Auditory event-related potentials are related to cognition at preschool age after very preterm birth

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BACKGROUND: Auditory event-related potentials (AERP) are neurophysiological correlates of sound perception and cognitive processes. Our aim was to study in very preterm born children at preschool age if AERP correlate with cognitive outcome.

METHODS: Seventy children (mean ± SD gestational age 27.4 ± 1.9 wk, birth weight 996 ± 288 g) were investigated at age 4.3–5.3 y with psychological testing (WPPSI-R, four subtests of NEPSY). Electroencephalogram was recorded while they listened to a repeated standard tone, randomly replaced by one of three deviants. Latencies and amplitudes for AERP components and mean amplitudes in successive 50-ms AERP time windows were measured.

RESULTS: Better cognitive test results and higher gestational age correlated with shorter P1 latencies and more positive mean amplitudes 150–500 ms after stimulus change onset. Neonatal brain damage was associated with a negative displacement of AERP curves. Neonatal morbidity had an impact on earlier time windows while gestational age and brain damage on both early and later time windows.

CONCLUSION: AERP measures were associated with cognitive outcome. Neonatal morbidity mainly affects early cortical auditory encoding, while immaturity and brain damage additionally influence higher cortical functions of auditory perception and distraction. Perinatal auditory environment might play a role in development of auditory processing.

Preterm children born at a gestational age less than 32 wk, even without neuromotor abnormalities, have as a group a lower mean intelligence quotient, an increased risk of neuropsychological deficits (such as attention, reading, learning, language, and memory impairment), neurosensory and visuospatial deficits, poor executive functions, behavioral problems, and low academic achievement (1,2). The structural and functional correlates of such impairments in preterm children are incompletely understood, and early diagnostic tools are needed, but still lacking.

Auditory event-related potentials (AERP) are measures of cortical brain activity related to auditory stimuli. They are neurophysiological correlates of cortical sound discrimination and sound processing and may be used to describe auditory system developmental plasticity (3).

Obligatory AERP responses reflect sound detection and the transient encoding of the physical stimulus features (4). They are highly dependent upon the acoustic characteristics of the stimulus and the integrity of the primary auditory pathway (2,5). At preschool age, they consist of a first positive peak around 100 ms (P1) and a second negative peak (N2) around 250 ms (2). Lower P1 and N2 amplitudes have been described in children with cognitive and/or behavioral problems (6,7). Both in preterm and full term born children, lower P1 and N2 amplitudes have been associated with less favorable outcome, especially in language domains (2,8).

Mismatch negativity (MMN) is an AERP component elicited by a change in auditory stimuli. It is a frontocentral distributed negativity peaking between 100 and 250 ms from the onset of a deviant stimulus, obtained by subtracting the average AERP to a frequent (standard) stimulus from that recorded after a rare (deviant) stimulus. The MMN, reflecting sound discrimination, is based on the automatic formation of neural memory traces for familiar auditory events and has been associated with preattentive cognitive processes in audition (9). While it is typically negative in adults, it may have a positive polarity in infants and young children (10). For salient sound changes, MMN is followed by the frontocentral P3a response, believed to represent an involuntary switch of attention (11).

In infants and children, pathological AERPs have been associated with a variety of neurocognitive impairments that have a high incidence after preterm birth (6,12,13). The survival rate of extremely preterm infants (< 28 gestational weeks (GW)) continues to increase, which might be associated with an increased prevalence of neurocognitive abnormalities (14). In preterm infants with birth weights below 1,500 g, AERP development during the first year of life differed from healthy term infants (15). Smaller P1 and larger N2 amplitudes were found in

5-y-old children born with mean gestational ages below 28 GW (2,16). In children born at less than 32 GW studied at 2 y of age, MMN responses reflected abnormal phoneme discrimination, which was related to a slower native language acquisition (17).

In this study, we aimed to investigate if AERP recorded at preschool age in children born very preterm (VP) at less than 32 GW are associated with neurocognitive outcome. We hypothesized that children who have abnormal results on cognitive or behavioral scales show AERP responses that differ from children who develop normally. As a secondary aim, we investigated the correlates of neonatal clinical risk factors with cortical auditory processing.

RESULTS

Subjects

Of the 87 VP infants recruited at birth, born with a gestational age less than 32 wk, three died during the neonatal period, one could not be contacted, and one had moved abroad. The parents of 10 children declined to participate in this study. Two children consequently declined the fixation of EEG electrodes. Thus, 70 VP children born at 23.9–31.7 GW had a complete AERP recording. Perinatal characteristics of these are shown in **Table 1**. The children were assessed at the age of 61.4 ± 2.4 mo (58.6 ± 2.5 mo corrected for gestational age). All children passed the national hearing test at 4 y of age and none used a hearing aid.

Table 1. Perinatal characteristics of all children with AERP recordings as well as of the subgroups with and without brain damage

	All children (n = 70)	Brain damage (n = 10)	No brain damage (n = 60)
Gestational age (weeks)	27.4 ± 1.9 (23.9–31.7)	27.0 ± 2.0 (25.1–31.7)	27.6 ± 1.9 (23.9–31.7)
Gestational age < 28 wk	44 (63)	7 (70)	37 (62)
Birth weight (g)	996 ± 288 (550–2025)	924 ± 231 (605–1,205)	1,009 ± 299 (550– 2,025)
Small for gestational age (≤ −2 SD)	21 (30)	3 (30)	18 (30)
Chorioamnionitis	2 (3)	1 (10)	1 (2)
Maternal pre-eclampsia	17 (24)	0 (0)	17 (28)
Antenatal steroids	69 (99)	10 (100)	59 (98)
Birth through cesarean section	49 (70)	5 (50)	44 (73)
Male gender	35 (50)	7 (70)	28 (47)
Twin	29 (41)	5 (50)	24 (40)
Triplet	5 (7)	0 (0)	5 (8)
Need for inotropics	29 (41)	6 (60)	23 (38)
Operation for patent ductus arteriosus	13 (19)	3 (30)	10 (17)
Sepsis (verified by blood culture)	18 (26)	4 (40)	14 (23)
Necrotizing enterocolitis	2 (3)	1 (10)	1 (2)
Intracranial hemorrhage (grade I-III or periventricular hemorrhagic infarction)	15 (21)	7 (70)	8 (13)
Severe intracranial hemorrhage (grade III or periventricular hemorrhagic infarction)	4 (6)	4 (40)	0 (0)
Shunt for posthemorrhagic hydrocephalus	2 (3)	2 (20)	0 (0)
Periventricular leukomalacia	8 (11)	8 (80)	0 (0)
Neonatal brain damage	10 (14)	10 (100)	0 (0)
Days on ventilator	6.7 ± 8.9	8.6 ± 8.0	6.2 ± 9.0
Days on nasal continuous positive airway pressure (CPAP)	19.4 ± 17.3	24.1 ± 17.1	18.5 ± 17.5
Days at hospital	86 ± 24	98 ± 28	84 ± 24
Laser therapy for retinopathy of prematurity	6 (9)	0 (0)	6 (10)
Bronchopulmonary dysplasia (oxygen at 36 GW)	35 (50)	5 (50)	30 (50)
Weight at term (g)	2995 ± 518	3079 ± 598	2976 ± 511
Head circumference at term (cm)	35.2 ± 1.4	35.5 ± 1.5	35.2 ± 1.4
Head circumference at AERP (cm)	50.6 ± 1.9	50.6 ± 2.8	50.6 ± 1.8

Values as numbers (%) or Mean ± SD (range).
AERP, auditory event-related potentials; CPAP,

Table 2. Cognitive test results and SDQ-scores for all children, and for children with and without neonatal brain damage

Test	Score		All children $n = 70$		Brain damage $n = 10$	No brain damage $n = 60$
		n	Mean ± SD	Abnormal (%)	Mean ± SD	Mean ± SD
WPPSI	VIQ	69	97.5 ± 12.0	9 (13)	92.0 ± 12.6	98.4 ± 11.8
	PIQ	70	97.1 ± 14.8	13 (19)	91.5 ± 20.7	98.0 ± 13.5
	PSQ	67	85.0 ± 11.6	30 (45)	74.8 ± 15.0	86.8 ± 10.0**
	FSIQ	69	94.2 ± 13.4	13 (19)	86.8 ± 16.4	95.5 ± 12.6
NEPSY	VAco	67	33.5 ± 9.1	11 (16)	26.7 ± 18.8	34.6 ± 6.2*
	VAt	67	208 ± 67	12 (18)	253 ± 71	202 ± 64*
	PP	69	11.8 ± 2.3	10 (14)	11.2 ± 2.6	11.9 ± 2.3
	NM	69	10.0 ± 4.8	18 (26)	7.5 ± 3.7	10.4 ± 4.8
	SR	68	17.3 ± 4.3	9 (13)	16.7 ± 6.0	17.4 ± 4.0
SDQ	Tot	70	9.1 ± 4.6	3 (4)	12.8 ± 5.3	8.5 ± 4.2**

Cut-off limits for abnormal test results are described in the Methods section.
FSIQ, full-scale IQ; NM, narrative memory; PIQ, performance IQ; PP, phonological processing; SDQ, strengths and difficulties questionnaire; SR, sentence repetition; Tot = total score; VIQ, verbal IQ.
P values for comparison between children with and without brain damage. *$P < 0.05$; **$P < 0.01$.

Cognitive Test Results

Cognitive test results are shown in **Table 2**. Children with neonatal brain damage (i.e., ultrasound abnormalities) had significantly lower processing speed quotients, less correct markings (VAco) and slower performance (VAt) at the visual attention subtest, as well as more difficulties according to the Strengths and Difficulties Questionnaire.

AERP and Neurocognition

Mean responses to the standard and deviant stimuli are shown in **Figure 1**.

As AERP components show a strong correlation with age at examination (16), all statistics including AERP data were corrected for age. Age at examination correlated significantly with the P1 latency ($r = -0.423$; $P < 0.001$), but not with any other AERP data.

Cognitive test results were related to AERP. Faster VAt correlated with shorter P1 ($r = 0.249$; $P = 0.048$) and N2 latencies ($r = 0.319$; $P = 0.010$). Children with abnormal VAt had longer N2 latencies ($266.0 ± 25.1$ vs. $244.9 ± 19.3$ ms; $P = 0.003$) and a trend to longer P1 latencies ($125.8 ± 8.4$ vs. $116.1 ± 16.7$ ms; $P = 0.065$). P1 and N2 amplitudes, however, were not related to cognitive test results.

The most consistent associations between cognitive test results and mean amplitudes in the time windows were found for the duration deviant (**Table 3**). From 150 ms after stimulus change onset, children with better cognitive test results (except for VAt) showed consistently more positive mean amplitudes in all time windows. At 300–350 ms, mean amplitudes were significantly higher for three of nine cognitive subtests for this deviant.

These associations were confirmed by comparing children with abnormal vs. normal cognitive test results in the three time windows 300–450 ms after change onset for the duration deviant (**Table 4**). Children with abnormal results in all nine subtests had lower mean amplitudes in these time windows
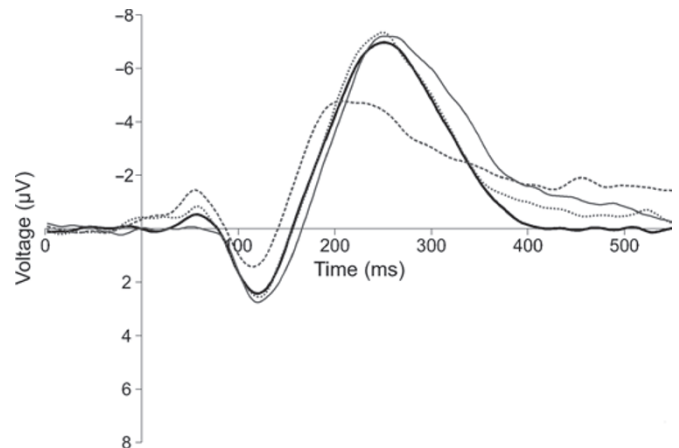

Figure 1. Grand average AERP responses to the standard stimulus and the three deviant stimuli for all $n = 70$ children. The positive peak around 100 ms is the P1, the negative peak around 250 ms the N2 response. Bold black line = standard. Dashed line = duration deviant; dotted line = direction deviant; grey line = frequency deviant.

than those with normal results, except for phonological processing in the 300–400 ms time windows. These more negative mean amplitudes reached significance for the VAco subtest in all three time windows and for the VAt subtest in the 400–450 ms time window.

Regarding the frequency deviant, children with abnormal processing speed quotients had more negative amplitudes in all seven time windows between 150–500 ms than children performing normally, reaching significance in the 350–400 ms time window ($-2.32 ± 1.78$ vs. $-1.25 ± 2.34$ μV; $P = 0.011$). Children with abnormal VAco scores had significantly lower mean amplitudes to the direction deviant in all seven time windows, reaching significance in the 200–250 ($-1.62 ± 2.74$ vs. $-0.02 ± 2.27$ μV; $P = 0.044$) and 300–350 ms time windows ($-1.72 ± 2.09$ vs. $0.23 ± 2.37$ μV; $P = 0.014$). In contrast, faster VAt (better performance) correlated with

Table 3. Correlation coefficients (*r* or β when corrected for head circumference) between mean amplitudes in 50-ms time windows after stimulus change onset for the duration deviant and cognitive test results

Test subset	*n*	100–150 ms	150–200 ms	200–250 ms	250–300 ms	300–350 ms	350–400 ms	400–450 ms
WPPSI								
VIQ	69	−0.072	0.069	0.156	0.148	0.229***	0.138	0.092
PIQ	70	−0.164	0.048	0.124	0.039	0.203***	0.211***	0.151
PSQ	67	−0.055	0.157	0.151	0.191	0.355**	0.354**	0.274*
FSIQ	69	−0.112	0.071	0.152	0.108	0.255*	0.197	0.145
NEPSY								
VAco	64	−0.138	0.151	0.067	0.022	0.221***	0.340**	0.235***
Vat	64	0.079	0.192	−0.030	0.025	0.006	−0.067	−0.254***
PP	65	0.109	0.267*	0.255*	0.166	0.207***	0.099	0.106
NM	65	−0.121	0.166	0.151	0.109	0.193	0.150	0.116
SR	65	0.008	0.140	0.116	0.070	0.252*	0.132	0.175

The time windows 250–300 ms after stimulus change onset is the window of the MMN response only, the window 400–450 ms is the window of the P3a response only. The time windows between 300–400 ms are overlapping time windows of the MMN and P3a reponses.
*$P < 0.05$; **$P < 0.01$; ***$P = 0.05$–0.1.
FSIQ, full-scale IQ; MMN, mismatch negativity; NM, narrative memory; PIQ, performance IQ; PP, phonological processing; SR, sentence repetition; VIQ, verbal IQ.

lower mean amplitudes to this deviant in all seven time windows (significant for 150–200 ms, $r = 0.249$; $P = 0.042$ and 250–300 ms, $r = 0.291$; $P = 0.017$).

AERP After Neonatal Brain Damage
Perinatal data for all children and children with and without brain damage are shown in **Table 1**. Mean amplitudes in time windows for children with and without neonatal brain damage are shown in **Table 5**. Average difference curves to the three deviants for both groups are shown in **Figure 2**.

Based on the grand average curves, we defined the MMN time windows for the frequency deviant as 200–350 ms, for the direction deviant as 150–300 ms, and for the duration deviant as 250–400 ms after stimulus change onset. The P3a time windows defined accordingly were 300–450 ms after stimulus change onset for all three deviants.

In the seven time windows between 100–450 ms, mean amplitudes of all three deviants were more negative in children with neonatal brain injury (i.e., stronger response in the MMN and weaker response in the P3a time windows), except for the 400–450 ms P3a time window for the frequency deviant. This group difference was significant in the 100–150 ms time window of the direction deviant and in the four time windows between 150–350 ms for the duration deviant.

No group differences in latencies and amplitudes of the P1 and N2 responses were found.

AERP Time Windows and Neonatal Morbidity
Correlations between mean amplitudes in time windows and neonatal morbidity are shown in **Supplementary Table S1** online.

Neonatal morbidity was associated with AERP changes. With decreasing GW, more negative mean amplitudes were found at 400–450 ms for the direction deviant and at 200–250 ms for the duration deviant.

Sepsis ($n = 18$) was associated with longer latencies of P1 (β = 0.345; $P = 0.020$) as well as with less negative mean amplitudes in early time windows of the direction (200–250 ms) and duration deviants (100–150 ms). Lower 5-min Apgar scores predicted more negative mean amplitudes in early time windows to the frequency (100–150 ms) and direction deviants (150–200 ms). Retinopathy of prematurity requiring laser therapy for ($n = 6$) predicted lower N2 amplitudes (β = −0.336; $P = 0.046$).

While sepsis and BPD ($n = 35$) correlated with less negative mean amplitudes in early time windows for the duration deviant (100–150 ms), longer mechanical ventilation strongly correlated with more negative mean amplitudes for this deviant (100–300 ms).

DISCUSSION
Our study shows that shorter latencies of the P1 and N2 components and more positive mean amplitudes in the MMN and P3a time windows were associated with better cognitive test results. As MMN by definition is a negative and P3a a positive deflection, more positive mean amplitudes in MMN and P3a time windows equal to weaker MMN and stronger P3a responses. Conversely, immaturity, most neonatal risk factors, and especially neonatal cerebral ultrasound abnormalities were associated with a negative displacement of the difference waveforms, generating an increase in MMN and a decrement in P3a amplitude.

Early AERP time windows reflect early cortical processes such as encoding and early processing while later time windows represent more advanced cognitive processes like change detection, auditory discrimination, and attentional switch (4,9,11). In our study, amplitudes in early time windows were influenced by gestational age, neonatal brain damage, sepsis, 5-min Apgar scores, days on a ventilator, and BPD. Conversely, amplitudes in later time windows were influenced

Table 4. Mean amplitudes in 50-ms time windows to the duration deviant in children with/without abnormal cognitive test results

Test subtest	n	100–150 ms	150–200 ms	200–250 ms	250–300 ms	300–350 ms	350–400 ms	400–450 ms
WPPSI								
VIQ	9	−0.84±2.37/−1.27±2.22	0.69±3.16/1.16±2.30	2.19±2.36/2.36±2.87	0.70±3.39/0.66±2.41	−1.51±2.27/−1.07±2.39	−2.51±3.39/−1.54±2.40	−2.93±3.21/−1.61±2.40
PIQ	13	−1.03±2.26/−1.25±2.22	0.58±3.22/1.20±2.18	1.91±2.75/2.43±2.79	1.13±2.83/0.55±2.45	−1.80±2.21/−1.01±2.39	−2.81±2.55/−1.43±2.48****	−2.95±2.64/−1.53±2.43****
PSQ	30	−0.76±1.97/−1.56±2.41	1.53±2.57/0.64±2.16	2.13±2.50/2.44±3.08	0.10±2.81/1.06±2.29	−1.79±2.33/−0.64±2.34****	−2.37±2.29/−1.22±2.65****	−2.23±2.49/−1.48±2.60
FSIQ	13	−0.99±2.18/−1.26±2.26	0.62±3.20/1.21±2.21	1.73±2.67/2.48±2.83	0.81±2.78/0.63±2.49	−1.77±2.23/−0.98±2.39	−2.54±2.77/−1.46±2.46	−2.99±2.48/−1.50±2.48****
NEPSY								
VACo	8	−0.27±2.47/−1.38±2.18	0.96±2.80/1.06±2.30	1.85±1.94/2.40±2.93	0.55±2.54/0.75±2.54	−2.45±2.39/−0.78±2.26*	−4.08±2.69/−1.24±2.28***	−4.04±2.84/−1.42±2.25**
Vat	11	−0.57±2.73/−1.35±2.12	0.09±2.17/1.28±2.37	2.13±2.37/2.35±2.90	0.66±2.67/0.73±2.51	−1.52±2.18/−0.95±2.39	−2.01±2.81/−1.64±2.52	−2.85±2.42/−1.61±2.52
PP	8	−1.89±2.76/−1.08±2.13	0.23±2.93/1.28±2.28	1.56±3.46/2.53±2.62	0.36±3.29/0.71±2.41	−0.87±2.38/−1.18±2.39	−0.94±3.05/−1.78±2.46	−2.00±3.05/−1.74±2.46
NM	15	−1.01±1.81/−1.24±2.36	0.51±2.33/1.31±2.42	2.06±2.33/2.43±2.95	1.17±2.73/0.45±2.45	−1.51±2.39/−1.07±2.37	−2.27±2.89/−1.54±2.38	−2.37±3.03/−1.60±2.33
SR	6	−0.62±2.71/−1.31±2.17	0.93±2.74/1.08±2.30	2.04±2.18/2.41±2.84	0.69±2.90/0.64±2.52	−2.10±1.90/−0.99±2.44	−3.12±3.15/−1.46±2.39****	−3.55±3.62/−1.54±2.25*

All amplitudes in µV. n = number of children with abnormal test results. Children with abnormal/children with normal test results.
Dir, direction deviant; Dur, duration deviant; FSIQ, full-scale IQ; Freq, frequency deviant; NM, narrative memory; PIQ, performance IQ; PP, phonological processing; SR, sentence repetition; VIQ, verbal IQ.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P = 0.05–0.1$.

by gestational age, neonatal brain damage, and 5-min Apgar scores only. Thus, different neonatal risk factors seem to influence the development of central auditory processing differently.

While neonatal morbidity mostly affected time windows before 250 ms, neuropsychological test performance was most strongly associated with later AERPs after 300 ms. This is reasonable as more advanced cortical auditory processing correlated with cognition (such as the MMN and P3a components) appears in later AERP time windows. Brain damage had an impact on all examined time points including the earliest time windows reflecting auditory encoding before the MMN. Thus, brain damage is influencing the whole spectrum of cortical sound encoding and processing. Interestingly, time windows affected by brain damage are identical with the time windows associated with neonatal morbidity (causing brain damage) and cognitive outcome (highly influenced by brain damage). As no detailed cerebral imaging was performed after the neonatal ultrasound scans in all children, it remains unclear whether other injuries than intraventricular hemorrhage and periventricular cysts might affect AERP.

Lower P1 amplitudes in children born VP have been described earlier (2,16). In this study, the P1 amplitude tended to increase with increasing gestational age, but it was not influenced by brain damage or other morbidity. Thus, environmental factors common to all VP infants rather than prematurity-related morbidity seem to determine the development of auditory encoding. Decreasing P1 with increasing prematurity and brain damage might reflect increased habituation to repetitive stimuli in these children (18). As the AERPs of the present study were recorded at preschool age, our results suggest that early extrauterine auditory environment in the neonatal period may modify the auditory network even in a longer perspective. The auditory environment is different between VP and term-born infants during the last trimester. Both favorable intrauterine influences and unfavorable effects of the NICU environment such as noisy ventilator support devices and disturbing alarms (19,20) may have an impact on later auditory processing.

In addition to stimulus characteristics and magnitude of stimulus change, component latencies in children are influenced by continued myelination, synaptic differentiation, and specialization (21,22). Advanced MRI studies have shown delayed microanatomical differentiation and myelination in white matter tracts in preterm infants (23). More mature auditory pathways in the brainstem and pons have been associated with shorter latencies on brainstem auditory-evoked potentials (24,25). While auditory connectivity is difficult to assess due to the small size and vicinity to adjacent structures of the relevant tracts, advanced volumetric brain studies in preterm children have revealed reduced volumes in temporal brain regions (26). Thus, it may be that both delayed myelination and impaired cortical differentiation may explain the increased AERP latencies in children with lower gestational age, sepsis, and lower 5-min Apgar scores.

Furthermore, our study shows significant correlations between AERP measures and cognitive outcome at preschool

Table 5. Mean amplitudes in µV (mean ± SD) of the deviant-minus-standard difference waves in the 50-ms time windows between 100–450 ms from stimulus change

Deviant time window	All children (*n* = 70)	Children with brain injury (*n* = 10)	Children without brain injury (*n* = 60)
Frequency			
100–150 ms	0.44 ± 2.38	−0.90 ± 1.92	0.67 ± 2.39***
150–200 ms	0.80 ± 2.49	−0.59 ± 1.41	1.03 ± 2.56***
200–250 ms[a]	−0.23 ± 2.70	−1.37 ± 2.59	−0.04 ± 2.69
250–300 ms[a]	−1.03 ± 2.72	−2.38 ± 2.11	−0.80 ± 2.76***
300–350 ms	−1.86 ± 2.77	−2.74 ± 2.09	−1.71 ± 2.86
350–400 ms[b]	−1.70 ± 2.28	−1.97 ± 1.73	−1.66 ± 2.36
400–450 ms[b]	−1.39 ± 2.44	−1.28 ± 1.79	−1.40 ± 2.54
Direction			
100–150 ms	0.07 ± 2.09	−1.54 ± 1.98	0.34 ± 2.00**
150–200 ms[a]	−0.09 ± 2.21	−0.80 ± 1.74	0.03 ± 2.26
200–250 ms[a]	−0.36 ± 2.44	−0.56 ± 3.31	−0.32 ± 2.30
250–300 ms[a]	−0.04 ± 2.42	−0.84 ± 3.06	0.09 ± 2.30
300–350 ms[b]	0.10 ± 2.25	−0.76 ± 2.04	0.24 ± 2.27
350–400 ms[b]	−0.41 ± 2.10	−1.34 ± 2.94	−0.26 ± 1.92
400–450 ms[b]	−0.74 ± 1.83	−1.06 ± 2.83	−0.68 ± 1.64
Duration			
100–150 ms	−1.21 ± 2.21	−1.54 ± 2.32	−1.15 ± 2.21
150–200 ms	1.08 ± 2.39	−0.64 ± 1.67	1.37 ± 2.38*
200–250 ms	2.33 ± 2.77	0.57 ± 2.70	2.62 ± 2.70*
250–300 ms[a]	0.66 ± 2.51	−1.11 ± 2.31	0.95 ± 2.44*
300–350 ms	−1.15 ± 2.36	−2.62 ± 1.73	−0.91 ± 2.37*
350–400 ms	−1.69 ± 2.53	−2.63 ± 2.30	−1.53 ± 2.55
400–450 ms[b]	−1.80 ± 2.51	−1.92 ± 2.50	−1.78 ± 2.53

[a]Time windows when only mismatch negativity appeared. [b]Time windows when only P3a appeared.
*$P < 0.05$; **$P < 0.01$; ***$P = 0.05–0.1$ for comparison between children with and without brain damage (adjusted for head circumference when appropriate).
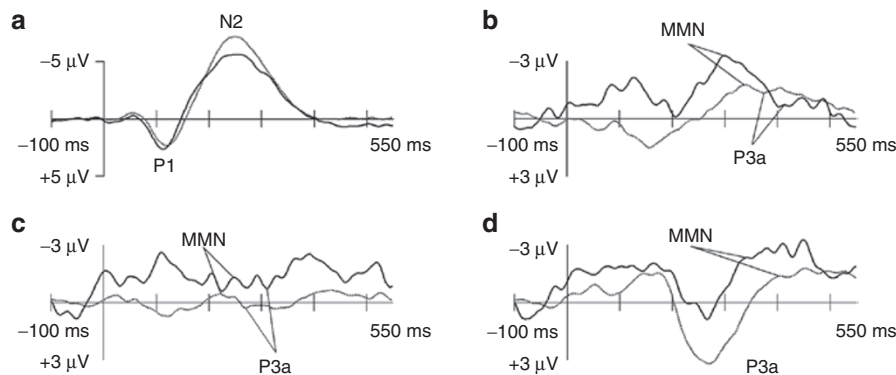

Figure 2. Comparison between children with and without neonatal brain damage. Average auditory event-related potentials standard curve (**a**) and deviant-minus-standard difference curves to the frequency (**b**), direction (**c**), and duration deviants (**d**) of children with (full line) and without (dotted line) brain damage. The main responses are marked on each curve. No P3a can be observed on the average curve of the duration. Stimulus onset and change onset is at 0 ms with the exception of change onset for the duration deviant (50 ms).

age. Very few earlier studies have addressed these correlations in preterm infants. One study has failed to show such correlations at 2 y of age (27), while a recent study using speech sounds on term-born and premature newborns showed that AERP at term was predictive of outcome in infancy (28).

Alterations in AERP and particularly MMN have been shown in children with learning disabilities (29), reading and language-related disorders (17), autism spectrum disorders (6,13,30), distractibility, and attention deficit hyperactivity disorder (30). In our study, AERP difference waves to all three deviants in children with brain damage and lower cognitive scores were displaced negatively, leading to stronger MMN and weaker P3a responses. This is in accordance with a study showing more negative responses to a frequency deviant during infancy in full-term children with neonatal brain damage (27). Perinatal brain damage together with plasticity during

subsequent brain development may considerably alter different phases of auditory processing (31). As ERP amplitudes and polarities depend on the magnitude of synaptic activation, the localization and orientation of the cortical or subcortical generators, excitatory or inhibitory nature of the input, and reception via synapses distal or proximal to the cell bodies (32), the negative AERP displacement is an additional indicator of altered brain maturation after neonatal brain damage and degree of immaturity at birth.

Investigation of AERP as a prognostic tool has only been evaluated recently and in small patient groups. This is so far the largest AERP study on preterm children, and the only study investigating the impact of prenatal and neonatal clinical factors on AERP responses beyond infancy. Strengths of our study are first that the study infants were consecutively recruited after birth, and more than 80% participated in the follow-up study at school age. Second, the success rate of the recordings was very high, with only two children (3%) not cooperating sufficiently for reliable recordings. In previous studies, up to 20% of recordings were rejected due to technical problems (e.g., refs (2,12)).

A caveat has been the use of multiple comparisons. A Bonferroni correction would have made most of the significant results disappear because of small group sizes and small differences between groups. Thus, in order to avoid reporting accidental correlations, we only present results that are consistent (or supported by adjacent—albeit only borderline significant—changes) between cognitive tests, adjacent time windows, or between at least two of the deviants. However, relevant findings may be excluded with this approach.

Unfortunately, our AERP paradigm was not designed to detect specific adverse neuropsychological outcomes. Other paradigms may increase the prognostic value for a specific impairment. However, AERP recordings and analyses are time consuming, and in spite of modern paradigms (7,33), the number of deviants testable is limited. Our aim was to apply an easy paradigm testing several important aspects of sound processing such as frequency, duration, and spatial perception. However, this paradigm does not seem to be sufficiently specific to be used as a prognostic tool on an individual basis.

We conclude that AERP measures at preschool age are influenced by gestational age at birth, neonatal brain damage and morbidity, and are associated with cognitive outcome at preschool age.

METHODS

Study Population
Preterm infants with a gestational age below 32 wk, born at Lund University Hospital between September 2000 and February 2003 and treated at the NICU were recruited into a prospective cohort study. Major congenital malformations were the only exclusion criterion. A total of 87 infants were enrolled.

Clinical data were collected prospectively during the neonatal period. Neonatal cerebral ultrasound scans were performed routinely at 1, 3, and 7 d, 3 wk, and at term. As severe intracranial hemorrhage, we defined intraventricular hemorrhage with ventricular dilation (grade III) and/or periventricular hemorrhagic infarction. As

neonatal brain damage, we defined severe intracranial hemorrhage and/or periventricular cysts on ultrasound at any time point up to term age.

The age at AERP examination was calculated from the time corresponding to term age. Informed, written parental consent was obtained both at recruitment and before the AERP recording at 4–5.5 y of age. The Regional Ethics Review Board, Lund, Sweden approved the study protocol prior to the start of the study.

AERP 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, as well as four electro-oculogram electrodes. The 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, Abbotsford, Australia).

The sound stimuli were presented as an oddball paradigm consisting of a standard tone (probability of 70%), randomly replaced by one of three infrequent deviant tones (10% probability for each). The time interval between the start of successive stimuli was 533 ms. The standard tone was a sinusoidal 1000 Hz tone with a duration of 100 ms. The frequency deviant differed from the standard by a 10% higher pitch (1100 Hz). 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. The third deviant differed in duration, lasting only 50 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. Each deviant was followed by at least one standard tone. In total, the standard tone was presented 1,290 times, while each deviant type was presented 180 times. The duration of the experiment was about 15 min.

AERP Averaging and Analysis
AERP data analysis was performed using a NeuroScan 4.5 system (Compumedics). The continuous EEG was filtered offline (bandpass 0.5–30 Hz). The data were divided into 650-ms epochs (100 ms before to 550 ms after stimulus onset). The epochs were baseline corrected to the prestimulus interval. Epochs with amplitudes exceeding ± 100 μV on any electrode were rejected, as well as all epochs following a deviant stimulus epoch. The epochs for the standard stimulus and those for the three deviant stimuli were averaged into separate averages for each subject and electrode. The final data set consisted of, on average, 101 accepted trials per deviant type (range: 41–162).

The AERP curves for standard and deviant stimuli in all subjects were averaged into grand average mean AERP curves. An averaged curve from the six frontal and central electrodes was used to define the individual latencies of the main peaks for each participant.

The P1 peak was defined as the most positive peak in the interval 130 ± 50 ms, and the N2 peak as the most negative peak in the interval 250 ± 80 ms.

Difference waveforms were obtained by subtracting the response to the standard from that to the deviant stimulus, individually for each child, using the averaged curves from the six frontal and central electrodes. In order to reduce the influence of noise, combined mean amplitudes for these six electrodes in successive 50 ms time windows from 100 to 450 ms after stimulus change onset were calculated for each subject. As MMN time window for each deviant, we defined the 50 ms time window with the MMN on the grand average mean curve and the previous and following 50 ms time windows (in total, three successive time windows). The P3a time windows were defined accordingly.

Neuropsychological Tests
On the same day as the AERP recordings, the children were tested using all subtests of the Wechsler Preschool and Primary Scale of intelligence—revised (WPPSI-R) (34) and the subtests Visual attention, Phonological Processing, Narrative memory and Sentence repetition of A Developmental Neuropsychological Assessment (NEPSY)

(35). The tests were performed by one of two psychologists trained in these test methods and blinded to both neonatal morbidity and AERP results.

The parents filled in the SDQ (36), in which we analyzed the total score. Length, body weight, and head circumference were registered.

The age range of the children at assessment was 4.3–5.3 y. In order to avoid effects of different test protocols in NEPSY for children below and above 5 y of age, all children were tested using the protocols for the age group below 5 y. Where no percentiles for 5-y olds were available for these protocols, percentiles for 4-y olds were used even for the children 5 to 5.3 mo of age. In order to elucidate different aspects of the visual attention subtest of NEPSY, we analyzed the number of correct markings (VAco) and the time to complete this test (VAt) separately.

Children scoring below 85 in WPPSI-R, on the 25th percentile or below on a NEPSY subtest and higher than 16 on the Strengths and Difficulties Questionnaire were considered abnormal for this subtest or score.

To exclude the effect of severe cognitive impairment on NEPSY test results, children with full-scale IQ ≤ 70 in WPPSI-R ($n = 4$) were not included in the NEPSY analysis.

Statistical Analyses

Statistical analyses were performed with PASW Statistics 18 for Windows software (IBM SPSS Statistics, Chicago, IL).

As we in an earlier study had found a significant association between age at examination and AERP latencies (16), and as head size may have an impact on AERP measures, all AERP measures correlating with these factors ($P < 0.1$ on Pearson bivariate correlations) were corrected for respective factor. Thus, we corrected for head circumference in the time windows between 150–250 and 350–400 ms for the frequency deviant, between 350–400 ms for the direction deviant, and between 200–250 and 350–450 ms for the duration deviant.

AERP measures and cognitive test results in children with and without neonatal brain damage were compared using *t*-test. Where correction for age at examination or head circumference was necessary, we used binary logistic regression analysis.

Associations between AERP measures and cognitive test results/ Strengths and Difficulties Questionnaire score were tested using bivariate correlations (Pearson). Where correction for age at examination or head circumference was necessary, we used linear or binary logistic regression analysis. Children with abnormal and normal test results/scores were compared using *t*-test.

The influence of neonatal clinical data on AERP measures were tested using multiple regression analysis, with AERP measures as dependent and neonatal clinical data as independent variables. In the primary model we included the prenatal factors sex, GA (continuous variable), and small for GA (SGA, defined as birth weight below −2 SD for gestation). In the secondary model, we further added the neonatal clinical variables 5-min Apgar, days on ventilator, sepsis, laser therapy for retinopathy of prematurity, and BPD (defined by need for additional oxygen at 36 GW), all known to have an impact on cognitive outcome. Correction for age at examination or head circumference was added where appropriate.

In order to avoid reporting accidental associations due to multiple comparisons, we only present results that are consistent between cognitive tests, adjacent time windows, or between at least two of the deviants. A *P* value < 0.05 was considered significant.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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