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# Reduction of the event-related potential P3 in preterm born 5-year-old healthy children

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HIGHLIGHTS

- We investigated attention functions in healthy preterm children by using EEG recording.
- Attention problems were not detectable on a symptom level in the preterm group.
- In contrast, preterm children showed alterations on the brain level (event-related potentials) in an attention driven task.

ABSTRACT

*Objectives:* An abbreviated gestational period may interrupt intrauterine brain development and constitutes a serious risk factor. Many preterm children show some form of attention deficits in later life. However, there is ambiguity about the nature and extent of these attention deficits in the literature. Moreover, the majority of studies investigated attention functions in preterm children on a symptom based level or using neuropsychological tasks. In contrast, neurophysiological studies have been comparatively scarce which will be addressed in the current study.
*Methods:* We investigated attention functioning in 27 low risk preterm children and 20 term children of 5–6 years of age by using EEG recording in an attention driven task (oddball task).
*Results:* Compared with term children, preterm children showed no attention deficits on a symptom level, but failed to show an increased oddball P3.
*Conclusion:* Current results suggest subclinical attentional changes in preterm children on the electrophysiological level in contrast to normal performance in attentional behavioral tests.
*Significance:* Our results emphasize to have a closer look at preterm children early in preschool age even though clinically relevant symptoms seem to be absent.


## 1. Introduction

Brain development starts soon after conception and continues until the second decade of life. The most vulnerable period for structural and functional brain development takes place throughout the 40 weeks of a pregnancy. Therefore, preterm delivery, i.e. delivery before 37 weeks of gestation, has a direct influence on, and interrupts the complex spatial and temporal sequence of brain development and regular brain maturation (Allin et al., 2011; Kesler et al., 2004, 2006; Nagy et al., 2011; Nosarti et al., 2008; Volpe, 2009a, 2009b; Volpe et al., 2011). The majority of preterm births occurs between 28 and 36 weeks of gestation. Around 1% is classified as extremely preterm, being born before 28 weeks of gestation. The prevalence of any impaired outcomes in the neonatal period and in the long term is inversely related to gestational age and birth weight and rises more steeply as gestational age falls (Abel et al., 2010; Gale and Martyn, 2004; Johnson et al., 2010;

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Linnet et al., 2006; Mathews and MacDorman, 2013; Moster et al., 2008; Singh et al., 2013; Singh and Kogan, 2007). Thus, one might predict that negative outcomes would be most prevalent in the smallest and youngest preterm infants, while late preterm children should be less at risk (Singh et al., 2013). In the neonatal period, preterm infants are at higher risk for multiple and interacting medical conditions such as respiratory distress syndrome, apnea, intraventricular hemorrhage, periventricular leukencephalopathy, temperature instability, feeding difficulties, hypoglycemia and seizures (Escobar et al., 2006; Kinney, 2006). In the long term, outcomes include neurosensory deficits (Moster et al., 2008; Volpe, 2009a, 2009b), cognitive disadvantages (Fan et al., 2013; Voigt et al., 2012), neuropsychological deficits, and psychiatric disorders (Aarnoudse-Moens et al., 2009; Arpino et al., 2010; Bhutta et al., 2002; Fan et al., 2013; Johnson et al., 2010; Johnson and Marlow, 2011; Marlow, 2004; Singh et al., 2013). The most prevalent psychiatric disorders following prematurity are attention deficits such as Attention Deficit Hyperactivity Disorder (ADHD) (Breeman et al., 2016; Elgen et al., 2004; Johnson, 2007; Johnson et al., 2010; Johnson and Marlow, 2011; Marlow, 2004; Mulder et al., 2011; Murray et al., 2016). However, the nature and presumably the origin of ADHD described in preterm cohorts differ from the typical clinical signs of ADHD in cohorts at term (for a review see (Johnson and Marlow, 2011)). Preterm cohorts have a higher risk for symptoms of inattention rather than hyperactivity/impulsivity (Brogan et al., 2014; de Kieviet et al., 2012; Indredavik et al., 2004; Jaekel et al., 2013) the male predominance in ADHD in the general population is typically not observed in preterm cohorts (for a review see (Johnson and Marlow, 2011)); the association with comorbid conduct disorders in the general population is lacking in preterm cohorts as there is no significant increase in conduct disorders (for a review see (Johnson and Marlow, 2011)); there appears to be a weaker association of ADHD with sociodemographic and family risk in preterm cohorts than in the general population, and there is a closer association between ADHD and medical variables than social factors (for a review see (Johnson and Marlow, 2011)). These findings suggest a more biologically determined form of attention deficits that has an impact on attention regulation rather than motor hyperactivity/impulsivity and is associated to the known neurologic sequelae of preterm birth and altered brain development (Allin et al., 2011; Eikenes et al., 2011; Indredavik et al., 2004; Murray et al., 2016; Nosarti et al., 2008; Skranes et al., 2008; Zubiaurre-Elorza et al., 2014). However, attention regulation in particular, is associated with poor school performance and might be the reason for poorer academic attainment of preterm children compared to their term peers (Brogan et al., 2014). Raising teachers' and especially kindergartens' awareness of inattention may enable them to identify children who may benefit from intervention. Based on these findings, further research is needed to elucidate the profile of impairment associated with such deficits to improve identification, management, and treatment of what is thought to be ADHD in preterm cohorts. Neurophysiological methods such as Event Related Potentials (ERPs) have the potential to increase the understanding of attention mechanisms, but have been used rarely in preterm cohorts. ERPs are a promising way to assess the neural architecture of cognitive functions during stimulus-response paradigms, such as the Oddball Task (Donchin et al., 1978; Polich and Criado, 2006; Pritchard, 1981). During this task a series of two different stimuli is presented with different probabilities in a random order (Squires et al., 1975). The subject is asked to discriminate the infrequent target stimulus from the frequent non-target stimulus by noting the occurrence of the target, typically by pressing a button or counting them mentally. The brain response is reflected in a difference of the averaged waveforms between both stimuli. A positive going amplitude can be observed at about 300 ms after stimulus onset (P3) for the infrequent stimulus, which is typically absent or attenuated after the presentation of the frequent stimulus (Folstein and Van Petten, 2008; Polich, 2007; Polich and Criado, 2006). There are several theories about the neural processes underlying the origin of the P3 component (Carrillo-de-la-Pena and Cadaveira, 2000; Donchin and Coles, 1988; Johnston et al., 1986; Wickens et al., 1983) and it has been used to study patient populations with a variety of neurologic and psychiatric disorders (Alexander et al., 2008; Bruder et al., 2009; Donkers et al., 2013). Commonly, the P3 amplitude can be seen as a measure of neural activity that is proportional to the amount of attentional resources (Polich, 2007; Polich and Criado, 2006; Sutton et al., 1965) and depends on the subject's level of arousal or physiologic state (Kok, 1990; Polich and Kok, 1995).

The current study aimed at extending the understanding of the nature and profile of attention functioning in preschool aged, healthy preterm children compared to term children by using EEG. To our knowledge this study is the first that included low risk preterm children without any clinically apparent problems to minimize possible confounding factors, i.e. gestational age > 27 weeks, IQ (in the normal range), no emotional deficits, no social problems or no typical ADHD/ADD symptoms, no high risk psychosocial environments, and no neurological disabilities. We hypothesize that the preterm children will show reduced P3 amplitudes in a visual Oddball Task.

## 2. Methods

The study was approved by the local ethics committee of the psychological faculty of the Ruhr University Bochum and adhered strictly to the requirements according to the Declaration of Helsinki and its subsequent amendments.

### 2.1. Sample

Eighty-one preschool children, aged between 60 and 78 month have been recruited from Dortmund and the surrounding areas. Participation was voluntary and parents gave written consent for their children to participate in this study. Testing took place in 2 sessions of 45 min. The same observers examined the study and comparison group. After testing, parents were informed about the test results in written and oral form. To minimize confounding factors and to guarantee higher group homogeneity, we excluded children from the data analysis when meeting one of the following criteria (1) IQ score < 85, (2) ADHD/ADD symptoms with clinical relevance, (3) significant conduct problems, (4) living in a high-risk psychosocial environment including the parental academic situation.

After exclusion, the group of preterm children included 27 children (7 females, 20 males, $M_{age}$ = 69, $SD_{age}$ = 6). Information on the child's demographic data, psychosocial environment, and place of residence were acquired using a special questionnaire. Neonatal data were available from the hospital database. Preterm children were all delivered in the same municipal hospital. Mean gestational age was 32 weeks (*SD* = *2.5*; range, 28–36) and mean birth weight was 1652 gram (*SD* = 578; range, 690–2570). Extremely preterm children with a gestational age below 28 weeks were excluded from this study. Preterm children stayed in hospital on average for 42 days after birth (*SD* = *24*; range, 13–82). Among the preterm children, 3 (11%) suffered intraventricular hemorrhage grade I or II and 23 (85%) had some kind of respiratory distress after birth, requiring assisted ventilation or respiratory support. No further medical risks such as periventricular leukomalacia, neonatal asphyxia, congenital malformations or neurosensory deficits were reported. All children were attending kindergarten at the time of this study.

The group of term children was recruited via postings in kindergartens. After exclusion according to the above described criteria, 20 children (8 females, 12 males, $M_{age}$ = 69, $SD_{age}$ = 5) were included in the analysis. Mean gestational age was 39 weeks (*SD* = 1.1; range, 38–41) with a mean birth weight of 3265 gram (*SD* = 560; range, 2300–4300). No pre-, peri-, or postnatal complications were reported, and no developmental disorders were known. Mean time in hospital after birth was 2.7 days (*SD = 1*; range, 1–5). All children were attending kindergarten at the time of this study.

Mean IQ score was estimated using the Kaufmann-Assessment Battery for children (Melchers and Preuß, 2009). Symptoms of attention deficit-/hyperactivity disorder (ADHD/ADD) were defined according to the criteria of ICD- 10 (F90.0/F90.1/F98.8) (World Health Organization (WHO), 1993) with the German parent rating scale (Fremdbeurteilungsbogen für Vorschulkinder mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen; FBB-ADHS-V) (Breuer and Döpfner, 2008). Conduct problems were assessed using the total difficulties score of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997). Psychosocial risks were assessed using the Family Adversity Index (FAI) (Rutter and Quinton, 1977) (see Table 1).

### 2.2. EEG recording and experimental procedure

In accordance with Jaeger et al. (2015) we used a visual Oddball Task with the image of a witch (non-target) and a wizard (target) to elicit the P3 component as a neuronal representation of attention. In visual Oddball Tasks, a characteristic brain response, the P3 component, which is a positive deflection that can be observed with a parietal-maximum around 300 ms after stimulus onset. The P3 wave should differentiate between a frequent target and infrequent non-target stimuli. Target and non-target stimuli were randomly presented during 100 trials, with 80 non-targets and 20 targets. Each stimulus was presented for 500 ms with an interstimulus interval of 1500 ms. Subjects were seated in a light and sound attenuated room fixating a computer screen and were instructed to attentively observe the wizard (target) and to ignore the witch (non-target). Before the experiment, they were informed that they should describe the wizard in detail after the session. This recall was not operationalized. During stimulus presentation a NIHON KOHDEN system continuously recorded the EEG from 20 scalp electrodes according to the international 10–20 system (Jasper, 1958). Linked earlobes were used as reference electrodes. The ground electrode was placed on the subject's forehead. Impedance was kept below 10 kΩ. Data digitized at a rate of 1000 Hz. All channels were filtered using a 0.1–35 Hz band pass and 50 Hz notch filter. ERP analyses were performed offline using the Brain Vision Analyzer software package (Brain Products GmbH, 2016). Epochs of 700 ms (200 ms pre-, 500 ms post stimulus) were segmented for each stimulus. Epochs including amplitude changes larger than 50 μV at frontal electrode sides were excluded from further analysis to control for eye-movement related artefacts. Remaining epochs were averaged separately for target and non-target stimuli. The summary of the average number of trials included in each participant's waveforms is listed in Table 2.

The two groups did not differ with respect to the average number of trials included from each condition (target: $F_{(1,\ 45)} = 0.67$, $p = 0.42$; non-target: $F_{(1,\ 45)} = 1.42$, $p = 0.24$), indicating that any group differences found on ERP measures are not based on differences in signal-to noise ratio between ERPs or total number of correct responses in each group. P3 was examined along the midline electrodes (Cz, Fz, Pz) and measured as the peak amplitude within a range of 250–400 ms after stimulus presentation. Grand-averages were calculated separately for target and non-target trials with respect to frontal-parietal amplitude and latency for each group.

### 2.3. Statistical analysis

Data were further analyzed using SPSS Statistics Version 23 (SPSS Inc., Chicago, Illinois, USA). One-way Analyses of Variance (ANOVA) were used for group comparisons of demographic variables for interval scaled variables and two-sided chi-squared analysis for group comparison for nominal scaled variables. Repeated measures analyses of variance (ANOVA) were used to compare neurophysiological data using Group (term children, preterm children) as the between subject factor and Condition (target, non-target) as well as Site (Cz, Fz, Pz) as within subject factors. Afterwards, separate ANOVAs were conducted for amplitude and latency for each electrode site (Cz, Fz, Pz). Greenhouse-Geisser corrections were used in cases where sphericity was violated. Partial eta-squared values ($\eta_p^2$) served as estimates of effect size of the ANOVAs. Non-paired *t*-tests were used to probe significant effects between groups and paired samples *t*-tests were used to probe significant effects within groups and between conditions. An alpha of 0.05 was defined as the threshold for statistically significant difference.

## 3. Results

### 3.1. Sample characteristics

Participant demographic data are summarized in Table 1. Groups were compared regarding gender, chronological age, and week of gestations, birth weight, lengths of stay in hospital, and neonatal complications such as any respiratory distress and intraventricular hemorrhage. Groups did not differ with respect to gender distribution ($\chi^2 = 1.05$, $p = 0.31$), chronological age ($F_{(1,\ 45)} = 0.093$, $p = 0.762$) or number of intraventricular hemorrhage ($\chi^2 = 2.374$, $p = 0.123$). As expected, groups differed with respect to the weeks of gestation ($F_{(1,\ 45)} = 157.513$, $p = 0.000$, $\eta^2 = 0.78$), the birth weight ($F_{(1,\ 45)} = 91.849$, $p = 0.000$, $\eta^2 = 0.67$) and the lengths of time stayed in hospital ($F_{(1,\ 45)} = 53.667$, $p = 0.000$, $\eta^2 = 0.55$). Additionally, groups differ according to respiratory distress after birth ($\chi^2 = 33.364$, $p = 0.000$).

**Table 1**
Demographic data in term children and preterm children. Only for significant differences the effect sizes are given as the proportion of variance accounted for $\eta_p^2$.

| | Term (*n* = 20) | Preterm (*n* = 27) | $\chi^2/F_{(1,45)}$ | *p*; $\eta_p^2$ |
|---|---|---|---|---|
| Female, *n* (%) | 8 (40) | 7 (26) | 1.05 | 0.59 |
| Age, month, Mean(*SD*) | 69 (5) | 69 (6) | 0.093 | 0.762 |
| GA, weeks, Mean(*SD*) | 39 (1.1.) | 32 (2.5) | 157.513 | 0.000; 0.78 |
| BW, gram, Mean (*SD*) | 3265 (560) | 1652 (578) | 91.849 | 0.000; 0.671 |
| Lengths of stay, days, Mean (*SD*) | 2.7 (1) | 42 (24) | 53.667 | 0.000; 0.54 |
| Medical risks | | | | |
| Any respiratory distress, *n* (%) | 0 (0) | 23 (85) | 33.364 | 0.000 |
| IVH grade I or II, *n* (%) | 0 (0) | 3 (11) | 2.374 | 0.123 |

*Note.* SD = Standard Deviation; GA = Gestational Age; BW = Birth Weight; RDS = Respiratory Distress Syndrome; IVH = IntraVentricular Hemorrhage.

**Table 2**
Average number of trials included in each participant's waveforms.

| | Preterm | Term |
|---|---|---|
| Target | 36.4 (3.3) | 37.4 (4.7) |
| Non-target | 146 (11) | 150 (12) |

*Note.* Statistics shown are mean (standard deviation).

### 3.2. P3 measures

Descriptive statistics of the P3 are shown in Table 3. Table 4 summarizes the results of the 3-way ANOVA for repeated measure with the factor Group (term children, preterm children), Condition (target and non-target) and Site (Cz, Fz, Pz). For P3 latencies, the main effect Condition ($F_{(1, 45)} = 6.06$, $p = 0.018$; $\eta^2 = 0.121$) yielded evidence for significance. No effects for the main effect Group or the Group × Condition interaction reached significance.

**Table 3**
P3 descriptive statistics.

| | Cz | Fz | Pz |
|---|---|---|---|
| *Peak amplitude* | | | |
| Target | | | |
| Preterm children | −5.28 (4.4) | −2.90 (3.1) | 2.43 (5.6) |
| Term children | −5.5 (4.3) | −5.59 (4.7) | 6.4 (6.1) |
| Non-target | | | |
| Preterm children | −3.4 (3.4) | −5.8 (2.7) | 1.29 (4.0) |
| Term children | −5.2 (4.1) | −6.5 (3.4) | 1.8 (4.6) |
| *Latency* | | | |
| Target | | | |
| Preterm children | | | 310 (61) |
| Term children | | | 326 (54) |
| Non-target | | | |
| Preterm children | | | 331 (65) |
| Term children | | | 359 (55) |

*Note.* Statistics shown are mean (standard deviation). Amplitude is in microvolt (μV), latency is in msec.

For the P3 amplitude, results show a significant main effect for Condition ($F_{(1, 45)} = 10.699$, $p = 0.002$; $\eta^2 = 0.196$) and Site ($F_{(1, 45)} = 70.112$, $p = 0.000$; $\eta^2 = 0.614$). Furthermore, significant interactions of Condition × Site ($F_{(1, 45)} = 13.537$, $p = 0.000$; $\eta^2 = 0.235$) and significant interaction of Group × Site ($F_{(1, 45)} = 3.839$, $p = 0.045$; $\eta^2 = 0.08$) were detected. The 3-way interaction Site × Condition × Group was also significant ($F_{(1, 45)} = 3.947$, $p = 0.033$; $\eta^2 = 0.082$). To resolve this three way interaction, separate 2-way analysis for each electrode sites were conducted including the factor Group (term children, preterm children) and the within factors Condition (target and non-target). Table 5 summarizes the results of this repeated measure ANOVAs. For peak amplitude at electrode position Pz, the main effect Condition ($F_{(1, 45)} = 25.98$, $p = 0.000$; $\eta^2 = 0.371$) and the Group × Condition interaction ($F_{(1, 45)} = 4.36$, $p = 0.043$; $\eta^2 = 0.09$) revealed significance. No effects for the main effect Group ($F_{(1, 45)} = 2.58$, $p = 0.116$) were found. To further elucidate the Group × Condition interaction at electrode position Pz, we first used paired samples *t*-tests to examine the differences in P3 peak amplitude among the condition, separately for each group. For term children the Oddball Task evoked higher P3 amplitudes during the target condition ($t_{(19)} = 5.012$, $p = 0.000$; $M = 6.3$, $SD = 6.1$) compared to the non-target condition ($M = 1.8$, $SD = 4.6$). For preterm children no such differences ($t_{(26)} = 1.014$, $p = 0.32$) were found, i.e. P3 peak amplitude did not differ significantly with respect to the factor Condition ($M_{target} = 2.43$, $SD = 5.64$; $M_{non\text{-}target} = 1.29$, $SD = 4.05$). Independent samples *t*-tests were used to examine differences in P3 peak amplitude between the groups and revealed that preterm children had significantly reduced P3 peak amplitude compared to term children at electrode position Pz in the target condition ($t_{(45)} = 2.259$, $p = 0.029$). Attenuation of P3 peak amplitude in preterm children compared to term children is illustrated in the grand averages (Fig. 1) and in the mean data in Table 3. For amplitudes at Fz and

**Table 4**
Repeated measures ANOVAS for ERP measures.

| | Effect | $F_{(1,45)}$ | $p$ | $\eta_p^2$ |
|---|---|---|---|---|
| P3 Amplitude (Condition X Site X Group) | **3-way interaction** | **3.947** | **0.033** | **0.082** |
| | **Condition X Site** | **13.537** | **0.000** | **0.235** |
| | **Group X Site** | **3.839** | **0.045** | **0.080** |
| | Group X Condition | 0.838 | 0.365 | |
| | **Condition** | **10.699** | **0.002** | **0.196** |
| | **Site** | **70.112** | **0.000** | **0.614** |
| | Group | 0.086 | 0.771 | |
| P3 Latency (Condition X Group) | **Condition** | **6.061** | **0.018** | **0.121** |
| | Group | 2.415 | 0.127 | |
| | Group X Condition | 0.351 | 0.556 | |

Bold indicates significant effect at $p < 0.05$.

**Table 5**
Repeated measures ANOVAS for ERP measures separate for each electrode site. Bold indicates significant effect at p < 0.05.

| | Effect | $F_{(1,45)}$ | $p$ | $\eta_p^2$ |
|---|---|---|---|---|
| Cz Amplitude | Condition | 1.926 | 0.162 | |
| | Group | 0.244 | 0.624 | |
| | Group X Condition | 0.248 | 0.621 | |
| Fz Amplitude | Condition | 0.013 | 0.909 | **0.09** |
| | **Group** | **4.667** | **0.036** | |
| | Group X Condition | 1.080 | 0.304 | |
| Pz Amplitude | **Condition** | **25.981** | **0.000** | **0.371** |
| | Group | 2.574 | 0.116 | |
| | Group X Condition | **4.356** | **0.043** | **0.09** |

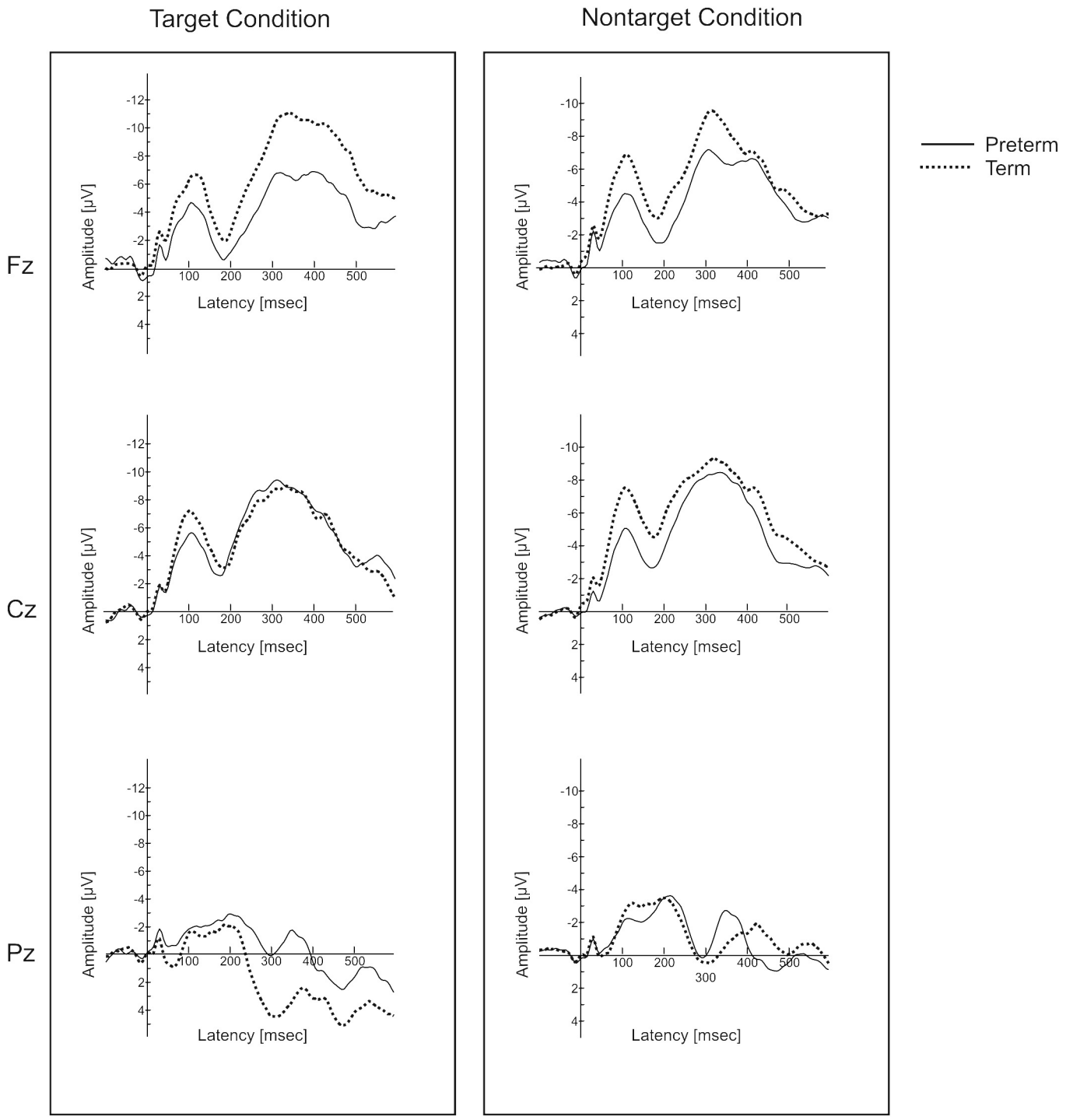


**Fig. 1.** Grand averaged ERP waveforms plotted for preterm children (solid line) and term children (dashed line) in the target condition (left column) and non-target condition (right column). ERPs are shown for electrode positions Fz (top row), Cz (middle row), and Pz (bottom row). Lower P3 amplitude responses were observed in preterm children compared to term children at Pz.

Cz position, no significant main effect for the factor Condition and the interaction Group × Condition were found. At electrode position Fz a significant main effect for the factor Group ($F_{(1,\ 45)}$ = 4.67, $p$ = 0.036; $\eta^2$ = 0.096) was found.

## 4. Discussion

This study investigated attention functioning in preschool aged, preterm children compared to term children by using event related potentials. To minimize confounding risk factors, we included low risk preterm children without any clinically apparent problems, such as gestational age > 27 weeks, IQ (in the normal range), with no emotional deficits, no social problems or no typical ADHD/ADD symptoms, no high risk psychosocial environments, and no neurological disabilities. The only significant medical risk in preterm children was respiratory distress after birth. Preterm children showed no typical symptoms of ADHD. However, EEG data yielded evidence for neurophysiological alterations. No increased P3

amplitude in response to a rare stimulus in an oddball task has been observed in preterm children.

The P3 component is a characteristic brain response upon repeated presentation of a rare stimulus and occurs around 300 milliseconds after stimulus onset. The Oddball paradigm allows to investigate differences in this brain response in more frequent and rare events, even before a conscious classification or recognition of an object has occurred. This is a very useful feature of the way processing incoming information: attending more to unusual, deviant, or rare events and spending less attention resources towards events that are constantly repeated and therefore probably less "relevant". Therefore, in the visual Oddball Task the typical EEG pattern consists of significantly increased P3 amplitudes upon the infrequent, target stimuli compared to the smaller P3 amplitudes for the frequent, non-target stimuli. In this study, only the term children showed the well-known characteristic response and the expected pattern of attention processes as reported earlier (Folstein and Van Petten, 2008; Polich, 2007; Polich and Criado, 2006). In contrast, the P3 component in preterm children did not differ significantly between target and non-target stimuli by showing a flattened P3 amplitude. These findings and the fact that only children without any clinically apparent problems or any typical ADHD/ADD symptoms were included in this study suggest long term subclinical attentional changes in preterm children. We suggest that these changes can be best explained due to a deficit in the subjects' general level of arousal, whereas the interpretation of the P3 as a phenomenon accompanying mental processes has many aspects to consider. Most commonly, P3 amplitude can be interpreted as a measure of neural activity that is proportional to the amount of attentional resources (Polich, 2007; Polich and Criado, 2006; Sutton et al., 1965). It is also related to the subject's level of arousal or physiologic state (Kok, 1990; Polich, 2007; Polich and Kok, 1995). Polich (2007) integrated two famous frameworks by Donchin and Coles (1988) and by Kahneman (1973), concluding that the P3 component in the Oddball Task depends on a subject's overall arousal level. This means that the overall arousal level determines the amount of processing capacity available for attention allocation/processing, which on the other hand is necessary to elicit the P3 in the Oddball Task. This interpretation is in line with earlier findings, which yield evidence that the arousal level affects the availability of attention processes to modulate P3 (Kok, 1990, 2001). Furthermore, in clinical studies the P3 amplitude flattening as found in the present experiment has often been associated with mental disorders and symptoms related to the patients' reduced arousal level such as chronic fatigue, lethargy, lack of motivation, endurance, and energy in schizophrenia (Donkers et al., 2013; Ergen et al., 2008) and major depression (for a recent review see (Bruder et al., 2009)). Additionally, in a study with preterm preschool aged children Gawehn (2009) found a deficit in the general state of alertness, which is comparable to the general state of arousal. At this time, our interpretation question cannot be finally clarified, as well as the influence of confounding factors in the preterm group. Confounding factors such as respiratory distress after birth or the long lasting time in hospital, which in turn cause stress and distress for the new born infants and their parents, might have an effect on the present results. The small sample size did however preclude investigation of the impact of these factors.

Given the precautions and limitations of the current results, we are confident that our study has also important implications. We found alterations on the neurophysiological brain level in an attention driven task, but these alterations were not detectable on a symptom level. This may question the common methods used in clinical praxis to detect attention deficits (FBB-ADHS-V; SDQ). Unfortunately, no estimation of the school performance of the children participating in this study has been made. However, current literature reports that minor dysfunctions become more apparent when children grow older i.e. at school age (for a review see (Aylward, 2005)). Accordingly, difficulties in preterm children become increasingly apparent at higher levels in school, even in children who performed appropriately in the first year at school (Smith and Knight-Jones, 1990). Furthermore, findings from the current literature report that preterm children without severe disabilities or/with normal intellectual potential, have problems in later academic achievement, and show behavioral and learning difficulties and further difficulties in everyday life (Aylward, 2002, 2005; Ornstein et al., 1991; Walther et al., 2000). Attention and attention regulation in particular may be the reason for poorer academic attainment in preterm children and may be one potential mechanism that can explain these findings (Brogan et al., 2014; van de Weijer-Bergsma et al., 2008). Attention problems without hyperactivity or deviant behavior are rarely identified, especially in the preschool period, as they usually pose no problem for the child during preschool activities. This may change during school period when higher demands have to be met. All these findings suggest a finer grained and longer lasting assessment of cognitive functions in preterm children ensuring interventions as early as the problems come to light.

In conclusion, a negative development cascade on learning might be prevented, if the typical attention problems in preterm children would be detected earlier in combination with appropriate support to overcome their attention problems early. Raising parents' and kindergartens' awareness of the expected, typical attention problems in preterm children may enable them to identify children who may benefit from early intervention. Therefore, diagnosis, measures and interventions must be adapted to the special needs of these children. In addition, psychoeducation and advice for parents have to emerge. For that, further research is needed to elucidate the profile of impairment associated with such deficits to improve identification, management, and treatment of what are the typical symptoms of attention problems in preterm children. Likewise, we suggest a follow up study to assess the academic development and to investigate whether the observed deficits are permanent or temporary. Furthermore, future research is needed to investigate the significance of the general arousal level in preterm children as a possible explanation for the observed EEG alterations. Our results support every effort to have a closer look at children premature early in preschool age even though clinically relevant symptoms are absent.

## Conflict of interest

None.

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