Biological Psychology 87 (2011) 350–357

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Auditory ERP components before and after transition to a first psychotic episode

Mirjam J. van Tricht[a,b,*], Dorien H. Nieman[a], Johannes H.T.M. Koelman[b], Lo J. Bour[b], Johan N. van der Meer[b], Thérèse A. van Amelsvoort[a], Don H. Linszen[a], Lieuwe de Haan[a]

[a] Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Meibergdreef 5, 1105 AZ Amsterdam, Netherlands
[b] Department of Neurology and Clinical Neurophysiology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands

ARTICLE INFO

Article history:
Received 19 October 2010
Accepted 17 April 2011
Available online 30 April 2011

Keywords:
Ultra High Risk subjects
Psychosis
ERP
N100
P300

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 (Yung et al., 2004, 2006; McGorry et al., 2003). 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 (Frommann et al., 2008; Bramon et al., 2008; Ozgürdal et al., 2008; van Tricht et al., 2010) and neuropsychological (Niendam et al., 2007; Brewer et al., 2006; 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 (Hawkins et al., 2008; Becker et al., 2010), 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 (van der Stelt et al., 2004; Nieman et al., 2002). 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 (Frommann et al., 2008; Bramon 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 com-

* Corresponding author at: Academic Medical Centre, Department of Neurology and Clinical Neurophysiology D2-136, P.O. Box 22660, 1100 DD Amsterdam, Netherlands. Tel.: +31 205668417; fax: +31 205669187.
E-mail address: m.j.vantricht@amc.uva.nl (M.J. van Tricht).

0301-0511/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2011.04.005

pared 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 first 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 (van Tricht et al., 2010; Bramon et al., 2008). Abnormalities in earlier ERP components have however been reported in both first episode and chronic schizophrenia patients (Potts et al., 1998; Salisbury et al., 2010; O'Donnell et al., 1993; Haenschel et al., 2007).

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 (Jeon and Polich, 2001; Faux et al., 1988). P3 amplitude asymmetry has also been reported in patients with a first psychotic episode (Salisbury et al., 1998; McCarley et al., 2002) 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 (Hirayasu et al., 1998; Renoult et al., 2007; van Tricht et al., 2010; Bramon et al., 2008).

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 GAF-score for at least 1 month).
2. *Attenuated Positive Symptoms (APS)*: subjects who have experienced subthreshold, 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 assessed with the Dutch 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 Academic Medical Center. 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; http://www.brainproducts.com). 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 (Salisbury et al., 2010; Ford et al., 2001; O'Donnell et al., 2004), 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 (Salisbury et al., 1994, 2010; Brockhaus-Dumke et al., 2008; Bramon et al., 2004), 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.