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Key words

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Highlights

- In auditory event-related potentials of preschool children, we found a faster decrease in latencies of P1 and N2 around the age of 5 years than previously described.

- At preschool age, children born very preterm had obligatory responses that differed from term-born and late preterm-born children.

- The decrease of N1 amplitude in the very preterm born children might reflect cognition, since similar amplitude findings have been described in term-born children with cognitive deficits.

Abstract

Objective: To assess auditory event-related potentials at preschool age in children born very preterm (VP, 27.4±1.9 gestational weeks, n=70) with a high risk of cognitive dysfunction.

Methods: We used an oddball paradigm consisting of a standard tone randomly replaced by one of three infrequent deviants (differing in frequency, sound direction or duration).

Results: The P1 and N2 latencies were inversely correlated to age (50-63 months) both in VP (r= -0.451, p <0.001, and r=-0.305, p =0.01, respectively) and term born controls (TC; n=15). VP children had smaller P1 than near-term (n=12) or TC (1.70±0.17 µV vs 2.68±0.41 and 2.92±0.43, respectively; p<0.05). Mismatch negativity response did not differ between groups.

Conclusions: Our data suggest a fast maturation of P1 and N2 responses with fast decrease in P1 and N2 latencies around the age of 5 years. Mismatch negativity response does not seem to be a robust measure for defining abnormalities in VP children.

Significance: In ERP studies in preschool children, even small, non-significant group differences in age at recording should be corrected for. Very preterm born children at preschool age have aERP patterns as earlier described in full-term born children with cognitive deficits.

1. Introduction

Children born very preterm, that is before 32 postmenstrual weeks, have a high prevalence of disabilities (Wilson-Costello et al., 2005; Platt et al., 2007). Even preterm children without neuromotor abnormalities have a lower mean IQ, an increased risk of neuropsychological deficits (such as attention, reading, learning, language, and memory disorders), neurosensory and visuospatial deficits, poor executive functions, behavioral problems, and low academic achievement (Mikkola et al., 2005; Aarnoudse-Moens et al., 2009). The anatomical and functional correlates of such impairments in preterm children are incompletely understood, and early diagnostic tools for cognitive dysfunction are still lacking.

Auditory event-related potentials (aERP) are measures of electrical brain activity related to auditory stimuli. They are neurophysiological correlates of cortical sound discrimination and sound processing and may be used to document auditory system developmental plasticity (Kral et al, 2007). At preschool age, at inter-stimulus intervals below 1 second, aERP consists of a P1 peak around 100 ms and a N2 peak around 250 ms (Ceponiene et al., 2002; Mikkola et al., 2007). The fronto-centrally predominant P1 is generated in the secondary auditory cortex (Liegeois-Chauvel et al., 1994). Lower P1 amplitudes have been described in children with cognitive and/or behavioral problems (Kemner et al., 1996, Lovio et al, 2010). N2 at preschool age is assumed to originate bilaterally in the auditory cortex of the superior temporal lobes with frontal predominance in scalp topography (Ceponiene et al., 2002). It has been linked to higher level, discriminative processes and attention orienting (Satterfield et al., 1994; Cunningham et al., 2000). In adults, it is described to be sensitive to task demands and attention (Näätänen and Picton, 1986). However, whether P1 and N2 in children represent similar neurophysiological processes as in adults has not yet been established.

Mismatch Negativity (MMN), a component of the event-related potentials has been used to investigate cortical sound discrimination capabilities across the lifespan (Kujala and Näätänen, 2010). In a stream of similar sounds, a deviating sound will elicit a negative deflection, the MMN response. It is based on the formation of neural memory traces for familiar auditory events and has been associated with pre-attentive cognitive processes in audition. Thus, MMN has been suggested to reflect 'primitive intelligence' in the auditory cortex (Näätanen et al., 2001). The MMN appears in difference curves obtained by subtracting responses to standard from deviant stimuli. In adults, it is typically negative, but may have a positive polarity in infants and children (Morr et al., 2002). Studies in infants suggest that the positive polarity is an immature feature. The neurophysiological correlates of this inverted polarity, however, are unknown (Carral et al., 2005; He et al., 2009).

Normal language development is largely dependent on normal sound and phoneme perception. Thus, studies have used MMN to assess speech sound perception (Lovio et al., 2009; Shafer et al., 2010; Partanen et al., 2011). Deficits in speech sound processing, such as impairment in discrimination of vowels or syllables, and in differentiation of sound frequency or duration, are hallmarks of language impairment, dyslexia, and reading problems (Bishop, 2007; Sharma et al., 2007). Moreover, in infants and children, association has been found between a variety of impairments and pathological aERPs. Abnormal MMN has been recorded in children with risk for dyslexia (Lovio et al., 2010) as well as in reading difficulties and attention deficit disorders (Huttunen-Scott et al., 2008).

The survival of very immature infants is continuously increasing, which might lead to a higher prevalence of neurocognitive abnormalities (Fellman et al., 2009). In these vulnerable infants, aERPs have not been studied. However, in more mature preterm infants, the development of aERPs during the first year differed from healthy term infants (Fellman et al.,

2004). At 5 years of age they had smaller P1 and larger N2 amplitudes (Mikkola et al., 2007). Further, in an MMN study at 2 years of age in preterm born children, phoneme discrimination was not dominated by the native language sounds. This was related to a slower native language acquisition and might be associated with later language development (Jansson-Verkasalo et al., 2010).

The rationale for this study was to investigate the possibility to use aERPs as a tool to define a risk group for neurocognitive abnormalities in children born very preterm. We hypothesized that very preterm infants with a high risk of cognitive dysfunction have changes in aERPs. Therefore, our aim was to investigate the aERPs at pre-school age in children born very preterm and compare these to those of term and late-preterm born children.

2. Methods

2.1. Study Population

Very preterm (VP) born infants in Lund University Hospital were recruited between September 2000 and February 2003 at the Neonatal Intensive Care Unit (NICU) into a prospective cohort study. Inclusion criteria were a gestational age below 32 weeks, dated with prenatal ultrasound at 17-18 gestational weeks (GW), and absence of major congenital malformations. As this NICU is a tertiary referral center providing regionalized care for extremely preterm infants, the major part of infants was born before 28 GW (N=55). A total of 87 infants were enrolled in the VP group.

Two control groups were included. A preterm control (PC) group (N=24) born at 32 to 35 GW with no major morbidity was recruited in the NICU and a healthy full-term control group (TC; N=24) born ≥37 GW at the maternity ward of the hospital.

All children underwent the national hearing screening at 4 years of age. The age at aERP examination was calculated from the time point corresponding to term age (40 GW). Parental informed written consent was obtained both at recruitment and before the aERP recording at 4-5.5 years of age. The Regional Ethics Review Board, Lund, Sweden approved the study protocol prior to the start of the study.

2.2. EEG recording and stimuli

Auditory stimuli were delivered binaurally through headsets at 60 dB Sound Pressure Level to the children while they watched a silenced movie in a sound-attenuated room. Ag/Ag–Cl electrodes were attached at electrode sites F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T3, and T4 according to the International 10–20 System. In addition, four electro-oculogram electrodes were used. EEG was referenced to the average of mastoid electrodes. An EEG (bandpass 0.1–70 Hz, sampling rate 500 Hz) was recorded using the NeuroScan 4.3 system (Compumedics; www.neuroscan.com).

The sound stimuli were presented as an oddball paradigm consisting of a standard tone (probability of 0.70), randomly replaced by one of three infrequent deviant tones (probability of 0.10 for each). Stimulus onset asynchrony was 533 ms. The standard tone was a sinusoidal 1000 Hz tone with a duration of 100 ms, including 10 ms onset and offset time. The

frequency deviant differed from the standard by a 10% higher pitch (1100 Hz; probability 0.10). An apparent direction deviant differed in perceived sound source location, achieved by a sound onset difference between the left and the right side of 750 µs, starting on the left or the right side (probability 0.05 each). The third deviant differed concerning the duration lasting only 50 ms and an onset and offset time of 5 ms. Otherwise, all deviants were identical to the standard tone.

Stimuli were presented in three blocks of 610 sounds, each block containing all deviant types. All blocks were introduced by a series of at least 10 standard tones. Each deviant was followed by at least one standard tone. Thus, during the whole recording, the standard tone was presented 1290 times, while each deviant type was presented 180 times. The duration of the experiment was about 15 min.

2.3. ERP averaging and analysis

Offline data analysis was performed using a NeuroScan 4.5 system (Compumedics; www.neuroscan.com). The continuous EEG was filtered offline (bandpass 0.5-30 Hz, 24 dB attenuation). After visual rejection of major artefacts, the data were divided into epochs from 100 ms pre-stimulus onset to 550 ms post-stimulus onset. The EEG was baseline corrected to the prestimulus interval. All epochs with amplitudes exceeding ±100 µV were rejected, as well as the first 3 epochs of every block and all epochs following a deviant stimulus epoch. The epochs for the standard stimulus and those for the three deviant stimuli were averaged separately. A minimum of 50 epochs for a given stimulus type was required in each subject to be included in further data analysis of this stimulus. The time from stimulus onset to 550 ms

post-stimulus onset was divided into 50 ms-periods, and the mean amplitude for each period was calculated.

The aERP curves for standard and deviant stimuli in all subjects within each of the three study groups were averaged into grand average mean aERP curves. An averaged curve from 6 electrodes (F3, Fz, F4, C3, Cz, C4) was used to define the individual latencies of the main positive (P1) and negative (N2) peaks for each participant. The P1 peak latency was defined as the time point for the maximum of the most positive peak in the interval 130 ms±50 ms, and the N2 peak as the time point for the most negative peak in the interval 250 ms±80 ms on this averaged curve. Mean amplitudes for the P1 and N2 peaks were calculated in the time window latency±30 ms using the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 electrodes.

Difference waveforms were obtained by subtracting the standard response from response to the deviant stimulus, individually for each participant, using the averaged curves from the 6 frontal and central electrodes as described above. From these difference waveforms, mean amplitudes were calculated for each 50 ms time window after stimulus onset for each participant.

The mismatch response (MMR) was measured in the difference curves for each child in the time window 150-350 ms after change onset (150-350 ms after stimulus onset for changes in perceived sound source location and frequency, 200-400 ms after stimulus onset for changes in duration). As MMR we defined the peak, positive or negative, with the largest mean amplitude for the interval of maximum peak ±30 ms, using the averaged curves from the 6 frontal and central electrodes. However, in order to exclude possible P3a-like responses from

being identified as MMR in the analysis (a late positive peak after MMR related to attentive functions), when a negative response preceded a positive in this time window, the negative response (MMN) was considered as MMR, and the following positive response was considered to be "Later positivity". From several positive peaks in this time window, we always defined the first positive peak as the MMR.

All latencies were defined as the time point for the maximum amplitude, and amplitudes as the mean amplitude for the time window defined by peak latency ±30 ms.

2.4. Statistics

Statistical analyses were performed with PASW Statistics 18 for Windows software. We used t-test for group comparison of clinical data. The effect of age at examination on amplitudes and latencies was assessed using the non-parametric Spearman correlation. Group differences in electrode effects and differences in scalp topography between MMN and positive MMR were analyzed with ANOVA for multiple measurements (group and electrode x group for group differences, MMN/positive MMR and electrode x MMN/positive MMR for differences in scalp topography between responses; Greenhouse-Geisser correction where the assumption of sphericity was violated). Univariate ANCOVA with correction for age at examination was used for group comparisons of time windows, peak latencies and amplitudes, using mean amplitudes for the in total 9 frontal, central and parietal electrodes. A p-value of < 0.05 was considered significant.

3. Results

3.1. Subjects

Of the 87 VP newborn infants recruited, three died during the neonatal period, one could not be contacted, and one had moved abroad. For ten children, the parents declined to participate in this study at pre-school age. Two children did not cooperate sufficiently for accurate recordings. Thus, 70 VP children born at 23.9 to 31.7 GW had a complete aERP recording (Table 1). Neonatal characteristics of them are shown in Supplementary Table S1. None of the children had pathological hearing test in child health center or used a hearing aid.

The parents of twelve PC children and nine TC children declined to participate in the study. Thus, complete aERP recordings were achieved in 12 PC children and in 15 TC children. At the time of the recording, the VP children were older than the control groups ($p<0.01$ for both groups), and the PC children were older than TC (Table 1). However, after correction for gestational age, the VP and PC groups were examined at similar ages, but their mean ages remained higher than that of TC ($p<0.05$). Therefore, all results have been corrected for age at examination.

3.2. Obligatory aERP responses

Mean amplitudes: The VP group had lower mean amplitudes to standard stimuli than both control groups in each 50 ms interval at 100-200 ms, and lower mean amplitude than the TC group at 200-250 ms (Table 2). No significant differences between the control groups were

observed. The time intervals for each electrode with different amplitudes in VP compared to control groups are shown in Supplementary Fig. S1.

P1 and N2: The main obligatory responses for the standards were the P1 and N2 responses (Fig. 1). The P1 amplitude was significantly lower in the VP group than in both control groups (Table 3). The P1 latency in the PC group was significantly longer than in both the VP and the TC groups.

Age effects on obligatory responses: Age at examination was negatively correlated to P1 and N2 latencies (r= -0.490; p <0.001 and r= -0.426; p <0.001, respectively; Fig.2), but not to the amplitudes of P1 (r=0.019; p =0.854) or N2 (r=0.141; p=0.167).

Significant correlations between age and P1 latency were present both in the VP (r= -0.451, p <0.001) and TC groups (r= -0.566, p =0.028), as also for N2 latency (r=-0.305, p =0.01 and r=-0.674, p =0.006, respectively) but not in the PC group.

Scalp distribution: We found a highly significant electrode effect, the frontal and central electrodes having higher amplitudes for P1 and N2 than the parietal electrodes in all groups (p<0.001 for all comparisons). For N2, the responses were highest centrally in all groups, as compared to left or right (p<0.001 for all comparisons).

3.3. Mismatch responses

The difference curves obtained by subtracting standard responses from each deviant response are presented by group in Fig. 3. For the duration deviant, in the typical MMN time window of 250-300 ms, the PC group response was more positive than in the VP (p=0.041) and TC (p=0.002) groups (Fig. 3).

The proportions of children presenting a MMR for all three deviants did not differ between the groups. Also, equal proportions of children showed an additional positive response after the MMR in the time window 200-350 ms after stimulus difference onset for all deviants (Table 4). No statistically significant differences in latency or amplitude of the MMR or of the following positive response between the study groups were found.

Both MMN and positive MMR were most prominent in the midline. For the frequency and duration deviants, there was no difference in anterio-posterior scalp topography, both responses being biggest fronto-centrally. For the direction deviant, the MMN amplitude was highest fronto-centrally while the positive MMR amplitude was highest centrally, but this topographical difference was not significant. No group differences were found in scalp distributions, neither for the MMN nor the positive MMR. Even combining positive and negative MMR, no different response patterns in scalp topography were found between the groups.

4. Discussion

Our main finding was that children born very preterm had at 4-5 years of age smaller P1 responses than children at the same age, born at term or late-preterm. This result is also

reflected in lower aERP amplitudes in the 100-200 ms time window.

A low peak amplitude may be caused by overlapping of successive peaks. An earlier start of the N2 component, overlapping P1, would cause a smaller P1 peak. On the other hand, an earlier start of the P1 peak would decrease a possible overlap with a starting N2 peak. On the grand average ERP curves, the N2 component in the VP group was not broader than in the two other groups. We did not find any significant group differences between very preterm and term children in P1 and N2 latency, and no significant correlations between the P1 amplitude and P1 and N2 latencies, respectively. Although we cannot rule out a latency effect of N2 on the P1 amplitude, we consider that the group differences in the P1 amplitude in our study are not explained by such a latency effect alone. Further, we have no reason to believe that our very preterm infants had a higher hearing threshold than control children explaining the lower P1 amplitude. Thus, we interpret the finding as an effect of decreased electrical generator activity. Some possible explanations are impairment in basic auditory encoding and local or general brain atrophy. Intracranial recordings suggest that the neural generators of the P1 originate from the secondary auditory cortex (Liegeois-Chauvel et al., 1994). Several magnetic resonance imaging studies on preterm born infants have shown decreased total brain volumes and decreased grey matter volumes, both at term and during childhood (Inder et al., 2005; Thompson et al., 2007). Regional vulnerabilities in temporal cortical areas in infants born prematurely leading to lower local cortical volumes, and correlation of these brain volumes with neurodevelopmental and cognitive outcome have been demonstrated both near term and at 8 years of age (Peterson et al., 2000; Peterson et al., 2003). No studies have shown a relation between aERPs and tissue abnormalities in preterm born, but several studies have shown an association between low P1 amplitudes and cognitive dysfunction.

Decreased P1 amplitudes have been shown in term-born children with ADHD (Kemner et al., 1996), autism spectrum disorders (Jansson-Verkasalo et al., 2003), and risk for dyslexia (Lovio et al., 2010). All of these disorders have an increased incidence in very preterm born children (Aarnoudse-Moens et al., 2009; Delobel-Ayoub et al., 2009; Guinchat et al., 2012). In an earlier, smaller follow-up study of low birth weight infants, we found a significant correlation between low P1 peak amplitudes and low performance in mainly verbal subtests of neurocognitive tests (Mikkola et al., 2007). Likewise, preterm children with ADHD had smaller visual P1 amplitudes than those without ADHD (Potgieter et al., 2003). The decreased P1 in our study may represent a general impairment in auditory encoding associated with an increased risk of cognitive dysfunction.

The degree of immaturity, that is gestational age, was not associated with amplitude or latency of P1 and N2. The longer P1 latencies in late-preterm children compared to the other groups may be related to a beta-error in the small sample size. However, as P1 latencies decreased fast with age in the preschool range, longer P1 latencies in the late preterm group may be a sign of delayed maturation of precortical or cortical sound transmission or cortical sound processing (Ceponiene et al., 2002; Eggermont and Ponton, 2003).

A second important finding was a significant correlation between age at examination and latencies of the obligatory P1 and N2 responses in very preterm and term-born children. This correlation was highly significant in the VP group and reached significance even in the relatively small TC group. However, there were only twelve PC children and they were of similar examination ages, which might explain why such an association was not found in this group.

Our results suggest that maturation of some middle-latency ERP components such as P1 and N2 at preschool age may not be as gradual as described earlier (Ponton et al., 2000; Wunderlich and Cone-Wesson, 2006). The present study points towards a phase of faster latency decrease in P1 and N2 around the age of 5 years. Such a fast maturation phase may have remained undetected as previous studies on P1 and N2 maturation in childhood have included only a few children of each age, and many studies had a larger age variation than ours (Wunderlich and Cone-Wesson, 2006). We studied the so far largest cohort of preschool children, which made it possible to assess the age effect in much greater detail than in previous studies. The latency decrease in pre-school children seems to be faster, 3 ms per month (P1 2.6 ± 1.1 ms; N2 3.4 ± 1.6 ms), than the 4-5 ms per year previously described (Wunderlich and Cone-Wesson, 2006). Although latency decrease seems to slow down with increasing age, we found even a faster decrease around 5 years of age than the latency decrease of P1 (2 ms per month) between 3 and 36 months of age in a recently published paper (Shafer et al., 2011).

However, because of limitations due to the cross-sectional design of this study, our results have to be confirmed in a longitudinal study with short inter-recording intervals on a sufficient number of preschool children. If our results prove to be true, the age effect needs to be considered when performing aERP studies at preschool age, implying that even small age differences at examination should be corrected for.

We did not find any significant differences in MMR between the study groups. Several previous studies have shown differences in MMR in preterm children as compared to term-born children (Fellman et al., 2004; Jansson-Verkasalo et al., 2004; Mikkola et al., 2007), whereas such were not noted in others (Lindgren et al., 2000; Gomot et al., 2007). Stimulus paradigms in these studies varied greatly, which may explain the differences. Definition of

MMN on difference waves in the individual child may be difficult, especially as younger children may have a positive MMR. Thus, a positive MMR seems to be a more immature response to a deviant than MMN and is more likely to be elicited with smaller deviants (Lee et al., 2012; Shafer et al., 2011). An equal distribution of children with positive and negative MMR in the study groups suggests that maturation of sound change detection for the deviants used in the current study was similar in the very preterm and control groups. A greater distractibility of preterm-born children, directing attention from a silent movie to the stimuli, might enhance MMN and thus mask a maturational deficit (Ahmmed et al., 2008; Shafer et al., 2011). However, it is not probable that such redirection of attention would have been sufficiently extensive and prolonged in our study to correct for maturational group differences. There are also differences in the ways of determining the presence of an MMN response in the different studies. Also, the effects may be varying due to the types of cognitive or behavioral difficulties that the child is encountering. For example, enhanced MMN to certain types of sound have been reported in children with autism and adults with Asperger's syndrome (Lepistö et al., 2005; Lepistö et al., 2007), whereas other studies show smaller MMN responses in, for example, children with dyslexia or risk of dyslexia (Lovio et al., 2010; Schulte-Körne and Bruder, 2010).

The strength of this study is a large, well-defined cohort of very immature newborn infants (half of them born before 28 GW) prospectively followed until preschool age. Only 12 percent of the families did not consent to the study. The experimental procedure is demanding for children at this age and thus completed assessments are usually not achieved in all subjects. We succeeded to obtain sufficient recordings in almost all (97%) children.

A weakness was the drop-off rate from recruitment at term to the aERP assessment years later in late-term and term-born children. As prenatal and perinatal complications as well as

sensory and neurological problems were exclusion criteria, we consider that the control children are representative of healthy late-preterm and term-born children. Anyhow, the size of the control groups corresponded to the number of subjects in most ERP studies - about 10-20 individuals (Wunderlich and Cone-Wesson, 2006; Bishop, 2007). As our focus was on the children born very preterm, and to assure a high reliability of our results, we prioritized a very high number of children in this group (70 children). For practical reasons, identical ages at examination (corrected for prematurity) could not be accomplished. The age difference between the groups, 4 months, should according to previous studies not influence the results (Wunderlich and Cone-Wesson, 2006). However, this small age difference turned out to have an important impact on group differences in latencies.

In conclusion, children born very preterm studied at pre-school age show changes in obligatory aERP responses that are comparable to changes reported in other studies in term-born children with cognitive deficits (Kemner et al., 1996; Jansson-Verkasalo et al., 2003; Lovio et al., 2010). The correlation between these aERP changes and neurodevelopmental outcome or specific deficits should be further investigated. As the MMR in preschool children can be either negative or positive or in some cases even both, this response does not seem to be a robust measure for defining a risk group for neurocognitive aberrations in very preterm born children of this age.

Latency decrease of P1 and N2 around the age of 5 years may be faster than earlier described. If our results are confirmed in future longitudinal investigations with sufficient recording frequency and sample size, the age effect of even a few months difference on obligatory responses must be taken into account when performing aERP studies on preschool children.

Acknowledgements

References

Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 2009;124:717-728.

Ahmmed AU, Clarke EM, Adams C. Mismatch Negativity and frequency representational width in children with specific language impairment. Dev Med Child Neurol 2008;50:938-944.

Bishop DV. Using mismatch negativity to study central auditory processing in developmental language and literacy impairments: where are we, and where should we be going? Psychol Bull 2007;133:651-672.

Carral V, Huotilainen M, Ruusuvirta T, Fellman V, Näätänen R,Escera C. A kind of auditory 'primitive intelligence' already present at birth. Eur J Neurosci 2005;21:3201-3204.

Ceponiene R, Rinne T,Näätänen R. Maturation of cortical sound processing as indexed by event-related potentials. Clin Neurophysiol 2002;113:870-882.

Cunningham J, Nicol T, Zecker S, Kraus N. Speech-evoked neurophysiologic responses in children with learning problems: development and behavioural correlates of perception. Ear Hear 2000;21:554-68.

Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M, et al. Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study. Pediatrics 2009;123:1485-1492.

Eggermont JJ, Ponton CW. Auditory-evoked potential studies of cortical maturation in normal hearing and implanted children: correlations with changes in structure and speech perception. Acta Otolaryngol 2003;123:249-252.

Fellman V, Kushnerenko E, Mikkola K, Ceponiene R, Leipälä J, Näätänen R. Atypical auditory event-related potentials in preterm infants during the first year of life: a possible sign of cognitive dysfunction? Pediatr Res 2004;56:291-297.

Fellman V, Hellström-Westas L, Norman M, Westgren M, Källén K, Lagercrantz H, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009;301:2225-2233.

Gomot M, Bruneau N, Laurent JP, Barthélémy C, Saliba E. Left temporal impairment of auditory information processing in prematurely born 9-year-old children: an electrophysiological study. Int J Psychophysiol 2007;64:123-129.

Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstet Gynecol Scand 2012;91:287-300.

He C, Hotson L, Trainor LJ. Development of infant mismatch responses to auditory pattern changes between 2 and 4 months old. Eur J Neurosci 2009;29:861-867.

Huttunen-Scott T, Kaartinen J, Tolvanen A, Lyytinen H. Mismatch negativity (MMN) elicited by duration deviations in children with reading disorder, attention deficit or both. Int J Psychophysiol 2008;69:69-77.

Inder TE, Warfield SK, Wang H, Hüppi PS,Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005;115:286-294.

Jansson-Verkasalo E, Ceponiene R, Kielinen M, Suominen K, Jäntti V, Linna SL, et al. Deficient auditory processing in children with Asperger Syndrome, as indexed by event-related potentials. Neurosci Lett 2003;338:197-200.

Jansson-Verkasalo E, Ruusuvirta T, Huotilainen M, Alku P, Kushnerenko E, Suominen K, et al. Atypical perceptual narrowing in prematurely born infants is associated with compromised language acquisition at 2 years of age. BMC Neurosci 2010;11:88.

Kemner C, Verbaten MN, Koelega HS, Buitelaar JK, van der Gaag RJ, Camfferman G, et al. Event-related brain potentials in children with attention-deficit and hyperactivity disorder: effects of stimulus deviancy and task relevance in the visual and auditory modality. Biol Psychiatry 1996;40:522-534.

Kral A, Eggermont JJ. What's to lose and what's to learn: development under auditory deprivation, cochlear implants and limits of cortical plasticity. Brain Res Rev 2007;56:259-269.

Kujala T, Näätänen R. The adaptive brain: a neurophysiological perspective. Prog Neurobiol 2010;91:55-67.

Lee CY, Yen HL, Yeh PW, Lin WH, Cheng YY, Tzeng YL, et al. Mismatch responses to lexical tone, initial consonant, and vowel in Mandarin-speaking preschoolers. Neuropsychologia 2012;50:3228-3239.

Lepistö T, Kujala T, Vanhala R, Alku P, Huotilainen M, Näätänen R. The discrimination of and orienting to speech and non-speech sounds in children with autism. Brain Res 2005;1066:147-157.

Lepistö T, Nieminen-von Wendt T, von Wendt L, Näätänen R, Kujala T. Auditory cortical change detection in adults with Asperger syndrome. Neurosci Lett 2007;414:136-140.

Liegeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P. Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. Electroencephalogr Clin Neurophysiol 1994;92:204–214.

Lindgren M, Stjernqvist K, Ors M, Rosén I. Event-related potential findings in healthy extremely pre-term (< week 29) children at age 10. Child Neuropsychol 2000;6:77-86.

Lovio R, Pakarinen S, Huotilainen M, Alku P, Silvennoinen S, Näätänen R, et al. Auditory discrimination profiles of speech sound changes in 6-year-old children as determined with the multi-feature MMN paradigm. Clin Neurophysiol 2009;120:916-921.

Lovio R, Näätänen R, Kujala T. Abnormal pattern of cortical speech feature discrimination in 6-year-old children at risk for dyslexia. Brain Res 2010;1335:53-62.

Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. Pediatrics 2005;116:1391-1400.

Mikkola K, Kushnerenko E, Partanen E, Serenius-Sirve S, Leipälä J, Huotilainen M, et al. Auditory event-related potentials and cognitive function of preterm children at five years of age. Clin Neurophysiol 2007;118:1494-1502.

Morr ML, Shafer VL, Kreuzer JA, Kurtzberg D. Maturation of mismatch negativity in typically developing infants and preschool children. Ear Hear 2002;23:118-136.

Näätanen R, Tervaniemi M, Sussman E, Paavilainen P, Winkler I. "Primitive intelligence" in the auditory cortex. Trends Neurosci 2001;24:283-288.

Partanen E, Vainio M, Kujala T, Huotilainen M. Linguistic multifeature MMN paradigm for extensive recording of auditory discrimination profiles. Psychophysiology 2011;48:1372-1380.

Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA 2000;284:1939-1947.

Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 2003;111:939-948.

Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. Lancet 2007;369:43-50.

Ponton CW, Eggermont JJ, Kwong B, Don M. Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. Clin Neurophysiol 2000;111:220-236.

Potgieter S, Vervisch J, Lagae L. Event related potentials during attention tasks in VLBW children with and without attention deficit disorder. Clin Neurophysiol 2003;114:1841-1849.

Satterfield JH, Schell AM, Nicholas T. Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys. Psychophysiology 1994;31:1-10.

Schulte-Körne G, Bruder J. Clinical neurophysiology of visual and auditory processing in dyslexia: a review. Clin Neurophysiol 2010;121:1794-1809.

Shafer VL, Yu YH, Datta H. Maturation of speech discrimination in 4- to 7-yr-old children as indexed by event-related potential mismatch responses. Ear Hear 2010;31:735-745.

Shafer VL, Yu YH, Datta H. The development of English vowel perception in monolingual and bilingual infants: Neurophysiological correlates. J Phonet 2011;39:527-45.

Sharma M, Purdy SC, Newall P, Wheldall K, Beaman R. Refractory effects on auditory-evoked responses in children with reading disorders. Neuroreport 2007;18:133-136.

Thompson DK, Warfield SK, Carlin JB, Pavlovic M, Wang HX, Bear M, et al. Perinatal risk factors altering regional brain structure in the preterm infant. Brain 2007;130:667-677.

Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115:997-1003.

Wunderlich JL, Cone-Wesson BK. Maturation of CAEP in infants and children: a review. Hear Res 2006;212:212-223.

Legends

Fig. 1. The grand average aERP response curve to standard stimulus in the very preterm (VP), preterm control (PC), and term control (TC) groups in the epoch from 100 ms pre-stimulus onset (-100) to 550 ms post-stimulus onset. On these aERP curves, two prominent peaks were identified: the first positive peak (P1) at 130 ms and the following negative peak (N2) at 250 ms from stimulus onset. P1 has a lower amplitude in the VP group than in the control groups ($p<0.05$). The waveforms are derived from the Fz electrode.

Fig. 2. Correlations between age at examination (corrected for gestational age) and P1 (r= -0.490; $p <0.001$) and N2 latencies (r= -0.426; $p <0.001$) in all groups combined. The individual values are marked as black dots (very preterm, VP), black circles (preterm control, PC), and grey dots (term control, TC). The correlation lines with 95% confidence interval are calculated for the whole study population of 97 children and show a latency decrease by 2.6±1.1 ms per month for P1 and 3.4±1.6 ms per month for N2.

Fig. 3. Difference curves obtained with the three deviants in the very preterm (VP), preterm control (PC), and term control (TC) groups in the time epoch from 100 ms before to 550 ms after stimulus onset. Waveforms are derived from the Fz electrode. The time window for the mismatch response (150-300 ms after change onset) is marked in grey for each deviant. PSSL = Perceived sound source location (direction deviant). No significant group differences were found.

The positivity dominating in the marked time window on the duration deviant difference wave is formed by a big and consistent positivity following the mismatch response in this time window in the vast majority of children (listed as "Later positivity" in Table 4).

aERPs for the standard stimuli
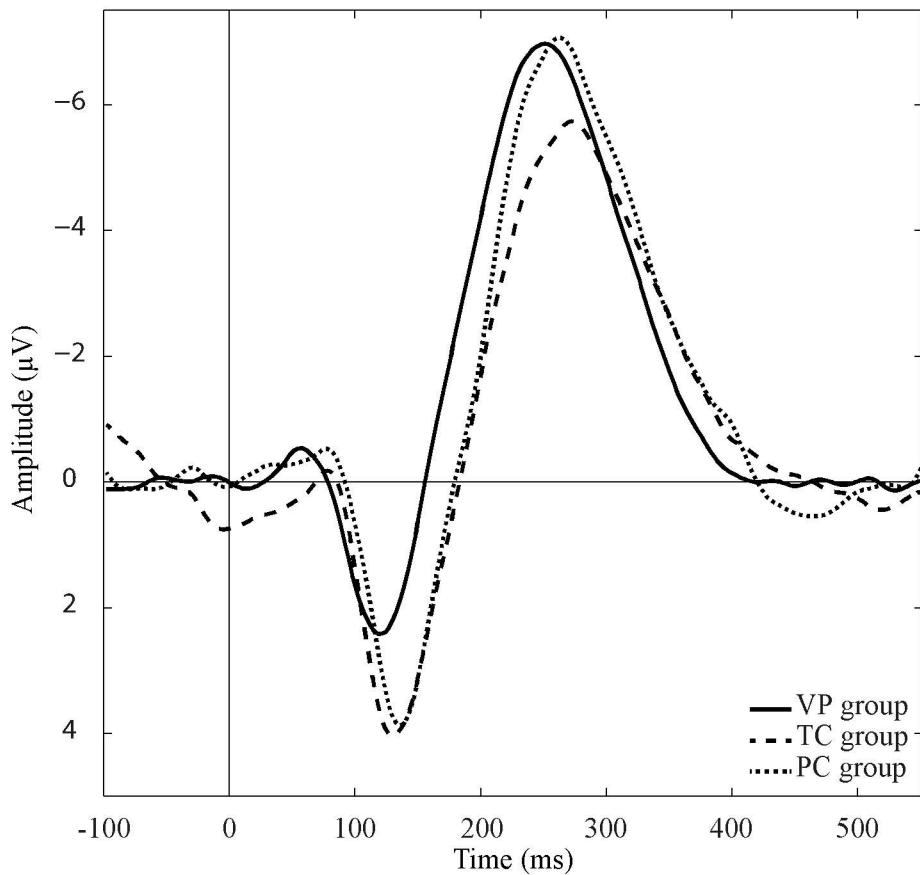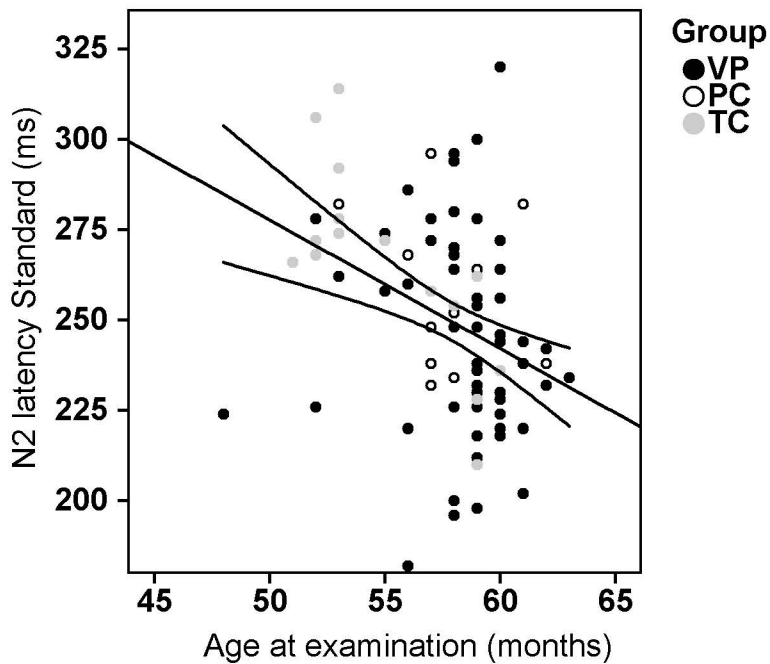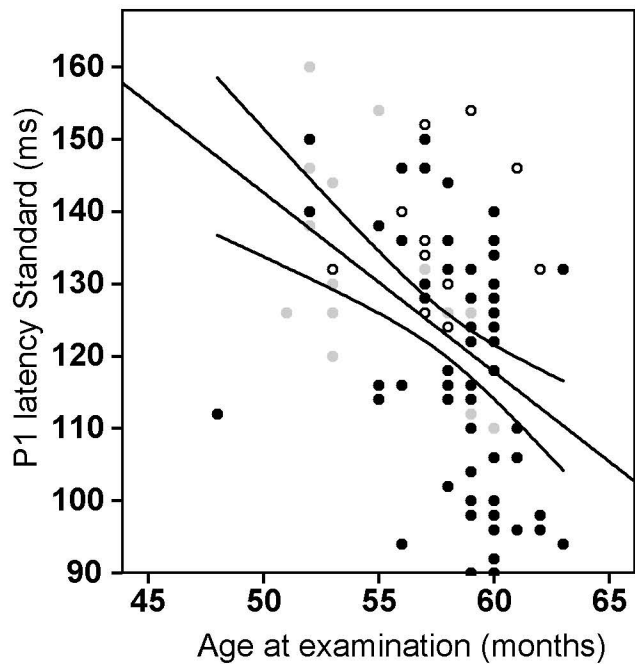
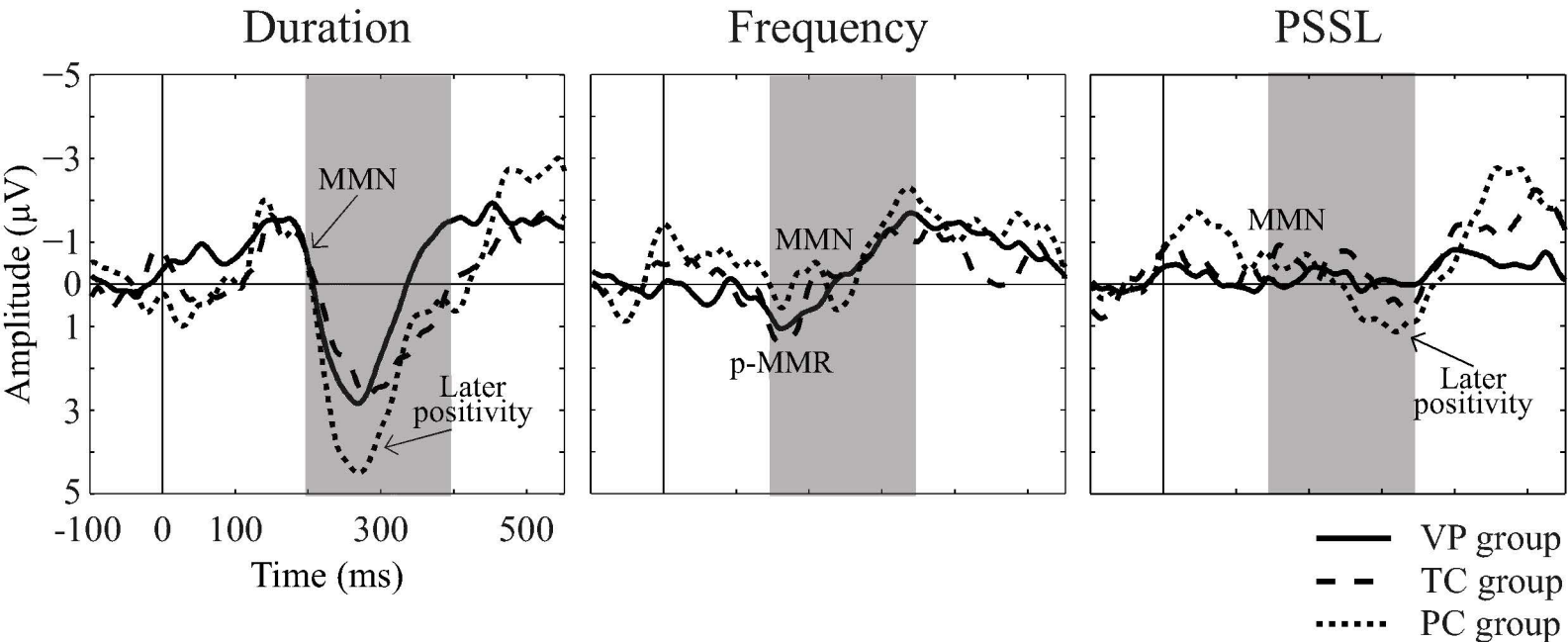Difference waveforms for the deviant stimuli

Table 1. Characteristics of the study groups. Values expressed as mean±SD or as numbers

(%), *p <0.01 **p ≤0.001 (vs. the very preterm group)

		Very preterm (VP, N=70)	**Preterm controls** (PC, N=12)	**Term controls** (TC, N=15)
Gestational age (weeks)		27.4±1.9	33.8±1.0	40.0±1.3
Birth weight (g)		996±288	2217±500	3725±393
Weight at term (g)		2995±518	3149±343	3725±393
At examination				
weight (kg)		18.5±3.1	18.8±2.8	19.3±3.3
head circumference (cm)		50.6±1.9	51.4±1.6	51.6±1.6
age (mths)		61.4±2.4	**59.3±2.2***	**55.1±3.2****
age corrected for prematurity (mths)		58.6±2.5	57.7±2.3 (NS)	**55.1±3.2****
Included into analysis of	Standard	70	12	15
	Frequency deviant	67	12	15
	Direction deviant	68	12	15
	Duration deviant	69	12	15

Table 2. Mean amplitudes (µV) of 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) to standard stimuli in successive 50 ms-intervals, after correction for age at examination. Values are mean±SEM. Significances: [1]VP vs PC $p=0.033$ and vs TC $p=0.013$, [2]VP vs PC $p=0.003$ and vs TC $p=0.009$, [3]VP vs TC $p=0.019$

Time window (ms)	Very Preterm (VP, N=70)	Preterm control (PC, N=12)	Term control (TC, N=15)
0 – 50	-0.08±0.09	-0.09±0.20	0.31±0.20
50-100	0.212±0.12	0.11±0.27	0.71±0.27
100-150	**1.51±0.20** [1]	**2.57±0.47**	**2.85±0.46**
150-200	**-1.57±0.26** [2]	**0.53±0.62**	**0.32±0.61**
200-250	**-4.89±0.25** [3]	-4.00±0.59	**-3.22±0.58**
250-300	-5.03±0.25	-5.33±0.60	-3.98±0.58
300-350	-2.60±0.21	-3.21±0.50	-2.30±0.49
350-400	-0.49±0.15	-1.15±0.35	-0.58±0.34
400-450	0.14±0.10	0.08±0.24	-0.04±0.24
450-500	0.11±0.08	0.20±0.19	-0.08±0.19
500-550	0.08±0.10	-0.07±0.25	0.15±0.24

Table 3. The P1 and N2 responses for the standard stimulus, after correction for age at examination. Values in mean±SEM, significances: [1]VP vs PC *p=0.001*, [2]VP vs PC *p=0.031* and VP vs TC *p=0.012*

|	Very Preterm (VP, N=70)	Preterm Control (PC, N=12)	Term controls (TC, N=15)
P1 latency, ms	**119.1±1.7** [1]	135.2±4.2	124.8±4.1
P1 amplitude, µV	**1.70±0.17** [2]	2.68±0.41	2.92±0.43
N2 latency, ms	245.0±3.2	256.3±7.7	257.4±7.5
N2 amplitude, µV	-5.60±0.26	-5.58±0.63	4.53±0.61

Table 4. Number (%) of children showing a mismatch response (MMR), either with main deflection peak negative (MMN) or positive (P-MMN) in the time window 150-350 ms after stimulus difference onset, and an additional positive response following the MMN response in this time window (here called Later positivity). There were no significant differences in the proportion of children showing MMN, positive MMR, or the later positivity between the groups for any of the deviants.

		Very Preterm (VP, N=70)	Preterm control (PC, N=12)	Term controls (TC, N=15)
Frequency deviant	MMR	69 (99)	12 (100)	15 (100)
	MMN	45 (65)	9 (75)	11 (73)
	Positive MMR	24 (34)	3 (25)	4 (27)
	Later positivity	32 (46)	6 (50)	8 (53)
Direction deviant	MMR	70 (100)	11 (92)	15 (100)
	MMN	48 (69)	5 (42)	9 (60)
	Positive MMR	22 (31)	6 (50)	6 (40)
	Later positivity	45 (64)	9 (75)	10 (67)
Duration deviant	MMR	57 (81)	10 (83)	12 (80)
	MMN	49 (70)	9 (75)	11 (73)
	Positive MMR	8 (11)	1 (8)	1 (7)
	Later positivity	68 (97)	12 (100)	14 (93)

Fig. S1 a-b Significance plots showing the intervals for each electrode where the very preterm group had significantly lower (orange) or higher (green) amplitude in response to the standard stimulus than the preterm or term control group, respectively. At all frontal, central and parietal electrodes, at 150-200 ms after stimulus onset, the very preterm group showed significantly lower amplitudes than the two control groups.

a. Very preterm group versus preterm control group

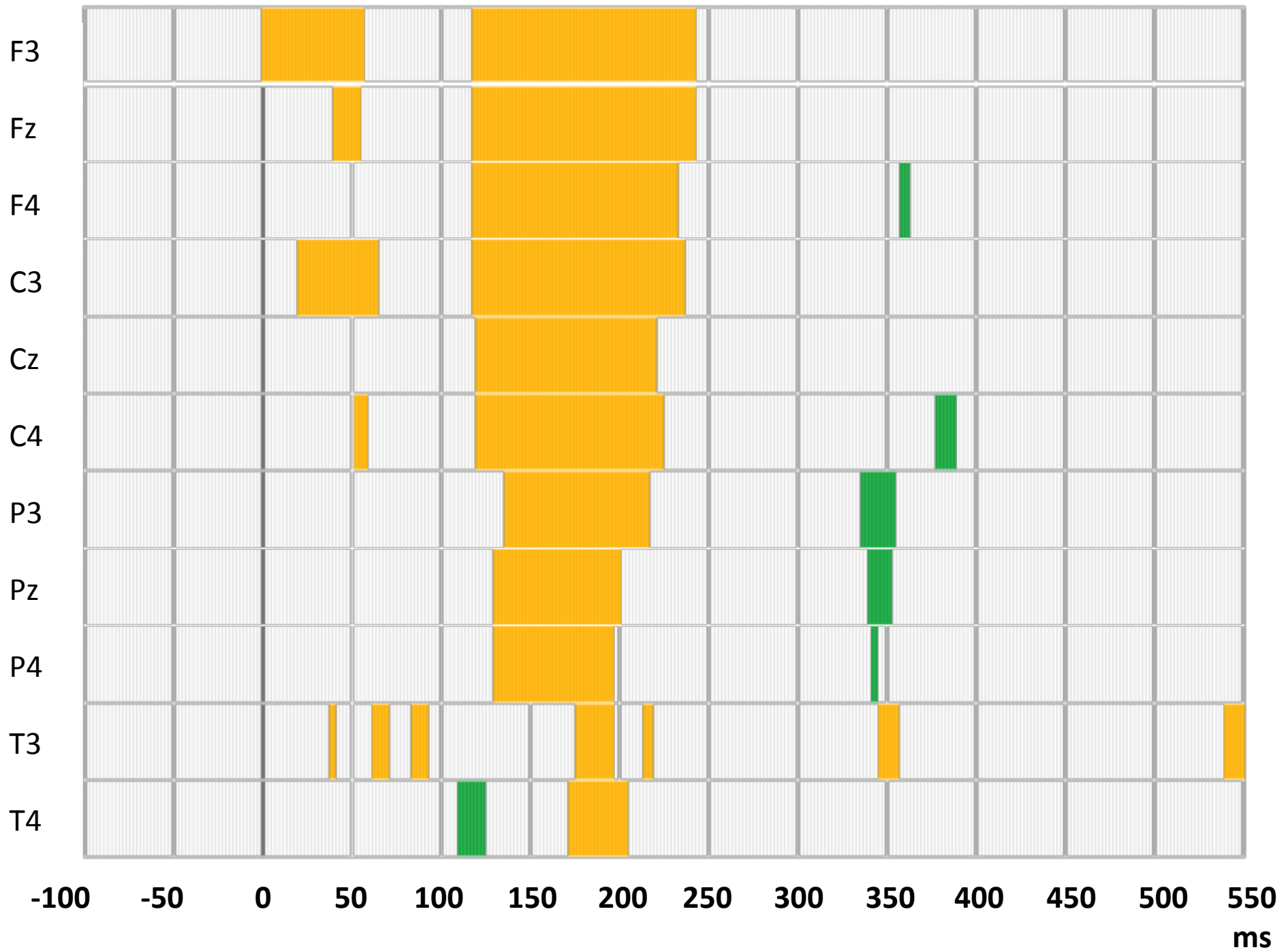b. Very preterm group versus term control group
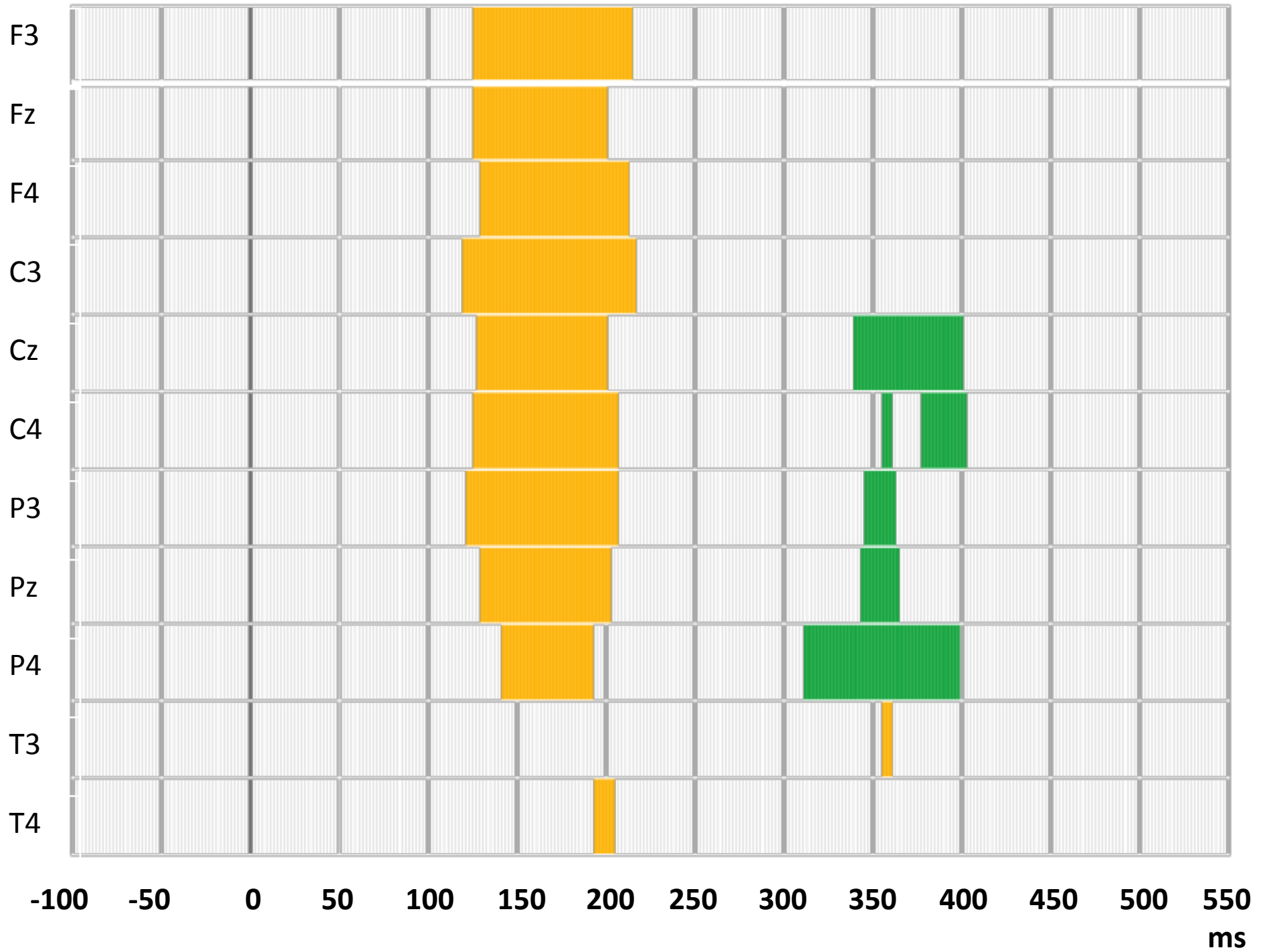
Table S1. Perinatal morbidity of the very preterm born children with aERP data analysis (N=70). Values expressed as mean±SD or as numbers (%). As severe intracranial hemorrhage, we defined intraventricular hemorrhage with ventricular dilation and/or parenchymal hemorrhage.

Days at hospital	86±24
Days on respirator	6.7±8.9
Days on nasal CPAP	19.4±17.3
Twin / triplet	29 (41) / 5 (7)
Chorioamnionitis	2 (3)
Maternal preeclampsia	17 (24)
Small for gestational age (birth weight ≤-2 SD)	21 (30)
Antenatal steroids	69 (98)
Birth through cesarean section	49 (70)
Need for inotropics	30 (42)
Sepsis	19 (27)
Necrotizing enterocolitis	2 (3)
Intracerebral hemorrhage	15 (21)
Severe intracerebral hemorrhage	4 (6)
Shunt for posthemorrhagic hydrocephalus	2 (3)
Periventricular leukomalacia	8 (11)
Severe retinopathy of prematurity	7 (10)
Bronchopulmonary dysplasia (oxygen at 36 GW)	35 (50)