i.e., N2 difference as reflected by target-minus-frequent N2 amplitude) is also thought to be affected in schizophrenia patients (O’Donnell et al., 1993). To our knowledge, no reports are yet available on the predictive value of these ERP components for the development of a first psychotic episode.

The present study focused on the predictive value of ERP parameters for transition to psychosis. With our longitudinal study, we aimed to investigate whether ERP abnormalities were also present in our UHR group and whether baseline differences existed between the UHR groups with and without transition to psychosis. We expected UHR subjects who made a transition to psychosis at follow up (UHR + T) to show smaller ERP amplitudes compared with UHR subjects without transition (UHR + NT) and healthy control subjects. Following the literature, we hypothesized that the amplitude reductions were most pronounced for the P3 component. The relation between ERP parameters and UHR symptoms was evaluated on an exploratory basis.

**METHODS**

**Participants**

**UHR Group**

Sixty-one subjects (19 women) with a UHR for developing psychosis were included (Table 1). The UHR subjects were referred to the Academic Medical Center (AMC), Amsterdam, the Netherlands, by professionals from mental health services for a second opinion with the question of whether a psychotic development was taking place. The subjects were examined within the Dutch Prediction of Psychosis Study of the AMC. The inclusion criteria for the UHR group were: age between 15 and 35 years, and belong to one or more of the following three groups (as described in McGorry et al. [2003] and Yung et al. [2003]):

**Genetic Risk in Combination with Reduced Functioning:** subjects who have a first-degree relative with a psychotic disorder or who themselves have a schizotypal personality disorder and who have experienced a significant decrease in functioning during the past year (i.e., 30% reduction of Global Assessment of Functioning (GAF) score for at least 1 month).

**Attenuated Positive Symptoms:** subjects who have experienced subthreshold, attenuated positive psychotic symptoms, defined by at least one of the following symptoms, appearing several times/week for at least 1 week within the last 3 months: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication, and odd behavior/appearance.

**Brief Limited Intermittent Psychotic Symptoms (BLIPS):** subjects who have experienced episodes of frank psychotic symptoms. BLIPS were defined by hallucinations, delusions, or formal thought disorders occurring within the last 3 months and resolving spontaneously within 1 week.

The exclusion criteria were: previous psychotic episode for more than 1 week, as assessed with the Structured Clinical Interview for Diagnosis, Sections B and C (Spitzer et al., 1992);
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Symptoms due to substance abuse, as assessed with the Comprehensive International Diagnostic Interview, Sections J and L; World Heath Organization (Wittchen et al., 2001) IQ below 85, as assessed with the Dutch National Adult Reading Test (NART; Schmand et al., 1991); vision disorders; endocrine disease; and known neuropsychological impairment (e.g., closed head injury). All participants gave written consent.

**Control Group**

Twenty-eight participants (15 women) served as a control group for ERP performance. Exclusion criteria were: visual disorders, endocrine disease, psychiatric illness present or in the past, familial history of psychiatric illness (evaluated for first- and second-degree relatives), known neurological impairment (e.g., closed head injury), and IQ below 85. They were matched as a group on age and estimated premorbid IQ of the UHR subjects. The control subjects received a fee for their participation of €40.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethical Committee of the AMC. Informed consent of all the participants was obtained after the nature of the procedures had been fully explained.

**Materials**

**ERP Recording**

ERPs were assessed with an active auditory-oddball paradigm. The subjects were seated in a comfortable chair with eyes open, in a dimly lit, quiet room. Target stimuli with a frequency of 2000 Hz and standard, nontarget stimuli with a frequency of 1000 Hz.
were presented binaurally through headphones at an intensity of 50 dB above hearing threshold. A total of 300 tones were presented, of which 80% were nontargets and 20% were targets, with a duration of 100 msec in a random sequence. The subjects were instructed to count the targets and respond to them with a button press. The total number of counted targets was asked at the end of each session. To familiarize the subjects with the task, three practice trials with target and nontarget stimuli were presented. The stimuli were generated with an interstimulus interval of 1480 ms (i.e., a stimulation frequency of .67 Hz).

Twenty-one silver–silver chloride disk electrodes were attached to electrode sites according to the international 10–20 system, with a reference electrode on linked mastoids and a ground electrode on the forehead. Additionally, four electrodes were attached at the outer canthi of both eyes and above and below the left eye for the registration of eye movements and blinks. The interelectrode impedances were always <5 kΩ in each subject investigated. The electroencephalograph was recorded with a band-pass filter of .04–300 Hz, with a sampling rate of 1000 Hz. Digitized data for each subject were stored in a database for subsequent offline analysis with Brainvision Analyzer (Brainproducts). After baseline correction, the signals were digitally filtered with a low-pass filter of 30 Hz and a high-pass filter of .10 Hz (24 dB/oct) and were epoched at 50 msec before stimulus and 450 msec after stimulus. The maximum allowed absolute difference between two values in one segment was 200 μV, and the maximum allowed voltage step was 50 μV. Segments in which these values were exceeded were removed. Both vertical and horizontal eye-movements were detected and removed with eye-movement detection measures developed by Gratton et al. (1982). Epochs were averaged separately for nontarget and target tones. If the number of artifact free trials was below 50%, the recording was excluded from further analyses.

Peak amplitudes were semi-automatically detected and calculated relative to pre-stimulus baseline of 50 msec (Duncan et al., 2009). The N1 and P2 were measured from averages elicited by nontarget tones. The N1 amplitudes were detected as the most negative point between 75 and 125 msec after stimulus (Buchsbaum, 1977; Golob et al., 2009; Potts et al., 1998; Rosburg et al., 2008; Turetsky et al., 2009). The P2 amplitudes were detected as the most positive point after the N1, with a latency range of 150–220 msec. The N2 and P3 components were calculated as waveforms generated by target tones. The N2 was scored within a timeframe of 180–320 msec after stimulus, whereas the P3 was defined as the largest positive value between 250 and 450 msec after stimulus. The N2b difference component was calculated by subtracting the most negative point after the nontarget stimulus from the most negative point after the target stimulus within the N2 time frame. The N1 and N2 components were assessed at central midline (Cz) scalp site, whereas P2 and P3 components were assessed at parietal (Pz) scalp site. Peak amplitudes and peak latencies were calculated with a computer algorithm. All peaks were visually inspected. If necessary, adjustments were made hereafter.
Laterality
To investigate possible laterality differences between the two groups, P3 waves were also assessed at T3 and T4 scalp positions. Following previous studies (Renoult et al., 2007; Salisbury et al., 1998) lateral analyses were conducted on normalized peak data. Each lateral voltage was normalized by dividing the lateral voltage by the mean group Cz amplitude. Asymmetry differences between the groups were investigated with ratios (amplitude T3/amplitude T4) and difference scores (amplitude T4 – amplitude T3).

Task Performance
Reaction times and the number of correct hits were calculated in all groups. Trials with no button press were excluded.

Instruments
All UHR subjects were assessed with the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003), the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), and the Premorbid Assessment Scale (PAS; Cannon-Spoor et al., 1982). The SIPS is a comprehensive diagnostic tool designed specifically for the assessment of the whole spectrum of prodromal signs and symptoms. The scale is composed of 19 items (5 positive, 6 negative, 4 disorganization, 4 general symptoms), each of which is given a score of zero to six according to defined criteria. A score between 3 and 5 on the positive symptoms indicates attenuated psychotic symptoms, and a score of 6 indicates a psychotic state or BLIPS. The PANSS is composed of 30 items, each of which is given a score of one to seven. Subscores for positive, negative, and disorganization symptoms can be calculated (Bryson et al., 1999; Lindenmayer et al., 1995). The PAS is a 28-item rating scale that assesses sociability and withdrawal, peer relationships, adaptation to school, and scholastic performance in four life stages (childhood, 11 years and younger; early adolescence, 12–15 years; late adolescence, 16–18 years; and adulthood, older than 18 years) as well as social aspects of life after age 15. Control subjects were also interviewed with the SIPS. When their scores surpassed the UHR threshold, they were excluded from the study.

Medication
For the analyses, all UHR subjects were divided into four categories: 1) antipsychotic medication (patients with antipsychotic medication and antidepressants and/or other medication, such as benzodiazepines, were also assigned to this category); 2) antidepressants or antidepressants with medication other than antipsychotic medication; 3) other, for instance, benzodiazepines, psychostimulants, and/or lithium carbonate; and 4) no medication (Table 1).

Procedure
In this longitudinal cohort study, subjects were followed up for 3 years. A transition to psychosis was operationalized as a score of 4 or more on PANSS for hallucinations,
delusions, or formal thought disorders for longer than 1 week. To establish a formal DSM-IV diagnosis, the Structured Clinical Interview for Diagnosis was administered to all subjects after transition to psychosis. After transition to psychosis, the subjects received the following diagnoses: schizophrenia ($n = 12$), schizophreniform disorder ($n = 3$), schizoaffective disorder ($n = 2$), and brief psychotic disorder ($n = 1$).

In all participants, ERPs were assessed in a session of approximately 20 min, within 1 week after the psychiatric questionnaires were administered. All participants were instructed not to smoke, use drugs, or drink coffee or other caffeinated drinks the day before the ERP recording.

**Statistical Analysis**

The ERP amplitudes of the three groups were compared by two-tailed $t$ tests, after separate multivariate analyses of variance. Differences between the UHR groups in psychiatric symptoms were evaluated with Mann–Whitney $U$ tests. A multivariate algorithm that optimizes prediction of conversion to psychosis was derived from a Cox proportional hazards model, with the Backward Stepwise method. This model was used to estimate the effects of the covariates on survival time. In this model, transition to psychosis was entered as the status variable, time to onset of psychosis or to follow-up was entered as the time variable, and ERP and clinical variables that differed significantly between the groups were entered as covariates. Given the small group sizes, only subscales of the psychiatric questionnaires were included in the Cox Model. In addition to the hazard ratio, sensitivity and specificity were calculated for the covariates that contributed significantly to the prediction of the event. Survival curves were obtained with Kaplan Meier survival analyses. Correlations between ERP parameters and psychiatric symptoms were examined with nonparametric correlation tests (Spearman’s $\rho$). Differences between groups in medication use and gender were analyzed with $\chi^2$ tests. For all tests, $p$ values of $< .05$ were accepted as significant. We did not correct the level of significance for multiple comparisons to reduce the probability of Type I error, because in these exploratory correlation analyses a Type II error (failure to detect an effect when it actually exists) is more serious than Type I error (considering an effect to be real when it is not). The data were analyzed with a statistical computer program (SPSS 17.0; SPSS, Chicago, Illinois).

**RESULTS**

**Demographic and Clinical Characteristics**

As shown in Table 1, 61 UHR subjects and 28 control subjects were included at baseline. Of the UHR subjects, 18 (30%) made a transition to psychosis over a 3-year follow-up period. The mean interval between inclusion and transition to psychosis in the UHR + T group was 9.4 months (range = 2–25 months, mean [SD] = 7.2). Three of the UHR subjects (5%) were lost to follow-up. These subjects did not differ significantly from subjects with follow-up information in terms of demographic or ERP parameters at baseline.
There were no differences between groups with respect to age \((F = .65, p = .53)\). The mean age of the UHR + T subjects was 20.4 years, whereas UHR + NT and healthy control subjects were 19.3 and 20.0 years of age, respectively. In addition, the groups did not differ in terms of gender \((\chi^2 = 4.2, p = .12)\) or premorbid IQ \((F = 1.74, p = .11)\). There were no differences between UHR groups in the amount of received treatment at baseline \((F = .98, p = .46)\). Finally, we found no differences between UHR groups in inclusion criteria at baseline \((\chi^2 = 6.8, p = .554)\).

**Event Related Potentials**

The groups did not differ significantly on the number of usable trials for the target \((F = .58, p = .56)\) or the non-target tone \((F = .41, p = .66)\). ERP amplitudes, hit rates, and reaction times are presented in Table 2. There were no differences in reaction times and hit rates between the groups. Baseline analyses revealed a significant difference between the groups in P3 amplitude \((F = 22.2, p < .0001)\). Subsequent t tests for independent samples showed significantly smaller P3 amplitudes of UHR + NT subjects compared with control subjects \((t = 3.99, p < .001)\). An even stronger effect was found when comparing P3 amplitudes between UHR + T subjects and control subjects \((t = 6.73, p < .0001)\). The P3 amplitudes were also significantly smaller in UHR + T subjects, compared with UHR + NT subjects \((t = 4.16, p < .001)\). We found no group differences in the N1, P2, or N2 components. However, our analyses did reveal significant differences in the N2b component between groups \((F = 3.66, p = .030)\). Subsequent t test showed that the N2b difference was larger in control subjects compared with both UHR + T \((t = 2.32, p = .025)\) and UHR + NT \((t = 2.44, p = .017)\) subjects. We found no differences in the N2b component between UHR + T and UHR + NT subjects. We found no differences in ERP measures between the distinct inclusion groups.

**Table 2 ERP parameters of UHR and control subjects at baseline**

<table>
<thead>
<tr>
<th></th>
<th>UHR+T (n = 18)</th>
<th>UHR+NT (n = 43)</th>
<th>Controls (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude N100 Cz</td>
<td>-6.9 (2.8)</td>
<td>-6.8 (2.8)</td>
<td>-7.8 (4.0)</td>
</tr>
<tr>
<td>Amplitude P200 Pz</td>
<td>3.7 (3.3)</td>
<td>3.3 (2.7)</td>
<td>4.5 (2.6)</td>
</tr>
<tr>
<td>Amplitude N200 target tone Cz</td>
<td>-25 (6.7)</td>
<td>-57 (6.1)</td>
<td>-21 (5.8)</td>
</tr>
<tr>
<td>Amplitude N200 standard tone Cz</td>
<td>-.97 (2.9)</td>
<td>-.80 (2.7)</td>
<td>1.1 (2.7)</td>
</tr>
<tr>
<td>N2b component Cz</td>
<td>.72 (5.9)</td>
<td>.23 (6.1)</td>
<td>3.2 (5.4) #</td>
</tr>
<tr>
<td>Amplitude P300 Pz</td>
<td>10.5 (2.3)</td>
<td>16.5 (6.0)</td>
<td>22.9 (7.6) *</td>
</tr>
<tr>
<td>Hit rate (%)</td>
<td>99.4</td>
<td>99.7</td>
<td>99.2</td>
</tr>
<tr>
<td>Reaction times (sec)</td>
<td>.43 (.1)</td>
<td>.42 (.1)</td>
<td>.40 (.1)</td>
</tr>
<tr>
<td>Artefact free trails target tones</td>
<td>46.0 (7.6)</td>
<td>46.4 (10.1)</td>
<td>48.6 (9.3)</td>
</tr>
<tr>
<td>Artefact free trails non-target tones</td>
<td>183.9 (36.3)</td>
<td>188.2 (40.3)</td>
<td>193.9 (33.6)</td>
</tr>
</tbody>
</table>

*p < 0.0001, #p < 0.03. Values are mean (SD). UHR = Ultra High Risk. UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis. N100 and P200 amplitudes were calculated from standard tones. N200 and P300 amplitudes were calculated from target tones. The N2b component was calculated by subtracting the N200 amplitude after standard (low) tones from the N200 amplitude following target (high) tones.
P3 Laterality

We found no baseline differences in P3 normalized amplitudes at T3 or T4 or in the T3/T4 ratio scores and T4 – T3 difference scores between the groups (Table 3).

Grand average ERP of the three groups after target and non-target tones are presented in Figure 1. See Figure S1 in Supplement 1 for the topographic maps of P3 distribution.

![Figure 1. Grand average ERP for UHR subjects and controls. (A) Grand average target waveforms for each group at Pz. (B) Grand average non-target waveforms for each group at Pz. (C) Grand average non-target waveforms for each group at Cz. Ultra High Risk subjects with transition to psychosis (UHR+T) = red lines. Ultra High Risk subjects without transition (UHR+NT) = green lines. Control group = dashed grey lines.](image)

P3 and psychiatric symptoms

See Table S1 in Supplement 1 for the SIPS, PANSS, and GAF data of the three groups. The score on the subscale negative symptoms of the SIPS was higher in UHR + T compared with UHR + NT subjects ($U = 251.0, p = .031$). In addition, UHR + T subjects showed a trend toward a higher score on the negative symptoms subscale of the PANSS ($U = 257.0, p = .063$). We found no differences between the groups on the positive symptom scales. Reduced P3 amplitude was related to increased social anhedonia and withdrawal as assessed with Item N1 of the SIPS ($\rho = -.313, p = .014$) and a higher rate of active social avoidance as assessed with Item G16 of the PANSS ($\rho = -.372, p = .003$). In addition, UHR subjects with smaller P3 amplitudes scored higher on the global assessment of the highest level of functioning of the PAS ($\rho = -.395, p = .002$), where the highest score reflects “unable to function in or enjoy any aspect of life.” Furthermore, UHR subjects with smaller P3 amplitudes scored higher at the item “social personal adjustment after the age of 15 years” ($\rho = -.267, p = .045$), where the highest score reflects “no desire to be with peers or others. Either asocial or antisocial.”
Effect of ERP and Clinical Variables on Survival Time

The following variables were entered in the final Cox model: P3 amplitude, N2b score, and negative symptoms subscales of the PANSS and the SIPS. With the Cox regression survival analysis, the strongest predictor of developing a psychosis was the P3 amplitude ($B = -.23$, $Wald = 10.4$, $p = .001$, hazard ratio = 1.37). This means that the relative risk of developing a psychosis increases 37% with a decrease of the P3 amplitude of 1 μV (Table S2 in Supplement 1). None of the other covariates contributed independently to the prediction of a first psychotic episode. The survival distribution (Figure 2) differed significantly between the groups with above and below UHR mean amplitudes (log rank (Mantel Cox) = 10.48, $p = .001$). We also attempted to assess the sensitivity and specificity

**Table 3** P3 laterality on T3 and T4 scalp positions of UHR and control subjects at baseline

<table>
<thead>
<tr>
<th></th>
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<th>UHR+NT (n = 43)</th>
<th>Controls (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3 amplitude at T3</td>
<td>.69 (.3)</td>
<td>.57 (.3)</td>
<td>.46 (.1)</td>
</tr>
<tr>
<td>P3 amplitude at T4</td>
<td>.67 (.2)</td>
<td>.50 (.2)</td>
<td>.47 (.2)</td>
</tr>
<tr>
<td>T3/T4 ratio</td>
<td>1.03 (.3)</td>
<td>1.14 (.5)</td>
<td>1.02 (.8)</td>
</tr>
<tr>
<td>T4-T3 difference</td>
<td>-.02 (.3)</td>
<td>-.07 (.5)</td>
<td>.01 (.4)</td>
</tr>
</tbody>
</table>

*normalized peak data: lateral voltage (μV) divided by the mean group Cz amplitude. Values are mean (SD). UHR = Ultra High Risk. UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis.

Figure 2. Survival curves for Ultra High Risk (UHR) subjects with P3 amplitudes above or below UHR group mean (14.7). The survival distribution differed significantly between the groups with above or below UHR mean amplitude (Log Rank (Mantel Cox) = 10.48, $p = .001$).
of the P3 amplitude. With the default cut value, the sensitivity and specificity of the P3 amplitudes was estimated as 83.3% and 79.1%, respectively. For the aim of obtaining a high sensitivity (thereby avoiding false negatives), the cut value for predicted group membership was set at .24, resulting in a sensitivity of 100% and a specificity of 69.8% for P3 amplitudes.

DISCUSSION

Our study shows that UHR subjects who eventually made a transition to psychosis have smaller parietal P3 amplitudes compared with subjects who did not make this transition. In addition, P3 amplitudes were the best predictor of a developing first psychotic episode in our UHR group. As such, P3 amplitudes seem to be a neurobiological predictor of future transition to psychosis. Our findings concur with other studies in high-risk populations, reporting midline P3 amplitudes reductions (Bramon et al., 2008; Ozgürdal et al., 2008; van der Stelt et al., 2005). We are the first, however, to report on the predictive value of P3 abnormalities.

We found no differences between the groups in N1 or P2 components. We did find a higher N2 difference score (N2b) in control subjects. The N2b component is used to index target detection and stimulus classification and is elicited by controlled deviance detection (Potts et al., 2007; Wood et al., 2007). This component, however, did not differ between the UHR groups. Thus, although both UHR groups showed impaired deviance detection, the N2b component did not attribute to predicting psychosis.

We found no evidence of P3 amplitude asymmetry differences between the groups. That our paradigm involved a button press, which is thought to diminish the abnormal P3 asymmetry in schizophrenia, could explain the absence of asymmetry differences (Bramon et al., 2008; Pfefferbaum et al., 1989; Renoult et al., 2007). However, our results replicate the findings of other studies on P3 asymmetry in UHR subjects (Bramon et al., 2008; Ozgurdal et al., 2008). Given that the laterality changes have repeatedly been found in later stages of the disease (Jeon & Polich, 2007), it is likely that these changes represent a marker of illness progression rather than a marker of susceptibility to schizophrenia. Replication studies are needed before any firm conclusions can be drawn.

As for the relations among P3, psychiatric symptoms, and social functions, some potential meaningful associations were found. Smaller P3 amplitudes were associated with a higher rating of social anhedonia and withdrawal as assessed with the SIPS and the PANSS. Moreover, reduced P3 amplitudes were related to a greater inability to function in or enjoy any aspect of life and a lower level of social personal adjustment as assessed with the PAS. Although these associations were modest, they point in the same direction, thus suggesting a relationship between P3 amplitudes and a decline in social functioning in daily life, which is a characteristic phenomenon in the prodromal phase of schizophrenia. Similar associations between ERPs, in particular Mismatch Negativity and the amplitude of the N2b component, and daily social functioning have been reported in schizophrenia patients (Light & Braff, 2005; Maeda et al., 2005). Our analysis failed to show associations
between P3 parameters and positive UHR symptoms. This might be due to a more modest symptom presentation in UHR subjects compared with schizophrenia patients.

In the present study, three subjects were lost to follow-up. Therefore, we cannot be certain about their current state of functioning. A transition to psychosis is highly unlikely, because we asked the practitioner who referred the subjects to contact us when they suspected a psychosis. Hence, we do not believe that we have incorrectly labelled these subjects as UHR + NT. Finally, these subjects did not differ from the other UHR subjects on any of the clinical or neurophysiological measures at baseline. It is therefore unlikely that these cases have influenced our results.

There is converging evidence that early intervention might prevent or delay the onset of psychosis (Harris et al., 2005; McGorry et al., 2002; McGorry et al., 2003). Our results suggest that P3 amplitudes might be helpful in improving prediction and therefore preventing transition to psychosis. Our forthcoming report will reveal whether P3 abnormalities show a progression after conversion to psychosis, as suggested by recent neuroimaging findings (Takahashi et al., 2009b).

We conclude that smaller parietal P3 amplitudes might be helpful in identifying an impending psychotic episode. Clinical variables, such as social withdrawal might also be a helpful measure, although these variables did not independently contribute to the prediction of a first psychotic episode in our study. If replicated, our findings might contribute to a more accurate prediction of a first psychotic episode in addition to other measures, such as neuroimaging and neurocognition.

ACKNOWLEDGEMENTS

The authors thank the EEG technicians of the Clinical Neurophysiology Unit for their assistance in the event-related potentials recordings. We also thank T. Boerée for his technical assistance. This study was supported by a grant for the Dutch Prediction of Psychosis Study from ZON-MW (ZorgOnderzoek Nederland/NWO-Medische Wetenschappen, project # 2630.0001) and a grant from the European Commission in Brussels, Belgium, for the European Prediction of Psychosis study (Grant QLGU-CT-2001-01081). The ZON-MW and the European Commission had no further role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

The authors reported no biomedical financial interests or potential conflicts of interest.
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REFERENCE LIST


Reduced Parietal P300 amplitude is associated with an increased risk for a first psychotic episode.


REDUCED PARIETAL P300 AMPLITUDE IS ASSOCIATED WITH AN INCREASED RISK FOR A FIRST PSYCHOTIC EPISODE


SUPPLEMENT 1

Table S1. Structured Interview for Prodromal Syndromes (SIPS), Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF) scores of Ultra High Risk (UHR) subjects and control subjects at baseline

<table>
<thead>
<tr>
<th></th>
<th>UHR+T (n = 18)</th>
<th>UHR+NT (n = 43)</th>
<th>Controls (n = 26)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structured Interview for Prodromal Syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>16.4 (6.8)</td>
<td>12.5 (6.9)</td>
<td>.85 (1.1)</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>11.7 (4.0)</td>
<td>10.8 (3.4)</td>
<td>1.2 (1.4)</td>
</tr>
<tr>
<td>General symptoms</td>
<td>9.4 (4.3)</td>
<td>8.9 (4.4)</td>
<td>.58 (1.0)</td>
</tr>
<tr>
<td>Disorganization symptoms</td>
<td>5.6 (2.9)</td>
<td>4.7 (2.8)</td>
<td>.65 (1.9)</td>
</tr>
<tr>
<td><strong>Positive and Negative Syndrome Scale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>12.3 (2.4)</td>
<td>11.9 (2.7)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>13.2 (4.7)</td>
<td>11.6 (4.9)</td>
<td>n.a.</td>
</tr>
<tr>
<td>General Psychopathology</td>
<td>25.3 (6.3)</td>
<td>24.1 (5.1)</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>Global Assessment of Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current GAF score</td>
<td>47.8 (12.7)</td>
<td>51.0 (11.7)</td>
<td>87.6 (6.5)</td>
</tr>
<tr>
<td>Highest GAF score in the last year</td>
<td>58.3 (14.2)</td>
<td>59.0 (11.4)</td>
<td>69.7 (35.1)</td>
</tr>
</tbody>
</table>

Values are mean (SD). UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis; n.a., not applicable; *data of two control subjects are missing

Table S2. Cox regression predicting relative risk of developing a psychosis

<table>
<thead>
<tr>
<th>Step</th>
<th>P3 amplitude</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p Value</th>
<th>Hazard Ratio</th>
<th>95.0% confidence interval for Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3 amplitude</td>
<td>-.274</td>
<td>.076</td>
<td>10.13</td>
<td>1</td>
<td>.001</td>
<td>1.38</td>
<td>1.25-1.47</td>
</tr>
<tr>
<td>N2b difference score</td>
<td>-.076</td>
<td>.048</td>
<td>2.56</td>
<td>1</td>
<td>.110</td>
<td>1.08</td>
<td>.98-1.19</td>
</tr>
<tr>
<td>SIPS^1 negative symptoms</td>
<td>.063</td>
<td>.045</td>
<td>1.98</td>
<td>1</td>
<td>.160</td>
<td>1.07</td>
<td>.98-1.16</td>
</tr>
<tr>
<td>PANSS^2 negative symptoms</td>
<td>.014</td>
<td>.048</td>
<td>.082</td>
<td>1</td>
<td>.774</td>
<td>1.01</td>
<td>.92-1.11</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3 amplitude</td>
<td>.247</td>
<td>.075</td>
<td>10.71</td>
<td>1</td>
<td>.001</td>
<td>1.39</td>
<td>1.26-1.51</td>
</tr>
<tr>
<td>N2b difference score</td>
<td>.076</td>
<td>.048</td>
<td>2.53</td>
<td>1</td>
<td>.112</td>
<td>1.08</td>
<td>.98-1.18</td>
</tr>
<tr>
<td>SIPS negative symptoms</td>
<td>.069</td>
<td>.040</td>
<td>2.98</td>
<td>1</td>
<td>.084</td>
<td>1.07</td>
<td>.99-1.16</td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3 amplitude</td>
<td>.225</td>
<td>.073</td>
<td>10.43</td>
<td>1</td>
<td>.001</td>
<td>1.37</td>
<td>1.28-1.49</td>
</tr>
<tr>
<td>SIPS negative symptoms</td>
<td>.071</td>
<td>.040</td>
<td>3.08</td>
<td>1</td>
<td>.079</td>
<td>1.07</td>
<td>.99-1.16</td>
</tr>
</tbody>
</table>

^1 Structured Interview for Prodromal Syndromes (SIPS); Positive and Negative Syndrome Scale (PANSS). **Bold** indicates significant p values
REduced Parietal P300 Amplitude Is Associated With an Increased Risk for a First Psychotic Episode

Figure S1. Colour-coded topographic maps of P3 distribution. A = P3 voltage activity for the three groups. B = T-statistics of P300 voltage activity for the UHR groups. UHR+T= Ultra High Risk patients with transition to psychosis. UHR+NT= Ultra High Risk patients without transition to psychosis.