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Prolonged Latencies of the N2 and P3 of the Auditory Event-Related Potential in Children at Risk for Schizophrenia

A Preliminary Report

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Summary. In previous studies investigating long latency components of the event-related potential (ERP), schizophrenic patients generally showed reduced P3 amplitudes and in some studies prolonged N2 or P3 latencies. As there is a higher risk of offspring of schizophrenics than of mentally healthy parents developing this disease, the present study was intended to clarify whether ERP components (in particular the N2 and P3) differ between these two groups of children. Twelve high-risk and 12 age-matched control children (aged 9–16 years) performed an auditory oddball task in order to assess late ERP components. This task required the subject to covertly count rare target tone pips ($P = 0.2$) irregularly interspersed among frequent standard tone pips ($P = 0.8$) in two series of 400 pips. ERPs were recorded from midline electrodes (Fz, Cz, Pz). The results indicated distinctly prolonged N2 and P3 latencies in ERPs to target stimuli in children of schizophrenic patients. These findings suggest a slowed target classification in these children.

Key words: Auditory event-related potential – N2 – P3 – Schizophrenia – Heredity – Children at risk

Introduction

The N2 and P3 component of the human event-related potential (ERP) are considered to form part of the brain's response to stimuli that deviate from a background of regularly repeated stimuli [12, 14, 15, 22]. Both components have been commonly linked to cognitive processes such as target detection, discrimination, or classification. They have also been identified as characteristic components of the more heterogeneous evoked response of children and adolescents [e.g. 5, 10].

In schizophrenic patients the latencies of the P3 and N2 components have been found to be prolonged in several studies [4, 13, 18]. Moreover, some studies have provided evidence that schizoprenic patients display reduced amplitudes of these components [e.g. 4, 13, 17, 19, 23].

It is widely accepted that there is a hereditary risk of developing schizophrenia [11, 16]. Assuming that ERP changes in schizophrenics reflect an underlying trait that is not necessarily linked to overt psychopathology, similar ERP alterations may also be present in biological relatives of schizophrenic patients. Thus, it has been found that compared with the normal controls, siblings of schizophrenics displayed reduced amplitudes of the late positive component to target stimuli in a syllable discrimination task, nearly equal to those of unmedicated schizophrenics [21]. Applying an auditory oddball task Friedman et al. [7] demonstrated lower amplitudes of the P350 and P400 components in children at risk of schizophrenia than in control children. We report preliminary results from a study aiming to clarify further whether the N2 and P3 of ERPs differ between children with at least one schizophrenic parent and children from mentally healthy parents.

Methods

Twelve high-risk and 12 control children (aged 9–16 years, mean: 12.6 years for both groups) of both sexes (6 females, 6 males) participated in the study (for details, see Table 1). At least one of the parents of the high-risk children suffered from schizophrenia according to the criteria of DSM III [2] (Three children had two schizophrenic parents). The disease had been diagnosed independently by at least two psychiatrists. All of the schizophrenic parents had been hospitalized at least three

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Table 1. Personal data for high-risk and matched control children. Age, sex (male = M, female = F); MI indicates practice inplaying a musical instrument; Educ. indicates educational background; Lo = level of high school, elementary school and lower; Me = intermediate level (German *Realschule*); Hi = college; Env. (environmental background) indicates whether the child lives at home (Ho), with foster parents or relatives (Fop), or in a foster home (Fho); Psy. indicates which parent (F = father, M = mother) suffered from schizophrenia

No.	Controls					High risk					
	Age (years)	Sex	MI	Educ.	Env.	Age (years)	Sex	MI	Educ.	Env.	Psy.
01	12.7	M	Yes	Hi	Ho	12.1	M	Yes	Me	Fop	M
02	12.8	M	No	Lo	Ho	12.6	M	No	Lo	Ho	F/M
03	15.9	F	No	Me	Ho	15.4	F	Yes	Hi	Ho	M
04	10.10	M	Yes	Lo	Ho	11.3	M	No	Hi	Ho	M
05	11.2	F	Yes	Lo	Ho	11.11	F	Yes	Lo	Ho	F/M
06	8.9	M	No	Lo	Ho	8.5	M	Yes	Lo	Ho	F
07	12.2	F	No	Lo	Ho	12.2	F	Yes	Me	Ho	M
08	14.4	F	No	Me	Ho	14.5	F	Yes	Hi	Fop	M
09	14.1	M	Yes	Lo	Ho	14.8	M	No	Lo	Fho	F/M
10	9.7	M	Yes	Lo	Ho	10.2	M	No	Lo	Ho	M
11	10.11	F	Yes	Lo	Ho	10.10	F	Yes	Hi	Fop	M
12	14.0	F	Yes	Me	Ho	13.2	F	Yes	Hi	Ho	F

times. One of them was permanently hospitalized because of severe residual symptomatology. Offspring of patients meeting distinct schizodepressive, schizopolar, or schizomaniac criteria were not included in the study because there is evidence that these subgroups are not only of schizophrenic but of more heterogeneous origin [1]. Control children (with no family history of psychiatric disorder) and high-risk children were matched according to age, sex and socioeconomic status, thus forming 12 comparable pairs. The high-risk children were found by studying family histories from clinical reports of patients hospitalized for schizophrenia. Permission to test the corresponding children was then obtained from their parents, foster parents, foster homes or communal Youth Welfare Offices. For exact selection of the control children according to matching criteria the research group benefitted from support from communal and ecclesiastical authorities.

For both groups, the mean IQs as measured by the Wechsler Intelligence Scales (WISC or WAIS) were nearly identical (mean ± standard deviation: controls: 114.9 ± 11.6; high-risks: 110.0 ± 13.7). The mean verbal IQ was 109.0 ± 10.4 in control children and 101.6 ± 13.6 in high-risk children; the mean performance IQ was 117.6 ± 15.1 and 116.4 ± 15.0, respectively, for the control and the high-risk group.

Auditory event-related potentials (AERPs) were recorded while the subject performed an oddball task. Two series of 400 tone pips (60 dB SPL, 60 ms duration) each were presented binaurally via earphones. Each series consisted of frequent (80% probable) standard tone pips (1200 Hz) and of rarer (20% probable) target tone pips (800 Hz) that were randomly interspersed among the standards. Interstimulus intervals varied randomly between 300 and 1100 ms (mean: 750 ms). The subject's task was to count covertly the more rare target tone pips.

Recordings were obtained of EEGs (5-s time constant, 30 Hz/3 dB high-frequency roll off) through Ag/AgCl electrodes from Fz, Cz and Pz leads referenced to linked earlobe electrode locations. Fpz served as ground. For artefact recognition, the vertical EOG was monitored. AERPs were averaged separately for each subject, type of tone pip (standard vs target) and electrode position. The averaging epoch covered a 40-ms pre-stimulus baseline and a 660-ms post-stimulus interval. Sweeps were excluded from analysis by a computer program if they contained eyeblinks, gross eye movements or other artefacts. Baseline-to-peak amplitudes and latencies were determined for maxima and minima within latency bins accounting for the N1 (60–140 ms post-stimulus onset), P2 (140–240 ms), N2 (180–360 ms), P3 (300–660 ms). P3 was identified only in AERPs to target pips. Differences in AERPs between high-risk children and matched control children were evaluated statistically by analysis of variance including the factors groups (high-risk vs. control) and topography (Fz, Cz, Pz), which were both treated as repeated measures factors.

Results

Counts of target tone pips in the oddball paradigm representing a crude estimate of vigilance performance seemed to deviate from the correct number of targets in each series slightly more in high-risk children than in controls (mean ± standard deviation: high-risks: 9.1 ± 9.5; controls: 6.6 ± 8.6). However, owing to the large variability this tendency failed to reach the 5% level of significance.

Figure 1 shows typical examples of averaged AERP waveforms to standard and target pips recorded from single subjects. AERPs to standard tone pips were similar in both experimental groups. Differences between the experimental groups, for amplitude as well as for latency of any of the AERP components to standard pips, did not reach statistical significance.

AERP waveforms from target pips, in general, were more variable than those elicited from standards. The early negative-positive component com-

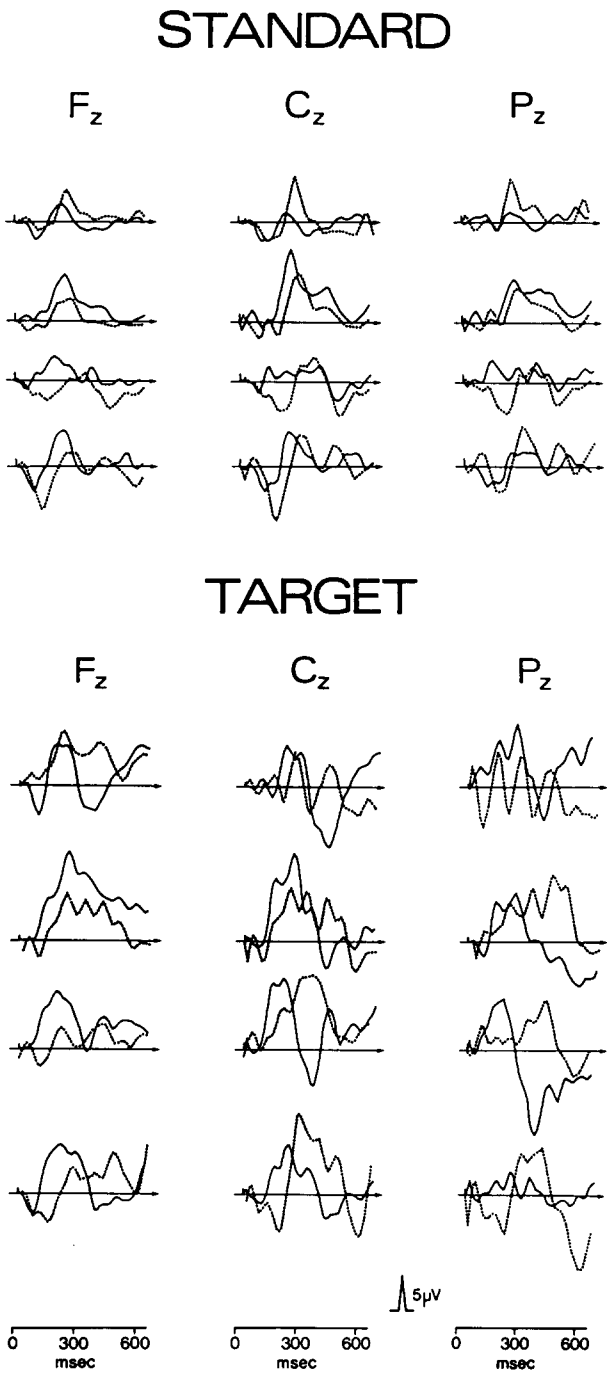

Fig. 1. Averaged AERPs to standard and to target pips from three high-risk subjects *(dotted lines)* and their matched controls *(solid lines)* recorded from frontal *(F_z)*, central *(C_z)* and parietal *(P_z)* midline electrode sites (vertex negative upward)

plex in AERPs to target tone pips appeared to be markedly overlapped by N2-related negativity. AERPs to targets were marked by an additional late positive component complex (P3) that was concentrated over parietal cortical areas.

N2 and early P3 amplitudes to target pips appeared to be smaller in the high-risk than in the control

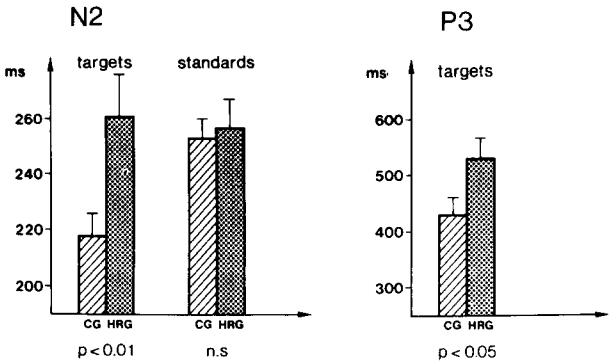

Fig. 2. N2 and P3 (at P_z) latencies in the high-risk group *(HRG)* and in the control group *(CG)*. P3 was identified following target pips only. Significant ($P<0.05$) differences between groups are indicated

group. However, owing to the variability among subjects the effect did not reach significance. N2 latencies in AERPs to targets were substantially shorter in controls (218 ms) than in children at risk (261 ms) (Fig. 2). The effect was statistically confirmed by analysis of variance (main effect on the group factor: $F(1,11) = 14.6$, $P<0.01$). it dominated over posterior cortical areas (group × topography: $F(2,22) = 8.5$, $P<0.01$). Maximum parietal positivity between 300 and 660 ms post-stimulus, too, displayed shorter latencies in the control than in the high-risk group (group: $F(1,11) = 5.3$, $P<0.05$; Fig. 2). Comparing single matched pairs revealed that N2 latency was longer in the high-risk than in the respective control child in 10 cases; for P3 latency this was true in 9 cases.

Discussion

The fundamental finding of the present investigation was that the two experimental groups of children, one being genetically at risk for schizophrenia, systematically differed in their event-related brain responses to the task relevant target stimuli of the applied oddball paradigm. AERP responses to standard pips were nearly identical in both groups. In AERPs to target pips latencies of the N2 and P3 components were distinctly longer in the high-risk than in the control group. Amplitudes were too variable to yield significant differences between both groups.

Differences in AERPs between both groups are not likely to be due to the subject sampling. Children were matched for age, sex and socioeconomic background. Education in terms of the type of school attended by the children seemed comparable. Moreover, behavioral performance on the Wechsler Intelligence Scales did not systematically differ between

experimental groups, giving no evidence of gross deficits of general cognitive performance in high-risk children.

Taking into consideration possible developmental changes in ERP components [8, 10] in connection with the wide age range of the present subject sample, conclusions with respect to the specific functional role of changes in late AERP components in high-risk children cannot be more than tentative. As AERPs differed significantly between experimental groups only after target stimuli but not after standard stimuli, it may be concluded that the discrimination of the task-relevant target stimuli is impaired in these children. This would fit observations in schizoprenics and their siblings supporting an alteration of ERP components in these subjects related to mechanisms of controlled (vs automatic) stimulus processing [e.g. 3, 5, 6, 17, 21]. Alternatively, the prolonged N2 and P3 latencies could reflect a deficit in maintaining attention, as typically seen in schizophrenia [3, 9, 20].

In conclusion, the present study demonstrates differences in AERPs reflecting cognitive processing of deviating task-relevant stimuli between offspring of schizophrenic patients and of mentally healthy parents. High-risk children displayed prolonged latencies of N2 and P3, indicating a slowed target classification in these children. The observed AERP alterations in the high-risk children may hint at an underlying predisposition for psychopathology. Further investigations (including assessment of reaction times, saccadic eye movements, and multiple ERP components) are in progress to verify the reported results in an extended subject sample.

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