Neurophysiological correlates of the pathway to the early stages of psychosis
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AUDITORY ERP COMPONENTS BEFORE AND AFTER TRANSITION TO A FIRST PSYCHOTIC EPISODE

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ABSTRACT

We investigated the course of Event Related Potentials (ERP) from prior to until shortly after a first psychotic episode in subjects at Ultra High Risk (UHR) for psychosis. N1, N2, N2b, P2 and P3 amplitudes were assessed using an auditory active oddball paradigm in 15 UHR subjects who made a transition to psychosis (UHR + T) at follow up, 23 subjects without a transition (UHR + NT) and 17 matched healthy controls at inclusion and again after approximately 18 months. Repeated-measures analyses revealed no significant time effects for any of the ERP components. However, an interaction effect was found for N1 amplitudes. Post-hoc analyses showed that N1 amplitudes were smaller at follow up compared to baseline only in UHR + T subjects. P3 amplitudes showed no further reduction after psychotic onset. These findings suggest that discernable ERP components behave differently during progression from the prodromal phase to the first psychotic episode. These findings may give insight in pathophysiological mechanisms underlying the genesis of psychosis.
1. INTRODUCTION

Early detection and prevention of psychotic disorders has caught the attention of many researchers worldwide. A frequently applied research strategy that aims at elucidating predictors of psychosis is investigating clinical samples of Ultra High Risk (UHR) subjects (McGorry et al., 2003; Yung et al., 2004; Yung et al., 2006). UHR subjects are thought to be at high risk for a first psychotic episode within a relatively short period based on one or more of the following symptoms: (1) Genetic risk in combination with reduced functioning; (2) Attenuated Positive Symptoms (APS) and (3) Brief Limited Intermittent Psychotic Symptoms (BLIPS).

In UHR subjects, before the onset of a first psychotic episode, abnormalities have been demonstrated at MRI neuro-imaging (Job et al., 2003; Pantelis et al., 2007; Takahashi et al., 2009a), neurophysiological (Bramon et al., 2008; Frommann et al., 2008; Ozgürdal et al., 2008; van Tricht et al., 2010) and neuropsychological (Brewer et al., 2006; Niendam et al., 2007; Seidman et al., 2010) assessments. In addition, imaging studies showed progression of structural brain abnormalities in prefrontal, inferior frontal and temporal lobe regions as well as in the medial and superior parietal cortex before and after the onset of the first psychotic episode (Sun et al., 2009; Takahashi et al., 2009b). Studies on the course of neuropsychological functions in UHR subjects before and after psychotic onset have yielded inconsistent results. Whereas two studies found no evidence of further neurocognitive deterioration after a first psychotic episode (Becker et al., 2010; Hawkins et al., 2008), evidence of a decline in visual memory and attentional set-shifting following psychosis onset was found in another study (Wood et al., 2007).

Event related potentials (ERPs) have frequently been examined in the search for biologic markers of schizophrenia and psychosis. An ERP that has been studied extensively in schizophrenia is the P300, also known as the P3 or P3b. The P3 is a scalp-recorded late ERP, which occurs about 300 ms after an attended unusual or task-relevant stimulus and has its maximum at parietal scalp position. It is a cognition related wave, closely associated with attention and memory (Nieman et al., 2002; van der Stelt et al., 2004). The P3b can be distinguished from the P3a, which is elicited by a rare event that is not task relevant and has an earlier peak latency and a scalp distribution with a midline fronto-central maximum (Polich, 2007). Although P3 abnormalities have been reported in a variety of disorders, including dementia, traumatic brain injury, ADHD and autism, P3 amplitude reductions are most consistently reported in schizophrenia (Duncan et al., 2009). Recent studies have demonstrated smaller P3 amplitudes prior to the onset of psychosis in UHR subjects (Bramon et al., 2008; Frommann et al., 2008, Ozgürdal et al., 2008). In a previous study of our group on ERP abnormalities in an UHR sample, subjects who made a transition to psychosis at follow up showed smaller parietal P3 amplitudes at baseline compared to UHR subjects who did not make this transition (van Tricht et al., 2010). Moreover, smaller parietal P3 amplitudes at baseline were the only independent predictor of a future psychotic episode. Other ERP components, including the N1, P2 and N2b however did not significantly contribute to the prediction of a first psychotic episode. To our knowledge, until now only one study
has reported abnormalities in these earlier ERP components in UHR subjects before a psychotic episode (Brockhaus-Dumke et al., 2008), whereas other studies in the field found no evidence of impairments in these components in the prodromal phase (Bramon et al., 2008; van Tricht et al., 2010). Abnormalities in earlier ERP components have however been reported in both first episode and chronic schizophrenia patients (Haenschel et al., 2007; O’Donnell et al., 1993; Potts et al., 1998; Salisbury et al., 2010).

Some studies in schizophrenia patients have also demonstrated P3 amplitude asymmetry, i.e. more pronounced amplitude reduction in the left compared to the right temporal lobe, in addition to amplitude reductions at midline scalp positions (Faux et al., 1988; Jeon & Polich, 2001). P3 amplitude asymmetry has also been reported in patients with a first psychotic episode (McCarley et al., 2002; Salisbury et al., 1998) and in UHR subjects before a possible transition to psychosis (Frommann et al., 2008), although most studies in high risk subjects and first episode patients found no evidence of P3 asymmetry (Bramon et al., 2008; Hirayasu et al., 1998, Renoult et al., 2007, van Tricht et al., 2010).

To our knowledge, no studies have yet explored the course of neurophysiological abnormalities before and after a first psychosis. Investigation of the course of neurophysiological alterations in UHR subjects who make a transition to psychosis may help to elucidate pathophysiological mechanisms that are primarily related to the development of psychosis. Thus, our main objective was to clarify the course of ERP abnormalities in UHR subjects from before until shortly after a first psychotic episode. We predicted that P3 abnormalities, as established in the prodromal phase, would show further progression after psychotic onset. In addition, at follow up, we expected P3 decrements in UHR subjects with a transition to psychosis to be more pronounced in left compared to right scalp positions. Finally, we expected a differential course of ERP amplitudes from baseline to the second assessment in the three groups: UHR subjects with a transition to psychosis were expected to show decreased mean N1, N2 and P2 amplitudes at follow up compared to baseline, whereas no temporal ERP changes were expected in UHR subjects without a transition to psychosis (UHR + NT) and a group of healthy controls.

2. METHODS

2.1. Participants

2.1.1. UHR group

Sixty-one subjects (19 women) with an UHR for developing psychosis were included at baseline. Demographic and clinical characteristics of these subjects have been described previously (van Tricht et al., 2010). Twenty-three UHR subjects were unavailable for the follow up assessment. Reasons for nonparticipation at follow up were refusal (n = 16), inability to be located (n = 6) and imprisonment (n = 1). The subjects who were available for a reassessment did not differ significantly from those lost to follow up in terms of demographic or ERP variables at baseline. Nevertheless, only UHR subjects with both baseline and follow up assessments (28 males, 10 females) were included in the current study. The subjects were examined within the Dutch Prediction of Psychosis Study (DUPS) at the Department of Early
Psychosis of the AMC. The inclusion criteria for the UHR group were: age between 15 and 35 years, and belonging to one or more of the following three groups:

1. **Genetic risk in combination with reduced functioning**: subjects who have a first degree relative with a psychotic disorder, or who themselves have a schizotypical 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).

2. **Attenuated Positive Symptoms (APS)**: subjects who have experienced sub-threshold, attenuated positive psychotic symptoms, defined by at least 1 of the following symptoms, appearing several times per 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 behaviour/appearance.

3. **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), symptoms due to substance abuse, as assessed with the Comprehensive International Diagnostic Interview, sections J and L (WHO, 1993; Wittchen, 1994), premorbid IQ below 85, as determined with the Dutch version of the National Adult Reading Test (NART; Schmand et al., 1991), severe vision and/or auditory disorders, endocrine disease and known neurological impairment (e.g. closed head injury).

### 2.1.2. Control group

Twenty-eight participants (15 women) served as a control group for ERP performance, of whom 17 subjects (6 women) were available for the second assessment. Reasons for nonparticipation at follow up in the control group were refusal (n = 7) and inability to be located (n = 4). Again, only subjects with baseline and follow up assessments were included. Exclusion criteria were similar to the UHR subjects, with the addition of psychiatric illness present or in the past and familial history of psychiatric illness (evaluated for first and second degree relatives). Controls were matched on age and estimated premorbid IQ of the UHR subjects.

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 participants was obtained after the nature of the procedures had been fully explained.

### 2.2. Materials

#### 2.2.1. ERP recording

ERPs were assessed using an active auditory-oddball paradigm. The subjects were seated in a comfortable chair with eyes open, in a dimly lit, quiet room. Tones consisting of target stimuli
with a frequency of 2000 Hz and standard, non-target 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, with a duration of 100 ms, were presented in a random sequence, of which 20% were targets and 80% non-targets. 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 non-target stimuli were presented. The inter-stimulus interval was 1480 ms.

Twenty-one silver silver disc electrodes (impedances <5 kΩ) were attached to electrode sites (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. Vertical and horizontal eye-movements were detected and removed using eye-movement detection measures developed by Gratton et al. (1982).

The EEG was recorded with an analogue band-pass filter of 0.04–300 Hz and digitally stored with a 1000-Hz sampling rate in a database for subsequent off line analysis using 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 0.10 Hz (24 dB/oct) and were epoched at 50 ms pre-stimulus and 450 ms post-stimulus. The maximum allowed absolute difference between two values in one segment was 200 μV and the maximum allowed voltage step was 50 μV. Epochs were averaged separately for non-target and target tones. For both target and non-target trials, the recording was excluded from further analyses if less than 50% of the trials included artefact free trials.

Peak amplitudes were semi-automatically detected and calculated relative to pre-stimulus baseline of 50 ms. Following previous studies (Ford et al., 2001; O’Donnell et al., 2004; Salisbury et al., 2010), N1 and P2 components were measured from averages elicited by non-target tones. N1 amplitudes were detected as the most negative point between 75 and 125 ms post stimulus whereas P2 amplitudes were detected as the most positive point following the N1, with a latency range of 150–220 ms. N2 and P3 components were calculated from waveforms generated by target tones. The N2 was scored as the most negative point within a timeframe of 180–320 ms post-stimulus, whereas the P3 was defined as the largest positive value between 250 and 450 ms post-stimulus. The N2b difference score was calculated by subtracting the most negative point following the non-target stimulus from the most negative point following the target stimulus within the N2 time frame. Based on the literature (Bramon et al., 2004; Salisbury et al., 1994, Salisbury et al., 2010), N1 and N2 components were assessed at central midline (Cz) scalp site, P2 at parietal scalp site (Pz), and P3 components at parietal, central and frontal (Fz) scalp sites. All peaks were visually inspected.

2.2.2. Laterality
Laterality differences were assessed by comparing P3 amplitudes at left (T3) and right (T4) scalp positions. In addition, group differences in P3 symmetry were assessed by comparing T4-T3 difference and T3/T4 ratio scores.
2.2.3. Task performance
Reaction times and the number of correct hits were calculated in all groups. Trials with no button press were excluded.

2.2.4. Medication
For the analyses, all UHR subjects were divided into four medication categories: (i) antipsychotic medication (patients using antipsychotic medication and other medication were also assigned to this category), (ii) antidepressants or antidepressants with medication other than antipsychotic medication, (iii) other, for instance benzodiazepines, methylphenidate, and/or lithium carbonate, and (iv) no medication. Possible medication effects on ERPs were assessed by comparing ERPs between these four groups and between the two categories ‘no medication’ and ‘medication’ (category one, two, and three combined). Because only one UHR subject used typical antipsychotics, no analyses were conducted comparing subjects using typical or atypical antipsychotics. Associations between the use of antipsychotics and ERP amplitudes were determined by correlating chlorpromazine equivalents with the mean amplitudes of the distinct ERP components.

2.3. Procedure
In this longitudinal cohort study, subjects were followed up for 3 years. UHR subjects were assessed shortly after inclusion. Eighteen months after the first assessment, all subjects were again contacted for a follow-up assessment. A transition to psychosis was defined as a score of 4 or more on the Positive and Negative Syndrome Scale (PANSS: Kay et al., 1987) for hallucinations, delusions or formal thought disorders for longer than 1 week. To establish a formal DSM-IV diagnosis, the SCID-I was administered to all subjects after transition to psychosis. Subjects who had experienced a psychotic episode were assessed when stabilized on medication.

ERPs were assessed in sessions of approximately 20 min. All participants were instructed not to smoke, use drugs or drink coffee or other caffeine holding drinks the day of the ERP recording. Before the ERP recording, participants were asked whether they complied with this instruction.

2.4. Statistical analyses
Temporal ERP changes were analyzed by means of nine separate repeated measures ANOVA’s, using ‘Group’ as between subjects factor and the distinct ERP components at the first and second assessment as within subjects variables (SPSS 17.0). Post hoc Tukey Honest Significant Difference (HSD) tests were subsequently applied to assess temporal changes in ERP components between groups. Exploratively, differences in the distinct ERP components between the three groups at follow up were assessed using ANOVA’s, followed by post hoc Tukey HSD tests. Correlations between ERP parameters, psychiatric symptoms and medication dosages were examined with nonparametric correlation tests (Spearman’s Rho). Group differences in age and premorbid IQ were evaluated using one-way ANOVA’s. Gender differences between the groups were assessed using
Chi² tests. Differences in GAF scores between the two UHR groups were assessed using Mann–Whitney U tests. Temporal changes in demographic and clinical variables were assessed using repeated measures ANOVA’s. For all tests, alpha of ≤0.05 was considered as statistically significant.

3. RESULTS

3.1. Demographic and clinical characteristics

Thirty-eight UHR subjects and 17 controls were assessed at baseline and follow up. The demographic and clinical characteristics of these subjects are presented in Table 1. Of the UHR subjects, 15 (39%) made a transition to psychosis over a 3-year follow-up period. These subjects received the following diagnoses: schizophrenia (n = 11), schizophreniform disorder (n = 2), schizoaffective disorder (n = 1) and brief psychotic disorder (n = 1). The mean interval between inclusion and transition to psychosis in the UHR + T group was 9.4 months (range = 2–25 months, SD = 7.2). The mean interval between baseline and follow up ERP recordings was larger in controls (37.1 months, range 14–66) compared to UHR + T (22.3 months, range 17–30) and UHR + NT subjects (21.7 months, range 19–36). At baseline, we found no differences between the two UHR groups in the percentage of subjects meeting the distinct inclusion criteria (all p values ≥.14). Moreover, there were no differences between both UHR groups in GAF scores at baseline (current: U = 155.0, p = .62; highest in past year: U = 160.5, p = .89) or follow up (current: U = 37.0, p = .28; highest in past year: U = 38.5, p = .31).

At baseline and follow-up, there were no differences between the groups with respect to age, gender distribution or premorbid IQ (all p values ≥.10). However, repeated measure analyses did reveal significant changes in age between the two assessments (time effect: F = 32.3, p < .001; interaction effect: F = 3.65, p = .001).

Post hoc analyses regarding the time effect yielded that the subjects in all three groups were older at the second assessment compared to baseline. With respect to the interaction effect, post hoc tests showed a statistical trend for a difference in the course of age between UHR + NT subjects and controls (p = .09). This finding can be explained by the fact that controls were assessed after a longer follow-up period than the UHR + NT subjects.

3.2. ERP

Repeated-measures analyses revealed no significant time effects for any of the ERP components (Table 2). However, a significant time x group interaction effect was found for N1 amplitudes. Thus, the course of N1 amplitudes from baseline to the second assessment differed significantly between the three groups. This effect would survive a Bonferroni correction for multiple comparisons. Post-hoc comparisons revealed that the mean difference in N1 amplitudes from baseline to follow up was larger in UHR + T subjects compared to controls (p = .006) and UHR + NT subjects (p = .06; statistical trend). No significant interaction effects were found for any of the other ERPs. Neither did we find time or interaction effects for the P3 amplitudes at T3 and T4, T4/T3 ratio or the T3-T4 difference scores (Table 3).
Table 1 Demographic and clinical characteristics at baseline and follow up

<table>
<thead>
<tr>
<th></th>
<th>UHR+T (n=15)</th>
<th>UHR+NT (n=23)</th>
<th>Controls (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>FU</td>
<td>Baseline</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>20.4 (4.4)</td>
<td>22.3 (4.3)</td>
<td>19.9 (4.3)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>11/4</td>
<td>11/4</td>
<td>17/6</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>6 (40)</td>
<td>7 (47)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Typical</td>
<td>1 (7)</td>
<td>0</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Atypical</td>
<td>5 (33)</td>
<td>7 (47)</td>
<td>0</td>
</tr>
<tr>
<td>Medication usage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (7)</td>
<td>4 (27)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>None</td>
<td>6 (40)</td>
<td>2 (13)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Chlorpromazine equivalents</td>
<td>120.8 (37.4)</td>
<td>223.0 (79.1)</td>
<td>130.5 (35.8)</td>
</tr>
<tr>
<td>NART IQ score (SD)</td>
<td>104.4 (8.4)</td>
<td>-</td>
<td>101.1 (9.5)</td>
</tr>
<tr>
<td>GAF Current</td>
<td>47.7 (13.4)</td>
<td>58.4 (14.7)</td>
<td>48.2 (11.0)</td>
</tr>
<tr>
<td>Highest in past year</td>
<td>58.3 (14.9)</td>
<td>59.4 (15.8)</td>
<td>56.8 (10.0)</td>
</tr>
<tr>
<td>Inclusion symptoms n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>10 (67)</td>
<td>-</td>
<td>18 (78)</td>
</tr>
<tr>
<td>BLIPS</td>
<td>2 (13)</td>
<td>-</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BLIPS and AS</td>
<td>1 (7)</td>
<td>-</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Genetic risk and reduced functioning</td>
<td>1 (7)</td>
<td>-</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Genetic risk, reduced functioning and AS</td>
<td>1 (7)</td>
<td>-</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: NART = National Adult Reading Test; GAF = Global Assessment of Functioning; AS = attenuated symptoms; BLIPS = Brief Limited Intermittent Psychotic Symptoms; UHR = Ultra High Risk, with (UHR+T) or without (UHR+NT) transition to psychosis.

There were no significant differences in the number of usable trials for target or non-target conditions, reaction times or hit rates between baseline and follow up. Moreover, we found no significant group differences in these variables at baseline or follow up. Grand average waveforms after target and non-target tones are presented in Fig. 1. Topographic maps of voltage activity after non-target tones for each group at follow up are presented in Fig. 2.

Exploratively, we investigated the neurophysiological profile of UHR + T patients shortly after a first psychotic episode. These additional analyses revealed group differences in P3 amplitudes at Pz (F = 11.5, p < .001). Post hoc Tukey HSD tests yielded that the P3 amplitude at Pz was smaller in UHR + T subjects compared to controls (p < .001). In addition, P3 amplitudes at Pz were significantly smaller in UHR + T patients compared to UHR + NT subjects (p < .001). We found no significant differences in P3 amplitudes between UHR + NT and control subjects. The analyses also revealed group differences in N1 amplitudes at Cz at follow up (F = 6.39, p = .003). Post hoc tests showed that the mean N1 amplitude was smaller in UHR + T patients compared to controls (p = .007) and UHR + NT subjects (p = .03). No group differences were found in any of the other ERPs or in the laterality scores.
Table 2 ERP parameters of Ultra High Risk (UHR) subjects and control subjects at baseline and follow up

<table>
<thead>
<tr>
<th></th>
<th>UHR+T (n=15)</th>
<th>UHR+NT (n=23)</th>
<th>Controls (n=17)</th>
<th>Time effect</th>
<th>Interaction effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow up</td>
<td>Baseline</td>
<td>Follow up</td>
<td>Baseline</td>
</tr>
<tr>
<td>Amplitude N1 standard (Cz)</td>
<td>-7.3 (2.4)</td>
<td>-5.6 (1.9)</td>
<td>-7.6 (2.7)</td>
<td>-8.2 (1.8)</td>
<td>-8.1 (1.6)</td>
</tr>
<tr>
<td>Amplitude P2 (Pz)</td>
<td>5.6 (5.1)</td>
<td>5.0 (3.9)</td>
<td>4.6 (5.2)</td>
<td>3.8 (3.9)</td>
<td>4.2 (3.7)</td>
</tr>
<tr>
<td>Amplitude N2 target (Cz)</td>
<td>-8.7 (5.6)</td>
<td>-4.7 (3.4)</td>
<td>-1.28 (5.2)</td>
<td>-2.3 (5.7)</td>
<td>-3.3 (4.9)</td>
</tr>
<tr>
<td>Amplitude N2 standard (Cz)</td>
<td>-93.2 (3.7)</td>
<td>1.0 (3.3)</td>
<td>-49.2 (2.7)</td>
<td>62.2 (2.2)</td>
<td>1.3 (2.9)</td>
</tr>
<tr>
<td>N2b difference</td>
<td>-0.6 (2.9)</td>
<td>-1.47 (5.3)</td>
<td>.79 (2.4)</td>
<td>2.92 (6.0)</td>
<td>4.4 (5.9)</td>
</tr>
<tr>
<td>Amplitude P3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pz</td>
<td>10.4 (2.0)</td>
<td>10.7 (3.1)</td>
<td>16.5 (6.0)</td>
<td>17.7 (5.5)</td>
<td>22.3 (6.4)</td>
</tr>
<tr>
<td>Cz</td>
<td>11.7 (4.0)</td>
<td>13.8 (6.2)</td>
<td>15.2 (7.0)</td>
<td>15.0 (7.0)</td>
<td>19.3 (6.6)</td>
</tr>
<tr>
<td>Fz</td>
<td>10.9 (5.2)</td>
<td>8.1 (4.7)</td>
<td>8.6 (4.7)</td>
<td>9.0 (5.2)</td>
<td>10.3 (5.4)</td>
</tr>
<tr>
<td>Hit rate (%)</td>
<td>99.4</td>
<td>99.6</td>
<td>99.7</td>
<td>99.7</td>
<td>99.2</td>
</tr>
<tr>
<td>Reaction times (sec)</td>
<td>.47</td>
<td>.48</td>
<td>.40</td>
<td>.41</td>
<td>.38</td>
</tr>
<tr>
<td>Usable trials target tone (no.)</td>
<td>45.1 (7.9)</td>
<td>48.9 (7.4)</td>
<td>47.5 (10.4)</td>
<td>51.7 (7.8)</td>
<td>51.9 (7.4)</td>
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<tr>
<td>Usable trials standard tone (no.)</td>
<td>183.2 (37.1)</td>
<td>187.7 (27.0)</td>
<td>196.0 (38.1)</td>
<td>209.3 (25.6)</td>
<td>202.5 (30.4)</td>
</tr>
</tbody>
</table>

Values are mean (SD). Abbreviations: UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis. N1 and P2 amplitudes were calculated from standard tones. N2 and P3 amplitudes were calculated from target tones. The N2b component was calculated by subtracting the N2 amplitude after standard (low) tones from the N2 amplitude following target (high) tones.

Table 3 P300 laterality at baseline and follow up

<table>
<thead>
<tr>
<th></th>
<th>UHR+T (n=15)</th>
<th>UHR+NT (n=23)</th>
<th>Controls (n=17)</th>
<th>Time effect</th>
<th>Interaction effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow up</td>
<td>Baseline</td>
<td>Follow up</td>
<td>Baseline</td>
</tr>
<tr>
<td>P3 amplitude at T3</td>
<td>8.16 (2.7)</td>
<td>8.01 (2.2)</td>
<td>8.87 (5.3)</td>
<td>8.9 (3.7)</td>
<td>8.92 (2.7)</td>
</tr>
<tr>
<td>P3 amplitude at T4</td>
<td>7.75 (2.9)</td>
<td>7.53 (2.8)</td>
<td>7.14 (3.4)</td>
<td>7.48 (3.5)</td>
<td>8.35 (2.8)</td>
</tr>
<tr>
<td>T3/T4 ratio</td>
<td>.99 (3.3)</td>
<td>.96 (3.3)</td>
<td>.91 (4.3)</td>
<td>.87 (3.3)</td>
<td>.97 (3.3)</td>
</tr>
<tr>
<td>T4-T3 difference</td>
<td>.41 (2.5)</td>
<td>.47 (2.3)</td>
<td>1.74 (3.8)</td>
<td>1.44 (2.7)</td>
<td>.57 (2.5)</td>
</tr>
</tbody>
</table>

Abbreviations: UHR = Ultra High Risk, with (UHR+T) or without (UHR+NT) transition to psychosis.
Figure 1. Grand average target waveforms for each group at Pz at baseline (A) and follow up (B); Grand average non-target waveforms for each group at Cz at baseline (C) and follow up (D). 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 black lines.

Figure 2. Colour-coded topographic maps of N1 voltage activity after non-target tones for each group at follow up. UHR+T= Ultra High Risk patients with transition to psychosis. UHR+NT= Ultra High Risk patients without transition to psychosis.
3.3. ERP and medication use in UHR subjects

We found no significant differences in ERPs between the four medication categories or between subjects who did or did not use medication at baseline or follow up. Repeated measures analyses regarding the chlorpromazine equivalent dosages revealed no time effects. However, we did find a threshold significant time x group interaction effect ($F = 3.25, p = .05$). Post hoc analyses showed that the mean change in chlorpromazine equivalent dosage from baseline to follow up differed between UHR + T and UHR + NT subjects ($p = .01$). However, we found no difference in chlorpromazine equivalents dosage in UHR + T subjects between baseline and follow-up. Moreover, correlation analyses revealed no significant associations between the dosage of antipsychotic medication and any of the ERP amplitudes (all $r$ values $<.38$, all $p$ values $>.15$).

4. DISCUSSION

Our study showed that there are no temporal changes in N2, P2 or P3 amplitudes from before until shortly after the onset of a first psychotic episode. However, the analyses did reveal an interaction effect for the N1 amplitudes. Post hoc analyses showed that N1 amplitudes were smaller at follow up compared to baseline only in UHR + T subjects. Although the UHR + T subjects showed smaller P3 amplitudes before and after transition to psychosis compared to controls and UHR + NT subjects, we found no evidence of P3 changes over the follow up period.

These results suggest that the course of neurophysiological disturbances from the prodromal phase until after the first psychotic episode is dissociable for the distinct ERP components. Whereas P3 abnormalities are already present before a psychotic episode and do not show progression shortly after psychotic onset, N1 amplitudes do show decrements after the onset of a first psychotic episode. There were no differences in N1 amplitudes between the groups at baseline (see also: van Tricht et al., 2010), suggesting that these abnormalities arise after the onset of a first psychosis.

In schizophrenia patients, smaller N1 amplitudes have been demonstrated using various experimental methods, including passive listening experiments, and passive or active oddball paradigms (for a review see Rosburg et al., 2008). Moreover, reduced N1 amplitudes have been demonstrated in first hospitalized subjects (Brown et al., 2002). The N1 is an obligate (i.e. produced regardless of whether the tone was attended; McCarley et al., 2003) response arising primarily from the auditory cortex (Turetsky et al., 2008). N1 decrements are thought to reflect impairments in early auditory sensory processing or reduced sensory registration (Ahveninen et al., 2006; Potts et al., 1998). However, the precise functional role of the N1 is still unclear. The N1 amplitude is related to stimulus characteristics (e.g. sound intensity). Moreover, many variables including arousal, motivation, fatigue, hearing thresholds and drug abuse influence N1 amplitudes (Rosburg et al., 2008). These findings suggest that the N1 can be classified as an exogenous or sensory potential. However, the N1 amplitude is also influenced by cognitive functions. For instance, it has been demonstrated that the N1 amplitude increases when subjects...
are asked to direct their attention to the stimuli (O’Donnell et al., 1994). Thus, the N1 amplitude seems to reflect both exogenous and endogenous processes, signifying both top-down and bottom-up stimulus processing (Butler et al., 2007).

Secondary cortical areas in the posterior region of the superior temporal cortex are thought to be principal generators of the N1 (Javitt et al., 1993; Salisbury et al., 2010). Moreover, it has been shown that compared to UHR subjects, patients with first episode schizophrenia show gray matter reductions in the superior temporal gyrus (STG) (Witthaus et al., 2009). Therefore, STG gray matter reductions may be an underlying mechanism of the reported N1 amplitude reductions. Longitudinal neuro-imaging studies following UHR subjects from before until after a first psychotic episode are necessary before any conclusions concerning the underlying pathology causing N1 impairments can be drawn.

As N1 amplitude abnormalities have also been demonstrated in first degree relatives of schizophrenia patients, it has been suggested that N1 amplitudes may reflect an auditory processing deficit related to the genetic vulnerability for schizophrenia, thus reflecting an endophenotypic trait marker for the disorder (Force et al., 2008). However, this study focused on a different population, i.e. a sample of help-seeking UHR subjects. In our UHR sample, as in a comparable group of UHR subjects (Bramon et al., 2008), we found no evidence of N1 impairments in UHR subjects before a first psychotic episode. Moreover, there is some evidence that N1 amplitude reductions are most pronounced in chronic schizophrenia patients compared to patients with a first psychotic episode (Brockhaus-Dumke et al., 2008; Salisbury et al., 2010). These findings suggest that N1 abnormalities may be related to disease progression.

The absence of P3 amplitude reductions from before until shortly after psychotic onset concurs with recently published data on neuropsychological functioning in UHR subjects (Becker et al., 2010; Hawkins et al., 2008, Seidman et al., 2010), thus suggesting that impairments in both neuropsychological and neurophysiological measures associated with attention and memory largely pre-exist before the first psychotic episode. Conversely, there is some evidence of neurophysiological deterioration following the prodromal phase. For instance, in a cross-sectional study it was suggested that P3 abnormalities may show a progressive course from the prodromal to the chronic stages of schizophrenia (Ozgürdal et al., 2008).

We found no group differences with respect to N2 or P2 amplitudes at baseline or follow up. To our knowledge, no other studies have yet investigated these ERP components in UHR subjects. However, there is some evidence of N2 and P2 abnormalities in first hospitalized schizophrenia patients (Brown et al., 2002; Salisbury et al., 2010). We could not confirm the presence of N2 or P2 deficits in UHR subjects after a first psychotic episode, nor did we find changes in these components between the prodrome and the onset of psychosis. Moreover, we found no evidence of P3 amplitude asymmetry in UHR + T subjects at baseline and follow-up. It has been suggested that this asymmetry develops later in the disease process, after a so-called “critical period”, which is thought to last approximately 5 years (Birchwood et al., 1998). In our study, UHR + T patients were assessed before the end of the critical period, with a mean follow up term of 11.3 months after psychotic onset.
A question that remains to be answered is whether these ERP abnormalities are specific to schizophrenia at disease onset. For instance, Salisbury and colleagues (Salisbury et al., 1998) found no differences in P3 midline amplitudes between first-episode affective psychotic patients and healthy controls, whereas their subjects with schizophrenia psychosis did show reduced P3 amplitudes at midline scalp position. In addition, first episode schizophrenia patients showed abnormal P3 symmetry at disease onset, whereas first-episode affective psychotic patients showed no P3 symmetry changes. Although the majority of our UHR + T developed schizophrenia or schizoaffective disorder, a few UHR + T patients were diagnosed with schizoaffective disorder or brief psychotic disorder. Unfortunately, the small subgroup samples did not allow us to compare ERP amplitudes between these diagnostic groups.

There are several limitations to the findings of this study. A major limitation is the small group samples, in particular the relatively small size of the UHR + T group. Another possible confounding factor that needs to be acknowledged is the effect of antipsychotic medication. Until now, there is no consensus of opinion on the relationship between medication and P3 amplitudes. Although antipsychotic medication enhanced P3 amplitudes in some studies (Bramon et al., 2004; Mathalon et al., 2000), P3 amplitudes are generally not restored to normal levels (Hirayasu et al., 1998; Jeon & Polich, 2003). As for the N1 it is believed that N1 reductions are more pronounced in medicated than unmedicated patients (Rosburg et al., 2008). The use of typical antipsychotics (e.g. haloperidol) has been associated with reduced cortical gray matter, which may account for the relationship with ERP amplitudes. The effect of atypical antipsychotics on cortical gray matter is however less clear (Lieberman et al., 2005). Our analyses revealed no differences between the four medication categories in ERP amplitudes, nor did we find evidence of a relationship between the dosage of antipsychotics and the ERP components. Moreover, there was no significant difference in the mean antipsychotics equivalent dosage between baseline and follow up in the UHR + T group. Finally, none of the UHR + T subjects used typical antipsychotics at follow up. These findings suggest that the reduced N1 amplitudes in UHR + T subjects are not a result of medication usage. Nevertheless, a secondary effect of medication cannot completely be ruled out.

In conclusion, our study showed no evidence of a progression of P3 abnormalities after a first psychotic episode. However, in the UHR + T group, N1 amplitudes did show reductions from before until after the onset of psychosis. These findings suggest that a differential breakdown occurs in processes that regulate the inflow of information from the environment. Whereas disturbances in relatively late, higher-level evaluative cognitive processes are already present in the prodromal phase, another pathological process, causing N1 deficits, may accompany the onset of a frank psychotic episode. Although speculative at this time, these ERP components may contribute to the diagnostic process of psychosis in the future. Longitudinal studies with larger samples are needed to follow UHR subjects with a transition to psychosis over years before any firm conclusions can be drawn.
DISCLOSURE STATEMENT
None of the authors report any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within 3 years of beginning the work submitted that could inappropriately influence our work.

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REFERENCE LIST


potentials in schizophrenia prior to treatment. Biol Psychiatry 43, 244-253.
compared to healthy controls. Psychiatr Res Neuroimaging 173, 163-169.

