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Auditory event-related potentials at preschool age in children born very preterm

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H I G H L I G H T S

- 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.

A B S T R A C T

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,

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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 and Eggermont, 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 to 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 32–35 GW with no major morbidity was recruited in the NICU and a healthy full-term control group (TC; $N = 24$) born $\geqslant 37$ 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