Neurophysiological correlates of the pathway to the early stages of psychosis
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SENSORY GATING IN SUBJECTS AT ULTRA HIGH RISK FOR DEVELOPING A PSYCHOSIS BEFORE AND AFTER A FIRST PSYCHOTIC EPISODE

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ABSTRACT

OBJECTIVES

To explore sensory gating deficits in subjects at Ultra High Risk (UHR) for psychosis before and after transition to a first psychotic episode.

METHODS

Sensory gating was assessed with the paired click paradigm in 61 UHR subjects, of whom 18 (30%) made a transition to psychosis (UHR + T) over a 3-year follow-up period and 28 matched healthy controls. Subjects were assessed at inclusion and again after approximately 18 months. P50, N100 (N1) and P200 (P2) sensory gating was established using the amplitude on the first (S1) and second (S2) click, the ratio- (S2/S1) and the difference score (S1-S2). Psychopathology was also assessed.

RESULTS

At baseline, UHR + T subjects presented smaller N1 difference scores compared to UHR + NT subjects and controls. The N1 difference score contributed modestly to the prediction of a first psychotic episode. Repeated measure analyses revealed smaller N1 and P2 S1 amplitudes, smaller P2 difference scores and larger P2 ratio’s at follow-up compared to baseline in UHR + T subjects.

CONCLUSIONS

The N1 difference score may be helpful in predicting a first psychosis. N1 and P2 sensory gating measures also showed alterations between the prodromal phase and the first psychosis, suggesting that these changes may relate to the onset of a frank psychotic episode.
INTRODUCTION

Neurophysiological research can contribute to the understanding of the neurobiological substrates of psychiatric diseases (Campanella & Guerit 2009). A widely used neurophysiological component in assessing auditory information processing is the P50, a small wave occurring about 50 ms after stimulus presentation. The P50 is an auditory evoked potential (AEP), i.e. a scalp EEG measure of the pre-attentive brain response to auditory stimuli (Arnfred 2006; Boutros & Belger 1999). A commonly used method to assess the P50 is the paired click paradigm in which two clicks, separated by an interval of 500 ms, are presented. The P50 amplitude to the first click (S1) is thought to assess the capacity of the central nervous system to register salient stimuli, whereas the amplitude after the second click (S2) is associated with suppression of redundant and irrelevant stimuli (Boutros & Belger 1999; Bramon et al. 2004).

Impairments in sensory gating, i.e. reduced suppression to S2, have been found in a number of psychiatric diseases, including bipolar disorder and cocaine users (Boutros et al. 2006; Schulze et al. 2007), but are most notably associated with schizophrenia (Boutros & Belger 1999; Olincy et al. 2010). Despite the ongoing debate about the methodology (Patterson et al. 2000; Potter et al. 2006; de Wilde et al. 2007), these impairments are a relatively consistent finding in schizophrenia patients (Arnfred 2006; Brenner et al. 2009). Different theories prevail concerning the processes leading to sensory gating deficits in schizophrenia. First, gating impairments were interpreted as a reduced ability to habituate to repeated auditory stimulation, i.e. lack of reduction of S2 amplitude (Adler et al. 1982; Clementz et al. 1998). However, more recent findings suggest that these impairments may also be due to reduced sensory registration, i.e. smaller S1 amplitudes (Arnfred 2006; Blumenfeld & Clementz 2001; Brockhaus-Dumke et al. 2008; Johannesen et al. 2005; Judd et al. 1992).

During the past few decades, the focus of schizophrenia research has shifted to the prodromal phase, i.e. the phase preceding psychotic illness in which a decline in premorbid functioning occurs (Yung 2003). In an attempt to delay or prevent the onset of a frank psychotic episode, research has concentrated on identifying subjects at high risk for a first psychotic episode. Attempts have been made to establish whether sensory gating deficits are also present in high risk subjects and thus may be helpful in predicting transition to psychosis. While one study found no significant differences between high risk subjects and healthy controls in P50 parameters (Cadenhead et al. 2005), others did find P50 impairments (Myles-Worsley et al. 2004), but only in those subjects who presented with clinically defined prodromal symptoms. Another approach to identify high risk subjects is the “Ultra High Risk (UHR) concept” (McGorry et al. 2003; Yung et al. 2006). These authors have developed operational criteria to identify subgroups at UHR of incipient psychosis. There is some evidence of gating deficits in UHR subjects compared to controls (Brockhaus-Dumke et al. 2008), but no differences in baseline sensory gating measures between UHR subjects with or without later conversion to psychosis were found, suggesting that P50 abnormalities are not helpful in predicting a first psychotic episode.
Using the paired click paradigm, abnormalities have also been demonstrated in later event related potentials (ERPs), such as the N100 (N1) (Brockhaus-Dumke et al. 2008) and P200 (P2) (Boutros et al. 2004b) in schizophrenia patients and UHR subjects, suggesting that gating deficits are also present beyond the pre-attentive phase of information processing. In fact, it has been demonstrated that compared to the P50 these later ERP components may be more reliable assessors of sensory gating (Fuerst et al. 2007; Rentzsch et al. 2008; Smith et al. 1994).

The aims of our study were twofold. First, we aimed at investigating whether P50, N1 and P2 sensory gating measures are helpful in predicting a first psychotic episode. We expected impaired sensory gating in UHR subjects who later develop a first psychotic episode. Second, we investigated the course of neurophysiological abnormalities from before until shortly after a first psychotic episode. We hypothesized that sensory gating abilities would show further deterioration after the onset of a first psychotic episode. Exploratively, the relationship between sensory gating and severity of psychopathology was investigated.

**METHODS**

**Participants**

**UHR group**

Sixty-one UHR subjects were included at baseline. They were referred to the Academic Medical Centre (AMC), Amsterdam, The Netherlands, for a second opinion with the question whether a psychotic development was taking place. The inclusion criteria for the Ultra High Risk group were: age between 15 and 35 years, and belong to one or more of the following three groups (McGorry et al. 2003; Yung et al. 2007):

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:** 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.

Exclusion criteria were: previous psychotic episode for more than 1 week (as assessed with the Structured Clinical Interview for DSM-IV Diagnosis, sections B and C (SCID-I: Spitzer et al. 1992), symptoms due to substance abuse, as assessed with the Comprehensive International Diagnostic Interview, sections J and L (WHO; Wittchen 1994), premorbid IQ below 85, as determined with the Dutch version of the National
Adult Reading Test (NART; Schmand et al. 1991); vision disorders, endocrine disease and known neurological impairment (e.g., closed head injury).

**Control group**

Twenty-eight demographically matched controls were included at baseline. Exclusion criteria for controls were similar to the UHR subjects, with the addition of psychiatric illness present or in the past, familial history of psychiatric illness (evaluated for first- and second-degree relatives).

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.

**Sensory gating procedure**

Auditory stimuli were presented binaurally through headphones at an intensity of 50 dB above hearing threshold. Initial series of continuing clicks were presented to determine the hearing threshold. During the dual-click paradigm, clicks were presented with square pulses of 0.04 ms duration with an interval of 500 ms between S1 and S2. 72 paired clicks were presented with a random time interval of 8 or 9 s. The subjects were comfortably lying on a hospital bed in a sound- and light-attenuated room. They were instructed to relax, keep their eyes open and fixated on one point and listen to the clicks.

**Recording method**

Twenty-one Ag–AgCl disc 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 inter-electrode impedances were less than 5 kΩ in each subject investigated. The EEG was recorded with a band-pass filter of 0.04–300 Hz, with a sampling rate of 1000 Hz. Digitized data for each subject were stored in a database for subsequent off line analysis using Brainvision Analyzer (Brainproducts). 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 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 N1 component was identified as the most negative deflection within 70–130 ms after stimulus presentation, whereas the P2 was identified as the largest positive deflection between 150 and 250 ms. N1 and P2 amplitudes were calculated relative to baseline. N1 and P2 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.

Instruments
All UHR subjects were assessed with the Structured Interview for Prodromal Syndromes (SIPS; Miller et al. 2003) and the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987). The SIPS is composed of 19 items (five positive, six negative, four disorganization, four 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. 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.

Medication
For the analyses, UHR subjects were ascribed to three medication categories: (i) antipsychotic medication (patients using antipsychotic medication and antidepressants, and/or other medication were also assigned to this category), (ii) other, i.e. antidepressants, benzodiazepines, methylphenidate, and/or lithium carbonate, (iii) no medication. Possible medication effects on ERPs were assessed by comparing ERPs between these three groups and between the categories “no medication” and “medication” (category one and two combined). Because only one UHR subject used typical antipsychotics at baseline and none of the subjects used typical antipsychotics at follow-up, no analyses were conducted comparing sensory gating in subjects using typical or atypical antipsychotics. Associations between the dosage of antipsychotics and ERP amplitudes were determined by correlating chlorpromazine equivalents with the mean amplitudes of the distinct ERP components.

Procedure
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 a SIPS interview at 9, 18 and 24 months and interviewed by telephone at 36 months. The first neurophysiological assessment was done shortly after inclusion. Approximately 18 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 PANSS for hallucinations, delusions or formal thought disorders for longer than one week. To establish a formal DSM-IV diagnosis, the SCID was administered to all subjects after transition to psychosis. Subjects who had experienced a psychotic episode were tested when stabilized on medication.

Sensory gating was assessed in sessions of approximately 10 min, within a week after the psychiatric questionnaires were administered. Participants were instructed not to consume caffeine containing drinks or smoke cigarettes the day preceding the recording. Before the recording, participants were asked whether they complied with this instruction.

**Statistical analysis**

Data were checked for normality, both visually and using the Kolmogorov–Smirnov test. The P50 parameters were not normally distributed. Therefore, we applied a stabilizing z-score transformation of cumulative proportions (estimated by Van der Waerden's formula) for the P50 parameters. After this transformation, parametric tests were used for the statistical analyses, using the transformed P50 scores. Group differences in sensory gating at baseline and follow-up were assessed using multivariate analyses of variance (MANOVAs), followed by Tukey honest significant difference (HSD) tests. With this strategy of statistical analysis we reduced the number of comparisons and corrected for experiment-wise error rate, hereby decreasing the probability of type 1 errors. The predictive value of sensory gating on conversion to psychosis was estimated using the Backward method of the logistic regression analyses. In addition, to assess the effects of the sensory gating measures on survival time, a multivariate algorithm that optimizes prediction of conversion to psychosis was derived from a Cox proportional hazards model, using the Backward Stepwise method. Temporal ERP changes were analyzed by means of repeated measures ANOVAs. If a significant effect emerged, post hoc repeated measure t-tests were applied to assess longitudinal effects within groups. Exploratively we looked at correlations between sensory gating parameters and psychopathology using Spearman Correlation coefficients. Differences between groups in gender distribution were analyzed using a Chi-square test. Group differences in age and premorbid IQ were analyzed using an ANOVA. Due to the unequal group distribution, differences in sensory gating between the three medication categories at baseline and follow-up were analyzed using non-parametric Kruskall–Wallis tests. Differences between subjects who did or did not use medication were assessed using Mann–Whitney U-test. For all tests, p values of ≤ 0.05 were accepted as significant. We chose not to correct for multiple comparisons, as the occurrence of a Type II error (failing to detect a difference) is increased in a smaller research population as ours, and corrections to prevent Type I error (detecting a difference where there is not) like a Bonferroni correction, will automatically inflate Type II errors (Rothman 1990; Perneger 1998).
RESULTS

Demographic and clinical characteristics

Sixty-one UHR subjects and twenty-eight controls were included at baseline. Demographic and clinical variables of these subjects are presented in Table I. At baseline and follow-up, there were no differences between the groups with respect to age, gender distribution or estimated premorbid IQ. Moreover, at baseline we found no differences in chlorpromazine equivalents between UHR + T and UHR + NT subjects. Of the UHR subjects, 18 (30%) made a transition to psychosis over a 3-year follow-up period. These subjects received the following diagnoses: schizophrenia (n = 12), schizophreniform disorder (n = 3), schizoaffective disorder (n = 2) and brief psychotic disorder (n = 1). At follow-up, we were able to assess 15 UHR subjects with transition to psychosis (UHR + T) and 23 UHR subjects without transition to psychosis (UHR + NT). Furthermore, 17 healthy control subjects (61%) were reassessed at follow-up. Reasons for nonparticipation at follow-up were refusal (n = 24), 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.

We found no significant correlations between sensory gating and the demographical variables. Moreover, there were no differences in sensory gating between male or female subjects, or between smokers and non-smokers. Therefore, none of these demographical variables were entered as covariates in the following statistical analyses.

Sensory gating

After applying the stabilizing transformation, the assumptions of equal covariance matrices (Box’s tests, p ≥ 0.56) and of homogeneity of variance (Levene’s tests, p ≥ 0.16) were met for all sensory gating measures. There were no differences between the three groups in the number of artifact free trials at baseline (F = 0.46, p = 0.62) or follow-up (F = 0.42, p = 0.66). Moreover, no group differences were found with respect to the latencies after the first or the second click at baseline or follow-up for any of the ERP components (all p values ≥ 0.14).

Baseline

ERP components at baseline are presented in Table II. Baseline analyses revealed significant group differences in the N1 difference score. Post hoc tests showed that the N1 difference score was smaller in UHR + T subjects compared to controls (p = 0.02) and UHR + NT subjects (p = 0.08; statistical trend). No group differences were found in the other ERP components. In addition, we found no differences in sensory gating measures between the distinct inclusion groups.

Effect of sensory gating parameters on survival

Only components which differed between the groups at baseline (i.e. N1 difference scores) were entered in the survival analyses. Using the backward method of the logistic regression analysis, we found that the N1 difference score contributed modestly to the predictive ability
Table 1 Socio-demographic characteristics 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>
<th>Statistics (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>20.4 (4.0)</td>
<td>19.3 (3.7)</td>
<td>20.0 (3.3)</td>
<td>p=.55(^1)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>13/5</td>
<td>29/14</td>
<td>13/15</td>
<td>p=.16(^2)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>7 (39)</td>
<td>9 (21)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2 (11)</td>
<td>7 (16)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>5 (12)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (44)</td>
<td>22 (51)</td>
<td>28 (100)</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalents</td>
<td>130.4 (30.4)</td>
<td>146.0 (67.2)</td>
<td>-</td>
<td>p=.18(^3)</td>
</tr>
<tr>
<td>DART IQ score (SD)</td>
<td>104.4 (8.4)</td>
<td>101.1 (9.5)</td>
<td>106.9 (10.4)</td>
<td>p=.11(^2)</td>
</tr>
<tr>
<td>Inclusion symptoms n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenuated symptoms</td>
<td>12 (67)</td>
<td>37 (86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLIPS</td>
<td>3 (17)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLIPS and attenuated symptoms</td>
<td>1 (6)</td>
<td>4 (9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Genetic risk and reduced functioning</td>
<td>1 (6)</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic risk, reduced functioning and attenuated symptoms</td>
<td>1 (6)</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NART = Dutch version of the National Adult Reading Test; BLIPS = Brief Limited Intermittent Psychotic Symptoms; UHR = Ultra High Risk; UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis. \(p\) = level of significance for one way ANOVA (1), Chi-square (2) and Mann Whitney U (3).

of the model \((B = -0.24, \text{Wald}=4.07, p = 0.04, \text{OR}=1.28, 95\% \text{CI for OR}=1.02–1.62)\). This means that the relative risk of developing a psychosis increases with 28% with a decrease of the N1 difference score of 1 \(\mu\)V. However, we found no significant effect of the N1 difference score on survival time, i.e. the time between inclusion and the onset of a first psychotic episode.

Longitudinal analyses

Repeated-measures analyses revealed several significant effects for the sensory gating measures (Table III). First, an interaction effect was found for the N1 S1 amplitude, indicating that the course of the N1 S1 amplitudes from baseline to the second assessment differed significantly between the three groups. An interaction effect was also found for the P2 ratio. Finally, significant time effects were found for the P2 S1 amplitude and P2 difference score. Post hoc paired sampled \(t\)-tests showed that UHR + T subjects presented smaller N1 S1 amplitudes \((t =2.38, p = 0.03)\), smaller P2 S1 amplitudes \((t =2.67, p = 0.02)\) and a smaller P2 difference score \((t =2.86, p = 0.01)\) at follow-up compared to baseline. In the UHR + NT and control group, no significant temporal changes were found for any of the ERP components. Grand average waveforms for S1 and S2 at baseline and follow-up are presented in Figure 1.

Follow-up assessment

Analyses on follow-up data revealed significant group differences in the P50 S2 amplitude \((F = 3.70, p = 0.03)\), the N1 S1 amplitude \((F = 15.51, p <0.001)\), the N1 difference score
Table 2 Sensory gating 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>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude P50 S1</td>
<td>2.54 (1.3)</td>
<td>2.41 (1.5)</td>
<td>2.76 (1.3)</td>
<td>F=.52, p=.60</td>
</tr>
<tr>
<td>Amplitude P50 S2</td>
<td>1.29 (.8)</td>
<td>1.20 (1.0)</td>
<td>1.50 (1.1)</td>
<td>F=.83, p=.44</td>
</tr>
<tr>
<td>P50 ratio</td>
<td>.59 (.3)</td>
<td>.59 (.7)</td>
<td>.64 (.5)</td>
<td>F=.07, p=.93</td>
</tr>
<tr>
<td>P50 difference score</td>
<td>1.25 (1.4)</td>
<td>1.21 (1.5)</td>
<td>1.23 (1.3)</td>
<td>F=.01, p=.99</td>
</tr>
<tr>
<td>Amplitude N100 S1</td>
<td>-3.16 (2.6)</td>
<td>-4.86 (3.5)</td>
<td>-5.19 (3.2)</td>
<td>F=2.41, p=.09</td>
</tr>
<tr>
<td>Amplitude N100 S2</td>
<td>-2.03 (2.3)</td>
<td>-1.72 (1.8)</td>
<td>-1.41 (2.3)</td>
<td>F=.52, p=.60</td>
</tr>
<tr>
<td>N100 ratio</td>
<td>.42 (1.1)</td>
<td>.42 (.5)</td>
<td>.82 (.5)</td>
<td>F=.47, p=.63</td>
</tr>
<tr>
<td>N100 difference score</td>
<td>1.13 (2.7)</td>
<td>3.14 (3.7)</td>
<td>3.78 (3.0)</td>
<td>F=3.74, p=.03</td>
</tr>
<tr>
<td>P200 amplitude S1</td>
<td>6.88 (5.8)</td>
<td>5.46 (4.6)</td>
<td>6.17 (4.3)</td>
<td>F=.81, p=.45</td>
</tr>
<tr>
<td>P200 amplitude S2</td>
<td>1.79 (2.2)</td>
<td>1.69 (2.2)</td>
<td>2.41 (2.2)</td>
<td>F=1.00, p=.37</td>
</tr>
<tr>
<td>P200 ratio</td>
<td>.34 (.5)</td>
<td>.24 (.7)</td>
<td>.43 (.3)</td>
<td>F=1.10, p=.34</td>
</tr>
<tr>
<td>P200 difference score</td>
<td>4.37 (5.2)</td>
<td>3.78 (4.6)</td>
<td>4.47 (4.5)</td>
<td>F=.22, p=.80</td>
</tr>
<tr>
<td>Artefact free trials</td>
<td>71.2 (1.0)</td>
<td>71.2 (1.9)</td>
<td>71.1 (1.9)</td>
<td>F=.19, p=.83</td>
</tr>
</tbody>
</table>

Values are mean (SD). Only vertex data (Cz) are reported. Abbreviations: UHR = Ultra High Risk; UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis. Bold indicates significant values.

Figure 1. N100 and P200 sensory gating in UHR subjects and healthy controls. Grand average waveforms for each group at Cz for the first (A) and second click (B) at baseline; grand average waveforms for each group at Cz for the first (C) and second click (D) at follow-up. 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. Only subjects with both baseline and follow up assessments were included in the figure. Note different scales and filter settings: values in the figure were calculated using a band pass filter of 0.5–50 Hz.
<table>
<thead>
<tr>
<th></th>
<th>UHR+T</th>
<th></th>
<th>UHR+NT</th>
<th></th>
<th>Healthy Controls</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n=15)</td>
<td></td>
<td>(n=23)</td>
<td></td>
<td>(n=17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow up</td>
<td>Baseline</td>
<td>Follow up</td>
<td>Baseline</td>
<td>Follow up</td>
</tr>
<tr>
<td><strong>P50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 amplitude</td>
<td>2.32 (1.1)</td>
<td>2.32 (1.7)</td>
<td>2.80 (1.5)</td>
<td>2.48 (0.9)</td>
<td>2.46 (1.3)</td>
<td>2.41 (1.1)</td>
</tr>
<tr>
<td>S2 amplitude</td>
<td>1.25 (0.8)</td>
<td>1.97 (1.0)</td>
<td>1.48 (1.0)</td>
<td>1.49 (0.9)</td>
<td>1.33 (0.9)</td>
<td>1.05 (0.9)</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.62 (4.1)</td>
<td>0.84 (8.6)</td>
<td>0.65 (5.1)</td>
<td>0.35 (5.9)</td>
<td>0.70 (5.1)</td>
<td>0.66 (1.3)</td>
</tr>
<tr>
<td>Difference score</td>
<td>1.07 (1.3)</td>
<td>0.35 (1.6)</td>
<td>1.31 (1.5)</td>
<td>0.98 (1.1)</td>
<td>1.12 (1.3)</td>
<td>1.36 (1.1)</td>
</tr>
<tr>
<td><strong>N100</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 amplitude</td>
<td>3.14 (2.7)</td>
<td>1.46 (4.1)</td>
<td>4.96 (2.9)</td>
<td>5.70 (2.0)</td>
<td>4.77 (2.6)</td>
<td>4.78 (1.5)</td>
</tr>
<tr>
<td>S2 amplitude</td>
<td>-2.18 (6.6)</td>
<td>-0.86 (1.7)</td>
<td>-1.90 (1.6)</td>
<td>-1.64 (1.7)</td>
<td>-2.20 (5.1)</td>
<td>-1.68 (1.1)</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.40 (1.2)</td>
<td>0.49 (1.8)</td>
<td>0.43 (3.1)</td>
<td>0.35 (5.9)</td>
<td>0.44 (5.1)</td>
<td>0.35 (3.1)</td>
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<tr>
<td>Difference score</td>
<td>0.95 (2.8)</td>
<td>0.60 (1.7)</td>
<td>3.06 (2.5)</td>
<td>4.05 (2.3)</td>
<td>3.06 (2.4)</td>
<td>3.10 (1.7)</td>
</tr>
<tr>
<td><strong>P200</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 amplitude</td>
<td>6.43 (6.2)</td>
<td>3.08 (4.6)</td>
<td>5.79 (4.4)</td>
<td>5.24 (3.4)</td>
<td>5.96 (3.4)</td>
<td>4.53 (2.9)</td>
</tr>
<tr>
<td>S2 amplitude</td>
<td>1.95 (2.2)</td>
<td>1.79 (1.7)</td>
<td>1.65 (2.2)</td>
<td>2.24 (1.0)</td>
<td>2.80 (2.3)</td>
<td>2.22 (1.7)</td>
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<tr>
<td>Ratio</td>
<td>0.35 (6.4)</td>
<td>0.64 (1.8)</td>
<td>0.35 (4.1)</td>
<td>0.55 (5.9)</td>
<td>0.51 (2.8)</td>
<td>0.49 (3.1)</td>
</tr>
<tr>
<td>Difference score</td>
<td>4.48 (5.8)</td>
<td>1.28 (1.7)</td>
<td>4.13 (4.6)</td>
<td>3.00 (3.8)</td>
<td>3.16 (2.6)</td>
<td>2.21 (1.7)</td>
</tr>
<tr>
<td>Artefact free trials</td>
<td>71.3 (8.0)</td>
<td>71.7 (5.5)</td>
<td>71.4 (9.9)</td>
<td>70.8 (1.5)</td>
<td>71.1 (9.9)</td>
<td>71.3 (8.0)</td>
</tr>
</tbody>
</table>

Values are mean (SD). S1=condition amplitude; S2=test amplitude. Abbreviations: UHR+T = UHR subjects with transition to psychosis; UHR+NT = UHR subjects without transition to psychosis. **Bold** indicates significant values. 'n=14 (one outlier removed).
(F = 13.91, p <0.001) and the P2 S1 amplitude (F = 3.79, p = 0.03). Post hoc Tukey HSD tests indicated that, compared to controls, UHR + T subjects presented with larger P50 S2 amplitudes (p = 0.02). The N1 S1 amplitude was smaller in UHR + T subjects compared to UHR + NT subjects (p < 0.001) and controls (p < 0.001), as was the N1 difference score (UHR + NT: p < 0.001; controls: p = 0.002). Finally, the P2 S1 amplitude was smaller in UHR + T subjects compared to UHR + NT subjects (p = 0.05) and controls (p = 0.04).

**Sensory gating and severity of psychopathology**

At baseline, no significant associations were found between the sensory gating measures and subscales of the PANSS or SIPS in UHR + T group or the UHR sample as a whole. At follow-up however, we found that a lower N1 difference score was related to higher scores on the subscales negative symptoms (rho = –0.63, p = 0.03) and general pathology (rho = –0.66, p = 0.02) of the SIPS in the UHR + T group.

**Sensory gating and medication use**

We found no differences in sensory gating measures between subjects who did or did not use medication, nor did the analyses reveal significant differences in sensory gating measures between the three medication categories. Moreover, within the UHR + T group at follow-up, we found no differences in sensory gating between subjects who did or did not use antipsychotic medication. Finally, our correlation analyses revealed no significant correlations between the dosage of antipsychotic medication and the sensory gating measures at baseline or follow-up. Nevertheless, we ran the analyses again using chlorpromazine equivalents as covariate. The temporal changes in the P2 S1 amplitudes lost significance after controlling for changes in the chlorpromazine equivalents from baseline to follow-up (F = 3.52, p = 0.07). Besides this, all discussed findings at baseline and follow-up persisted after covarying chlorpromazine equivalents.

**DISCUSSION**

The present study examined the course of sensory gating abnormalities from before until shortly after a first psychotic episode. We found some evidence of sensory gating deficits before the onset of a first psychotic episode: at baseline the N1 difference scores were smaller in UHR + T subjects compared to UHR + NT subjects and healthy controls. Moreover, the N1 difference score contributed modestly to the prediction of a first psychotic episode. No group differences were found with respect to the P50 or P200 components at baseline.

Interestingly, our analyses also revealed temporal changes in sensory gating measures from before until shortly after a first psychotic episode. From baseline to follow-up, reduced N1 and P2 S1 amplitudes and P2 difference scores were demonstrated only in UHR + T subjects. Moreover, compared to healthy controls, UHR + T subjects presented with larger P50 S2 amplitudes, smaller N1 S1 amplitudes and smaller N1 difference scores at follow-up. Analyses on follow-up data also showed smaller N1 and P2 S1 amplitudes and smaller N1 difference scores in UHR + T compared to UHR + NT subjects.
These findings suggest that impairments in sensory gating may partly arise before the onset of a first psychotic episode. Specifically, the N1 difference score may be viewed as a vulnerability marker of psychosis and may aid in the difficult process of predicting psychosis. Along with other studies however (Boutros et al. 2004a; Brockhaus-Dumke et al. 2008; van Tricht et al. 2010) our results challenge the view that sensory gating deficits are solely a result of reduced suppression to S2: although group differences were found for the P50 S2 amplitude at follow-up, UHR + T subjects were most impaired on the N1 and P2 S1 amplitudes. Moreover, at baseline, UHR + T subjects only demonstrated smaller N1 difference scores, whereas no group differences were found with respect to the S2 amplitudes or ratio scores. As has been documented in previous studies (i.e. Arnfred 2006; Blumenfeld & Clementz 2001; Brockhaus-Dumke et al. 2008; Johannesen et al. 2005), the N1 difference score and N1 ratio may be reflective of distinct gating or stimulus registration measures. For instance, in the study of Brockhaus-Dumcke and colleagues, the difference score was highly correlated with the S1 amplitude but only modestly with the S2 amplitude, implying that the difference score mainly reflects impaired stimulus registration represented by the S1 amplitude. The S2/S1 ratio in contrast, was strongly correlated with the S2 amplitude but not with the S1 amplitude, implying that this measure seems to primarily reflect reduced gating. In accordance with these findings, we found no evidence of smaller S2 amplitudes in UHR + T subjects at baseline, whereas a trend for group differences in N1 S1 amplitudes was found. In sum, these findings support the hypothesis that UHR subjects are mostly impaired on registration measures, whereas impairments in sensory gating (as assessed by S2 amplitudes and ratio scores), only arise after the onset of a first psychotic episode and may be related to disease progression.

Abnormalities in the generation of the N1 component have been interpreted as diminished early auditory sensory-perceptual processing or involuntary attention. Moreover, some researchers have hypothesized that N1 amplitudes may reflect an abnormality in readiness, i.e. a decrease in expectancy during repeated stimulation (Arnfred 2006). Smaller N1 amplitudes have been reported in chronic schizophrenia patients, patients with a first episode of schizophrenia as well as first degree relatives of schizophrenia patients (Foxe et al. 2010). These findings have led investigators to hypothesize that N1 deficits may be viewed as an endophenotypic marker for schizophrenia, linked to the underlying genetic risk of developing this disorder. Our findings support the view that the N1 may be viewed as a risk marker to the disease. Along with studies reporting N1 impairments in other stages of the disease, one might therefore conclude that N1 deficits are a trait marker of psychosis. However, the picture is far from clear. First, N1 S1 amplitudes also showed changes from the prodromal phase until after psychotic onset, supporting the view that the N1 may in fact be viewed as a (partial) state marker of the disease. This is supported by our correlation analyses, in which modest associations between the N1 S1 amplitude and measures of negative symptoms and general pathology were found at follow-up. Moreover, other studies in UHR subjects and patients with a first episode of psychosis have not reported N1
impairments (Bramon et al. 2008; van Tricht et al. 2010, 2011). As suggested by Foxe and colleagues (Foxe et al. 2010), the absence of N1 impairments in UHR subjects and patients with a first episode of schizophrenia may be a result of a lack of power or the use of a relatively low number of sweeps. Moreover, these inconsistencies may be due to a difference in employed paradigms. Whereas studies that used the oddball paradigm generally do not find evidence of N1 abnormalities in UHR subjects (Bramon et al. 2008; van Tricht et al. 2010, 2011), using the paired click paradigm differences in N1 components between UHR subjects and controls have been previously demonstrated (Brockhaus-Dumke et al. 2008; Myles-Worsley et al. 2004). In sum, no firm conclusions can yet be drawn on the robustness of the N1 as a marker of schizophrenia.

Limitations need to be addressed. First, several studies have described effects of antipsychotic medication on ERP components (Adler et al. 2004; Light et al. 2000). However, our analyses showed no associations between the sensory gating measures and chlorpromazine equivalents, neither did we find differences in ERPs between the distinct medication categories. In addition, with exception of the P2 S1 amplitudes in the longitudinal analyses, all effects persisted after controlling for chlorpromazine equivalents. Therefore, medication use should not have biased our results. We hypothesize that the absence of medication effects on ERPs in our study might be due to the relatively low medication dosages in our UHR sample. Another limitation of our study is the small group sizes. Moreover, we did not apply a Bonferroni correction for multiple comparisons. This decision was made because decreasing Type 1 errors (detect a difference when there is actually not a difference) would automatically inflate the probability of making Type 2 errors (Rothman 1990; Perneger 1998). By using Tukey HSD tests, which corrects for experiment-wise error rate, we already decreased the probability of making type 1 errors. Nevertheless, due to the small sample and large number of comparisons, some caution is warranted in the interpretation of our results. Finally, there is an ongoing debate on methodological issues concerning ERP measurement (e.g. Patterson et al. 2008; de Wilde et al. 2007). This debate concerns a large array of topics, including the effects of the use of high- or low pass filters, click intensity and duration, stimulus presentation methods and peak detection methods. Standards for ERP data collection and measurements (as for example proposed by Patterson et al. 2008), should be applied in future studies to enhance comparability across research groups.

We conclude that the N1 difference score may be helpful in predicting a first psychotic episode in UHR subjects. Moreover, some sensory gating parameters showed changes from before until shortly after a first psychotic episode in UHR + T subjects. These findings suggest that impairments in sensory gating may partly be present before the onset of a first psychotic episode, but also show changes associated with psychotic onset. By demonstrating that worsening of sensory gating impairments is related to experiencing a psychotic episode, our study contributes to the understanding of the pathophysiological mechanisms associated with psychosis. Replication studies using larger samples are warranted before firm conclusions can be drawn.
ACKNOWLEDGEMENTS

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