Neurophysiological correlates of the pathway to the early stages of psychosis
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STATE AND TRAIT ASPECTS OF INFORMATION PROCESSING DEFICITS ASSOCIATED WITH TRANSITION: A LONGITUDINAL STUDY FROM PRODROMAL STATE TO FIRST PSYCHOSIS

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ABSTRACT

BACKGROUND
Information processing deficits are a core feature of schizophrenia. However, the profile and longitudinal course of information processing deficits from the prodrome until after a first psychotic episode have not yet been established.

METHODS
Information processing abilities as assessed using several Event-Related Potential (ERP) and oculomotor movement paradigms were determined in 138 subjects. Sixty-one subjects were at Ultra High Risk (UHR) for developing psychosis, of whom 18 subjects made a transition to a first episode of psychosis (FEP) within the 36 month follow up period (UHR-T) and 43 did not (UHR-NT). An additional 47 patients with a FEP and 30 demographically matched healthy control subjects were investigated. Fifteen UHR-T (83%), 23 UHR-NT (53%) and 17 healthy control subjects (57%) were reassessed at follow up.

RESULTS
UHR-T and FEP subjects showed comparable P300 and antisaccade abnormalities at baseline. Additionally, repeated measure analyses yielded no significant changes in these parameters from baseline to follow up in UHR-T. In contrast, UHR-T showed reduced N100 and P200 amplitudes as well as decreased SPEM performances after psychotic onset.

CONCLUSIONS
Abnormalities in neurophysiological components related to higher order, cognitive functions, including P300 and antisaccades, show temporal stability during the prodromal phase and the onset of a first psychosis and may thus be viewed as trait factors of schizophrenia. In contrast, deficits in earlier information processing seem to be related to the onset of florid psychosis and may reflect state markers of the disease.
INTRODUCTION

Information processing deficits may be a fundamental factor of psychosis (Bhattacharyya et al., 2012; Kapur, 2003). In fact, abnormalities in stimulus detection and processing may underlie the “downstream” clinical and cognitive impairments as observed in schizophrenia patients (Rissling et al., 2012). More specifically, the clinical phenomena of schizophrenia may at least in part result from dysfunctions in the coordination of neural activity at the earliest stages of sensory and cognitive information processing (Hermens et al., 2009; Kirihara et al., 2009; Turetsky et al., 2009) and may contribute to the psychosocial disability observed in patients with schizophrenia (Jahshan et al., 2012; Green et al., 2003; Rissling et al., 2012).

Efficient information processing requires a variety of abilities, including adequate pre-attentive processing of stimuli to process novel stimuli and inhibit responses to irrelevant stimuli, but also intact higher order, cognitive processing. With the aid of neurophysiological paradigms, attempts have been made to identify the neurobiological substrates of information processing deficits during these distinct time phases. Event Related Potentials (ERPs) following an auditory or visual stimulus, for instance, are uniquely suited to study temporal sources of brain fluctuations (Jahshan et al., 2012). ERPs reflect the sequence of neural processing of information from early automatic sensory to more controlled and conscious processing (Rissling et al., 2010). It is well known that schizophrenia patients demonstrate reduced auditory ERP amplitudes across the different stages of stimulus processing, i.e. varying from early (pre-attentive) components (Patterson et al., 2008; Salisbury et al., 2010) to later, attention dependent components such as the P300 (Turetsky et al., 2007; Umbricht et al., 2006).

Abnormalities in eye movements are also believed to be a reflection of disturbances in neuronal circuits that are relevant in the investigation of the neurobiology of schizophrenia (Benson et al., 2012; Nieman et al., 2000). Using several eye movement paradigms, abnormalities in the processing of visual stimuli can be examined. For example, the antisaccade test, in which subjects are asked to fixate on a central cue and then inhibit a reflexive saccade to a suddenly appearing peripheral visual target and look in the opposite direction from the cue, can be used to assess higher cognitive functions (Nieman et al., 2007), whereas the ability to track a moving object with the eyes is often assessed using Smooth Pursuit Eye Movement (SPEM) tasks.

Several studies have tried to elucidate whether ERPs and eye movement components vary with clinical fluctuations (i.e. a ‘state’ factor) or if they show stability over the different stages and clinical states of schizophrenia (i.e. ‘trait’ marker). There is increasing evidence that auditory P300 amplitude reductions may be longitudinally stable in schizophrenia patients, although there seem to be some state-dependent modulation of these deficits (Mathalon et al., 2000; Turetsky et al., 1998a). Abnormalities in earlier ERP components, including P50 and N100, may already be present in first-hospitalized patients but seem to be most prominent in chronic schizophrenia patients (Brockhaus-Dumke et al., 2008) and seem to correlate with clinical symptoms (Boutros et al., 2009). With regard to the
eye movement tasks, both pursuit and antisaccade performance seem to be stable over time in schizophrenia (Gooding et al., 1994; Turetsky et al., 2007), although associations of SPEM performance with symptomatology, in particular disorganisation symptoms, has been reported (Lee & Williams, 2000). Importantly, these studies have investigated state and trait aspects of neurophysiological impairments in patients diagnosed with schizophrenia without inclusion of the prodromal period. Furthermore, many studies investigating trait and state aspects of neurophysiological impairments in schizophrenia are cross-sectional. Thus, longitudinal studies investigating the course of these deficits across the different disease stages, including the prodromal period, are needed.

During the past few decades, evidence has emerged that information processing deficits are already present in subjects at risk for psychosis, particularly in subjects at Ultra High Risk (UHR) for a first psychotic episode (McGorry et al., 2003; Miller et al., 2003; Yung et al., 2006). In addition to the studies demonstrating neurophysiological abnormalities in UHR subjects, evidence is emerging that the inclusion of neurophysiological (often endophenotype; Braff et al., 2007; Gottesman et al., 2003) parameters, such as P300 and mismatch negativity (MMN) amplitudes, into predictive models may be helpful in predicting future transition to psychosis (Bodatsch et al., 2011; van Tricht et al., 2010a). However, to the best of our knowledge, no studies have yet examined the profile and course of several neurophysiological abnormalities, including ERPs and eye movements, in a single cohort of patients from the prodrome until after a first psychotic episode.

The primary aim of this longitudinal cohort study was to develop an integrative multi-system model of neurophysiologic abnormalities related to information processing deficits associated with a first psychotic episode. Using complementary and well replicated neurophysiological biomarkers we aimed to identify a profile of information processing deficits in UHR subjects and schizophrenia patients with a First Episode of Psychosis (FEP). We hypothesized that, compared to controls, both UHR and FEP patients would show information processing impairments, as reflected by smaller ERP amplitudes and prolonged latencies and increased error rates and decreased gain on oculomotor tests. Most pronounced deficits were expected in the FEP group. Moreover, we expected differences in neurophysiological parameters at baseline between subjects with (UHR-T) and without (UHR-NT) later transition to psychosis and more severe information processing deficits in UHR-T subjects at follow up compared to baseline.

METHODS
Two ERP (oddball and paired click) and oculomotor movement paradigms (smooth pursuit eye movements and antisaccade test) were administered in groups of FEP patients, UHR subjects and healthy controls. The latter two groups were examined at baseline and again at follow up (i.e. after approximately 18 months).
Participants

UHR Group
Sixty-one UHR subjects were included at baseline. The UHR subjects were referred to the Academic Medical Center (AMC) in Amsterdam by professionals from mental health services because the referring clinician suspected a development towards a first psychosis. The inclusion criteria for the UHR group were: a) age between 15 and 35 years, and b) subjects met one or more of the following inclusion criteria: 1) Genetic risk in combination with reduced functioning, 2) Attenuated psychotic symptoms appearing several times per week for at least 1 week within the last three months and 3) Brief Limited Intermittent Psychotic Symptoms (BLIPS): i.e. frank psychotic symptoms occurring within the last 3 months and resolving spontaneously within 1 week (for a more detailed description of the inclusion criteria, see Miller et al., 2003).

FEP patients
Forty-seven patients (4 females) with a first episode of schizophrenia were included. All patients were admitted to the Department of Early Psychosis of the AMC. Inclusion criteria for this group were age between 15–35 years with a first episode of schizophrenia psychosis (i.e. patients who relapsed to a second psychotic episode were excluded). All subjects fulfilled DSM-IV diagnostic criteria for schizophrenia as determined by the Mini International Neuropsychiatric Interview (MINI) Plus for DSM-IV disorders (Sheehan et al., 1998). This interview was also used to exclude affective disorders and substance abuse disorders.

Control Group
Thirty healthy subjects (16 women) aged between 15 and 35 years without psychiatric illness present or in the past, or familial history of psychiatric illness (evaluated for first and second degree relatives) served as a control group. They were matched on age and education level of the UHR subjects.

For all groups, exclusion criteria were: having symptoms relevant for inclusion arising from a known general medical disorder or drugs or alcohol dependency and estimated premorbid verbal IQ below 85. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Medical Ethical Committee of the AMC approved the study design. Informed consent of all participants was obtained after the nature of the procedures had been fully explained.

Neurophysiological assessment
Event Related Potentials
A paired click paradigm and an oddball paradigm were administered. In the paired-click paradigm, 72 paired clicks were presented binaurally through headphones at an intensity of 50 dB above hearing threshold, with a random time interval of 8 or 9 seconds and interval of 500 ms between the first (S1) and second (S2) click (for details see: van
Tricht et al., 2012). In the oddball paradigm, a total of 300 tones were presented, of which 80% were non-targets (1000Hz) and 20% were targets (2000Hz), with a duration of 100 ms in a random sequence. The subjects were instructed to count the targets and respond to them with a button press. Details on recording methods, artefact rejection and calculation of ERP components are presented in Supplement 1.

**Eye movement recordings**

**Smooth pursuit eye movement (SPEM)**

Eye movements were recorded using the double magnetic induction method (DMI-method) developed by Bour et al. (Bour et al., 1984). Subjects were asked to follow the target (i.e. a red dot), which moved with a constant velocity of 10 degrees/sec from left to right and vice versa (triangular tracking), as closely as possible. Values of interest for this paradigm were the smooth pursuit gain and the saccadic rate (for details: van Tricht et al., 2010b). Pursuit gain was defined as the ratio between target velocity and eye velocity. Regarding the saccadic rate, we differentiated between saccades that correct for SPEM deficiencies (corrective saccades) and saccades that disrupt tracking (non-corrective saccades).

**Antisaccade test**

In this task, subjects are required to fixate on a central cue and to inhibit a reflexive saccade to a suddenly appearing visual target and look in the opposite direction with the same distance. Values of interest for this paradigm were the error rate, mean latency of the correct and incorrect antisaccades and antisaccade gain (Nieman et al., 2007).

**Procedure**

In this longitudinal cohort study, UHR subjects were followed up for three years. Subjects, their parents or caretakers and the referring instances were asked to contact us in case of increasing symptoms. In addition, they were seen for follow-up interviews at 9 and 18 months, including assessments of the SIPS. Transition to psychosis was operationalized as a continuation of BLIPS, i.e., any single item on the Positive subscale of SIPS with a score of 6 for more than 7 days. Following identification of full-blown psychotic symptoms, the diagnostic category of transition was determined by applying DSM-IV criteria for psychotic disorders and affective disorders with psychotic features. The first neurophysiological assessment was done shortly after inclusion. Approximately eighteen months after the first assessment, all subjects were again contacted for a follow-up assessment.

**Statistical Analyses**

Differences in neurophysiologic parameters between the four groups (i.e. UHR-T, UHR-NT, FEP and controls) were investigated by three separate MANOVAs (one for dual click parameters, one for the oddball paradigm and one for eye movement parameters). Post hoc Bonferroni tests were applied to correct for multiple comparisons. Temporal changes in neurophysiological components from baseline to follow-up were analyzed using repeated measures ANOVAs. To exclude confounding effects of medication,
differences in neurophysiological components between the distinct medication categories (Table 1) were assessed using a Kruskal Wallis test. Associations between the dosage of antipsychotics and neurophysiological parameters were determined by correlating chlorpromazine equivalents with the distinct neurophysiological components. If not described otherwise, \( p \) values of \( \leq 0.05 \) were accepted as significant.

**RESULTS**

A total of 138 subjects were enrolled in this study at baseline: 61 UHR subjects, 47 FEP patients and 30 healthy control subjects. Of the participants included at baseline, 121 subjects completed all the neurophysiological paradigms; eye movement data of 17 subjects were missing (refusal: \( n=14 \); technical difficulties: \( n=3 \)), whereas EEG/ERP data of 2 subjects were missing (refusal: \( n=1 \); small number of artefact free trials: \( n=1 \)).
Of the UHR subjects, 18 (30%) made a transition to psychosis over a 3-year follow-up period. These subjects received the following DSM IV diagnoses: schizophrenia (n=12), schizophreniform disorder (n=3), schizoaffective disorder (n=2) 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). At follow up, we were able to assess 15 UHR-T, 23 UHR-NT subjects and 17 controls. Reasons for nonparticipation at follow up were refusal (n=26), inability to be located (n=9) and imprisonment (n=1). Importantly, the subjects with follow up assessments did not differ significantly from those lost to follow up in terms of demographic or ERP parameters at baseline. The mean interval between baseline and follow up neurophysiological 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, there were significant differences between the groups with respect to sex, age and IQ scores (Table 1). There were more men in the FEP group compared to the three other groups. Moreover, FEP patients were older at the time of assessment compared to UHR-NT subjects (p=.01). FEP patients demonstrated lower IQ scores compared to UHR-T (p=.02) and controls (p<.001). In view of these differences, we also applied MANCOVAs while co-varying for demographic variables (i.e. IQ, age). As preliminary analyses yielded no significant differences in ERP and eye movement components between the male or female subjects included in our study (all p values > .16), controlling for sex in the analyses does not seem warranted.

BASELINE
Event Related Potentials
Paired click paradigm
Multivariate analyses of variance yielded a significant effect (Wilks’ Lambda: F=3.55, p<.001). Univariate tests revealed significant group differences in N100 S1 amplitudes, N100 and P200 difference scores and the P200 ratio (Table 2). Post hoc Bonferroni tests yielded smaller N100 S1 amplitudes in FEP compared to controls (p=.03) and UHR-NT subjects (p=.01). Moreover, UHR-T subjects tended to demonstrate smaller N1 amplitudes compared to controls (p=.08). With regard to the N100 difference score, we found differences between FEP and controls (p=.05) and between UHR-T subjects and controls (p=.01). FEP patients also demonstrated larger P200 ratio's compared to UHR-T (p=.04) and UHR-NT (p=.04) subjects. No group differences were found for P50 amplitudes, or for ERP latencies (all p values ≥.14). Grand average waveforms for S1 and S2 at baseline are presented in Figure 1.

Oddball paradigm
Multivariate analyses of variance for oddball parameters yielded a significant effect (Wilks’ Lambda: F=3.97, p<.001). Group differences were found with respect to the N100 amplitudes at Cz and for P300 amplitudes at Fz, Cz and Pz (Table 3). Regarding the ERP latencies, we only found group differences in P200 latencies. Post hoc tests showed that the N100 amplitudes were smaller in FEP compared to controls (p=.04). With respect to the P300 amplitudes we
Table 2 Sensory gating parameters of FEP patients and UHR and control subjects at baseline

<table>
<thead>
<tr>
<th></th>
<th>FEP (n=47)</th>
<th>UHR-T (n = 18)</th>
<th>UHR-NT (n = 43)</th>
<th>Controls (n = 29)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude P50 S1</td>
<td>2.30 (1.5)</td>
<td>2.54 (1.3)</td>
<td>2.41 (1.5)</td>
<td>2.76 (1.3)</td>
<td>F=.63, p=.60</td>
</tr>
<tr>
<td>Amplitude P50 S2</td>
<td>1.13 (.7)</td>
<td>1.29 (.8)</td>
<td>1.20 (1.0)</td>
<td>1.56 (1.1)</td>
<td>F=1.40, p=.25</td>
</tr>
<tr>
<td>P50 ratio</td>
<td>.61 (.53)</td>
<td>.59 (.3)</td>
<td>.59 (.7)</td>
<td>.65 (.5)</td>
<td>F=.04, p=.99</td>
</tr>
<tr>
<td>P50 difference score</td>
<td>1.19 (1.4)</td>
<td>1.25 (1.4)</td>
<td>1.21 (1.5)</td>
<td>1.20 (1.3)</td>
<td>F=.04, p=.99</td>
</tr>
<tr>
<td>Amplitude N100 S1</td>
<td>-2.95 (1.7)</td>
<td>-3.16 (2.6)</td>
<td>-4.86 (3.5)</td>
<td>-5.19 (3.2)</td>
<td>F=5.73, p=.001</td>
</tr>
<tr>
<td>Amplitude N100 S2</td>
<td>-.87 (1.7)</td>
<td>-.20 (2.3)</td>
<td>-1.72 (1.8)</td>
<td>-1.41 (2.3)</td>
<td>F=2.11, p=.10</td>
</tr>
<tr>
<td>P100 ratio</td>
<td>.21 (2.0)</td>
<td>.42 (1.1)</td>
<td>.47 (.5)</td>
<td>.28 (.5)</td>
<td>F=.65, p=.58</td>
</tr>
<tr>
<td>N100 difference score</td>
<td>2.07 (2.0)</td>
<td>1.13 (2.7)</td>
<td>3.14 (3.7)</td>
<td>3.77 (3.0)</td>
<td>F=4.31, p=.006</td>
</tr>
<tr>
<td>P200 amplitude S1</td>
<td>3.98 (3.5)</td>
<td>6.88 (5.8)</td>
<td>5.46 (4.6)</td>
<td>6.13 (4.3)</td>
<td>F=2.50, p=.06</td>
</tr>
<tr>
<td>P200 amplitude S2</td>
<td>1.97 (2.5)</td>
<td>1.79 (2.2)</td>
<td>1.69 (2.2)</td>
<td>2.41 (2.2)</td>
<td>F=.40, p=.40</td>
</tr>
<tr>
<td>P200 ratio</td>
<td>.77 (1.3)</td>
<td>.34 (.5)</td>
<td>.24 (.7)</td>
<td>.53 (.5)</td>
<td>F=3.82, p=.01</td>
</tr>
<tr>
<td>P200 difference score</td>
<td>2.01 (3.9)</td>
<td>4.37 (5.2)</td>
<td>3.78 (4.6)</td>
<td>3.81 (3.9)</td>
<td>F=2.79, p=.04</td>
</tr>
<tr>
<td>Artefact free trials</td>
<td>70.8 (1.0)</td>
<td>71.2 (1.0)</td>
<td>71.2 (.9)</td>
<td>71.1 (.9)</td>
<td>F=.19, p=.83</td>
</tr>
</tbody>
</table>

Values are mean (SD). Only vertex data (Cz) are reported. Bold indicates significant values. \textsuperscript{1}n=42 (one outlier removed). Abbreviations: FEP= First Episode Psychosis; UHR = Ultra High Risk; UHR-T = UHR subjects with transition to psychosis; UHR-NT = UHR subjects without transition to psychosis.

Table 3 ERP parameters of FEP patients, UHR and control subjects at baseline

<table>
<thead>
<tr>
<th></th>
<th>FEP (n=46)</th>
<th>UHR-T (n = 18)</th>
<th>UHR-NT (n = 43)</th>
<th>Controls (n =28)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude N100</td>
<td>-5.57 (2.8)</td>
<td>-6.92 (2.8)</td>
<td>-6.84 (2.8)</td>
<td>-7.48 (2.9)</td>
<td>F=3.35, p=.02</td>
</tr>
<tr>
<td>Amplitude P200</td>
<td>3.76 (3.4)</td>
<td>5.18 (3.3)</td>
<td>5.38 (2.7)</td>
<td>4.98 (3.3)</td>
<td>F=.84, p=.49</td>
</tr>
<tr>
<td>Amplitude N200</td>
<td>-3.55 (5.9)</td>
<td>-.25 (6.7)</td>
<td>-.57 (6.1)</td>
<td>-2.11 (5.78)</td>
<td>F=1.98, p=.12</td>
</tr>
<tr>
<td>Amplitude P300 Fz</td>
<td>5.85 (5.1)</td>
<td>7.66 (5.5)</td>
<td>7.74 (4.8)</td>
<td>10.59 (6.2)</td>
<td>F=6.45, p&lt;.001</td>
</tr>
<tr>
<td>Amplitude P300 Cz</td>
<td>10.90 (6.6)</td>
<td>10.97 (3.72)</td>
<td>14.48 (6.98)</td>
<td>19.47 (7.6)</td>
<td>F=11.01, p&lt;.001</td>
</tr>
<tr>
<td>Amplitude P300 Pz</td>
<td>11.08 (6.0)</td>
<td>10.54 (2.3)</td>
<td>16.5 (6.0)</td>
<td>22.69 (7.5)</td>
<td>F=20.22, p&lt;.001</td>
</tr>
<tr>
<td>Artefact free trials target</td>
<td>45.9 (12.0)</td>
<td>46.0 (7.6)</td>
<td>46.4 (10.1)</td>
<td>46.2 (10.5)</td>
<td>F=.32, p=.81</td>
</tr>
<tr>
<td>Artefact free trials standard</td>
<td>186.6 (45.3)</td>
<td>183.9 (36.3)</td>
<td>188.2 (40.3)</td>
<td>180.5 (43.4)</td>
<td>F=.03, p=.99</td>
</tr>
</tbody>
</table>

Values are mean (SD). Bold indicates significant values. Abbreviations: FEP= First Episode Psychosis; UHR = Ultra High Risk; UHR-T = UHR subjects with transition to psychosis; UHR-NT = UHR subjects without transition to psychosis.

found that P300 Fz amplitudes were smaller in FEP compared to UHR-NT subjects (p=.001) and controls (p=.004). At Cz and Pz, we found larger P300 amplitudes in controls compared to the other groups (Cz: UHR-NT: p=.01; UHR-T: p=.001; FEP: p=.002; Pz: UHR-NT: p=.003; UHR-T: p<.001; FEP: p<.001). Moreover, P300 Pz amplitudes were smaller in UHR-T subjects compared to UHR-NT subjects (p=.003). P200 latencies were longer in FEP compared to controls (p=.004) and UHR-NT (p=.002). No differences in oddball parameters were found between FEP and UHR-T. Grand average waveforms are presented in Figure 2.
Eye movements

**SPEM**

We found differences between the groups in the pursuit gain and the rate of corrective and non-corrective saccades during pursuit (Table 4). Post hoc tests revealed that the pursuit gain was lower in FEP compared to UHR-NT (p=.03) subjects. The total rate of saccades during pursuit was higher in FEP compared to UHR-T (p=.02), UHR-NT (p=.01) and controls (p<.001), and in UHR-NT compared to controls (p=.01). The rate of corrective saccades was higher in FEP compared to controls (p<.001) and in UHR-NT compared to controls (p=.02). Finally, control subjects showed a lower rate of non-corrective saccades compared to FEP (p<.001) and UHR-NT subjects (p=.02).

**Saccade – antisaccade**

We found group differences for the error rate and the mean latency of correct antisaccades (Table 4). Post hoc test showed a higher antisaccade error rate in FEP compared to the three other groups (all p values <.001). Moreover, FEP patients showed prolonged correct antisaccadic latencies compared to UHR-T (p=.02), UHR-NT (p=.05) and control (p=.01) subjects.

All significant results for ERP and oculomotor data persisted after covarying for age and IQ scores.
**LONGITUDINAL ANALYSES**

**Evoked and Event Related Potentials**

Findings of longitudinal analyses on ERP components in UHR subjects from prior to until shortly after the onset of a first psychotic episode showed smaller N100 and P200 S1 amplitudes, smaller P200 difference scores and larger P200 ratio's at follow up compared to baseline in UHR-T subjects. With regard to the oddball paradigm, we found that N100 amplitudes were smaller at follow up compared to baseline only in UHR-T subjects.

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**Figure 2.** Grand average waveforms as derived from the oddball paradigm for each group at Fz (A), Cz (B) and Pz (C) at baseline. Ultra High Risk subjects with transition to psychosis (UHR+T) = red lines. Ultra High Risk subjects without transition (UHR+NT) = green lines. First Episode Psychosis (FEP) = blue line. Control group = dashed black lines.
In contrast, P300 amplitudes showed no further reduction after psychotic onset (for details: van Tricht et al., 2011; van Tricht et al., 2012).

**Eye movements**

**SPEM**

Repeated-measures analyses revealed several significant interaction effects for the SPEM parameters. First, we found an interaction effect for the pursuit gain (F=4.47, p=.02). Thus, the course of pursuit gain from baseline to follow up differed significantly between the three groups. We also found interaction effects for the saccadic rate during pursuit (F=4.12, p=.02) and the rate of non-corrective saccades (F=4.90, p=.01). Post-hoc comparisons showed that the pursuit gain was lower in UHR-T subjects at follow up compared to baseline (t=3.21, p=.008). UHR-T also showed a higher rate of non-corrective saccades at follow up compared to baseline (t=3.49, p=.005). On the contrary, UHR-NT demonstrated a lower saccadic rate during pursuit at follow up (t=2.10, p=.05). No changes over time were found in the control group.

Analyses on follow up data yielded group differences in all SPEM variables, except the rate of back up saccades. Post hoc Bonferroni tests showed that the pursuit gain was lower in UHR-T subjects compared to UHR-NT (<.001) and controls (p=.003). The rates of corrective (controls: p=.003; UHR-NT: p=.04) and non-corrective (controls: p=.01; UHR-NT: p=.01) saccades during pursuit were higher in UHR-T subjects.

| Table 4 Eye movement parameters in FEP patients and UHR and control subjects at baseline |
|-----------------------------------------------|-------------------|-------------------|-------------------|-------------------|
|                  | FEP               | UHR-T             | UHR-NT            | Controls          |
| **SPEM**         |                   |                   |                   |                   |
| Saccades (total) | 2.12 (.6)         | 1.59 (.3)         | 1.89 (1.1)        | 1.21 (.4)         |
| Corrective       | 1.51 (.5)         | 1.07 (.2)         | 1.36 (1.0)        | .86 (.2)          |
| Catch-up saccades| 1.33 (.6)         | .97 (.2)          | 1.12 (.6)         | .76 (.2)          |
| Back-up saccades | .18 (.2)          | .14 (.1)          | .25 (.5)          | .10 (.1)          |
| Non-corrective   | .65 (.3)          | .51 (.2)          | .56 (.3)          | .33 (.2)          |
| Forward          | .50 (.3)          | .35 (.2)          | .36 (.2)          | .26 (.2)          |
| Backward         | .14 (.12)         | .16 (.1)          | .21 (.2)          | .06 (.1)          |
| Square wave jerks| .02 (.02)         | .03 (.02)         | .02 (.03)         | .01 (.01)         |
| Pursuit gain     | .87 (.1)          | .94 (.1)          | .93 (.1)          | .92 (.1)          |
| Pursuit ramps    | 28.9 (.2)         | 28.5 (.3)         | 28.9 (.2)         | 28.9 (.2)         |
| **Saccade / anti-saccade** |       |                   |                   |                   |
| Error rate (%)   | 53.9 (26.0)       | 27.2 (16.4)       | 30.5 (19.7)       | 18.1 (12.2)       |
| Latency correct antisaccades | 432.6 (134.3) | 347.99 (44.6)    | 377.5 (70.4)      | 363.4 (59.0)      |
| Latency incorrect antisaccades | 228.5 (44.2) | 227.6 (43.0) | 229.7 (66.2) | 221.9 (53.9) |
| Gain correct antisaccades | .96 (.6) | .86 (.2) | .83 (.3) | .97 (.4) |
| Gain incorrect antisaccades | .75 (.1) | .75 (.2) | .75 (.1) | .68 (.2) |

Values are mean (SD). **Bold** indicates significant p values. Abbreviations: FEP = First Episode Psychosis; UHR = Ultra High Risk; UHR-T = UHR subjects with transition to psychosis; SPEM = smooth pursuit eye movements; UHR-NT = UHR subjects without transition to psychosis.
Saccade – antisaccade

No significant time or interaction effects were found for the antisaccade parameters. Analyses on follow up data yielded group differences in the mean saccadic gain and the antisaccade error rate. Post hoc comparisons showed that the saccadic gain was lower in UHR-T subjects compared to controls (p=.01). The antisaccade error rate was higher in UHR-T subjects compared to controls (p=.01) and UHR-NT subjects (p=.08; statistical trend).

Medication

We found no differences between the three medication categories in neurophysiological components. However, in the patient groups, correlation analyses yielded modest associations between the chlorpromazine equivalent and N100 S1 amplitudes (rho=.21, p=.04), P200 latencies (rho=.21, p=.04), the pursuit gain (rho=.22, p=.04), the rate of corrective saccades (rho=.34, p=.002) and the antisaccade error rate (rho=.37, p=.002). Due to these findings, we ran the analyses again with medication prescription (i.e. the three categories of medication use) as a covariate. With exception of the P200 latencies (F=1.76, p=.16), all group effects persisted after controlling for medication prescription.

DISCUSSION

The aim of our study was to develop an integrative multi-system model of neurophysiologic abnormalities related to information processing, associated with a first psychotic episode. With regard to the ERPs we found that P300 abnormalities are already present before the onset of psychosis and no changes were observed after psychotic onset. Interestingly however, repeated measure analyses revealed changes over time in earlier components from baseline to follow up in UHR-T subjects. On the eye movement examination, we found increased saccadic rates during pursuit in our UHR sample at baseline. Whereas no temporal changes were found in antisaccade parameters, we found decreased pursuit gain and increased saccadic rates on the SPEM task in UHR-T subjects only after psychotic onset.

Along with previous studies in schizophrenia (Mathalon et al., 2000; Turetsky et al., 1998), our findings support the hypothesis that P300 abnormalities may be viewed as a trait marker of psychosis. Thus, deficits in the top down allocation of attention, as reflected by smaller P300 amplitudes, are stable from the prodromal phase to the onset of a first psychosis and during the progression of the disease. On the contrary, earlier ERP components, including N100 and P200 amplitudes and latencies, more likely reflect a state marker of the disease: we found changes in these components over time, suggesting that abnormalities in these components are related to the onset of frank psychosis. These findings persisted after controlling for (fluctuations in) medication dosage. In accordance with a previous study in UHR subjects (Brockhaus-Dumke et al., 2008), using the paired click paradigm we found some evidence of reduced N100 S1 amplitudes in UHR-T subjects at baseline. However, we also found temporal changes in N100 components from baseline to after psychotic onset in both the oddball and double
click paradigm. Confirming the findings of both cross-sectional (Jahshan et al., 2012), and longitudinal (Salisbury et al., 2007) studies regarding the mismatch negativity, we conclude that abnormalities in the automatic processing of stimuli and orienting of attention may to some extent be present in the early phases of schizophrenia, but also show progressive worsening after the onset of psychosis. Thus, early ERP measure may index progressive structural changes. We found no evidence of P50 abnormalities in our UHR or FEP sample. As has been hypothesized in a previous study of our group (de Wilde et al., 2007), the absence of P50 deficits in our young FEP and UHR subjects suggest an effect of age on the P50 ERP. That is, the P50 deficit may be the result of an ongoing neurodevelopmental process independent of disease onset.

To summarize, our results imply that early ERP components are more state dependent, i.e. fluctuating with symptom severity and psychotic onset, whereas the later ERP components are stably impaired during the different phases of psychotic development. Moreover, our finding of preserved automatic processing in light of impaired higher order, cognitive processing in UHR-T subjects before psychotic onset suggest a dissociation of early and later stages of stimulus processing. Although these findings could be viewed as ‘counter-intuitive’, it has been previously described that higher level information-processing deficits do not originate from deficits in lower levels of sensory perceptual processing (van der Stelt et al., 2004; Wölwer et al., 2011). Moreover, the stability of the P300 component over time matches the finding of another study of our group, demonstrating temporal stability of cognitive deficits in a UHR sample before, during and after a first psychotic episode (Becker et al., 2010). A possible explanation for the instability of the early components might be the use of antipsychotics. Indeed, previous studies have demonstrated a relationship between the use of 1st and 2nd generation antipsychotics and reduction of early ERP amplitudes specifically (Rissling et al., 2012; Rosburg et al., 2008).

With regard to the eye movement assessment, our results showed no evidence of SPEM deficits in UHR-T subjects at baseline, whereas UHR-NT subjects did significantly differ from controls. A possible explanation for these findings could be that the inability to suppress unwanted saccades is not specific for the psychosis prodrome, but related to the presence of psychopathology in general. Indeed, from baseline to follow up, a decreased saccadic rate during pursuit was observed only in UHR-NT subjects. Although this may be a chance finding, it may also signify a recovery of neurobiological impairments related to psychopathology: previous studies have documented a reduction in positive, negative, disorganization and general symptoms and an increased level of global functioning during follow-up of UHR-NT subjects (Velthorst et al., 2010). Alternatively, the (non significant) lower saccadic rate during pursuit in UHR-T compared to UHR-NT may also be ascribed to the increased presynaptic dopaminergic activity that may predate the onset of psychotic symptoms (Bloemen et al., 2012). Indeed, several studies have yielded associations between dopamine and SPEM performance, where studies generally report better SPEM performance in healthy control subjects after dopamine administration (Malaspina et al., 1994).
On the antisaccade test, we found increased error rates in FEP patients as well as in UHR-T subjects at follow up compared to controls and UHR-NT subjects, reflecting impairments in working memory and top down, volitional control associated with fronto-striatal dysfunction in these groups after the onset of psychosis (Hutton & Ettinger, 2006). Moreover, in contrast to the SPEM measures, no changes over time were found in the error rate in UHR-T subjects, suggesting that antisaccade abnormalities are stable across different stages of the disease. Along with previous studies demonstrating temporal stability of the antisaccade error rate in schizophrenia patients during different stages of the disease (Calkins et al., 2008; Gooding et al., 2004), our findings cautiously support the candidacy of the antisaccade error rate as a trait factor of schizophrenia.

We acknowledge several limitations of this study. First, although most of our results persisted after controlling for medication dosages, we cannot rule out that medication use has biased our results. Therefore, future studies should aim at including medication naïve subjects. Second, differences between the groups were present with respect to some demographic variables (i.e. age, sex and IQ). Although we controlled for age and IQ differences in the covariate analyses, and preliminary analyses yielded no effect of these parameters on neurophysiological components in our sample, we cannot completely rule out that these variables may account for part of our results. Indeed, ERP differences between male and female subjects have been previously described (Turetsky et al., 1998b; Yuan et al., 2008). Third, a substantial amount of variables were taken into account, whereas our research sample, specifically the UHR-T group, was relatively small. We controlled for multiple comparisons by using MANOVAs and post hoc Bonferroni corrections, to rule out Type 1 errors as much as possible. Additionally, the within subject design in the longitudinal study partly compensates for this caveat. Moreover, to our knowledge, we are the first to report on the course of different neurophysiologic markers from the prodrome to the first episode of psychosis in one sample, thereby contributing to the knowledge on neurophysiological correlates of schizophrenia.

We conclude that abnormalities in feedback, higher order information processing, including P300 amplitudes and the antisaccade error rate remain stable from the prodromal phase until after the onset of a first psychosis and may thus be viewed as trait factors of schizophrenia. On the contrary, we found no evident impairments in earlier ERP components and SPEM parameters in UHR-T subjects at baseline, although results with respect to the N100 were inconsistent. Moreover, analyses yielded temporal instability of these components over the distinct disease stages. Thus, deficits in automatic, early processing, are related to the onset of a first psychosis in this sample and may reflect a state marker of the disease. Future studies should investigate whether P300 and antisaccade abnormalities are specifically associated with the onset of schizophrenia psychosis, and not other psychiatric disorders. If so, at risk individuals with impaired P300 and antisaccade performance may be good candidates for benign, low side-effect psychosocial interventions such as cognitive behavioural therapy and other potentially prophylactic interventions (Braff, 2012; Swerdlow, 2011; van der Gaag et al., 2012).
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FINANCIAL DISCLOSURE

None reported
REFERENCE LIST


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SUPPLEMENT 1:
DETAILS ON ERP RECORDING AND CALCULATION

Recording method
Recordings were done using Brainlab EEG systems (OSG, Rumst, Belgium). Twenty-one Ag–AgCl disc electrodes were attached to the scalp (10-20 system; impedances <5 kΩ), with reference electrodes 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 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; http://www.brainproducts.com).

Paired click paradigm
After baseline correction, the signals were epoched at 50 ms pre- to 450 ms post stimulus (Knott et al., 2009). Following previous studies (Jerger et al., 1992; Rentzsch et al., 2008), the trials were filtered with different filter settings to optimize scoring of the three components. For the P50 analysis signals were digitally filtered with a low-pass filter of 50 Hz and a high-pass filter of 10 Hz (24 dB/oct). This band pass filter was chosen to optimally detect relatively small differences in this frequency band. For the N100 and P200 analyses, a band pass filter of 0.5 – 50 Hz was applied. Trials with voltages exceeding ± 75 μV during the recorded epoch were rejected and excluded. Eye-movements were detected and removed using eye-movement detection measures developed by Gratton and colleagues (Gratton et al., 1982).

An algorithm was designed to identify the distinct ERP components of the filtered mean EEG traces. The P50 amplitude was defined as the difference between the amplitude of the positive peak (P50) and the preceding negative trough (N40). The N40 was identified as the most negative deflection between 25 and 60 ms post stimulus, whereas the P50 was selected as the most positive peak between 40 and 80 ms post stimulus. P50 ratio (P50 S2 amplitude/ P50 S1 amplitude) and difference score (P50 S1 – P50 S2) were subsequently calculated.

The N100 component was identified as the most negative deflection within 70 to 130 msec after stimulus presentation, whereas the P200 was identified as the largest positive deflection between 150 and 250 ms. N100 and P200 amplitudes were calculated relative to baseline. N100 and P200 ratio and difference scores were calculated similar to the P50 gating parameters.

For all components, the ERP wave had to be present in at least one additional midline recording channel besides Cz (i.e. Pz or Fz), as it has been demonstrated that this criterion helps in avoiding spurious or non-physiological components (Boutros et al., 1991). Moreover, for the S2 amplitudes the latency had to be in a 10 ms range of the latency on S1. The segments were averaged for each stimulus separately. Only data from the vertex (Cz) are reported. Finally, all peaks were visually inspected, while blinded for patient/control status.
Oddball paradigm

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 percent 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), N100 components were measured from averages elicited by non-target tones. N100 amplitudes were detected as the most negative point between 75 and 125 ms post stimulus. P200 amplitudes were calculated for target and non-targets (Ferreira-Santos et al., 2012), and were detected as the most positive point following the N100, with a latency range of 150-220 ms. N200 and P300 components were calculated as waveforms generated by target tones. The N200 was scored within a timeframe of 180-320 ms post-stimulus, whereas the P300 was defined as the largest positive value between 250 and 450 ms post-stimulus. In line with previous studies demonstrating that these components typically reach their maximum at these scalp positions (Bramon et al., 2004; Brockhaus-Dumke et al., 2008; Salisbury et al., 1994; Salisbury et al., 2010), and to reduce the number of comparisons, N100 and N200 components were only assessed at central midline (Cz) scalp site, P200 at parietal scalp site (Pz), and P300 components at parietal, central and frontal (Fz) scalp sites. All peaks were visually inspected.
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