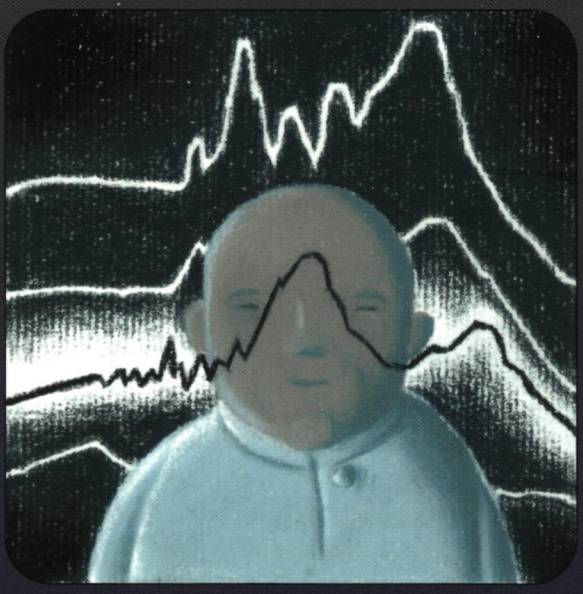
AUDITORY EVOKED RESPONSES IN PRETERM INFANTS



developmental aspects and clinical value

J.W. PASMAN

AUDITORY EVOKED RESPONSES IN PRETERM INFANTS:

Developmental Aspects And Clinical Value

AUDITORY EVOKED RESPONSES IN PRETERM INFANTS:

Developmental Aspects And Clinical Value

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CONTENTS

Abbreviations

ABR	Auditory Brainstem Evoked Response
ACR	Auditory Cortical Evoked Response
ADIT	Auditory Discrimination Test
AER	Auditory Evoked Response
AERF	Auditory Evoked Response Factor
BMC-AER	Brainstem, Middle Latency and Cortical Auditory Evoked Response
BWVK	Bourdon-Wiersma Concentration Test Voor Kinderen
CA	Conceptional Age
EEG	Electroencephalogram
GA	Gestational Age
GAF	Gestational Age Factor
GAG	Gestational Age Group
IPL	Interpeak Latency
IVH	Intraventricular Haemorrhage
LDT	Leiden Diagnostic Test
MLR	Middle Latency Auditory Evoked Response
NBRS	Neurobiologic Risk Score
NNI	Neonatal Neurological Inventory
NPV	Negative Predictive Value
PPA	Peak-Peak Amplitude
PERI	Perinatal Risk Inventory
PIQ	Performance Intelligence Quotient
PPV	Positive Predictive Value
PVL	Periventricular Leukomalacia
SER	Somatosensory Evoked Response
SPL	Sound Pressure Level
TIQ	Total Intelligence Quotient
VER	Visual Evoked Response
VIQ	Verbal Intelligence Quotient
VMI	Visual Motor Integration Test
WHO	World Health Organization
WISC-R	Wechsler Intelligence Scale for Children - Revised

Chapter 1

General introduction

Prematurity predisposes the infant to a number of neurological, neuropsychological and educational sequelae [Drillien *et al.* 1980, Klein *et al.* 1989, Abel Smith and Knight-Jones 1990]. During the past three decades the survival rates of preterm infants have increased because facilities for perinatal intensive care have improved. Nevertheless, the prevalence of major handicap in surviving preterm infants has remained stable [Stewart *et al.* 1981, Grogaard *et al.* 1990]. The increased survival rate will therefore result in an increasing number of preterm infants with handicaps. The incidence of major handicaps varies from 5% to 22%, depending on the maturity of the patient population, the classification of neurological and neuropsychological abnormalities and the duration of follow-up [Collin *et al.* 1991, Ornstein *et al.* 1991, Veen *et al.* 1991, Fazzi *et al.* 1992, Graziani *et al.* 1992]. Minor handicaps such as mild developmental delays, educational problems and poor school performance are found in up to 60% of the preterm infants. Early detection of handicaps in preterm infants is not only important for adequate treatment and preventive strategies in the neonatal period, but also for long-term medical, educational and psychosocial management.

Efforts have been made to determine neonatal risk factors predicting neurodevelopmental outcome in full-term and preterm infants [Kitchen *et al.* 1980, Michelsson *et al.* 1984, Stewart *et al.* 1989, Vohr *et al.* 1989, Den Ouden *et al.* 1990, Brazy *et al.* 1991, Scheiner and Sexton 1991]. Several reports have identified low birth weight and fetal growth retardation as neonatal risk factors [Abel Smith and Knight-Jones 1990, Zubrick *et al.* 1988]. Especially the combination of these factors with early, abnormal neurological signs results in an unfavourable prognosis, regarding neurodevelopmental and motor outcome, learning capabilities, and language acquisition [Kitchen *et al.* 1980, Michelsson *et al.* 1984, Powell *et al.* 1986, Stewart *et al.* 1989, Vohr *et al.* 1989]. Furthermore, gestational age GA), intraventricular haemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, socioeconomic status, assisted ventilation and hyperbilirubinaemia are reported to be important neonatal risk factors for neurodevelopmental outcome of preterm infants [Bozynski *et al.* 1987, Den Ouden *et al.* 1990, Brazy *et al.* 1991, Graziani *et al.* 1992, Litmann and Parmalee 1972, Scheiner and Sexton 1991, Stewart *et al.* 1989, Van de Bor *et al.* 1989]. However, with respect to socioeconomic status, assisted ventilation and hyperbilirubinaemia these studies are equivocal [Brazy *et al.* 1991]. Only a few neonatal risk scores, in which these neonatal risk factors are combined, were developed to improve the prediction of neurodevelopmental outcome in preterm infants and/or low birth weight infants. These risk scores show a high specificity and positive predictive value (PPV). However, the sensitivity and negative predictive value (NPV) of these risk scores

are rather low [Brazy *et al.* 1991, Scheiner and Sexton 1991]. In other words a considerable number of preterm infants are considered as low-risk infants, although they show an unfavourable long-term neurodevelopmental outcome.

Neurophysiological methods such as electroencephalography (EEG) and evoked responses are useful noninvasive techniques for evaluating brain function at the bedside in newborn infants [Watanabe 1992]. Furthermore, some authors have stated that early physiologic indices can be used to predict long-term developmental trends [Karmel *et al.* 1988, Molfese 1989].

EEG abnormalities in term and preterm infants have been described in relation to a variety of perinatal sequelae. In perinatal encephalopathy, the EEG background is closely related to the degree of later neurological abnormalities [Lombroso 1985, Pezzani *et al.* 1986, Grigg-Damberger *et al.* 1989]. Furthermore, in both term and preterm infants the prognostic value of the neonatal EEG is increased by performing serial recordings [Takeuchi and Watanabe 1989, Tharp *et al.* 1989, Watanabe *et al.* 1989, Holmes and Lombroso 1993].

Somatosensory evoked responses (SERs) are a sensitive measure of the integrity of the sensory pathways in newborn infants [Mercuri *et al.* 1994]. The close anatomical relation between sensory pathways and motor tracts cause that lesions of the central motor system also affect SERs. Over the past fifteen years SERs have been used to predict neuromotor outcome in newborn infants [Görke 1986, Klimach and Cooke 1988]. Several authors have found a strong correlation between abnormal motor outcome and median nerve SERs (i.e., prolonged N1 peak latency). They have also shown that a single normal SER was of relatively little prognostic value, whereas two or more normal SERs indicated a normal outcome [Klimach and Cooke 1988, Willes *et al.* 1989].

The visual evoked responses (VERs) in newborns have been studied over a longer period than the other evoked responses. Most reports indicate that VERs provide an objective measure of visual function in both term and preterm infants [Placzek *et al.* 1985, McCulloch *et al.* 1991, Roy *et al.* 1995]. Only a few reports exist on VERs in preterm infants. In these studies it is stated that in preterm infants VERs can be used in the assessment of the degree of brain damage. However, in preterm infants VERs are not useful in either diagnosis or prognosis [Watanabe *et al.* 1981, Pryds *et al.* 1989].

Auditory evoked responses (AERs) primarily reflect the function of the peripheral and central auditory pathways. To a certain extent the AERs also yield information on the integrity of those parts of the central nervous system closely related to the auditory system. Auditory evoked responses can be subdivided according to their latency in brainstem (ABR), middle latency (MLR) and cortical

(ACR) auditory evoked responses (BMC-AERs). ABRs include early responses time-locked to click stimuli occurring within 10 ms. MLRs consist of negative and positive peaks occurring between 10 and 50 ms. ACR waves are recorded during the 50-1000 ms latency range following the acoustic stimulus. See Figure 1.

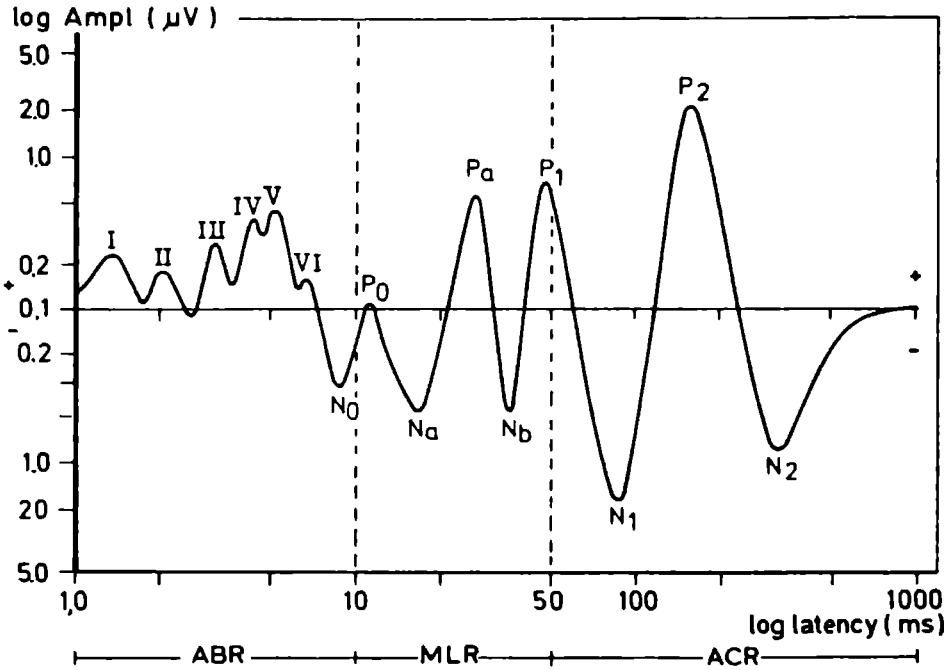

Fig. 1. *Brainstem (ABR), middle latency (MLR) and cortical (ACR) auditory evoked responses (BMC-AERs).*

Although referred to as brainstem auditory evoked response, part of the response reflects the compound action potential in the peripheral portion of the cochlear nerve and corresponds to the N1 potential of the electrocochleogram. Although the ABR components II and III are generally believed to originate in the auditory pathways in the pons, there is disagreement as to their precise sources. Recent studies suggest that ABR component II is at least partly generated in the intracranial portion of the cochlear nerve close to the brainstem. Furthermore, it is suggested that auditory pathways in the ipsilateral pons contribute to wave II. Wave III is generated in the caudal pons, probably in the region of the trapezoid body and the superior olivary complex. ABR waves IV and V are often fused into

a single broad complex. The major sources of these two components are considered to be the lateral lemniscus and/or inferior colliculus on both sides [Hashimoto *et al.* 1981, Oh *et al.* 1981, Møller and Janetta 1983, Møller *et al.* 1988, Wada and Starr 1983, Markand *et al.* 1989, Markand 1994].

Some disagreement remains concerning the generators of the MLR. Some reports have suggested that both Na and Pa are generated in the primary auditory cortex [Scherg and von Cramon 1986]. Other authors agree that component Pa is generated in the auditory cortex. Nevertheless, they have found evidence that there is a more deeply situated, subcortical source for Na [Wood and Wolpaw 1982, Deiber *et al.* 1988, Ibañez *et al* 1989].

The ACR components N100 and P200 reach their maximum amplitude at the vertex in the frontocentral region. Recent source localization studies have suggested that two dipolar sources are active in the latency range of the N100 in each temporal lobe. One has a tangential orientation and the other has a radial orientation creating a potential field centered in the midtemporal region [Wolpaw and Wood 1982, Scherg and von Cramon 1986]. These results only apply to mature ACRs, because in infants the waveform and latencies of ACR components are strongly related to maturational changes in the central nervous system, in particular the auditory cortex. ACR data in infants and young children can therefore only be used if these data are related to age-specific normative data.

Over the past twenty years many authors have presented normative data on ABRs for preterm and term infants. Furthermore, various studies have reported on the maturation of ABRs in the preterm period. [Hecox and Galambos 1974, Salamy and McKean 1976, Goldstein *et al.* 1979, Despland and Galambos 1980, Cox *et al.* 1981, Roberts *et al.* 1982, Salamy 1984, Rotteveel *et al.* 1985, Salamy *et al.* 1985, Rotteveel *et al.* 1986a, 1987a, 1987b, Lauffer and Wenzel 1990, Eggermont 1992, Ponton *et al.* 1993]. In comparison to the number of reports on ABRs, there are only a limited number of reports relating to normative data and maturation of MLR and ACR in preterm infants [Weitzman and Graziani 1968, Mendel *et al.* 1977, Ohlrich *et al.* 1978, Özdamar and Kraus 1983, Okitsu 1984, Kraus and McGee 1993]. Only a few studies exist in which the maturation of ABR, MLR and ACR is studied longitudinally in the same cohort of preterm infants [Rotteveel *et al.* 1985, 1986a, 1986b, 1986c, 1987a, 1987b, 1987c, 1987d, 1987e].

Several authors have reported selective vulnerability of auditory relay nuclei in the preterm period, especially between 28 and 40 weeks GA [Dobbing and Sands 1973, Griffiths and Laurence 1974, Leech and Alvord 1977]. Over the past 15 years several authors have reported on the clinical importance of brainstem

auditory evoked responses (ABRs) in newborn infants. Most of these studies have focussed primarily on term infants, in particular on term infants with asphyxia or hyperbilirubinaemia and on term infants at risk of hearing loss [Stein *et al.* 1983, Guerit 1985, Cycowisz *et al.* 1988, Murray 1988, Guinard *et al.* 1989, Durieux Smith *et al.* 1991, Yang *et al.* 1993]. Other studies have concentrated on the predictive power of ABRs in relation to neurodevelopmental outcome or later language skills in term infants [Stockard *et al.* 1983, Majnemer *et al.* 1988, Molfese 1989]. The relation between ABR findings and neurodevelopmental outcome in preterm infants is assessed in various studies [Majnemer *et al.* 1988, Beverly *et al.* 1990, Cox *et al.* 1992, Salamy and Eldredge 1994]. Majnemer *et al.* [1988] found evidence for the usefulness of the ABR as a diagnostic test for high-risk neonates. Cox *et al.* [1992] suggested that early ABR may predict long-term neurobehavioural development in low birth weight infants. Salamy and Eldredge [1994] reported that infants with neurological signs or demonstrable brain anomalies were 4-5 times more likely to exhibit deviant ABRs. They also reported that the synergistic effects of selected predictor variables further increased the risk associated with abnormal ABRs. On the other hand, Beverly *et al.* [1990] found that neither flash VERs nor ABRs provide a good prognostic indicator for neurodevelopmental outcome. Only a few reports have focussed on the predictive value of the MLR and ACR for neurodevelopmental outcome in newborn infants [Molfese 1989]. To the best of our knowledge, MLR and ACR have not been evaluated with respect to diagnostic properties or predictive value in preterm infants. Furthermore, BMC-AER measures have not been assessed as neonatal risk factors or integrated in neonatal risk scores.

Aim of the study

The aim of this study is to determine the clinical value of BMC-AERs obtained in the neonatal period in preterm infants and, more specifically, to assess the validity and predictive value of BMC-AERs with respect to the long-term neurodevelopmental outcome in these infants. In order to answer these key question, it was necessary to carry out two specific developmental studies of BMC-AERs in preterm infants. First, it was necessary to determine the (cumulative) detectability for all BMC-AER components in low-risk preterm infants (i.e., preterm infants expected to show a normal long-term neurodevelopmental outcome). A sufficient detectability of BMC-AER components during the preterm period is a prerequisite for the clinical application of BMC-AERs in this age group. Second, it is neces-

sary to identify the effects of preterm birth on the maturation of BMC-AERs in low-risk preterm infants before the effects of perinatal pathology on BMC-AERs can be assessed.

In order to allow the assessment of the predictive value of BMC-AERs, the long-term neurodevelopmental outcome in the preterm infants must be established. A follow-up study at 5-7 years of age determines both the neurological and the neuropsychological outcome in high-risk and low-risk preterm infants. In determining this, it is necessary to investigate whether neuropsychological impairments in low-risk preterm infants are due to moderate-severe impairment in a few preterm infants, or to slight impairment in the majority.

The clinical and predictive value of BMC-AERs as a single neonatal risk factor is then determined, taking into account the results of the developmental studies and based on the results of the follow-up study. This is done first for subgroups of preterm infants (high-risk/low-risk, early/late preterm and normal/abnormal outcome). These analyses are then performed for the individual preterm infants.

The predictive power of neonatal risk factors can be improved by combining separate neonatal risk factors in a neonatal risk score. This study therefore evaluates two neonatal risk scores with respect to long-term neurological and neuropsychological outcome. In order to improve the predictive power of one of these risk scores (NBRS), a BMC-AER factor and a GA factor were added to the 13 items combined in the NBRS.

Materials and methods

Eighty-one preterm infants (GA 25-34 weeks) and 25 healthy, term infants (GA 38-42 weeks) were included in this prospective study. The preterm group consisted of preterm infants admitted to the Neonatal Intensive Care Unit of the University Hospital Nijmegen. The term group consisted of healthy term infants born in the same hospital. This group served as a control group. Infants with dysgenetic brain lesions, major congenital anomalies or well-defined clinical syndromes were excluded.

The preterm infants were classified as high-risk or low-risk infants according to the semi-quantitative Neonatal Neurological Inventory (NNI). The NNI is based on four elements: 1) clinical neurological examination, 2) echoencephalography, 3) arterial or capillary blood pH and 4) Apgar score. With respect to the clinical neurological examination infants with neonatal seizures, cranial nerve palsies, asymmetric neurological syndromes or persistent abnormalities on neurological

examination according to Dubowitz *et al* [1980] were classified as high-risk infants The neurological examination also contained a qualitative analysis of spontaneous and evoked motility In order to determine structural ischemic and/or haemorrhagic brain lesions transfontanellar echoencephalographic studies were performed daily in the first week of life and thereafter at least once biweekly until discharge In the case of haemorrhage the echoencephalographic results with respect to intracranial haemorrhages were classified according to Papile *et al* [1978] Periventricular leukomalacia was assessed as present or absent The NNI assessment was also based on blood pH and Apgar score In low-risk infants the blood pH had to be above 7 10 (arterial) or 7 00 (capillary) and the Apgar score had to be above seven at five minutes On basis of the NNI 65 of the 81 preterm infants were classified as low-risk and 16 were classified as high-risk (i e , at least one of the four NNI high-risk criteria is present) Five of the 65 low-risk preterm infants and 7 of the 16 high-risk preterm infants died in the neonatal period Forty-four of the surviving low-risk preterm infants, all of the surviving high-risk preterm infants and 18 of the 25 term infants had a complete follow-up The other infants were not available for follow-up because of migration or withdrawal by the parents

Brainstem (ABR), Middle Latency (MLR) and Cortical (ACR) Auditory Evoked Responses were obtained at 40 weeks conceptional age (CA), 52 weeks CA and five years of age The state of vigilance was monitored by the technician Where possible the ABR and MLR were obtained from sleeping subjects, but data from wakeful subjects were accepted The waveform labelling and classification criteria of the BMC-AERs have been described by Rotteveel *et al* [1985, 1986*a*, 1986*b*, 1986*c*, 1987*a*] Grand composite group averages were used as templates for individual records An auditory evoked response factor (AERF) was designed, based on ABR and MLR

At the age of 5-7 years the infants were invited to participate in a follow-up investigation consisting of a neurological and neuropsychological evaluation An experienced child neurologist carried out the clinical neurological examination using standard pediatric neurological examination methods The WHO classification of Impairments, Disabilities and Handicaps was used to classify the neurological abnormalities [1980] Neurological abnormalities were classified as minor if they did not result in disability and/or handicap, and were classified as major if they did result in these The infants of both the preterm and the term group were divided into two subgroups on the basis of the neurological examination 1) the neurologically normal group consisting of infants with no or minor

neurological abnormalities and 2) the neurologically abnormal group consisting of infants with major neurological abnormalities.

The neuropsychological diagnostic work-up consisted of standardized tests: the Visual-Motor Integration Test (VMI), the 'Leiden Diagnostic Test' (LDT) or the Revised Wechsler Intelligence Scale for Children (WISC-R) depending on the test age of the child, the Bourdon-Wiersma-Vos concentration test for infants (BWVK) and the Auditory Discrimination Test (ADIT) [Haassen *et al.* 1974, Crul and Peters 1976, Schroots and Alphen de Veer 1976, Vos 1988, Beery 1989]. Since age-norms exist for the VMI, LDT and WISC-R, results from these tests could be converted into standard scores. For the BWVK and ADIT, group performances were compared on the basis of raw scores.

The Neurobiologic Risk Score (NBRS) and revised NBRS were conceived for the preterm infants in our study. The NBRS assessment was based on data obtained within the first four weeks after birth. The results were analysed for both neurological and neuropsychological outcome.

Chapter 2

Detectability of auditory evoked response components in preterm infants

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Early Human Development 1991; 26: 129-141

Summary

In determining the detectability of Brainstem, Middle Latency and Cortical Auditory Evoked Responses in preterm newborns, one has to deal with the ongoing maturation of the auditory system. In the preterm period the detectability of evoked responses is closely related to the appearance of the individual evoked response components. The detectability of the individual evoked response components in preterm infants is important, because low detectability rates make the absence of a particular evoked response component irrelevant with respect to the clinical-neurophysiological correlation. In a longitudinal study we determined the detectability and cumulative detectability, i.e., the presence of individual evoked response components in one or more recordings of evoked response components in 37 low-risk preterm infants between 30 and 41 weeks conceptional age. On the basis of their detectability it is concluded that evoked response components, determined between 30 to 34 weeks CA, are generally of limited use for clinical application, except for Auditory Brainstem Response (ABR) components I, IIn, V and Vc and Middle Latency Response (MLR) component Na. Our study made clear that improvement can be achieved by performing more than one examination within a period of approximately 4 weeks between the recording sessions. The cumulative detectability rates after two recordings showed improvement for all components involved in this study. The cumulative detectability rates of ABR components I, II, IIN, III, V, IIc, IIINc, Vc, MLR components Na and P0, and Auditory Cortical Response (ACR) components PbP1 and N2p are sufficient to use as measure in the neurophysiological judgement of functional integrity of the central auditory pathway in preterm infants.

Detectability, a prerequisite for clinical applicability, is one of the least documented aspects of auditory evoked response testing in newborns and especially in preterm newborns In determining the detectability of auditory evoked responses (Brainstem, Middle latency and Cortical Auditory Evoked Responses) in preterm born infants, one has to deal with both the ongoing anatomical as well as the physiological maturation of the peripheral and central auditory system In the preterm period the detectability of evoked responses is closely related to the appearance of the individual evoked response components It is clear that knowledge about the detectability of the individual evoked response components in preterm infants and the timing of the recordings is of great importance, because low detectability rates make the absence of a particular evoked response component irrelevant with respect to the clinical-neurophysiological correlation

The Auditory Brainstem Responses (ABRs) comprise the wave sequence within the first 10 ms after stimulation In the last decade detailed latency data on ABRs in preterm infants have been reported [Starr *et al* 1977, Rotteveel *et al* 1978a, Goldstein *et al* 1979, Krumholz *et al* 1985, Salamy *et al* 1985] In these studies the latency changes are extensively described, the detectability rate, however, is mentioned sparsely The most relevant ABR components show a rapid increase in detectability from 25 to 32 weeks [Rotteveel *et al* 1978a] The most stable components of the ABRs are the ipsilateral positive peaks I, II, III and V, the contralateral positive peaks IIc and Vc, the ipsilateral negative peak IIN, the contralateral negative peak IIINc See Figure 1

In contrast to the quantity of reports on the maturation of ABRs in preterm infants, there are only a few reports on the maturation of Middle Latency Responses (MLRs) and Auditory Cortical Responses (ACRs) [Ohlrich *et al* 1978, Rotteveel *et al* 1978b, Rotteveel *et al* 1978c, Kraus *et al* 1985, Rogers *et al* 1989]

The Middle Latency Responses (MLRs) are defined as the peaks and troughs occurring 10 to 100 ms after acoustic stimulation The MLR waveform components are denominated by the prefix P for positive and prefix N for negative components The additional suffices characterize the sequence in the wave complex N0, P0, Na, Pa, Nb, etc [Goldstein and Rodman 1967, Picton *et al* 1974] P0, Na and Pa are the most reproducible components in MLRs in preterm infants The detectability rates show a remarkable age dependency and Na reaches a higher detectability rate than Pa at any conceptional age (CA) level [Kraus *et al* 1985, Okitsu 1984, Rotteveel *et al* 1978b] See Figure 2

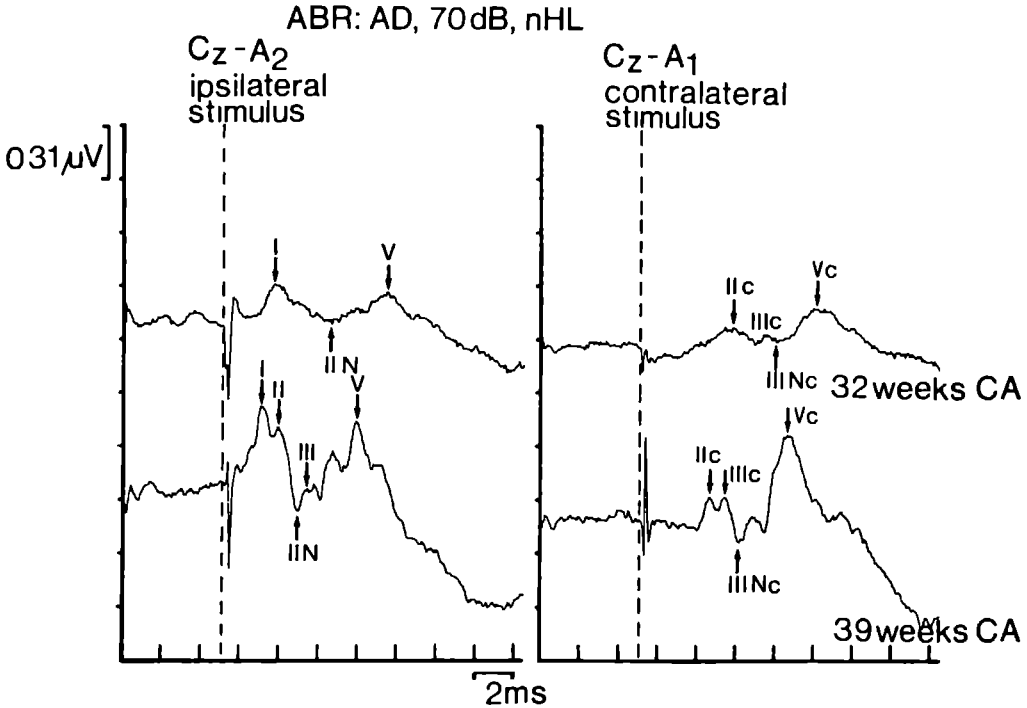

Fig. 1. *Brainstem Auditory Evoked Response obtained after stimulation right ear (AD) and recorded ipsilateral (Cz-A2) and contralateral (Cz-A1) at 32 and 39 weeks CA Symbols used are N – negative, c – contralateral*

The Auditory Cortical Responses (ACRs) constitute the third level of the auditory evoked response complex and consists of relatively low voltage fast waves (primary complex Na, Pb, Nc, P1, N1), followed by high voltage slow waves (secondary complex P2, N2, P3, N3, P4) [Akiyama *et al* 1969, Monod and Garma 1971, Schulte *et al* 1977, Weitzman and Graziani 1968] The ACR waveform components are denominated by the prefix P for positive and prefix N for negative components The additional suffices characterize the sequence in the wave complex Denomination after their latencies in this age group is not useful in view of the continuous changes in the complex composition of the waveform and the latency changes of the various components The first ACR waves appear at about 25 weeks CA, initiating the premature stage, followed by a transitional stage around term date, and gradually developing into a more mature 'posttransitional' stage, achieved at about 3 months after term date [Rotteveel *et al* 1978c] In the

premature stage the components of the secondary complex are additionally characterized by the suffix p [Rotteveel *et al* 1978c] The ACR waves occur within 1000 ms after stimulation. The most reproducible components of the ACR are Na, PbP1, P2p, N2p, P3p and N3p [Rotteveel *et al* 1978c] See Figure 3.

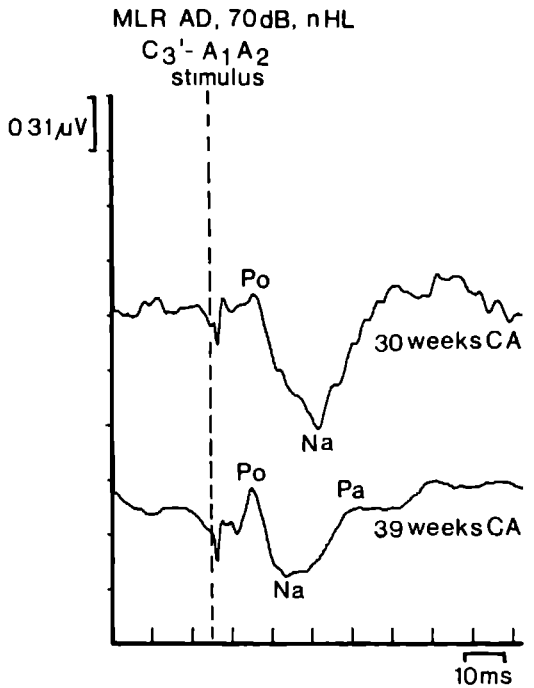

Fig. 2. *Middle Latency Auditory Evoked Response obtained after right ear stimulation (AD) and recorded contralateral (C3'-A1A2) at 30 and 39 weeks CA Symbols used are N=negative; P=positive.*

In a longitudinal study we examined the detectability of evoked response components in 37 low-risk preterm infants between 30 and 41 weeks CA The results were analyzed and the (cumulative) detectability rates of the most important evoked response components after 2, or if necessary, 3 recordings were determined.

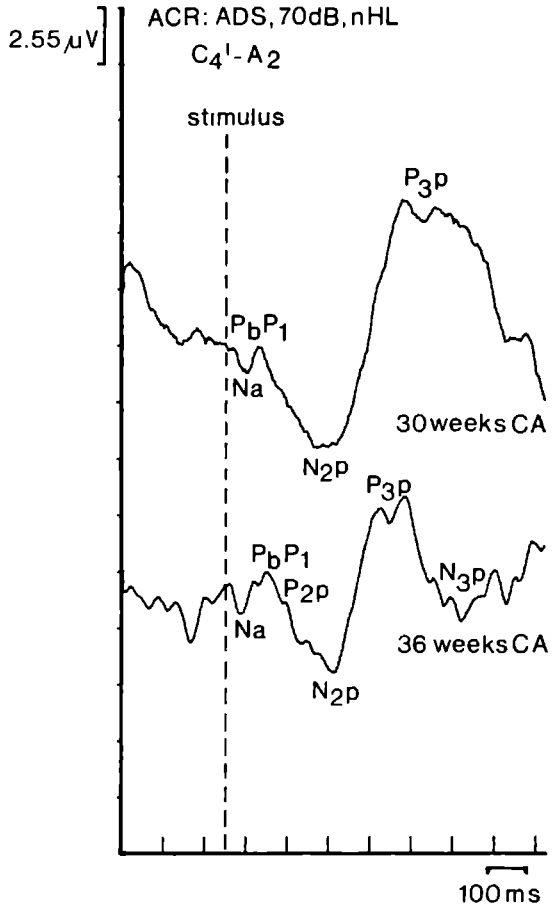

Fig. 3. *Cortical Auditory Evoked Response obtained after stimulation of both ears (ADS) and recorded at 30 and 36 weeks CA. Symbols used are: prefix P= positive; prefix N=negative; suffix p=premature.*

Subjects and methods

Brainstem, Middle Latency and Cortical Auditory Evoked Responses (BMC-AERs) were obtained in 37 low-risk preterm infants between 30 and 41 weeks CA (CA = GA + chronological age), using a Nicolet CA-1000 evoked potential unit. Subjects, test conditions, instrumentation and test parameters have been described previously [Rotteveel *et al.* 1985, Rotteveel *et al.* 1987d]. The test parameters are

summarized in Table 1 The gestational age (GA) varied from 25 to 34 weeks and was determined by the last menstruation date of the mother In doubtful cases the complete Dubowitz Newborn Maturation Scale was used to assess GA [Dubowitz *et al* 1970] Body weight, length and head circumference at birth were within normal limits (> P3)

Infants with structural haemorrhagic, hypoxic, infectious or dysgenetic brain lesions were excluded from the study Neonatal seizures, cranial nerve palsies or asymmetric syndromes also led to exclusion Structural brain lesions were established by neurologic examination, polygraphic electroencephalography and transfontanellar echoencephalography To exclude hypoxic events without structural damage the blood pH had to be above 7 10 (umbilical) or above 7 00 (heel) The Apgar scores had to be above 5 after 1 minute or above 7 after 5 minutes In four infants the last mentioned criteria (pH or Apgar) were not met, however, these infants were excepted in the study because of their excellent clinical condition and performance at time of the study The actual condition during the examination was assessed by an adapted neurological examination according to Dubowitz [Dubowitz *et al* 1980]

The first recording was obtained between 30-34 weeks CA, the second and third one between 35-41 weeks CA (ABR and MLR) or 35-37 weeks CA (ACR) The second recording period of the ACRs was limited to the period between 35 and 37 weeks CA because of the complex changes of the ACR in the transition of the premature ACR wave form to the infantile ('posttransitional') ACR wave form The subtests (ABR, MLR and ACR) were performed twice at each recording session in order to assess the reproducibility of the individual evoked response components At each recording session a threshold using intensities of 30, 40, 50 and 80 dB was performed to establish the integrity of the peripheral acoustic apparatus Only infants with comparable thresholds in relation to their conceptional age were included in the study The state of vigilance was observed by the technician To avoid 'crossover' effects the appearance of a contralateral peak I led to exclusion from the study The state in which the recordings were obtained were defined as sleep state, awake state, transitional state or restlessness The recordings in the study were preferably obtained while the infants were awake (ACR) and while the infants were asleep (ABR and MLR) The criteria upon which a deflection in a waveform is classified and labelled is previously described by one of the authors [Rotteveel *et al* 1987a, 1987b, 1987c]

Because the major aim of our study is about the clinical applicability of auditory evoked responses in preterm infants we have focussed on the most stable components in respect to their latencies

Table 1. *Test parameters*

	ABR	MLR	ACR
Click duration (μs)	100	999	999
Intensity* (dB)	70	70	70
Threshold (dB)	80/50/40/30		
Rate (Hz)	11 1	4 7	mean 0 5
Mode (rarefaction)	regular	regular	random
Binaural/monaural	monaural	monaural	binaural
Sensitivity (μV)	12 5 or 25	25 or 50	50 or 125
High pass filter** (Hz)	30	5	1
Low pass filter (Hz)	3000	250	30
Contralateral masking	+	+	-
Channels	2	4	4
Time base (ms)	20	100	1000
Prestimulus time (ms)	5	25	250
Sweeps	2000	256 or 512	64 or 128
Sample points	512	256	256
Sample frequency (kHz)	25 6	2 56	0 256
Active sites	Cz	Cz, C4', C3'	Cz, C4', C3'
Reference	A2, A1	A2A1 (linked)	A2, A1
Ground	Fz	Fz	Fz
Derivations	Cz-A2	Cz-(A2A1)	Cz-A2
	Cz-A1	C4'-C3'	Cz-A1
		C4'-(A2A1)	C4'-A2
		C3'-(A2A1)	C3'-A1

* *Zero dB setting = 30 dB peak equivalent SPL*

** *Filter roll-off 12 dB/octave*

Because grand composite group averages illustrate the interindividual stability of evoked responses, the stability of evoked response components was assessed by creating grand composite group averages [Rotteveel *et al.* 1985, Rotteveel *et al.* 1987d]. The ABR records were analysed independently by two investigators. The results of prior recordings were not known to the investigators. For analysis the investigators used visual inspection of the ipsilateral records in connection with the contralateral records, superimposition of the two averages for each subtest at each recording session, the intensity series and the grand composite group averages, which were obtained by summation of the individual records of all

subjects for each CA level. See Figure 4. The MLR and ACR records were analysed in the same manner. See Figure 4

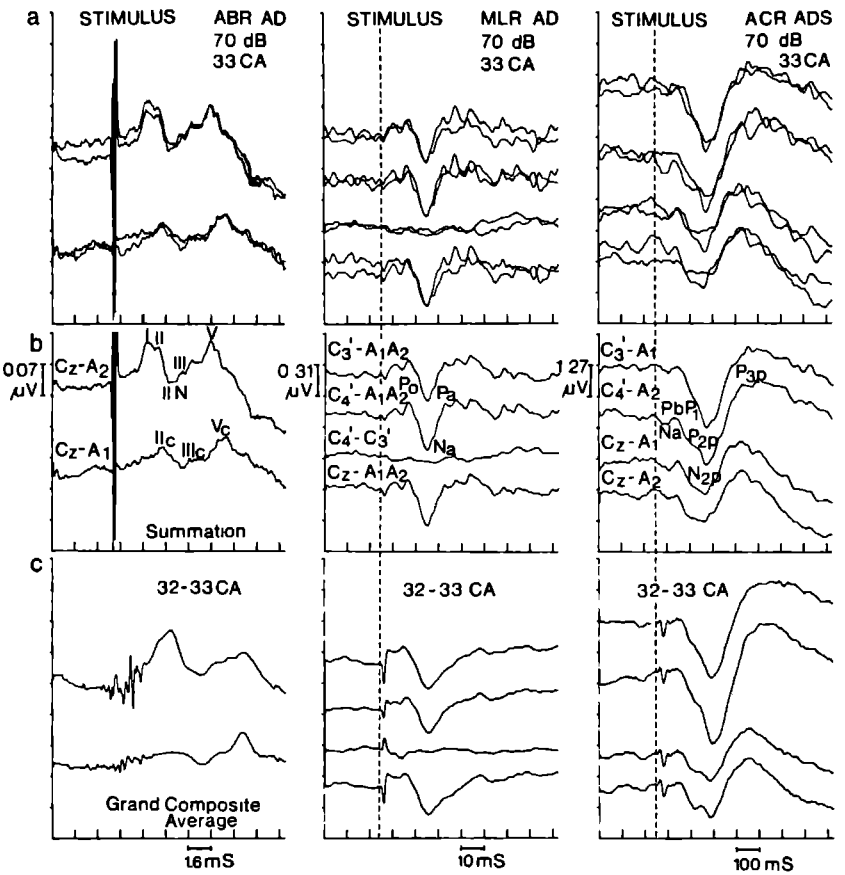

Fig. 4. *Brainstem (ABR), Middle Latency and Cortical (ACR) Auditory evoked Response obtained in representative preterm born infants at 33 weeks CA a) superimposedduplo records; b) summation of the duplo records; c) grand composite averages, obtained by summation of individual records of 39 preterm born infants recorded at 32 or 33 weeks CA.*

The records were examined qualitatively only for the presence or absence of the ipsilateral positive peaks I, II, III and V, the ipsilateral negative peak IIN, the contralateral positive peaks IIc and Vc and the contralateral negative peak IIINc

for the Auditory Brainstem Evoked Responses (ABRs), the positive peaks P0 and Pa and the negative peak Na for the Middle Latency Responses (MLRs) and the negative peaks Na, N2p, N3p and the positive peaks PbP1, P2p and P3p for the Auditory Cortical Responses (ACRs) The choice of the selected components was based on previous observations with regard to the detectability for each CA level [Rotteveel *et al* 1987c] The detectability rate of the individual BMC-AER components was determined after the first recording and expressed in percentages together with the limits of a 95% confidence interval

After the second recording the cumulative detectability rate, i e , the presence of individual evoked response components in either or both recordings, was calculated and expressed in percentages (with 95% limits of a confidence interval) for the ABR, MLR and ACR separately For the MLR components it was possible to calculate the cumulative detectability rate after three recordings However, the number of subjects was reduced because some infants were only tested once in the period between 35 and 41 weeks CA The cumulative detectability rate of ACR components after three recordings was not established because the second testing period was restricted to the time period between 35-37 weeks CA This study has been approved by the Ethics Committee of the University Hospital Nijmegen and the parents of the subjects gave informed consent to the work

Results

Auditory Brainstem Response (ABR)

Table 2 shows the detectability rates for the most prominent ABR components in a group of 37 preterm born infants after the first recording performed between 30-34 weeks CA For the ABR peaks I and V the detectability rates are at least 92%, the other ABR components (II, IIN, III, IIc, IIINc and Vc) showed slightly lower percentages (at least 76% to 89%) After two recordings (firstly between 30-34 weeks CA, and subsequently between 35-41 weeks CA) the cumulative detectability rates for the ABR components reached values of 100% except for the ABR peaks II, III and IIINc after stimulation of the left ear (95% and 97% respectively) The cumulative detectability rates for ABR components after right-sided stimulation compared to the cumulative detectability rates after left-sided stimulation demonstrated no significant differences (Mc Nemar tests $p > 0\ 25$) Lower detectability rates are observed for the right-sided stimulations after the first recording However, with the exception of component IIN ($p = 0\ 03$) neither of these right-left differences are significant ($p > 0\ 25$)

Table 2. *Detectability rate of ABR-waves after one recording (between 30-34 weeks conceptional age, n=37) and cumulative detectability rate after two recordings (second recording between 35-41 weeks conceptional age, n=37)*

	Detectability rate after first recording in percent with 95% confidence interval		Cumulative detectability rate after 2 recordings in percent with 95% confidence interval	
Waves	ABR AD	ABR AS	ABR AD	ABR AS
I	92 (78-98)	100 (91-100)	100 (91-100)	100 (91-100)
II	76 (59-88)	81 (65-92)	100 (91-100)	95 (82-99)
IIN	84 (68-94)	100 (91-100)	100 (91-100)	100 (91-100)
III	87 (71-96)	92 (78-98)	100 (91-100)	97 (86-100)
V	92 (78-98)	100 (91-100)	100 (91-100)	100 (91-100)
IIc	89 (75-97)	92 (78-98)	100 (91-100)	100 (91-100)
IIINc	78 (62-90)	84 (68-94)	100 (91-100)	97 (86-100)
Vc	89 (75-97)	97 (86-100)	100 (91-100)	100 (91-100)

Middle Latency Response (MLR)

The detectability rates for the most prominent MLR components (P0, Na, Pa) after the first recording are comparable to the detectability rates found for the ABR components after the first recording, except for Pa Pa shows rather low detectability rates of 43% or less, depending on the derivation, the side of stimulation and state of vigilance The same holds for the cumulative detectability rates of MLR components after two recordings The cumulative detectability rates for MLR component Pa reached percentages of 61% to 66%, also depending on the derivation and stimulus side considered The cumulative detectability rates after 2 and 3 recordings are similar (63% to 79% for Pa) No or very slight differences were found comparing detectability rates for ipsilateral, contralateral and central derivations See Table 3 Comparing detectability rates for right-sided stimulation with left-sided stimulation neither after one nor after two recordings significant differences could be established (Mc Nemar tests $p > 0\ 25$)

Auditory Cortical Response (ACR)

Tables 4 and 5 show the (cumulative) detectability rates for the most prominent ACR components (Na, PbP1, P2p, N2p, P3p, N3p)

Table 3. *Detectability rate of MLR-waves after one recording (between 30-34 weeks conceptional age) and cumulative detectability rate after two recordings (second recording between 35-41 weeks conceptional age) For right-sided stimulation n=36, for left-sided stimulation n=35*

	Detectability rate after first recording in percent with 95% confidence interval		
	P0	Na	Pa
AD Cz	89 (74-97)	100 (90-100)	31 (16-48)
AS Cz	89 (74-97)	97 (85-100)	43 (26-61)
AD C4'	89 (74-97)	100 (90-100)	31 (16-48)
AS C3'	86 (70-95)	97 (85-100)	40 (24-58)
AD C3'	89 (74-97)	100 (90-100)	33 (19-60)
AS C4'	89 (74-97)	97 (85-100)	37 (22-55)
	Cumulative detectability rate after 2 recordings in percent with 95% confidence interval		
	P0	Na	Pa
AD Cz	97 (86-100)	100 (90-100)	61 (44-77)
AS Cz	97 (85-100)	100 (90-100)	66 (48-81)
AD C4'	97 (86-100)	100 (90-100)	61 (44-77)
AS C3'	97 (85-100)	100 (90-100)	66 (48-81)
AD C3'	97 (86-100)	100 (90-100)	61 (44-77)
AS C4'	97 (85-100)	100 (90-100)	63 (45-79)

Table 4. *Detectability rate of early ACR-waves after one recording (between 30-34 weeks CA, n=28) and cumulative detectability rate of early ACR-waves after two recordings (second recording between 35-41 weeks CA, n=28)*

	Detectability rate after first recording in percent with 95% confidence interval		Cumulative detectability rate after 2 recordings in percent with 95% confidence interval	
	Na	PbP1	Na	PbP1
Cz-A2	73 (56-86)	68 (50-82)	87 (71-96)	97 (86-100)
Cz-A1	73 (56-86)	70 (53-84)	87 (71-96)	97 (86-100)
C4'	78 (62-90)	73 (56-86)	96 (82-99)	95 (82-99)
C3'	65 (48-80)	81 (65-92)	92 (78-98)	100 (91-100)

Table 5. *Detectability rate of late ACR-waves after one recording (between 30-34 weeks CA, n=28) and cumulative detectability rate of late ACR-waves after two recordings (second recording between 35-37 weeks CA, n=28)*

	Detectability rate after first recording in percent with 95% confidence interval			
	P2p	N2p	P3p	N3p
Cz-A2	39 (22-59)	75 (55-89)	61 (41-45)	25 (11-45)
Cz-A1	36 (19-56)	79 (59-92)	57 (37-76)	25 (11-45)
C4'	54 (34-73)	86 (67-96)	64 (44-81)	(11-25 45)
C3'	43 (25-63)	86 (67-96)	68 (48-84)	25 (11-45)
	Cumulative detectability rate after two recordings in percent with 95% confidence interval			
	P2p	N2p	P3p	N3p
Cz-A2	71 (51-87)	93 (77-99)	89 (72-98)	68 (48-84)
Cz-A1	64 (44-81)	89 (72-98)	86 (67-96)	64 (44-81)
C4'	79 (59-92)	96 (82-100)	86 (67-96)	54 (34-73)
C3'	82 (63-94)	100 (88-100)	89 (72-98)	43 (25-63)

The detectability rates after the first recording, performed between 30-34 weeks CA, were generally lower then the detectability rates of the ABR and MLR components, except for Pa After the first recording, the ACR components Na, PbP1, N2p and P3p showed detectability rates varying from 57% to 86% The ACR component P2p demonstrated lower detectability rates of 36% to 54%, depending on the derivation The ACR component N3p showed the lowest detectability rates (25%) After two recordings (the second recording performed between 35-37 weeks CA) the cumulative detectability rates for all ACR components revealed higher percentages, varying from 86% to 100% for components Na, PbP1, N2p, P3p and 43% to 82% for components P2p and N3p No significant differences for detectability rates of ACR components were found, comparing central and temporal derivations (Mc Nemar tests $p = 0\ 07$ for the left derivations of component N3p after two recordings, otherwise $p > 0\ 10$) or comparing right-sided and left-sided derivations ($p > 0\ 10$)

To determine the clinical applicability of BMC-AERs in preterm and full-term born infants, one has to establish which of the individual evoked response components, during the neonatal period, are suitable for clinical use. Several authors have reported that the ongoing maturation of evoked responses during the preterm period, especially between 30 to 40 weeks CA, is associated with increasing detectability rates of the most prominent evoked response components [Starr *et al.* 1977, Ohlrich *et al.* 1978, Okitsu 1984, Kraus *et al.* 1985, Rotteveel *et al.* 1987a, Rotteveel *et al.* 1987b, Rotteveel *et al.* 1987c, Rogers *et al.* 1989]. For this reason one has to be aware of the detectability of the individual evoked response components, because low detectability rates make the absence of a particular evoked response component irrelevant with respect to the clinical-neurophysiological correlation.

In our study we found the ABR components I, IIN, V, IIc and Vc to be the most stable with detectability rates of 87% to 100% and therefore clinically suitable. This is in agreement with detectability rates reported by Goldstein *et al.* [1967] and Krumholz *et al.* [1985]. However, considerably lower detectability rates are reported by Roberts *et al.* [1982] and Salamy *et al.* [1985]. This is probably due to protocol design differences and different analysis methods. Improvement can be achieved in determining cumulative detectability rates after two recording sessions. In the same group preterm infants the cumulative detectability rates for the ABR components shows an increase up to 100%.

In accordance with the sparse reports concerning the detectability rates of MLR components, we found P0 and Na the most stable and detectable. The detectability rates after the first recording session varied from 86% to 100%. Also in agreement with most reports are the considerably lower detectability rates of Pa [Okitsu 1984, Kraus *et al.* 1985, Rogers *et al.* 1989]. The cumulative detectability rates after two recording sessions showed clearly increased percentages; P0 and Na reached values of 97 to 100%, whereas Pa reached only values of 61% to 66%.

Studies on ACRs report mainly latencies and amplitudes of the peaks and troughs. Only briefly the detectability of the ACR components is discussed [Ellingson *et al.* 1974, Graziani *et al.* 1974, Ohlrich *et al.* 1978]. Comparison of the results of these reports is arduous due to the lack of uniformity in denomination of the various components. Our components N2p and P3p correspond respectively with component N1 and P2 as described by Graziani *et al.* [1974]. In our study after the first recording session components Na, PbP1, N2p and P3p showed moderate detectability rates (57%-86%). Taking in account the differences

in nomenclature our results with respect to the detectability are in agreement with the reports mentioned. After the second recording session only ACR component PbP1 achieved detectability rates of nearly 100% (95%-100%), whereas components N2p (89%-100%) and P3p (86%-89%) reaches slightly lower values.

From our study it is concluded that the detectability rates of evoked response components, determined between 30 to 34 weeks CA, are too low to use the absence or presence of these components for clinical application, yet an exception has to be made for ABR components I, IIn, V and Vc and MLR component Na. However, our study made clear that improvement can be achieved by performing more than one examination within an average period of approximately 4 weeks between the recording sessions. The cumulative detectability rates after two recordings, i.e., the detectability rate of a certain component in either or both recordings, showed improvement for all components involved in this study. The cumulative detectability rates of ABR components I, II, IIN, III, V, IIc, IIINc, Vc, and MLR components Na and P0 are sufficient to serve as a diagnostic measure. The same holds for fast ACR component PbP1 and the slow ACR component N2p, although after 37 weeks CA the transition from the premature ACR waveform into the infantile waveform is accompanied by a considerable loss of detectability around the term period. In our opinion no clinical decisions based on auditory evoked responses in preterm infants should be made until at least two recordings (spaced at least a month apart) have been made.

Chapter 3

The effect of preterm birth on brainstem, middle latency and cortical auditory evoked responses (BMC-AERs)

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Summary

Recent studies on the maturation of Auditory Brainstem Evoked Responses (ABRs) present conflicting results, whereas only sparse reports exist with respect to extrauterine maturation of Middle Latency Auditory Evoked Responses (MLRs) and Auditory Cortical Evoked Responses (ACRs). The present study reports the effect of preterm birth on the maturation of auditory evoked responses in low-risk preterm infants (28-36 weeks conceptional age). The ABRs indicate a consistent trend towards longer latencies for all individual ABR components and towards longer interpeak latencies in preterm infants. The MLR shows longer latencies for early component P0 in preterm infants. The ACRs show a remarkable difference between preterm and term infants. At 40 weeks CA the latencies of ACR components Na and P2 are significantly longer in term infants, whereas at 52 weeks CA the latencies of the same ACR components are shorter in term infants. The results support the hypothesis that retarded myelination of the central auditory pathway is partially responsible for differences found between preterm infants and term infants with respect to late ABR components and early MLR component P0. Furthermore, mild conductive hearing loss in preterm infants may also play its role. A more complex mechanism is implicated to account for the findings noted with respect to MLR component Na and ACR components Na, and P2.

The effects of preterm birth on the rate of maturation of the auditory system remains an issue of both theoretical and clinical importance [Eggermont and Salamy 1988, Collet *et al.* 1989]. Important elements involved in the neurophysiologic maturation of the auditory system are peripherally the maturation of the cochlea and centrally the increasing synaptic efficiency, dendritic growth and axonal myelination [Despland 1985, Eggermont and Salamy 1988]. The cochlea becomes functional at about 20 weeks conceptional age (CA). At this time other portions of the auditory pathway are capable of signalling its function. The peripheral portions of the auditory pathway reach their full morpho-functional growth during the first weeks of post-term life. Centrally, in the human there is considerable synaptogenesis in the perinatal and postnatal period and a tremendous growth of dendrites after term [Norman 1975, Yakovlev and Lecour 1967]. Myelination occurs during the second growth spurt of the brain, which takes place in the second half of gestation and lasts well into the second postnatal year or later [Dobbing and Sands 1973, Dobbing 1974]. The vestibular and auditory pathways in the brainstem myelinate early and rapidly before term, whereas other fibre systems at the level of the brainstem myelinate later and at a slower rate [Yakovlev and Lecour 1967, Lemir *et al.* 1975, Brody *et al.* 1987]. Developmental, neuroanatomical and magnetic resonance imaging (MRI) studies have shown that myelination progresses in the centripetal direction [Yakovlev and Lecour 1967, Gilles 1976, Gilles *et al.* 1983, Salamy *et al.* 1985, Holland *et al.* 1986, McArdle *et al.* 1987, Martin *et al.* 1988]. The neurophysiological maturation of the auditory system also proceeds from the periphery to the cortex. Hence, the maturation of the caudal brainstem is somewhat faster than that of the upper brainstem [Ruben and Rapin 1980, Lauffer and Wenzel 1990, Hafner *et al.* 1991, Jiang *et al.* 1991]. At term the auditory pathway is myelinated in 95% of infants [Gilles 1976, Eggermont and Salamy 1988].

In view of the fast rate of maturation of both the peripheral and the central nervous system between 28 and 40 weeks CA, one can expect that the human auditory pathway is very vulnerable to anoxic-ischemic insults in this period. Indeed, several experiments have demonstrated selective vulnerability of auditory relay nuclei, such as the cochlear nuclei, superior olives and inferior colliculi [Dobbing and Sands 1973, Griffiths and Laurence 1974, Myers 1975, Norman 1975, Leech and Alvord 1977, Salamy *et al.* 1982].

Various studies concerning the effect of preterm birth on the maturation of ABRs present partly equivocal results. Starr *et al.* [1977], Despland *et al.* [1980] and Fawer *et al.* [1982] did not find differences between term and preterm infants

at the same conceptional age with respect to the latencies and interpeak latencies of the ABR [Starr *et al.* 1977, Despland and Galambos 1980, Fawer and Dubowitz 1982]. Delorme *et al.* [1986] and Collet *et al.* [1989], however, found significantly shorter latencies of ABR components III and V and decreased interpeak latencies I-III and I-V in infants with an extrauterine life longer than 2 weeks compared with infants at the same conceptional age but an extrauterine life less than 2 weeks [Delorme *et al.* 1986, Collet *et al.* 1989]. Furthermore, Eggermont and Salamy [1988] showed longer latencies for ABR components I, III and V in preterm infants compared to infants born at term, but no differences in interpeak latencies I-III, III-V and I-V.

Only sparse reports exist on intrauterine maturation versus extrauterine maturation of MLRs and ACRs. Schulte *et al.* [1977] reported that the maturation of ACRs was not influenced by premature exposure to the extrauterine acoustic environment and that three or more weeks of exposure to continuous incubator noise does not influence the auditory evoked responses.

We studied the differences between the auditory evoked responses in healthy, term infants compared to low-risk preterm infants, born between 28 and 36 weeks CA. It can be hypothesized that extrauterine preterm exposure leads to a delayed development of the auditory system, reflected by longer latencies, interpeak latencies and lower amplitudes of auditory evoked responses. Alternatively, extrauterine preterm exposure may lead to enhanced auditory system development, reflected by shorter latencies and higher amplitudes of auditory evoked responses. In this study ABR, MLR and ACR latencies and interpeak latencies, amplitudes, peak-peak amplitudes, peak-peak ratios and waveform morphology of the most important auditory evoked response components are analysed in both term, healthy infants and low-risk preterm infants. The low-risk preterm infants have been studied previously with respect to the maturation of auditory evoked responses during the preterm period.

Subjects

Twenty-three healthy, term infants (mean gestational age (GA) 39.9 weeks, sd = 1.0 week) and 49 low-risk preterm infants born between 28 and 36 weeks GA (mean GA 30.7 weeks, sd = 2.3 weeks) were studied at term and 3 months thereafter. Subjects have been described and reported previously [Rotteveel *et al.* 1987a, Rotteveel *et al.* 1987b, Rotteveel *et al.* 1987c]. The gestational age was determined by the mother's last menstruation. In doubtful cases the complete

Dubowitz Newborn Maturation Scale was used to assess GA [Dubowitz *et al.* 1970]. Body weight, length and head circumference at birth were within normal limits (> P3 and < P97).

Infants with structural, haemorrhagic, hypoxic, infectious or dysgenetic brain lesions were excluded from the study. Neonatal seizures, cranial nerve palsies or asymmetric syndromes also led to exclusion from this study. Structural, haemorrhagic and cystic hypoxic brain lesions were established by neurologic examination, polygraphic electroencephalography and transfontanellar echoencephalography. The mean blood pH in the preterm group was 7.23 (sd = 0.11) (umbilical) and 7.21 (sd = 0.11) (heel). In the term group this was respectively 7.26 (sd = 0.07) and 7.26 (sd = 0.06). The Apgar scores had to be above 5 after 1 minute or above 7 after 5 minutes for study inclusion. The actual clinical condition at the time of each recording session was assessed by neurological examination according to Dubowitz *et al.* [1980].

This study has been approved by the Ethics Committee of the University Hospital of Nijmegen. Informed consent was obtained from all parents of infants enrolled in the study.

Methods

Brainstem (ABR), Middle Latency (MLR) and Cortical (ACR) Auditory Evoked Responses were obtained at term (40 weeks CA) and 3 months thereafter using a Nicolet CA-1000 evoked potential unit. Test conditions, instrumentation, test parameters and nomenclature have been described previously [Rotteveel *et al.* 1987a, Rotteveel *et al.* 1987b, Rotteveel *et al.* 1987c]. The test parameters are summarized in Table 1.

In each recording session ABR, MLR and ACR recordings were replicated in order to visually assess the reproducibility of the individual evoked response components. To avoid 'crossover' effects, the appearance of a contralateral peak I led to exclusion of the recording from the study. The state of vigilance was monitored by the technician. The state in which the recordings were obtained were defined as: sleep state, awake state, transitional state or restlessness. EEG monitoring for state definition was not performed. The ACR recordings were preferentially obtained while the infants were awake and the ABR and MLR during sleep although awake state was accepted. The criteria upon which a deflection in a waveform is classified and labelled is previously described [Rotteveel *et al.* 1987a, Rotteveel *et al.* 1987b, Rotteveel *et al.* 1987c].

Table 1. *Test parameters*

	ABR	MLR	ACR
Click duration (μs)	100	999	999
Intensity* (dB)	70	70	70
Threshold (dB)	80/50/40/30		
Rate (Hz)	11 1	4.7	mean 0 5
Mode (rarefaction)	regular	regular	random
Binaural/monaural	monaural	monaural	binaural
Sensitivity (μV)	12.5 or 25	25 or 50	50 or 125
High pass filter** (Hz)	30	5	1
Low pass filter (Hz)	3000	250	30
Contralateral masking	+	+	-
Channels	2	4	4
Time base (ms)	20	100	1000
Prestimulus time (ms)	5	25	250
Sweeps	2000	256 or 512	64 or 128
Sample points	512	256	256
Sample frequency (kHz)	25.6	2 56	0 256
Active sites	Cz	Cz, C4', C3'	Cz, C4', C3'
Reference	A2, A1	A2A1 linked	A2, A1
Ground	Fz	Fz	Fz
Derivations	Cz-A2	Cz-(A2A1)	Cz-A2
	Cz-A1	C4'-C3'	Cz-A1
		C4'-A2	C4'-A2
		C3'-A1	C3'-A1

* Zero dB setting = 30 dB peak equivalent SPL

** Filter roll-off 12 dB/octave

The ABR, MLR and ACR records were analyzed independently by two investigators. The analysis required visual inspection of the ipsilateral records in connection with the contralateral records and superimposition of the two averages for each subtest at each recording session. Threshold was determined using intensities of 30, 40, 50 and 80 dB SPL. The threshold responses were used to identify ABR component I and/or V. Grand composite group averages were used as templates for individual records. The grand composite group averages were obtained by summation of the individual records for each CA level and for the term and preterm groups separately.

ABR latencies of the ipsilateral components I, II, III and V, the latencies of contralateral components IIc and Vc, the ipsilateral interpeak latencies I-III, III-V

and I-V, the contralateral interpeak latency IIc-Vc, the amplitudes of ipsilateral components II and V and the ipsilateral amplitude ratio V/I after monaural stimulation were analyzed. See Figure 1.

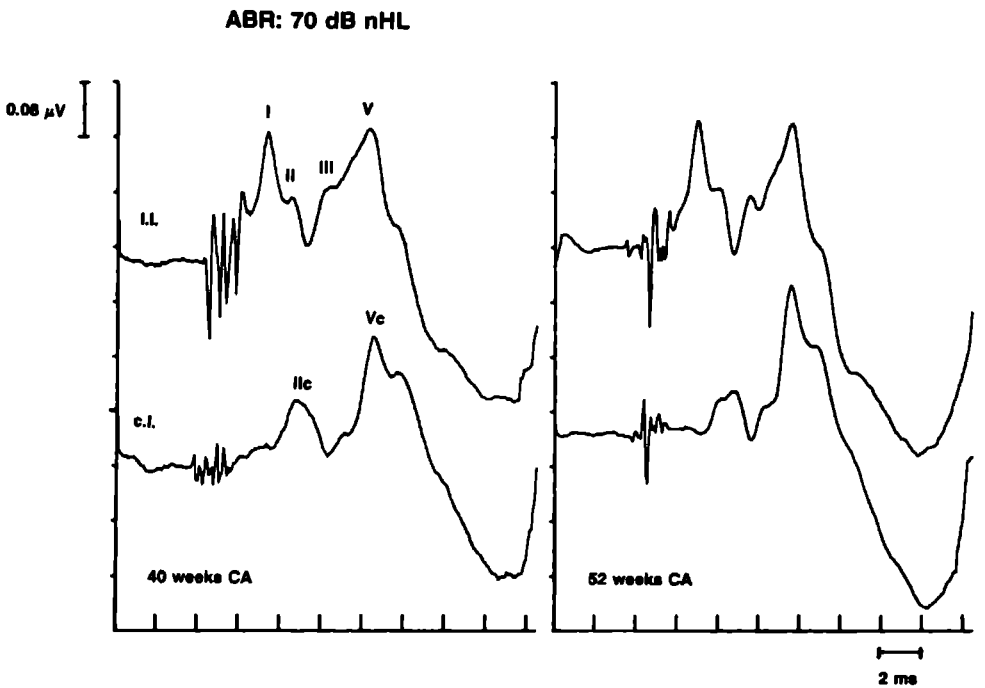

Fig. 1. *Grand composite group averages of ABRs obtained ipsilateral and contralateral to stimulation in full term and 3 months old infants. An upward deflection indicates positivity at the Cz electrode. The synchronization procedure of peak I results in a jitter of the stimulus artefact, avoiding a I-V interpeak latency difference jitter. (i.l.= ipsilateral; c.l.=contralateral; prestimulus interval=5 ms).*

MLR latencies and amplitudes of components P0 and Na, the interpeak latency P0-Na and the peak-peak amplitude P0-Na for each derivation after monaural stimulation were determined See Figure 2.

ACR latencies and amplitudes of components Na, N1, P2 and N2 at 40 and 52 weeks CA and P3 at 52 weeks CA for each derivation after binaural stimulation

were analysed. See Figure 3. Waveform morphology was determined by visual inspection.

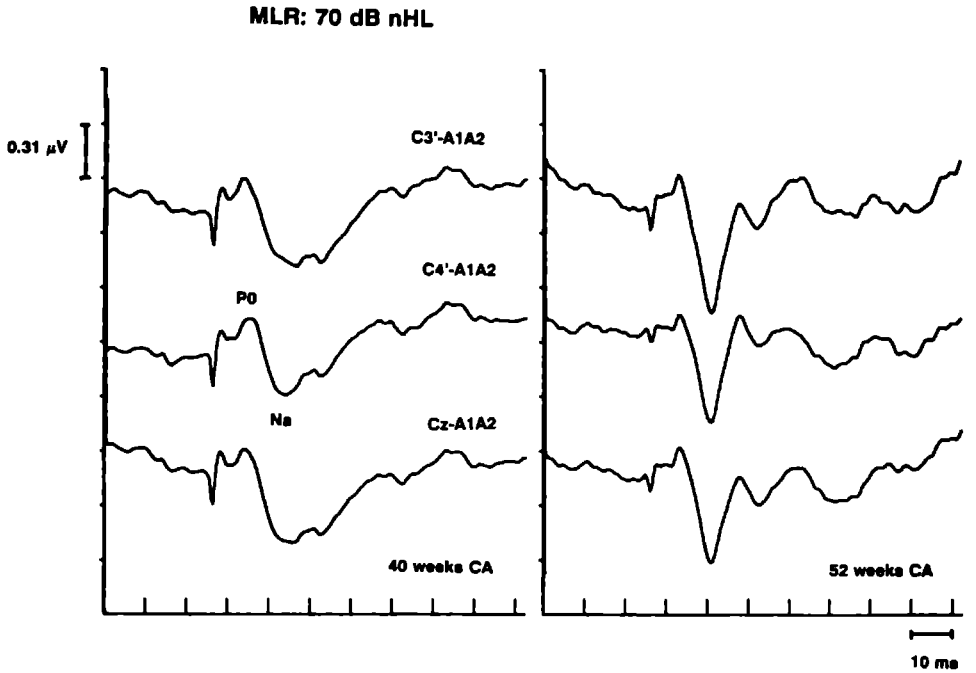

Fig. 2. *Grand composite group averages of ABRs obtained ipsilateral and contralateral to stimulation in full term and 3 months old infants. An upward deflection indicates positivity at the Cz electrode.*

Using *t*-tests for paired samples, in general, no clear differences were found between left-sided and right-sided stimulation for ABR and MLR parameters. In addition, no imbalance could be observed between the number of positive and negative mean left-right differences. Consequently, the corresponding derivations, i.e. the ipsilateral derivation after right- and left-sided stimulation, respectively the contralateral derivation after right- and left-sided stimulation were averaged. For the same reasons the left and right temporal derivations and left and right central derivations concerning the ACR were averaged. The results of ABRs, MLRs and

ACRs at term and 3 months thereafter were analysed for each derivation in both the preterm and term infants.

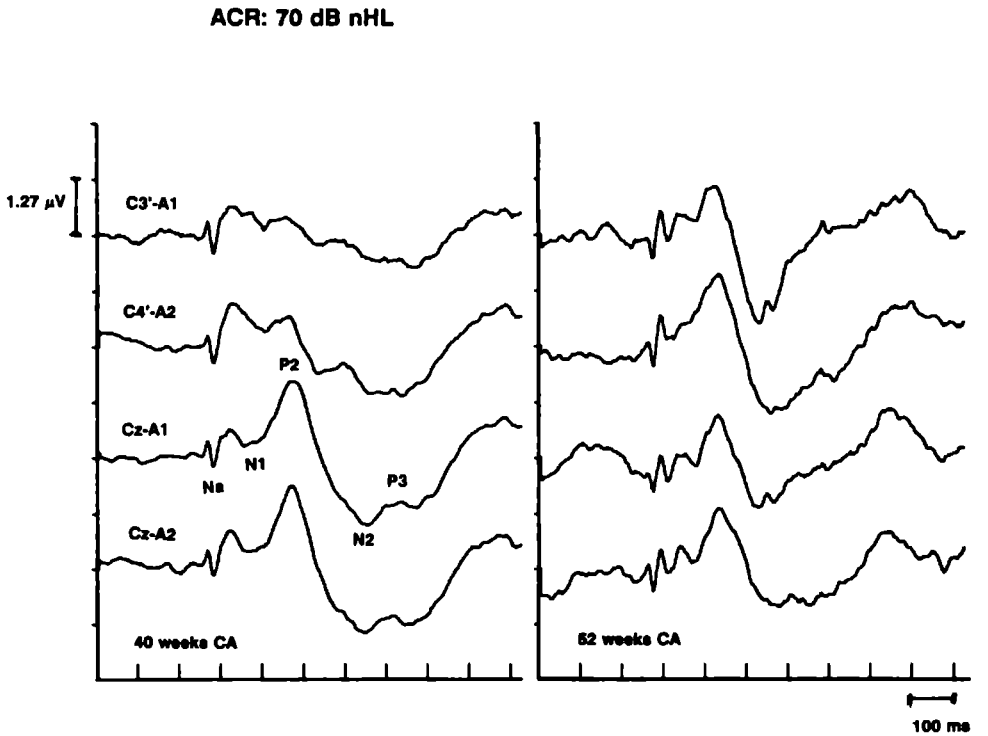

Fig. 3. *Grand composite group averages of ACRs obtained after binaural stimulation in full term and 3 months old infants. An upward deflection indicates positivity at the Cz, C4' and C3' electrodes.*

First, these analyses were made for subjects with complete observations for the latencies and amplitudes at each derivation and stimulus side. Because missing observations may not necessarily indicate pathology, the analyses were done next for complete observations with the addition of incomplete observations, i.e. observations with missing values for one of both stimulation and/or derivation sides [Pasman *et al.* 1991].

Statistical methods

First, the multivariate Hotelling T^2-test for two samples was performed to determine a possible difference between the preterm group and term group considering the joint response components. Next, if a difference between the term group and the preterm group was established, it was followed by a simultaneous test procedure as described by Morrison [1967]. This procedure was used to identify the response components accountable for the difference found. Furthermore, the univariate Student's t-test for two samples was performed to determine differences between the preterm and term group with respect to separate auditory evoked response components. Any difference was considered to be statistically significant if a p-value ≤ 0.05 was found. In cases when the p-value was $0.05 < p \leq 0.10$ the testing result was said to be nearly significant.

Results

A summary of significant and nearly significant differences between the preterm and term group with respect to latencies and amplitudes of ABR, MLR and ACR components according to the Student's t-test are given in Table 2. In general, results of the analyses concerning left/right complete observations are similar to those extended by incomplete observations. With the exception of the ABR latencies. This may be a reflection of the larger fraction of preterm infants with incomplete observations compared to term infants in this group. The latencies in infants with incomplete observations are increased. The results concerning complete/incomplete observations are presented in detail because incompleteness may be related to retarded maturation of auditory evoked responses [Pasman *et al.* 1991].

ABR

No differences concerning ABR waveform morphology, i.e. the morphology of the various peaks and troughs, between preterm and term infants were found.

There was a tendency towards longer latencies for all ABR components in the preterm group. See Table 3. However, as per Hotelling T^2-test no statistical differences between term infants and preterm infants at term and 3 months thereafter with respect to the joint latencies and amplitudes were found. According to Student's t-tests at 3 months the latency of ABR component V was significantly longer in preterm infants. Latencies of component III and Vc and the interpeak

latency I-V were nearly significantly longer in preterm versus term infants at 3 months. A significant increase in the amplitude ratio V\I in preterm infants was found at term.

MLR

No differences in MLR waveform morphology were seen between preterm infants and term infants.

According to the Hotelling T^2-test significant or nearly significant differences between the preterm infants and term infants were found for the central and contralateral derivations at term and 3 months thereafter. Using the simultaneous test procedure it was found that these differences were primarily due to the latency of component P0 for central derivations at 3 months ($p = 0.04$) and for contralateral derivations at term as well as at 3 months ($p \leq 0.01$).

Generally, the latencies of MLR components P0 and Na were increased in preterm infants compared to term born infants for each derivation (ipsilateral, contralateral and central) at both time periods tested. See Tables 4a, 4b and 4c. However, based upon Student's t-tests these differences were only significant for MLR component P0 in the contralateral and central derivations at term and 3 months and in the ipsilateral derivation at 3 months. No significant differences concerning the MLR component Na were found. The interpeak latency P0-Na was always shorter in preterm infants, but significance was only reached for the contralateral derivations at term, and nearly significance was reached at 3 months. This is in accordance with findings concerning the absolute latencies of components P0 and Na. In general, the amplitudes of MLR components P0 and Na were decreased and the peak-peak amplitude P0-Na was reduced in preterm infants. This was statistically significant with regard to the amplitude of MLR component P0 at term in the ipsilateral derivation and with regard to component Na at term and 3 months in the contralateral derivation. Peak-peak amplitudes P0-Na were significantly reduced in preterm infants versus term infants at 3 months in the contralateral derivation and nearly significantly reduced at term in the contralateral derivation and at 3 months in the central derivation.

ACR

Differences in latencies and amplitudes of various ACR components between preterm and term infants, as well as differences concerning the ACR waveform morphology were found. At term and 3 months the ACR composite group average waveform showed a more mature shape in term infants compared to preterm infants. See Figure 4.

Table 2. *Summary of differential developmental differences of Auditory Evoked between preterm infants and term infants. Significant and nearly significant to Student's t-tests are indicated*

		Recorded at term	
		Complete	Complete/incomplete
ABR		n_p/n_t = 20/20	n_p/n_t = 33/23
Latency	III	-	-
	V	-	-
	I-V	-	-
	Vc	-	-
Amplitude	V	preterm < term	-
	ratio V/I	-	preterm < term
MLR		$n_p^1/n_p^2/n_p^3$ = 25/24/25	$n_p^1/n_p^2/n_p^3$ = 33/33/32
		$n_t^1/n_t^2/n_t^3$ = 16/8/11	$n_t^1/n_t^2/n_t^3$ = 25/20/19
Latency	P0	preterm > term [1 3]	preterm > term [1 3]
	P0-Na	(preterm < term [3])[1]	preterm < term [3]
Amplitude	P0	(preterm < term)[1]	preterm < term [2]
	Na	(preterm < term)[3]	preterm < term[3]
	P0-Na	(preterm < term)[3]	(preterm < term)[3]
ACR		n_p^4/n_p^5 = 9/10, n_t^4/n_t^5 = 14/6	n_p^4/n_p^5 = 18/19, n_t^4/n_t^5 = 22/15
Latency	Na	preterm < term [4 5]	preterm < term [4 5]
	N1	preterm < term [4]	-
	P2	preterm < term [4]	preterm < term [4 5]
Amplitude	Na	preterm > term [4 5]	(preterm > term [5]) [4]
	N1	preterm < term [5]	-
	P2	preterm < term [4]	(preterm < term) [4]
	N2	-	(preterm < term) [4]

MLR
1 central derivations
2 ipsilateral derivations
3 contralateral derivations

ACR
4 central derivations
5 temporal derivations

n_p number of preterm infants
n_t number of term infants

Table 2. *(continued)*

		Recorded 3 months after term	
		Complete	Complete/incomplete
ABR		n_p/n_t = 24/19	n_p/n_t = 44/22
Latency	III	-	(preterm > term)
	V	-	preterm > term
	I-V	-	(preterm > term)
	Vc	-	(preterm > term)
Amplitude	V	-	-
	ratio V/I	-	-
MLR		$n_p^1/n_p^2/n_p^3$ = 43/42/42	$n_p^1/n_p^2/n_p^3$ = 49/49/48
		$n_t^1/n_t^2/n_t^3$ = 18/10/18	$n_t^1/n_t^2/n_t^3$ = 22/22/22
Latency	P0	preterm > term [1 3]	(preterm > term [1 3])[2]
	P0-Na	-	(preterm < term) [3]
Amplitude	P0	-	-
	Na	(preterm < term)[3]	preterm < term[3]
	P0-Na	(preterm < term[3])[2]	(preterm < term[3])[1]
ACR		n_p^4/n_p^5 = 14/13, n_t^4/n_t^5 = 12/11	n_p^4/n_p^5 = 18/19, n_t^4/n_t^5 = 22/15
Latency	Na	preterm > term [4 5]	preterm > term [4 5]
	N1	-	-
	P2	preterm > term [4]	preterm > term [4 5]
Amplitude	Na	-	-
	N1	-	-
	P2	-	-
	N2	-	-

- $p > 0.10$

() $0.05 < p \leq 0.10$ for the derivations indicated outside the brackets

Table 3. *ABR*

	Recorded at term					Recorded 3 months after term				
	Term (n=23)		Preterm (n=33)		T^2-test $p > 0\ 10$	Term (n=22)		Preterm (n=44)		T^2-test $p > 0\ 10$
Latency (ms)	mean	sd	mean	sd	*t*-test	mean	sd	mean	sd	*t*-test
I	2 56	0 50	2 75	0 39	-	2 15	0 37	2 31	0 36	-
II	3 64	0 47	3 73	0 43	-	3 18	0 38	3 36	0 53	-
III	5 43	0 54	5 55	0 55	-	4 62	0 41	4 83	0 46	$p = 0\ 07$
V	7 51	0 43	7 63	0 44	-	6 72	0 32	6 98	0 44	$p = 0\ 02$
I-III	2 88	0 38	2 81	0 40	-	2 47	0 23	2 53	0 26	-
III-V	2 08	0 33	2 07	0 38	-	2 10	0 25	2 15	0 22	-
I-V	4 95	0 25	4 88	0 33	-	4 57	0 22	4 68	0 22	$p = 0\ 07$
IIc	4 12	0 43	4 19	0 42	-	3 59	0 47	3 73	0 43	-
Vc	8 01	0 42	8 04	0 48	-	7 09	0 34	7 29	0 46	$p = 0\ 08$
IIc-Vc	3 89	0 29	3 85	0 34	-	3 50	0 35	3 56	0 32	-
Amplitude (μV)										
II	0 12	0 06	0 12	0 07	-	0 12	0 08	0 12	0 09	-
V	0 22	0 08	0 19	0 07	-	0 24	0 09	0 22	0 09	-
V/I	1 43	0 67	1 11	0 49	$p = 0\ 04$	1 36	0 69	1 23	0 60	-

- $p > 0\ 10$

Table 4a *MLR· derivations ipsilateral to stimulation*

	Recorded at term					Recorded 3 months after term				
	Term (n=20)		Preterm (n=33)		T^2-test $p > 0\ 10$	Term (n=22)		Preterm (n=49)		T^2-test $p > 0\ 10$
Latency (ms)	mean	sd	mean	sd	*t*-test	mean	sd	mean	sd	*t*-test
P0	8 6	0 8	8 8	1 0	-	7 6	0 8	8 1	1 0	$p = 0\ 05$
Na	18 4	1 7	18 4	1 8	-	15 8	1 9	15 9	1 4	-
P0-Na	9 8	1 7	9 6	1 6	-	8 1	1 9	7 8	1 5	-
Amplitude (μV)										
P0	0 18	0 13	0 09	0 14	$p = 0\ 04$	0 18	0 18	0 09	0 30	-
Na	-0 40	0 20	-0 48	0 19	-	-0 67	0 43	-0 62	0 43	-
P0-Na	0 57	0 24	0 57	0 24	-	0 85	0 43	0 70	0 41	-

- $p > 0\ 10$

Table 4b. *MLR central derivations*

	Recorded at term					Recorded 3 months after term				
	Term (n=25)		Preterm (n=33)		T^2-test $p = 0\ 06$	Term (n=22)		Preterm (n=49)		T^2-test $p = 0\ 009$
Latency (ms)	mean	sd	mean	sd	*t*-test	mean	sd	mean	sd	*t*-test
P0	8 3	0 6	8 9	0 8	$p = 0\ 005$	7 7	0 7	8 3	0 7	$p = 0\ 002$
Na	18 5	1 5	18 4	1 7	-	15 6	1 3	16 0	1 3	-
P0-Na	10 2	1 5	9 5	1 5	-	7 9	1 3	7 6	1 2	-
Amplitude (μV)										
P0	0 17	0 28	0 13	0 14	-	0 22	0 25	0 15	0 26	-
Na	-0 46	0 22	-0 43	0 18	-	-0 65	0 45	-0 53	0 39	-
P0-Na	0 63	0 24	0 56	0 23	-	0 87	0 45	0 68	0 39	$p = 0\ 08$

- $p > 0\ 10$

Table 4c. *MLR: derivations contralateral to stimulation*

	Recorded at term					Recorded 3 months after term				
	Term (n=19)		Preterm (n=32)		T^2-test $p < 0.001$	Term (n=22)		Preterm (n=48)		T^2-test $p < 0.001$
Latency (ms)	mean	sd	mean	sd	*t*-test	mean	sd	mean	sd	*t*-test
P0	8.0	0.7	9.1	0.9	$p < 0.001$	7.5	0.8	8.5	0.8	$p < 0.001$
Na	18.6	2.3	18.4	1.6	-	15.7	1.4	16.0	1.4	-
P0-Na	10.6	2.3	9.3	1.4	$p = 0.01$	8.2	1.6	7.5	1.4	$p = 0.06$
Amplitude (μV)										
P0	0.16	0.12	0.16	0.12	-	0.22	0.22	0.16	0.26	-
Na	-0.50	0.16	-0.39	0.20	$p = 0.05$	-0.74	0.52	-0.50	0.37	$p = 0.03$
P0-Na	0.66	0.21	0.55	0.23	$p = 0.09$	0.96	0.45	0.66	0.40	$p = 0.006$

- $p > 0.10$

Table 5a. *ACR: central derivations*

	Recorded at term					Recorded 3 months after term				
	Term (n=22)		Preterm (n=18)		T^2-test $p = 0\ 02$	Term (n=16)		Preterm (n=23)		T^2-test $p = 0\ 10$
Latency (ms)	mean	sd	mean	sd	*t*-test	mean	sd	mean	sd	*t*-test
Na	27	5	22	4	$p = 0\ 002$	16	3	18	3	$p = 0\ 02$
N1	140	25	128	19	-	115	14	119	20	-
P2	209	22	187	17	$p = 0\ 001$	174	19	191	17	$p = 0\ 007$
N2	344	54	347	44	-	294	40	292	32	-
P3	*	*	*	*	*	375	46	389	51	-
Amplitude (μV)										
Na	-0 1	1 0	-0 7	0 8	$p = 0\ 06$	-0 9	1 5	-0 8	1 4	-
N1	0 2	0 9	0 3	0 8	-	-0 2	1 3	-0 8	0 9	-
P2	2 5	1 7	1 6	1 1	$p = 0\ 07$	1 8	1 3	2 1	1 3	-
N2	-2 3	1 9	-1 4	1 0	$p = 0\ 08$	-1 5	1 2	-1 6	1 3	-
P3	*	*	*	*	*	0 1	1 4	0 3	1 6	-

\- $p > 0\ 10$

* P3 not analysed at 40 weeks

Table 5b. *ACR: temporal derivations*

	Recorded at term					Recorded 3 months after term				
	Term (n=15)		Preterm (n=19)		T^2-test $p = 0.003$	Term (n=12)		Preterm (n=24)		T^2-test $p > 0.10$
Latency (ms)	mean	sd	mean	sd	*t*-test	mean	sd	mean	sd	*t*-test
Na	27	5	22	4	$p = 0.002$	15	2	18	3	$p = 0.01$
N1	137	23	128	21	-	112	16	114	19	-
P2	203	22	182	19	$p = 0.006$	168	21	184	19	$p = 0.03$
N2	357	59	340	52	-	287	30	290	29	-
P3	*	*	*	*	*	381	52	395	39	-
Amplitude (μV)										
Na	-0.2	0.7	-0.8	0.7	$p = 0.03$	-1.0	1.3	-0.5	0.8	-
N1	0.5	1.0	-0.0	0.8	-	0.0	1.3	-0.5	1.2	-
P2	1.2	1.0	1.1	0.7	-	2.3	1.4	2.2	1.6	-
N2	-1.5	1.5	-1.1	0.7	-	-2.6	1.6	-2.8	1.6	-
P3	*	*	*	*	*	0.2	1.5	0.4	1.4	-

- $p > 0.10$

* P3 not analysed at 40 weeks

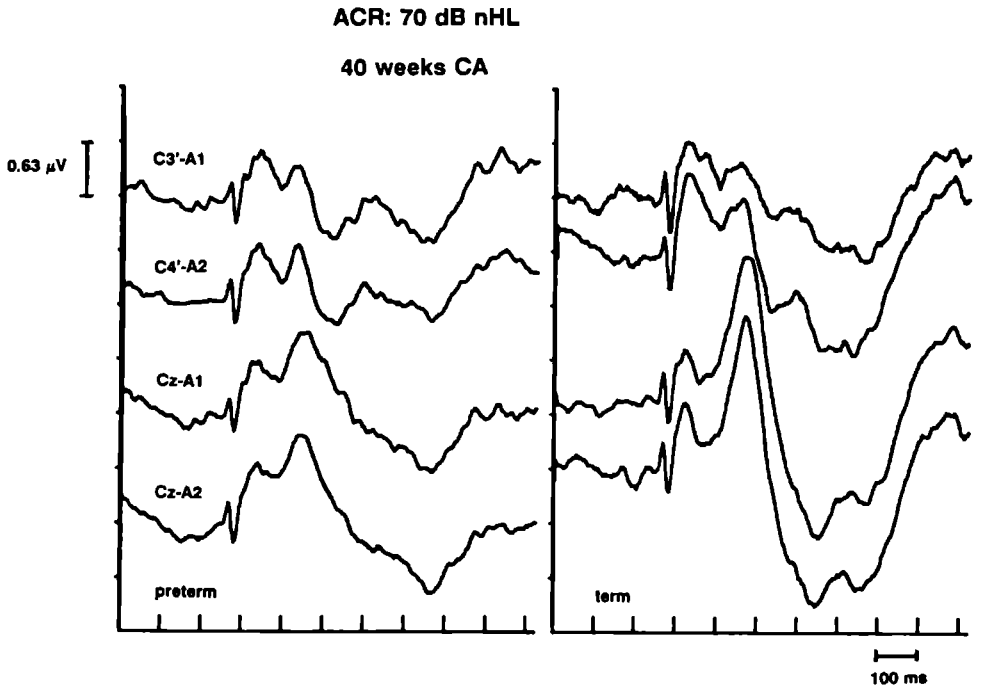

Fig. 4. *Waveform morphology of grand composite group averages of ACRs obtained after binaural stimulation in full term and preterm infants at 40 weeks CA. An upward deflection indicates positivity at the Cz, C4' and C3' electrodes.*

The Hotelling T^2-test revealed a significant difference between the preterm and term group tested at term with respect to the joint latencies and amplitudes of the ACR. See Tables 5a and 5b. However, the simultaneous test procedure did not indicate a particular latency or amplitude to which this difference could be attributed ($p > 0.10$). At 3 months no significant differences were established using the Hotelling T^2-test. In preterm infants at term the ACR showed shorter latencies for components Na, N1 and P2 in the central and temporal derivations. According to Student's t-tests these latency differences between preterm and term infants were statistically significant for ACR components Na and P2 in both derivations.

By contrast, at 3 months the ACR components Na and P2 and to a lesser extent N1 showed longer latencies in preterm infants compared to term infants. For the components Na and P2 both in the central and temporal derivations a significant difference was found.

At term the absolute value of the mean amplitude of ACR component Na was significantly higher in the temporal derivation in preterm infants. For the central derivation a nearly significant increase in amplitude was found. In addition, for the latter derivation at term nearly significantly reduced absolute values of the mean amplitude of the components P2 and N2 were found in preterm infants. At 3 months no significant differences with respect to the amplitudes of the ACR components was observed.

Discussion

In the last decade, neurobehavioural studies indicated that preterm infants tend to have lower scores on mental and psychomotor tests than term infants [Drillien 1972, Saint-Anne Dargassies 1977, Astbury *et al.* 1983, Forslund and Bjerre 1983, Hadders-Algra *et al.* 1988]. The incidence and severity of these abnormalities is negatively correlated with birth weight and gestational age [Marlow *et al.* 1987]. Additionally, recent studies on magnetic resonance imaging (MRI) of the neonatal brain revealed delayed myelination in preterm infants compared to term infants [Dietrich *et al.* 1986, McArdle *et al.* 1987, Lauffer and Wenzel 1990]. And furthermore, pathologic conditions occurring in the maturing human may cause retarded maturation of myelin sheath and synaptogenesis [Astbury *et al.* 1983].

With respect to the ABRs our results show only a tendency towards longer latencies for the individual ABR components and at 3 months the results show also increased interpeak latencies in preterm infants compared to term infants. However, significance or near significance was only reached for components III, V and Vc and interpeak latency I-V at 3 months. Furthermore, it must be emphasized that in the preterm group there are relatively more infants with incomplete observations than in the term group. This may be due to a higher percentage of preterm infants with conductive hearing loss compared to term infants. Conductive hearing loss may cause longer absolute latencies, lower amplitudes and a less well-developed waveform of the ABR. However, generally mild conductive hearing loss does not affect ABR interpeak latencies. So, longer latencies, lower amplitudes and a poorer waveform of the ABR can also be attributed to a retarded myelination of the central auditory pathway at the level of the brainstem. Because myelination progresses in a centripetal direction, delayed myelination may affect late ABR components more than early ABR components, leading to longer interpeak latencies [Gilles 1976, Gilles *et al.* 1983, Salamy *et al.* 1985, Dietrich *et al.*

1986, Holland 1986, McArdle *et al.* 1987, Martin *et al.* 1988]. Therefore, our results concerning the ABR support the hypothesis of a delayed myelination, possibly in combination with conductive hearing loss. Eggermont and Salamy [1988] also found longer latencies in preterm infants and attributed this finding to the high incidence of middle ear effusions in preterm infants resulting in mild conductive hearing loss. Delorme [1986] and Collet [1989] reported significantly shorter latencies for ABR components III and V, and shorter I-III and I-V intervals in preterm infants with an extrauterine life longer than 2 weeks compared to preterm infants with an extrauterine life less than 2 weeks. They concluded that these shorter latencies and decreased interpeak latencies in infants with a longer extrauterine life are due to anatomical factors rather than an enhanced maturation of the auditory system. However, in a previous study we did not find significant changes in central conduction time due to the effect of gestational age at a specific conceptional age level [Rotteveel *et al.* 1987a]. Furthermore, it is important to emphasize that the infant groups used in the studies of Delorme *et al.* [1986] and Collet *et al.* [1989] did not correspond with the infant groups in the study of Eggermont and Salamy [1988] and our present study. Collet *et al.* [1989] compared two groups of preterm infants at a conceptional age between 36 and 37 weeks, whereas Eggermont and Salamy [1988] studied both preterm and term infants. So, the results mentioned in these studies are not simply comparable and therefore need not to be conflicting.

To our knowledge there are no studies on the effect of preterm birth on the maturation of the MLR. In our study the early MLR components Na and P0 showed longer latencies in preterm infants, but significant differences were only reached for component P0 with regard to the contralateral and central derivations at term and at 3 months. Longer latencies for MLR component P0 in preterm infants can be attributed to a delayed centripetal myelination of the central auditory system. However, if the primary mechanism is delayed myelination, one would expect even longer latencies for MLR component Na in preterm infants. In our study this was not found. A more complex mechanism than delayed myelination may account for the results found. One could think, for instance, of an enhanced synchronization due to decreased dendritic complexity.

There are only sparse reports in the literature addressing the subject of intrauterine versus extrauterine maturation of ACRs. In one such study, it was stated that the development of the ACR was not influenced by earlier exposure to the extrauterine environment [Schulte *et al.* 1977]. In our study, we found that at term the ACR latencies of components Na, N1 and P2 are longer in term infants compared to preterm infants, whereas at 3 months the latencies of the same ACR

components are shorter in term infants compared to preterm infants. The differences with respect to Na and P2 were significant. Furthermore, at term as well as at 3 months the ACR continued to exhibit an immature waveform morphology in preterm infants whereas in term infants a more mature morphology was found. These findings are even more complex than the findings concerning MLR component Na. One has to realize that little is known regarding the generators of ACR activity, particularly during the maturation of the auditory system in preterm and term infants. In addition to myelination, an important role may be attributed to compromised synaptic efficacy and dendritic growth resulting in a shifting in the localization and orientation of electric sources underlying the ACR components.

In conclusion, this study supports the hypothesis that middle ear effusions in combination with retarded myelination of the central auditory pathway may be responsible for the latency and interpeak latency differences noted between preterm infants and term infants studied at term and 3 months thereafter with respect to late ABR components and early MLR component P0. The differences found between preterm and term infants with respect to the MLR component Na and the ACR components Na, N1 and P2 are the result of a complex mechanism. Additional research concerning localization and orientation of electromagnetic sources and their changes during the maturation of the auditory cortex is a possible way to unravel the complex mechanism involved.

Chapter 4

Neurodevelopmental profile in low-risk preterm infants at five years of age

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(Submitted)

Summary

The goal of this study is to determine the neurodevelopmental profile of a group of low-risk preterm infants and to determine whether the potentially unfavourable outcome is due to a few infants with moderate to severe impairments or to a majority of infants with only slight impairments. In a prospective study 44 low-risk preterm infants, i.e., infants with a neonatal risk score indicating a favourable outcome, born between 25-34 weeks gestational age, and 18 healthy term infants were neurologically examined and neuropsychologically tested at five years of age. As a group the low-risk preterm infants had a more unfavourable neurological and neuropsychological outcome than the term infants. The group differences were largely attributable to neurological abnormalities and/or a poorer neuropsychological outcome in 12 of the 44 low-risk preterm infants. The remaining low-risk preterm infants, however, showed quite similar test scores when compared with the term infants. From these results we conclude that the unfavourable neurodevelopmental outcome of low-risk preterm infants when compared with the outcome of term infants is due to moderate to severe impairment in a few low-risk preterm infants, rather than slight impairment in the majority. The low-risk preterm infants with an unfavourable neurodevelopmental outcome showed particular impairment on measures of visual-motor integration, concentration and auditory memory in combination with integrative functions.

Attempts have been made to determine neonatal risk factors and to design neonatal risk scores predicting neurodevelopmental outcome in preterm infants and/or infants with low birth weight [Kitchen *et al.* 1980, Michelsson *et al.* 1984, Stewart *et al.* 1989, Vohr *et al.* 1989, Den Ouden *et al.* 1990, Brazy *et al.* 1991, Scheiner and Sexton 1991]. Current neonatal risk scores (i.e., NBRS and PERI) have limited validity and predictive value, mainly because the sensitivity and negative predictive value (NPV) is relatively low [Brazy *et al.* 1991, Scheiner and Sexton 1991]. The low sensitivity and NPV show that some low-risk infants are falsely classified. Thus, we need to know more about the neurodevelopmental profile in low-risk preterm infants.

For the relationship between neuropsychological outcome and neonatal risk factors Abel Smith and Knight-Jones [1990] reviewed 11 controlled studies. Although a considerable overlap was reported between preterm and term children's test scores, eight studies still demonstrated some significant impairment. In a prospective cohort-study of 611 infants with a birth weight of 1750 g or less, Mutch *et al.* [1993] showed that relatively few infants with birth weight below 1000 g performed within the normal range on all tests, and that many of them demonstrated moderate to severe disability at age 4.5 years. The latter subgroup had had elevated perinatal risk factors. In mildly impaired children no significant relationship was found between birth weight and perinatal factors on the one hand, and outcome on the other hand (social class excepted). A recent study by Herrgard *et al.* [1993] is similarly inconclusive on perinatal risk factors. They found a lower IQ at age five years for a group of 60 preterm children when compared with control children, even if 14 handicapped children were excluded, but insufficient perinatal data were available to separate high-risk from low-risk infants. From these studies it is not clear whether a potentially unfavourable outcome for the preterm group as a whole is due to moderate to severe impairment in a few of these infants, or to slight impairment in the majority. The latter condition is referred to as handicaps of 'low-severity-high-incidence' [Aylward and Pfeiffer 1989, Herrgard *et al.* 1993] or as 'hidden handicap' [Zubrick *et al.* 1988].

Determination of long-term neuropsychological outcome should address the issue of the typical preterm neuropsychological profile, if any. Michelsson *et al.* [1984] found a higher incidence of impaired motor function, speech defects and impaired school achievement in low birth weight infants. Several authors found that preterm infants performed less well at age five years on spatial relation and visual-motor integration tasks [Klein *et al.* 1985, Herrgard *et al.*, 1993]. Other

authors found that very-low-birth-weight infants scored significantly lower than did controls in expressive language, memory, visuomotor, and fine motor function [Hack *et al.* 1992, Taylor *et al.* 1995]. Mutch *et al.* [1993] concluded that in the absence of neuromotor deficits, the relationship of intellectual impairment to birth weight is unclear. Thus, motor, visual-motor and visual-spatial abilities seem the most affected in preterm infants.

In this prospective study we determined the neurodevelopmental profile at five years of age of a well-defined group of low-risk preterm infants and of a group of term infants. This study is part of a larger study on the development of neurophysiological parameters and on the nature of the neurodevelopmental outcome of 81 preterm infants born between 25 and 34 weeks gestational age (GA) and 25 healthy term infants [Rotteveel *et al.* 1987a,1987b, 1987c, Pasman *et al.* 1991, 1992, 1996]. In the neonatal period the preterm infants were classified as low-risk or high-risk based a neonatal risk score (Neonatal Neurological Inventory). The high-risk infants were excluded from this part of the study. The term infants served as a control group. The aim of this study is to give answers to the following questions: 1) What is the long-term outcome in this particular group of low-risk preterm infants? 2) Are differences between low-risk preterm infants and term infants due to moderate to severe impairment in a few preterm infants, or to slight impairment in the majority? 3) What is the typical neuropsychological profile of these preterm infants?

Subjects and methods

Forty-four low-risk preterm infants (GA 25-34 weeks) and 18 healthy, term infants (GA 38-42 weeks) were included in this prospective study. The preterm group consisted of inborn and outborn preterm infants who were admitted to the Neonatal Intensive Care Unit of the University Hospital Nijmegen between March 1983 and June 1984. The term group consisted of healthy, term infants born in the University Hospital Nijmegen in the same period and served as a control group. Infants with dysgenetic brain lesions, major congenital anomalies or well-defined clinical syndromes were excluded from the study.

In the neonatal period a cohort of 81 preterm infants was classified as high-risk or low-risk according to the semi-quantitative Neonatal Neurological Inventory (NNI). The NNI assessment was performed in the first two weeks after birth. The NNI is based on four items: 1) clinical neurological examination, 2) echoencephalography, 3) arterial or capillary blood pH and 4) Apgar score. The clinical

neurological examination was performed according to the neurological assessment described by Dubowitz *et al.* [1980]. In addition to the items of the Dubowitz score the examination also included a qualitative analysis of spontaneous and evoked motility. Albers and Jorch [1994] have subsequently also described such an approach. To determine structural and haemorrhagic brain lesions transfontanellar echoencephalographic studies were performed in the first days of life and at least once biweekly until discharge. Haemorrhagic brain lesions detected by echoencephalographic examination were classified according to Papile *et al.* [1978]. The NNI assessment also was based on blood pH and Apgar score. In low-risk infants the blood pH had to be above 7.10 (arterial) or 7.00 (capillary) and the Apgar score had to be above seven at five minutes. In order to validate the NNI, the NNI results were compared, retrospectively, with the results according to the Neurobiologic Risk Score (NBRS) described by Brazy *et al.* [1991]. Based on the NNI, 65 of the 81 preterm infants were classified as low-risk and 16 as high-risk (i.e., having one or more of the four NNI high-risk criteria). The results of NNI and NBRS were almost the same (sensitivity 0.47; specificity 0.95, resp. 0.97; positive predictive value 0.78, resp. 0.88; and negative predictive value 0.82). The low-risk preterm infants were divided into two GA groups: the early low-risk preterm group (25-30 weeks GA) and the late low-risk preterm group (31-34 weeks GA). Five of the 65 low-risk preterm infants and seven of the 16 high-risk infants died in the neonatal period. The high-risk infants were excluded from further analyses.

At the age of five years the infants were invited to participate in a follow-up investigation consisting of a neurophysiological, neurological and neuropsychological evaluation. Clinical neurological examination was performed by an experienced child neurologist using standard pediatric neurological examination methods. To classify the neurological abnormalities the WHO classification of Impairments, Disabilities and Handicaps was used [WHO 1980]. Neurological abnormalities were classified as minor if they did not result in disability and/or handicaps. The neurological examination was used to divide the infants of the low-risk preterm group and the term group into a neurologically normal subgroup consisting of infants with no or minor neurological abnormalities and a neurologically abnormal subgroup consisting of infants with neurological disability and/or handicaps ('major neurological abnormalities'). Socioeconomic Status (SES) was determined for each child according to the method described by Westerlaak [Schroots and Alphen de Veer 1976]. Sixteen of the surviving 60 low-risk preterm infants (27%) and seven of the 25 term infants (28%) were not available for the complete follow-up period because of migration or withdrawal by

the parents. So, 44 low-risk preterm infants and 18 term infants had a complete follow-up at five years of age. Table 1 summarizes the subject population.

Questionnaires

The parents received two questionnaires, one to be filled out by them, the other to be filled out by the child's teacher. These questionnaires were used to signal developmental and/or educational problems. The teachers had no substantial knowledge of the child's medical history. The parent questionnaire contained questions related to the medical history and present functioning of their child. To evaluate the parental responses the questions and answers were classified into 11 categories: 1) medical history, 2) history of physical therapy, 3) history of speech therapy, 4) hearing, 5) vision, 6) toilet training, 7) motor development and motor skills, 8) language and speech, 9) daily skills, 10) social skills, and 11) (hyper)activity and/or sleeping problems. Two investigators in consensus evaluated the responses to each category on a three-point scale as follows: 1) no problems now or in the past, 2) some question regarding the child's functioning, and 3) rather serious problems indicated now or in the past.

The questionnaire filled out by the teachers was designed to assess the infant's present performance. Responses were classified into nine categories: 1) hearing, 2) vision, 3) toilet training, 4) motor skills, 5) language and speech, 6) daily skills, 7) social skills, 8) (hyper)activity, and 9) a prognosis regarding the child's ability to receive normal academic education. The same three-point rating scale developed for the parent questionnaire was used to evaluate the teacher questionnaire. The teacher of one child with major neurological abnormalities did not respond.

Neuropsychological testing

The low-risk preterm and term infants were tested at five years of age. The neuropsychological test battery consisted of the Visual-Motor Integration Test (VMI), the 'Leiden Diagnostic Test' (LDT), the Bourdon-Wiersma-Vos concentration test for infants (BWVK), and the Auditory Discrimination Test (ADIT) [Beery 1982, Crul and Peters 1976, Schroots and Alphen de Veer 1976, Vos 1988].

The VMI, in which the child is requested to copy line-drawings, assesses visual (input) and fine-motoric (output) integration skills. Performance is expressed in standard scores that have a normal distribution, with a population mean of 10 and a standard deviation of three.

Table 1 *Subject description of term, late low-risk preterm and early low-risk preterm infants*

Group	n	GA ± sd (in weeks)	Mean birth weight ± sd (in grams)	Mean head circumference ± sd (in cm)	Test age + range (months)
Term (≥ 40 weeks GA)	18				
male	14	39 5 ± 0 9	3128 ± 481	34 5 ± 1 4	59 (58-61)
female	4	40 3 ± 0 8	3170 ± 726	34 0 ± 1 9	60 (59-61)
Late low-risk preterm (31-34 weeks GA)	23				
male	14	32 1 ± 0 9	1590 ± 391	30 0 ± 3 1	62 (56-67)
female	9	33 3 ± 0 9	1534 ± 297	29 0 ± 1 9	62 (59-65)
Early low-risk preterm (25-30 weeks GA)	21				
male	9	29 6 ± 1 1	1134 ± 309	27 0 ± 2 3	61 (57-64)
female	12	28 4 ± 1 6	1023 ± 237	25 2 ± 2 3	60 (56-66)

The LDT is a Dutch intelligence test. The standard score of the LDT is called total IQ (TIQ), a score that follows a normal distribution, with a mean of 100 and a standard deviation of 15. The test consists of eight subtests. The first three subtests assess performance IQ (PIQ); in these tests the input is visual and the output involves fine motor skills. The remaining five subtests assess verbal IQ (VIQ); here the input is either auditory or auditory and visual, and the output involves oral speech or fine motor skills. A comprehensive description of the LDT is given in Appendix 1.

In the BWVK concentration test, the child is presented with a test form consisting of 11 rows of 24 figures each. The figures are triangles, quadrilaterals, and pentagons, and the child is required to cross all the quadrilaterals with a pencil. The variable for evaluation of performance was whether or not the infant passed the task (the criterion for passing was a total number of less than 30 errors).

In the ADIT the child is presented with monosyllabic (consonant-vowel-consonant) words played back from audio tape. The task consists of selecting from two pictures the one that corresponds to the auditorily presented test word. The alternative, incorrect picture represents a word, that differs from the test word with respect to either the initial consonant, the vowel, or the final consonant. Raw scores, the number of correct items from a total of 30 presentations, served as the performance index.

One of the eight low-risk preterm infants who exhibited neurological abnormalities couldn't perform the neuropsychological tests.

Test procedure

The infants were tested by a psychological assistant. After a short introduction, the parents were asked to leave the test room. Four infants did not accept the absence of their parents, in which case one of the parents stayed during the test. The tests were administered in the following order: VMI, ADIT, BWVK, short break, LDT. This study was approved by the Ethics Committee of the University Hospital Nijmegen. Before testing, parental consent was obtained.

Statistical analyses

For the VMI and LDT age-norms are available so performances on these tests could be transformed to standard scores. Because the standard score of the BWVK and ADIT is expressed in steps of 1 standard deviation, we decided to use more refined raw scores instead; this procedure is justified if age-matched groups are compared.

Based on the neuropsychological test results, children who obtained a score in

the lowest 10% range on the VMI (i.e., VMI: < 7) and/or the intelligence test (i.e., TIQ < 80) were classified as poor performers. Also, children with a moderately poor VMI score of seven combined with a below average score (i.e., TIQ < 100) on the intelligence test, were identified as poor performers. The significance of the difference between the poor performers and the remaining (preterm born) children was tested using a randomization test [Edgington 1987].

To test the significance of the differences in test and subtest scores between the term group and preterm groups, two separate analyses of variance were conducted. In the first analysis, the term group was compared with that part of the early low-risk preterm group with a normal outcome plus that part of the late low-risk preterm group with a normal outcome. In the second analysis the term group was compared with the low-risk preterm group with an unfavourable neurodevelopmental outcome, i.e., the low-risk preterm infants with an abnormal neurological and/or neuropsychological development at five years of age. In both of the analyses of variance the three factors in the analyses were: gestational age group (GAG), Gender (Gn), and socioeconomic status (SES).

Responses to both the parent and teacher questionnaires were averaged across categories to obtain a composite score; results were tested for significance by analysis of variance. Differences were considered to be statistically significant if a p-value ≤ 0.05 was found. The statistical analyses were conducted with SPSS for Windows 6.0.

Results

Neurological outcome

In the term group no major neurological abnormalities were found at five years of age, whereas eight of the 44 surviving low-risk preterm infants (18%) had major neurological abnormalities. These neurological deficits consisted of mental retardation, epilepsy, infantile encephalopathy with diplegia, hemiplegia, quadriplegia or extrapyramidal movement disorders, and visual, auditory or sensory disturbances.

Questionnaires

The mean scores on the questionnaires for the entire low-risk preterm and term groups and the results of the analysis of variance are presented in Table 2. The parent and teacher questionnaires reported more problems in the preterm groups than in the term group, except for the early preterm girls (teacher questionnaires).

For the parent questionnaires GAG reached significance In the preterm groups more problems were noted in boys than in girls For both parent and teacher questionnaires significant differences were found In addition, a significant interaction between GAG and Gender was found for the parents questionnaires

Neuropsychological test results

The neuropsychological test results are summarized in Table 2 For socioeconomic status (SES) no significant differences were found between the groups The results show that there is a trend for the IQ-scores of the LDT (LDT-TIQ, LDT -PIQ and LDT -VIQ) to be highest for the term group, intermediate for the late low-risk preterm group (31-34 weeks GA) and lowest for the early low-risk preterm group (25-30 weeks GA) There are two exceptions girls in the late low-risk preterm group had higher VIQ scores than the girls in the term group, resulting in a similar TIQ score Girls generally performed better than boys For the VMI, there is a trend toward decreasing scores with decreasing GAG On the ADIT, early low-risk preterm infants had lower scores than the term and late low-risk preterm infants Percentages of infants passing the BWVK dropped from 100% for the term group, to 83% for the early preterm girls, 71% for the late preterm boys and 44% for the early preterm boys The differences were significant for LDT-PIQ and BWVK with respect to the factor GAG These differences were primarily due to the lower test scores in the early low-risk preterm group The differences with respect to the factor Gender were significant for LDT-TIQ, LDT-PIQ, VMI and BWVK

Identification of neuropsychological poor performers

The test scores of VMI and TIQ for each individual child of the term and preterm groups are given in Figure 1

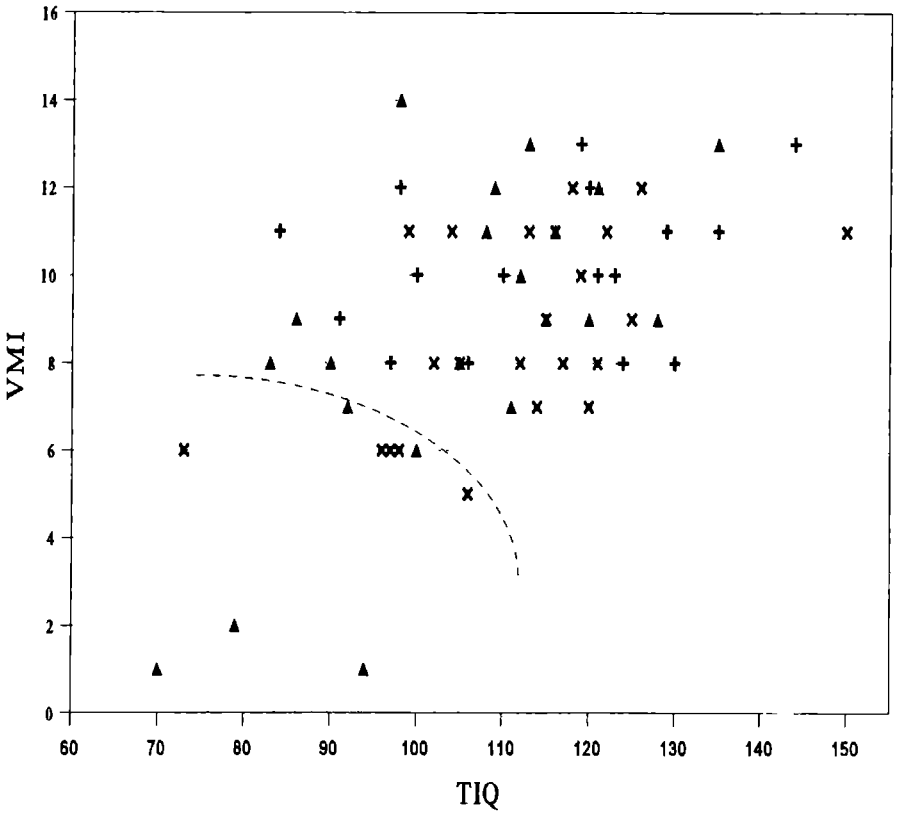
The VMI and TIQ criteria mentioned before were applied to identify neuropsychological poor performers According to these criteria ten low-risk preterm children were identified as neuropsychological poor performers To validate the classification of these neuropsychological poor performers, a randomization test (Edgington, 1989) was used As a group, the ten neuropsychological poor performers had a composite z-score based on VMI, BWVK and LDT, which was significantly different from the composite z-score of the remaining low-risk preterm children ($p < 0.001$) There was a considerable overlap between neuropsychological poor performers and infants with neurological abnormalities at five years six of the ten neuropsychological poor performers were also classified as neurologically abnormal, four born between 25-30 weeks GA and two born between 31-34 weeks GA

Table 2. *Ratings from parent and teacher questionnaires and neuropsychological (sub)test scores for the term, early and late low-risk preterm infants*

	Term		Late low-risk preterm		Early low-risk preterm		Analysis of variance	*p*-value
Gestational age	38-42 weeks		31-34 weeks		25-30 weeks			
Gender	♂ (n=14)	♀ (n=4)	♂ (n=14)	♀ (n=9)	♂ (n=9)	♀ (n=12)		
SES	1 64	1 5	1 79	1 78	1 89	1 58	-	ns
Questionnaires								
Parents	1 06	1 09	1 34	1 18	1 66	1 35	Gender*	0 01
							GAG*	0 001
Teachers	1 1	1 11	1 3	1 21	1 48	1 06	Gender*	0 02
Psychological tests								
LDT-TIQ	113	118	107	118	98	112	Gender	0 03
LDT-PIQ	108	119	104	108	96	109	Gender	0 008
							GAG	0 04
LDT-VIQ	113	113	108	120	101	111	-	ns
VMI	10 3	11	8 1	9 7	8 6	7 4	Gender	0 003
ADIT	28 2	27 8	28 4	29	27 7	27 6	-	ns
BWVK	100	100	71	100	44	83	Gender	0 02
							GAG	0 053

Note Ratings from parent and teacher questionnaires expressed on a three-point scale See text One teacher questionnaire was not filled out (preterm group) BWVK performance is expressed in the percentage of infants passing the test One preterm infant was not able to perform the tests Ns not significant

* There is a significant interaction between Gender and GAG $p = 0\ 052$ (parent questionnaires) and $p = 0\ 03$ (teacher questionnaires)



✚ term
✖ late low-risk preterm infants (31-34 weeks GA)
▲ early low-risk preterm infants (25-30 weeks GA)

Fig. 1. *VMI and TIQ performance of 18 term and 44 low-risk preterm infants.*

Two infants with neurological abnormalities had normal neuropsychological outcome. Thus, a total number of 12 low-risk preterm infants emerge with an unfavourable outcome at age five years. The results of the post hoc analyses are summarized in Table 3.

Comparison of term infants and low-risk preterm infants with a normal outcome

The neuropsychological test results of the term group were compared to the results of the early and late low-risk preterm groups with a normal neurodevelopmental outcome at five years of age. The results are presented in Table 3.

Table 3. *Test scores of twelve preterm infants with an unfavourable outcome at age 5 years as compared to the mean Test scores of the term infants, early and late preterm infants with a normal outcome at 5 years of age*

Group	*GA*	n	Neurol Class	VMI	VIQ	PIQ	TIQ	BWVK	ADIT	Parent	Teacher
Term	≥ 40	18	1-2	10 4	113	111	114	100%	28 1	1 06	1 1
Low-risk preterm with a normal outcome	31-34	18	1-2	9 6	117	108	116 3	83%	28 8	1 2	1 22
	25-30	14	1-2	10 4	108	107	108 9	86%	27 4	1 33	1 13
Low-risk preterm with an unfavourable outcome	27-33	12	1-3	6 1	99 2	94 1	96 4	50%	28	1 7	146
Neuropsychological + neurological	27	1	3	nt	nt	nt	nt	nt	nt	1 91	1 11
unfavourable outcome	29	1	3	6	89	108	100	0	29	1 82	1 44
	30	1	3	7	94	94	94	0	29	2 27	1 89
	30	1	3	2	74	86	79	0	26	1 73	2
	31	1	3	6	101	89	96	0	28	1 36	1 67
	33	1	3	6	98	97	98	1	28	1 64	1 33
Neurological abnormalities	30	1	3	9	118	117	120	1	28	1 91	1 33
	30	1	3	8	113	90	105	0	28	1 64	1 55
Neuropsychological poor performers	29	1	1	7	91	97	92	1	29	1 18	1
	32	1	1	6	70	88	73	1	25	1 91	1 89
	33	1	1	5	108	100	105	1	30	1 27	1 33
	33	1	2	6	99	100	99	1	28	1 73	1

nt = not testable

BWVK 0 = fail, 1=pass

For both the parent and teacher questionnaires the factor GAG was significant ($p \leq 0\ 004$) Thus, more problems were indicated by parents and teachers of infants in the low-risk preterm groups These problems were more often expressed in boys than in girls The teachers, who were unaware of the infants medical histories, reported fewer severe problems than the parents for the early preterm group The development problems indicated were related to a history of physical therapy, a history of speech therapy, vision problems and (hyper)activity

In the analyses of the neuropsychological test results the factor Gender reached significance for VMI ($p < 0\ 01$) and for the LDT subtest Paper-Folding ($p < 0\ 05$) On these (sub)tests girls performed better than boys, a rather consistent finding, that also seems to hold for the non-significant differences Gestational age was a significant factor for the ADIT ($p < 0\ 05$) Early low-risk preterm infants (25-30 weeks GA) scored lower on the ADIT than late low-risk preterm (31-34 weeks GA) and term infants In contrast with the significant differences found between the term group and the complete low-risk preterm group for GAG, the comparison of the term group with that part of the low-risk preterm groups with a normal outcome only showed significant differences for the parent questionnaires

Comparison of term infants and low-risk preterm infants with an unfavourable outcome

The term infants were compared to the low-risk preterm infants with an unfavourable outcome, i e , the low-risk preterm infants with major neurological abnormalities and/or neuropsychological poor performers The results of the questionnaires, neuropsychological tests and the analyses of variance are given in Table 4 In the analysis of both the parents and the teacher questionnaires the term infants and preterm infants with unfavourable outcome showed significant differences That is, more problems were reported for low-risk preterm infants with an unfavourable outcome than for term infants Five categories were most frequently marked as problematic history of speech therapy, language problems, vision problems, toilet training, (hyper)activity and motoric problems

For the neuropsychological test results larger differences were found between term and low-risk preterm infants with an unfavourable outcome than between term infants and late and early low-risk preterm infants with a normal outcome The factor GAG was significant for LDT-TIQ, LDT-PIQ, VMI and BWVK For the LDT-subtest Block-Design and Word-Order the GAG was also significant The term infants clearly performed better than the low-risk preterm infants with an unfavourable outcome For the LDT-PIQ and LDT subtest Paper-Folding girls per-

formed significantly better than boys This is also true for the BWVK results for the low-risk preterm infants with an unfavourable outcome

Discussion

Long-term outcome of the low-risk preterm infants

In our study, the incidence of major neurological abnormalities established by clinical examination at age five, (i e , abnormalities leading to disability and/or handicap), was higher in the low-risk preterm group (18%) than in the term group (0%) It has to be emphasized that six of the eight low-risk infants with major neurological abnormalities were born between 25-30 weeks GA The percentage neurological dysfunction is of the same magnitude as that reported by other authors [Drillien *et al* 1980, Kitchen *et al* 1980, Stewart *et al* 1989] From the teacher and parent questionnaires it is clear that more problems are seen in the early and late preterm group than in the term group For these findings it is important to stress that in our study no differences in socioeconomic status (SES) were found between the term and preterm groups Although the high-risk infants were not included in this study it is of importance to report that eight of the nine surviving high-risk infants showed an unfavourable neurodevelopmental outcome

High-incidence/low-morbidity or low-incidence/high-morbidity?

From the literature it is not clear if the differences between term and preterm infants are caused by few infants with a moderate to severe disability (low incidence-high morbidity) or by a majority of these infants with only slight impairment (high incidence-low morbidity) In a post hoc analysis of both the term and preterm group, twelve infants with an unfavourable outcome at five years of age were identified based on the neurological examination and neuropsychological tests Six of these infants were not only neuropsychological poor performers but also belonged to the low-risk preterm infants with major neurological abnormalities Although neurological and neuropsychological diagnoses are based on different aspects of the neurodevelopmental profile, so that the diagnoses cannot be directly compared, the neuropsychological criteria for 'poor performers' might be more rigorous than the neurological criteria for 'handicap and/or disability' Nevertheless, a pronounced (overall) difference was found between the term group and these low-risk preterm infants with an unfavourable outcome These differences were significant for LDT-TIQ, LDT-PIQ, VMI and BWVK

Table 4. *Ratings from parent and teacher questionnaires and neuropsychological (sub)test scores for the term group and the low-risk preterm group with an unfavourable outcome*

	Term group		Preterm group with an unfavourable outcome		Analyses of variance	*p*-value
Gender	♂ (n=14)	♀ (n=4)	♂ (n=8)	♀ (n=4)		
SES	1.64	1 5	1.63	1 75	-	ns
Questionnaires						
parents	1.06	1.09	1.72	1 66	abnormal preterm > term	0 001
teachers	1 1	1 11	1.6	1 22	abnormal preterm > term	0 004
Psychological tests						
LDT-TIQ	113	118	94	103	abnormal preterm > term	0.03
LDT-PIQ	108	119	90	104	abnormal preterm > term boys < girls	0 006 0 04
LDT-VIQ	113	113	98	102	-	ns
VMI	10.3	11	5 6	7.3	abnormal preterm > term	0 001
ADIT	28 2	27 8	27.9	28.3	-	ns
BWVK	100	100	38	75	abnormal preterm > term* boys < girls*	0 03 0 03

Note Ratings from parent- and teacher questionnaires expressed on a three-point scale. One teacher questionnaire was not filled out (preterm poor performer group). BWVK performance is expressed in the percentage of infants passing the test. One infant with an unfavourable outcome was not able to perform the tests

* For BWVK there is also a significant interaction between GAG and Gender (p = 0 03). the difference between term and preterm poor performers is more pronounced for boys.

Table 4. *(continued). Ratings from parent and teacher questionnaires and neuropsychological (sub)test scores for the term group and the low-risk preterm group with an unfavourable outcome*

	Term group		Preterm group with an unfavourable outcome		Analyses of variance	*p*-value
Gender	♂ (n=14)	♀ (n=4)	♂ (n=8)	♀ (n=4)		
Subtests LDT						
Block-design	105	111	85	96	abnormal preterm > term	0 002
Paper-folding	106	120	92	110	boys < girls	0 02
Knox-cubes	109	114	100	102	-	ns
Word-span	111	102	97	95	-	ns
Word-order	113	111	102	94	abnormal preterm > term	0 04
Sentence-Repetition	110	114	96	108	-	ns
Question-Answering	103	104	95	104	-	ns
Comprehension	113	117	103	112	-	ns

In contrast, in the comparison of the term group with the early and late low-risk preterm groups with a normal outcome no significant differences were found with respect to GAG, except for the parent questionnaires. In other words, the majority of the low-risk preterm infants showed no differences if compared to the term group, whereas a number of the low-risk preterm infants showed moderate to severe neurological and/or neuropsychological abnormalities. Our findings are compatible with the results presented by some other authors. Smedler *et al.* [1992] investigated sensi-motor and cognitive development in 14 medically healthy, very-low-birth-weight and small-for-gestational-age children and 14 control children. At 8.7-11.2 years the very-low-birth-weight and small-for-gestational-age group scored significantly lower on measures of visuospatial ability, nonverbal reasoning, strategy formation and gross-motor coordination. The group differences were largely attributable to the subnormal performance of eight of the 14 very-low-birth-weight and small-for-gestational-age children. In a study of low-birth-weight infants (< 1750 g) at 4.5 years of age Mutch *et al.* [1993] performed a cluster analysis. The children in two of the six clusters (75.3%) showed average to above-average IQs. Cluster membership correlated highly with language attainment, ability to copy shapes. In other reports more evidence has been found for the condition referred to as handicaps of 'low-severity-high-incidence' [Aylward and Pfeiffer 1989, Herrgard *et al.* 1993] or as 'hidden handicap' [Zubrick *et al.* 1988].

Neurodevelopmental profile at five years

Looking more in detail at the differences between the term group and the low-risk preterm group with an unfavourable outcome, the mean ratings obtained from parent and teacher questionnaires were relatively unfavourable for the low-risk preterm infants when compared with the term infants. Furthermore, only two of the eight low-risk preterm infants with major neurological abnormalities did not belong to the group of neuropsychological poor performers. One of these two showed a disharmonic LDT profile with a low PIQ score compared with the VIQ score. Based on the significant differences in neuropsychological test results between the term group and the low-risk preterm infants with an unfavourable outcome it is shown that the preterm infants did less well on performance tasks (LDT-PIQ and LDT-subtest Block-Design). The LDT-subtest Block-Design assesses primarily visual-motoric performance. The low-risk preterm infants also showed significant lower results on the VMI. Our findings of poor visual-motor performance on the VMI and LDT corroborate other studies [Drillien *et al.* 1980, Klein *et al.* 1985, Vohr *et al.* 1989, Saigal *et al.* 1990, Hack *et al.* 1992, Smedler *et al.* 1992, Taylor *et al.* 1995]. However, unlike our study, these reports made no

distinction between high-risk and low-risk infants. The significant lower score on the BWVK in our study, for the low-risk preterm infants with an unfavourable outcome, highlights the concentration problems that are part of the developmental deficits of these infants. Herrgard *et al.* [1993] found problems with attention, as well as difficulties in gross motor, fine motor and visual-motor performance, in the infants with lower IQ values. The significant result for the LDT-subtest Word-Order indicate that low-risk preterm infants with an unfavourable outcome have more problems with auditory sequential memory tasks. Although the memory tasks used were not strictly related to our auditory memory tasks, it may be noted that other authors have reported memory deficits in preterm and low birth weight infants [Drillien *et al.* 1980, Saigal *et al.* 1990]. To summarize the neuropsychological deficits in low-risk preterm infants with an unfavourable neurodevelopmental outcome: visual-motor integration, concentration and auditory memory in combination with integrative functions seem most affected. This profile largely corroborates the data in the literature.

Conclusions

The present study demonstrated that low-risk preterm infants as a group have a more unfavourable outcome than term infants. This is due to a small subgroup of low-risk preterm infants with neurological abnormalities combined with a poorer neuropsychological outcome at age five years. However, the remaining low-risk preterm infants showed no neurological and/or neuropsychological disabilities when compared to the term infants. Thus, the results strongly suggest that the unfavourable outcome of the preterm group as a whole is due to moderate to severe impairment of the few, rather than slight impairment of the majority. The children with an unfavourable outcome showed particular impairment on visual-motor integration, concentration and auditory memory in combination with integrative functions.

Appendix 1 *Characterization of the subtests of the Dutch 'Leiden Diagnostic Test' (LDT) subtest name, abbreviation, input and output modality and type of information processing*

Subtest	Input	Output	Information process
Block Design	visual	fine-motoric	matching, pattern perception, perceptual analysis and synthesis, eye-hand coordination
Paper Folding	visual	fine-motoric	sequential and spatial memory, memory for spatial transformations, eye-hand coordination
Knox Cube	visual	fine-motoric	spatial sequential memory, eye-hand coordination
Word Span	auditory	speech-motoric	verbal sequential memory
Word Order	auditory + visual	fine-motoric	verbal sequential memory, matching
Sentence Repetition	auditory	speech-motoric	sentence memory
Question Answering	auditory	speech-motoric	semantic memory, (re)productive language
Comprehension	auditory	speech-motoric	understanding questions, logic reasoning (based on experiential knowledge and knowledge of social relations), productive language ability

Chapter 5

The effects of early and late preterm birth on brainstem and middle-latency auditory evoked responses in children with normal neurodevelopment

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In preterm and term infants, brainstem and middle latency auditory evoked responses (ABR and MLR) were obtained at 40 and 52 weeks conceptional age (CA) and at 5 years of age. A neurological and neuropsychological evaluation was performed at 5 years of age. To study the effect of preterm birth on the maturation of the ABR and MLR, the preterm infants were divided into early and late preterm groups. Only children with a normal neurodevelopmental outcome at 5 years of age were entered into the study. For ABR, the late preterm group showed significantly longer mean latencies IIc, III, V and Vc when compared with the term group at 52 weeks CA. There was a trend to longer ABR latencies I in the early preterm group compared with the term group. At 52 weeks CA the late preterm group showed longer mean inter-peak latencies III-I and V-I when compared with the term as well as the early preterm group. At 5 years the late preterm group showed significantly longer mean ABR latencies IIc and III when compared to the early preterm group. For MLR, the early preterm group showed significantly longer mean latencies of MLR component P0 when compared with the term group at 40 weeks CA. At 52 weeks the late preterm group also had longer mean MLR latencies P0 than the term group. At 5 years of age the term group showed higher mean peak-peak amplitudes Na-P0 than the early as well as the late preterm group. To a large extent, the ABR results support the hypothesis that middle ear effusions in combination with retarded myelination of the central auditory pathway are responsible for the ABR differences found between term and preterm infants with a normal neurodevelopmental outcome at 5 years of age. The longer latencies and inter-peak latencies found in late preterm infants when compared with early preterm infants might be explained by an augmented vulnerability of the auditory pathway between 30 and 34 weeks CA. The MLR differences found between term and preterm infants might be explained by a difference in the maturation of primary and nonprimary MLR components.

Introduction

Earlier we reported on the effect of preterm birth on brainstem, middle latency and cortical auditory evoked responses obtained at 40 and 52 weeks conceptional age (CA) in low-risk preterm infants (estimated gestational age (GA) 25-34 weeks) and healthy, term control infants [Pasman *et al.* 1992]. For the auditory brainstem evoked responses (ABR), significantly or nearly significantly longer means were found for the latencies of components III, V and Vc and inter-peak latency V-I at 52 weeks CA in preterm infants. At 40 weeks CA, a significant increase in the mean amplitude ratio V\I was found in preterm infants. For the middle latency auditory evoked responses (MLRs), the mean latencies of P0 components were longer, and the mean inter-peak latencies Na-P0 shorter, in preterm infants at 40 and 52 weeks CA. The ABR findings conformed, to some extent, to the findings of Eggermont and Salamy [1988] and Küttner *et al.* [1991]. However, other authors found shorter latencies for ABR components III and V and decreased inter-peak latencies III-I and V-I for preterm infants [Delorme *et al.* 1986, Collet *et al.* 1989]. At the time of the earlier study there were no reports on the effect of preterm birth on the MLR.

Recently a follow-up study of the same preterm and term infants was carried out at 5 years of age. In this study we found that a considerable number of low risk-preterm infants had an abnormal neurodevelopmental outcome. So we re-assessed the effect of preterm birth on ABR and MLR. To eliminate the influence of neurological and/or neuropsychological abnormalities on the effect of prematurity, in this study we only looked at infants with a normal neurodevelopmental outcome. To study the effect of the degree of prematurity on the maturation of ABR and MLR, we divided the preterm infants into an early preterm group (25-30 weeks GA) and late preterm group (31-34 weeks GA). The results of the present study will be discussed and contrasted with the results of our earlier work.

Patients and methods

Eighty-one preterm infants (GA 25-34 weeks) and 25 healthy, term control infants (GA 38-42 weeks) entered this prospective study. The preterm group consisted of preterm infants who were admitted to the Neonatal Intensive Care Unit of the University Hospital Nijmegen. The term control group consisted of healthy, term infants born in the same hospital in the same period. Gestational age was determined by the mother's last menstruation. In doubtful cases the complete Dubowitz

Newborn Maturation Scale was used to assess GA [Dubowitz *et al.* 1970]. Body weight, length and head circumference at birth were within normal limits (> P3 and < P97). Infants with dysgenetic brain lesions, major congenital anomalies or well-defined clinical syndromes were excluded from the study.

Twelve of the 81 preterm infants (15%) and none of the term infants died in the neonatal period. Sixteen of the 81 preterm infants (20%) and 7 of the 25 term infants (28%) were not available for the complete follow-up period because of migration or withdrawal by the parents. The remaining 53 preterm infants were divided in a group of 28 early preterm infants (24-30 weeks GA) and a group of 25 late preterm infants (31-34 weeks GA). At the age of 5-6 years the infants were invited to participate in a neurophysiological, neurological and neuropsychological evaluation.

Clinical neurological examination was performed by an experienced child neurologist using standard pediatric neurological examination methods. The results were classified on a three-point abnormality scale (none-minor-major), based on the WHO classification of Impairments, Disabilities and Handicaps [WHO 1980]. Neurological abnormalities were classified as minor if they did not result in disability and/or handicap and as major if they did. Based on this examination, the infants of both the preterm and the term groups were divided into two groups: infants with no or minor neurological abnormalities, and infants with major neurological abnormalities.

The neuropsychological diagnostic battery consisted of standardized tests: Visual-Motor Integration Test (VMI), Leiden Diagnostic Test (LDT) or the WISC-R, Bourdon-Wiersma-Vos concentration test for infants (BWVK) and Auditory Discrimination Test (ADIT) [Haassen *et al.* 1974, Crul and Peters 1976, Schroots and van Alphen de Veer 1976, Vos 1988, Beery 1989].

The ABRs and MLRs were obtained at 40 weeks CA, 52 weeks CA and 5 years of age using a Nicolet CA-1000 or a Nicolet PII evoked potential unit. Test conditions, instrumentation, test parameters and nomenclature have been described elsewhere. The test parameters are summarized in Table 1. In each recording session the auditory evoked responses were replicated to visually assess the reproducibility of the individual evoked response components. The state of vigilance was monitored by the technician. Where possible we tried to get ABR and MLR from sleeping subjects, but data from wakeful subjects were accepted. The waveform labelling and classification criteria have been described elsewhere [Rotteveel *et al.* 1987a, 1987b, Pasman *et al.* 1992].

Table 1. *Test parameters*

	ABR	MLR
Click duration (μs)	100	999
Intensity (dB)*	70	70
(threshold (dB))	80\50\40\30	
Rate (Hz)	11	4 7
Mode (rarefaction)	regular	regular
Side of stimulation (AD/AS)	AD + AS	AD + AS
High pass filter (Hz)**	30	5
Low pass filter (Hz)	3000	250
Number of channels	2	4
Time base (ms)	20	100
Prestimulus interval (ms)	5	25
Number of sweeps	2000	256 or 512
Sample points	512	256
Active sites	Cz	Cz, C4', C3'
Reference	A2, A1	A2A1 linked
Ground	Fz	Fz
Derivations	Cz-A2	Cz-(A2A1)
	Cz-A1	C4'-C3'
		C4'-(A2A1)
		C3'-(A2A1)

* Zero dB setting = 30 dB peak equivalent SPL

** Filter roll-off 12 dB/octave

The recordings were analysed independently by two investigators We used grand composite group averages as templates for individual records The grand composite group averages were obtained by summing the individual records for each CA level and for the term and preterm groups separately ABR latencies of the ipsilateral components I, III and V, the latencies of contralateral components IIc and Vc, the ipsilateral inter-peak latencies III-I, V-III and V-I, the contralateral inter-peak latency Vc-IIc, the ipsilateral amplitude ratio V/I and the inter-peak latency ratio V-III/III-I after monaural stimulation were analysed MLR latencies of components P0 and Na, the inter-peak latency Na-P0 and the peak-peak amplitude P0-Na for ipsilateral, contralateral and central (i e , ipsicentral at 5 years) derivations after monaural stimulation were determined Waveform morphology was determined by visual inspection

Using Student's *t*-tests for paired samples, no clear differences were found between left-sided and right-sided stimulation for ABR and MLR parameters [Pasman *et al.* 1992]. In addition, no imbalance could be observed between the number of positive and negative mean left-right differences. Consequently, the corresponding derivations, viz. the ipsilateral, the contralateral or the central (i.e., ipsicentral at 5 years) derivations after right-sided and left-sided stimulation were averaged. The ABR and MLR results at 40 weeks CA, 52 weeks CA and 5 years of age were analysed for each derivation in both preterm and term infants. Incomplete left-right observations were also included, because missing observations may not necessarily indicate pathology [Pasman *et al.* 1991].

For the different auditory evoked response components, analyses of variance were used to determine possible differences between the 3 groups: early preterm, late preterm and term group. If an overall difference was established, a comparison of each pair of groups was carried out according to the Scheffé method. Any difference was considered statistically significant if a p-value ≤ 0.05 was found. In cases where $0.05 < p \leq 0.10$ the result was taken to indicate a trend. The statistical analyses were carried out with the SAS statistical package [SAS Institute Inc. 1985] and an SAS-macro.

This study was approved by the Ethics Committee of the University Hospital of Nijmegen. Informed consent was obtained from all parents of infants enrolled in the study.

Results

Based on the neurological and neuropsychological examination at 5 years of age, infants with a normal neurodevelopmental outcome were selected. All term control infants (n = 18) had a normal outcome, while 15 of the 28 early preterm infants (54%) and 18 of the 25 late preterm infants (72%) had a normal neurodevelopmental outcome. Gestational age, birth weight and head circumferences of the early preterm infants, late preterm infants and term infants with a complete follow-up and normal neurodevelopmental outcome are summarized in Table 2.

A summary of significant differences between the early preterm, late preterm and term group with respect to latencies and amplitudes of ABR and MLR components are listed in Tables 3 and 4. For details see Appendix 1 and 2.

Table 2. *Gestational age, birth weight and head circumferences of the term and preterm infants in the study*

		Gestational age	Birth weight	Head circumference
	n	mean ± sd	mean ± sd	mean ± sd
Early preterm infants (25-30 weeks GA)	15	28.2 ± 1.6	1037 ± 228	25.1 ± 1.9
Late preterm infants (31-34 weeks GA)	18	32.2 ± 1.2	1567 ± 342	29.7 ± 3.0
Term infants (38-42 weeks GA)	18	39.4 ± 1.1	3144 ± 516	34.2 ± 1.3

Auditory Brainstem Evoked Responses (ABRs)

We found no differences in the ABR waveform morphology between the 3 groups. At 40 and 52 weeks CA, longer latencies for all ABR components were observed in the preterm groups when compared with the term group. At 5 years of age this was true for the late preterm group but only for component I in the early preterm group. Remarkably, the longest latencies were found in the late preterm group, except ABR component I at 40 and 52 weeks CA and component IIc and III at 40 weeks CA. However, significant results were obtained only at 52 weeks CA and 5 years of age. Furthermore, at 52 weeks CA component I showed a trend towards longer latencies in early preterm infants when compared with term infants. The latencies of component IIc, III, V and Vc at 52 weeks CA were significantly longer in the late preterm group when compared with the term group. The same holds for the latencies IIc and III at 5 years of age in the late preterm group when compared with the early preterm group. The inter-peak latencies III-I and V-I at 52 weeks CA were significantly longer in late preterm infants when compared with term infants. This was also the case in late preterm infants when compared with early preterm infants. In addition, at 52 weeks CA a trend towards lower latency ratios V-III/III-I was found for the late preterm group when compared with the early preterm group. See Table 3 and Appendix 1.

Middle Latency Auditory Evoked Responses (MLRs)

No differences in MLR waveform morphology were found between the preterm and term groups. In general, at 40 and 52 weeks CA and at 5 years of age, longer latencies of the MLR components P0 and Na were observed for the preterm groups.

Table 3. *ABR: Significant differences (and trends to differences) between term infants, early preterm infants and late preterm infants at 40 weeks CA, 52 weeks CA and 5 years of age according to the multiple comparison method of Scheffé*

	40 weeks CA		52 weeks CA		5 years	
	Difference	*p* - value	Difference	*p* - value	Difference	*p* - value
I latency	-	-	early preterm > term	0 10	-	-
IIc latency	-	-	late preterm > term	0 04	late preterm > early preterm	0 05
III latency	-	-	late preterm > term	0 007	late preterm > early preterm	0 01
V latency	-	-	late preterm > term	0 002	-	-
Vc latency	-	-	late preterm > term	0 007	-	-
III-I latency	-	-	late preterm > early preterm late preterm > term	0 001 0 002	-	-
V-III latency	-	-	-	-	-	-
V-I latency	-	-	late preterm > early preterm late preterm > term	0 007 0 03	-	-
Vc-IIc latency	-	-	-	-	-	-
V-III/III-I latency ratio	-	-	late preterm < early preterm	0 05	-	-
V/I amplitude ratio	-	-	-	-	-	-

The most important exception relates to MLR component Na in early preterm infants at 40 and 52 weeks CA, where shorter mean latencies were seen in early preterm infants when they were compared with both late preterm and term infants. The results were only significant for P0 at 40 and 52 weeks CA. When comparing late preterm and early preterm infants, longer (but not significantly longer) latencies were observed for the late preterm group, except for P0 at 40 weeks CA and at 5 years of age. Shorter inter-peak latencies Na-P0 at 40 and 52 weeks CA were seen in the preterm groups (especially the early preterm group) when compared with the term group. At 5 years of age, the inter-peak latencies Na-P0 were generally longer in the preterm groups (especially the late preterm group) when they were compared with the term group. Significant differences were not found at 40 and 52 weeks CA, nor at 5 years. Generally, the Na-P0 peak-peak amplitudes were smaller in the preterm groups at 40 weeks CA, 52 weeks CA and 5 years of age. Although the differences showed a consistent pattern, significant results were only found at 5 years of age, scattered over the various derivations. See Table 4 and Appendix 2.

Discussion

Earlier we reported on the effect of prematurity on the maturation of BMC-AERs obtained in low-risk preterm infants and term control infants at term date, and 3 months later [Pasman *et al.* 1992]. In a follow-up study we evaluated the same preterm and term infants at 5 years of age. A considerable number of the low-risk preterm infants showed an abnormal neurodevelopmental outcome at this age. To eliminate the influence of neurological and/or neuropsychological abnormalities on the maturation of ABR and MLR, in the present study we excluded infants with an abnormal neurodevelopmental outcome. To assess the influence of the degree of prematurity on the maturation of BM(C)-AERs, we divided the preterm group in an early preterm group (25-30 weeks GA) and a late preterm group (31-34 weeks GA).

Remarkable differences in ABR, especially in the latencies, were found when we compared the early and late preterm groups. The mean latencies of most ABR components were longer in late preterm infants than in early preterm infants, especially at 5 years CA. At 52 weeks CA the greater lengths of the inter-peak latencies III-I and V-I in late preterm infants compared with early preterm infants were particularly pronounced. No clear effects of the degree of prematurity were found in the latencies, inter-peak latencies or peak-peak amplitudes of the MLR.

Table 4. *MLR: Significant differences (and trends to differences) between term infants, early preterm infants and late preterm infants at 40 weeks CA, 52 weeks CA and 5 years of age according to the multiple comparison method of Scheffé*

	40 weeks CA		52 weeks CA		5 years	
	Difference	*p* - value	Difference	*p* - value	Difference	*p* - value
P0 latency	early preterm > term[1]	0 002	late preterm > term[1]	0 002	-	-
	early preterm > term[2]	0 02	late preterm > term[2]	0 001	-	-
	late preterm > term[3]	0 06	early preterm > term[2]	0 08	-	-
	early preterm > term[3]	0 005	late preterm > term[3]	0 01	-	-
Na latency	-	-	-	-	-	-
Na-P0 latency	-	-	-	-	late preterm > term[1]	0 08
Na-P0 amplitude	early preterm < term[3]	0 09	-	-	early preterm < term[1]	0 002
	-	-	-	-	late preterm < term[1]	0 03
	-	-	-	-	early preterm < term[2]	0 01
	-	-	-	-	late preterm < term[2]	0 09
	-	-	-	-	early preterm < term[3]	0 01
	-	-	-	-	late preterm < term[3]	0 03

[1]) (ipsi)central derivation

[2]) ipsilateral derivation

[3]) contralateral derivation

In the present study, we compared the ABR and MLR of early and late preterm infants with a normal neurodevelopmental outcome with the ABR and MLR of term infants, where in the previous study we compared the entire low-risk preterm group with the term group. The mean ABR latencies were longer in both early (40 and 52 weeks CA) and late preterm infants (40 and 52 weeks CA and 5 years) when compared with the ABR latencies in term infants. This was specially marked for ABR components IIc, III, V and Vc at 52 weeks CA in late preterm infants when compared with term infants. At 52 weeks component I showed a trend towards longer latencies in early preterm infants compared with term infants. Longer mean inter-peak latencies III-I and V-I were obtained for late preterm infants compared with term infants at 52 weeks CA. For the MLR component P0, the results showed increased mean latencies in both the early and late preterm group when compared with the term group at 40 and 52 weeks CA. For the MLR component Na no clear differences were found, although the mean latencies of MLR component Na were overall longer in the late preterm group when compared with the term group at 40 and 52 weeks CA and 5 years of age.

Generally, for both ABR and MLR, the present results agree with our earlier report [Pasman *et al.* 1992]. For the ABR latencies, our findings are supported by the findings of Eggermont and Salamy [1988], and Küttner *et al.* [1991]. Küttner *et al.* also found longer inter-peak latencies V-I in preterm infants, where Eggermont and Salamy did not find such an effect. Few studies report on the maturation of MLR, and we know of no reports on the effect of preterm birth on the maturation of the MLR [Kraus *et al.* 1985, Rotteveel *et al.* 1987b, Rogers *et al.* 1989, Kraus and McGee 1993].

To explain our findings concerning the effect of early and late preterm birth on ABR and MLR it is necessary to consider the mechanisms involved in the neurophysiological maturation of the auditory system. These mechanisms are: maturation of outer/middle ear, maturation of the cochlea, axonal myelination, dendritic growth and increasing synaptic efficiency [Shah *et al.* 1978, Goldstein *et al.* 1979, Salamy 1984, Starr 1984, Despland 1985, Eggermont and Salamy 1988]. In short, the cochlea becomes functional at about 20 weeks CA. The peripheral portions of the auditory pathway reach their full morpho-functional growth during the first weeks of post-term life. Centrally, there is a considerable synaptogenesis in the perinatal and postnatal period and a tremendous growth of dendrites after term [Yakovlev and Lecour 1967, Norman 1975]. Myelination occurs during the second growth spurt of the brain, which starts in the second half of gestation and lasts well into the second postnatal year or later [Dobbing and Sands 1973, Dobbing 1974]. The vestibular and auditory pathways in the brainstem myelinate early and

rapidly before term, whereas other fibre systems at the level of the brainstem myelinate later and at a slower rate. Developmental, neuroanatomical and magnetic resonance imaging studies have shown that myelination progresses in a centripetal direction [Yakovlev and Lecour 1967, Gilles 1976, Gilles *et al.* 1983, Salamy *et al.* 1985, Holland *et al.* 1986, McArdle *et al.* 1987, Martin *et al.* 1988].

Our results show possibly increased latencies of early ABR component I in preterm infants, especially in early preterm infants. This finding might relate to the high incidence of middle ear effusions in (early) preterm infants [Eggermont and Salamy 1988]. The fact that the other ABR latencies and inter-peak latencies are longer in preterm infants tends to support the hypothesis of a delayed myelination in preterm infants.

ABR latency differences were also observed between early preterm and late preterm infants indicating that the effect of preterm birth on the ABR in late preterm infants is greater than the effect on the ABR in early preterm infants. These differences might be due to the relatively fast rate of myelination of the auditory system between 30 and 34 weeks CA leading to a higher vulnerability of the auditory system in this period. It is known that in the preterm and perinatal period the auditory pathway is indeed vulnerable to various exogenous influences, such as anoxic-ischemic insults, hypotension and hypoglycemia. Furthermore, several experiments have demonstrated selective vulnerability of auditory relay nuclei, such as the cochlear nuclei, superior olives and inferior colliculi, in this period [Dobbing and Sands 1973, Griffiths and Laurence 1974, Myers 1975, Norman 1975, Leech and Alvord 1977, Salamy *et al.* 1982].

Increased latencies for MLR component P0 in preterm infants can also be attributed to a delayed centripetal myelination of the central auditory system. However, if the primary mechanism is delayed myelination, one would expect the latency of MLR component Na and the inter-peak latency Na-P0 to be increased in preterm infants. In our study this effect was not found. Thus, a more complex mechanism than delayed myelination alone, might be required to explain the results presented. Recent reports suggest that within the MLR generating system the primary and nonprimary components may mature at different rates. The nonprimary components appear to develop early and are probably sleep-state-dependent, whereas the primary components develop later and are reliable even in sleep [Kraus and McGee 1993, McGee *et al.* 1993].

Conclusions

Preterm birth effects the maturation of brainstem auditory evoked responses, even in preterm infants with a normal neurodevelopmental outcome at 5 years of age. These differences are probably related to a combination of middle ear effusions and retarded myelination of the central auditory pathway. The results of our previous report are largely in agreement with the present results. This concordance may imply that neurological and neuropsychological abnormalities resulting in an abnormal neurodevelopmental outcome at 5 years of age are not substantially associated with a disturbed maturation of ABR and MLR in a low-risk preterm population. The degree of prematurity also influences the brainstem evoked responses. This can be explained by a time-dependent vulnerability of the auditory pathway during the early and late preterm periods. The effect of preterm birth on the maturation of the middle latency auditory evoked responses might be explained by a differential maturation of the primary and nonprimary components of the MLR. To disentangle the mechanism involved, further research is needed. Determination of the location and orientation of the electromagnetic sources and their changes during the maturation of the central auditory pathway might be useful.

Appendix 1. *Mean and sd of ABR latencies, inter-peak latencies (IPLs), amplitude ratios and inter-peak latency ratios (IPL ratios)*

	40 weeks CA			52 weeks CA			5 years		
ABR	Early preterm	Late preterm	Term	Early preterm	Late preterm	Term	Early preterm	Late preterm	Term
Latency	n = 11	n = 14	n = 18	n = 15	n = 18	n = 18	n = 15	n = 17	n = 17
I	2 75 ± 0 26	2 69 ± 0 48	2 56 ± 0 41	2 39 ± 0 32	2 31* ± 0 46	2 11 ± 0 29	1 66 ± 0 27	1 73 ± 0 31	1 61 ± 0 19
IIc	4 20 ± 0 39	4 14 ± 0 48	4 05* ± 0 36	3 75 ± 0 37	3 85* ± 0 39	3 53* ± 0 29	2 68* ± 0 13	2 91 ± 0 36	2 79 ± 0 18
III	5 63 ± 0 37	5 48 ± 0 60	5 47 ± 0 49	4 78 ± 0 44	5 06 ± 0 51	4 60 ± 0 28	3 64* ± 0 14	3 87 ± 0 27	3 73 ± 0 15
V	7 58 ± 0 31	7 61 ± 0 39	7 53 ± 0 41	6 94 ± 0 33	7 23 ± 0 60	6 71 ± 0 20	5 64 ± 0 22	5 79 ± 0 31	5 65 ± 0 20
Vc	8 07 ± 0 27	8 08 ± 0 44	8 01* ± 0 35	7 23 ± 0 34	7 50 ± 0 48	7 07 ± 0 31	5 77 ± 0 22	5 93 ± 0 28	5 78 ± 0 22
IPL									
III-I	2 87 ± 0 26	2 82 ± 0 51	2 91 ± 0 44	2 38 ± 0 17	2 74* ± 0 20	2 49 ± 0 22	2 04* ± 0 18	2 14 ± 0 14	2 12 ± 0 13
V-III	1 96 ± 0 23	2 11 ± 0 52	2 04* ± 0 37	2 17 ± 0 18	2 17 ± 0 37	2 11 ± 0 26	1 94* ± 0 13	1 92 ± 0 13	1 91 ± 0 14
V-I	4 83 ± 0 25	4 93 ± 0 33	4 98 ± 0 29	4 55 ± 0 12	4 81** ± 0 29	4 60 ± 0 20	3 98 ± 0 13	4 06 ± 0 21	4 04 ± 0 20
Vc-IIc	3 83 ± 0 22	3 88 ± 0 33	3 96* ± 0 35	3 49 ± 0 31	3 63* ± 0 33	3 55* ± 0 32	3 04* ± 0 10	3 01 ± 0 21	2 97 ± 0 18
Amplitude ratio									
V/I	1 09 ± 0 55	1 16 ± 0 39	1 52 ± 0 71	1 21 ± 0 49	1 08*** ± 0 57	1 41 ± 0 77	1 47 ± 0 69	1 40* ± 0 80	1 53 ± 0 49
IPL ratio									
V-III/III-I	0 70 ± 0 12	0 84 ± 0 42	0 74* ± 0 24	0 93 ± 0 12	0 81** ± 0 12	0 88 ± 0 16	0 96* ± 0 14	0 90 ± 0 08	0 91 ± 0 08

* one missing
** two missings
*** three missings

Appendix 2. *Mean and sd of MLR latencies, interpeak latencies (IPLs) and peak-peak amplitudes*

	40 weeks CA			52 weeks CA			5 years		
	Early preterm	Late preterm	Term	Early preterm	Late preterm	Term	Early preterm	Late preterm	Term
Latency	n = 11	n = 14	n = 18	n = 15	n = 18	n = 18	n = 15	n = 17	n = 17
P0#	93 ± 10	88** ± 05	82 ± 06	82 ± 09	87 ± 07	77 ± 07	113 ± 15	108* ± 18	109 ± 12
P0##	94* ± 11	91** ± 06	85** ± 08	84 ± 09	88 ± 07	77 ± 09	110 ± 14	108* ± 20	109 ± 11
P0###	91 ± 10	88** ± 08	80* ± 07	80 ± 12	84 ± 08	75 ± 07	117 ± 20	112* ± 18	110 ± 11
Na#	187 ± 19	192 ± 18	190 ± 13	156 ± 17	161 ± 09	157 ± 14	165 ± 26	169 ± 23	158 ± 16
Na##	185* ± 18	193 ± 16	189 ± 15	155 ± 17	161 ± 10	160 ± 17	162 ± 25	169 ± 24	157 ± 17
Na###	185 ± 21	195 ± 18	189 ± 16	154 ± 17	161 ± 10	157 ± 16	165 ± 26	175 ± 21	163 ± 22
IPL									
Na-P0#	94 ± 16	100** ± 16	105 ± 14	74 ± 11	75 ± 10	79 ± 13	51 ± 14	61* ± 16	49 ± 12
Na-P0##	91* ± 15	98** ± 16	102** ± 18	72 ± 14	73 ± 12	82 ± 20	51 ± 14	59* ± 20	48 ± 12
Na-P0###	95 ± 18	103** ± 17	108* ± 17	74 ± 14	77 ± 13	82 ± 14	48 ± 15	59* ± 18	53 ± 16
Peak-peak amplitude									
P0-Na#	0 50 ± 0 19	0 62** ± 0 26	0 67 ± 0 24	0 69 ± 0 25	0 68 ± 0 44	0 82 ± 0 43	0 56 ± 0 26	0 69* ± 0 34	1 01 ± 0 40
P0-Na##	0 51* ± 0 21	0 61** ± 0 27	0 60**** ± 0 27	0 65 ± 0 26	0 68* ± 0 45	0 81 ± 0 40	0 50 ± 0 21	0 61* ± 0 37	0 88 ± 0 39
P0-Na###	0 48 ± 0 21	0 62** ± 0 25	0 69**** ± 0 21	0 75 ± 0 28	0 66 ± 0 45	0 90 ± 0 38	0 54 ± 0 35	0 61* ± 0 35	0 99 ± 0 50

* one missing
** two missings
*** three missings
**** four missings

\# = central for 40 weeks and 52 weeks CA (ipsicentral for 5 years)
\## = ipsilateral
\### = contralateral

Chapter 6

Diagnostic and Predictive Value of Auditory Evoked Responses in Preterm Infants

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(submitted)

In this study, the diagnostic and predictive value of brainstem, middle latency and cortical auditory evoked responses (BMC-AERs) obtained in the neonatal period in 81 preterm infants was assessed in relation to neurodevelopmental outcome. The preterm infants were neonatally classified according to risk category and gestational age (GA). The BMC-AERs were analysed with respect to detectability, latencies, and amplitudes as well as derived latency and amplitude measures. At 5 years of age the neurodevelopmental outcome was assessed from neurological and neuropsychological evaluations. The results showed that BMC-AER differences mainly correlated with risk category (low-risk/high-risk) and to some extent correlated with degree of prematurity. In view of these findings the degree of prematurity and the effect of risk category on the BMC-AERs have to be taken into account when relating BMC-AERs obtained in the preterm period to the neurodevelopmental outcome. In this study we found that the BMC-AERs for infants with abnormal neurodevelopmental outcomes were scarcely distinguishable from the BMC-AERs for infants with normal neurodevelopmental outcomes. Thus far, BMC-AERs in preterm infants have proved useful in maturational studies and with infants showing symptoms suggesting lesions or dysfunction of the peripheral and/or central auditory system. For predicting neurodevelopmental outcome in preterm infants, BMC-AERs are of limited clinical value.

The relatively high short-term and long-term morbidity in preterm infants has encouraged many authors to focus on the determination of neonatal risk factors in order to improve the prediction of neurodevelopmental outcome [Kitchen *et al.* 1980, Michelsson *et al.* 1984, Vohr *et al.* 1989, Scheiner and Sexton 1991, Abel Smith and Knight-Jones 1990]. Several neonatal risk factors and risk scores have been proposed as predictors of neurodevelopmental outcome in preterm infants and/or infants with low-birth-weight [Scheiner and Sexton 1991, Brazy *et al.* 1991]. However, these neonatal risk factors and risk scores are of limited clinical value, because a considerable number of preterm infants predicted to be at low-risk develop neurodevelopmental impairments during infancy or childhood.

Brainstem (ABR), middle latency (MLR) and cortical (ACR) auditory evoked responses (BMC-AERs) primarily reflect the function of the peripheral and central auditory pathways. To a certain extent the BMC-AERs also give information on the integrity of adjacent parts of the central nervous system. Several experiments have demonstrated selective vulnerability of auditory relay nuclei in the preterm period, especially between 28 and 40 weeks GA [Dobbing and Sands 1973, Griffiths and Laurence 1974, Leech and Alvord 1977]. In the past 15 years several authors have reported on the clinical importance of ABRs in newborn infants. Most of these studies have focused primarily on term infants, in particular on term infants with asphyxia or hyperbilirubinaemia and on term infants at risk for hearing loss [Stein *et al.* 1983, Guerit 1985, Guinard *et al.* 1989, Durieux Smith *et al.* 1991, Yang *et al.* 1993]. Neonatal ABR abnormalities have been described in infants with perinatal complications [Kraus *et al.* 1984, Nwaesi *et al.* 1984, Yasuhara *et al.* 1986, Cycowisz *et al.* 1988, Murray 1988]. Some authors have stated that early physiologic indices can be used to predict long-term developmental trends [Karmel *et al.* 1988, Molfese 1989]. Some studies have concentrated on the predictive value of ABRs in relation to neurodevelopmental outcome or later language skills in term infants [Stockard *et al.* 1983, Majnemer *et al.* 1988, Molfese 1989]. Only few authors have reported on ABR findings related to neurodevelopmental outcome in preterm infants [Majnemer *et al.* 1988, Beverly *et al.* 1990, Cox *et al.* 1992, Salamy and Eldredge 1994]. Majnemer *et al.* [1988] found evidence for the usefulness of the ABR as a diagnostic test for high-risk neonates. Cox *et al.* [1992] put forward that early ABR may predict long-term neurobehavioural development in low birth weight infants. Salamy and Eldredge [1994] reported that infants with neurological signs or demonstrable brain anomalies were 4-5 times more likely to exhibit deviant ABRs. They also reported

that the synergistic effects of selected predictor variables further increased the risk associated with abnormal ABRs. On the other hand, Beverly *et al.* [1990] found that neither flash VERs nor ABRs provide a good prognostic indicator for neurodevelopmental outcome. Only a few reports have focused on the predictive value of the MLR and ACR for neurodevelopmental outcome in newborn infants [Molfese 1989]. To the best of our knowledge, BMC-AER abnormalities are not evaluated as a neonatal risk factor in preterm infants.

In the present study the diagnostic and predictive value of BMC-AERs obtained in preterm infants in the neonatal period is assessed in relation to the long-term neurodevelopmental outcome. Firstly, we studied the differences in (cumulative) detectability of the various BMC-AER components obtained in the preterm period, and compared the results for low-risk and for high-risk preterm infants. For limited subgroups, the same analysis was also performed to evaluate the differences between early and late preterm infants and between infants with and without a normal neurological outcome at 5-7 years of age. We also compared BMC-AERs obtained at 29-32 weeks CA and at 33-35 weeks CA, for early low-risk infants against early high-risk infants with neurological/neuropsychological abnormalities at age 5-7 years. Subsequently, for low-risk infants, we analysed the BMC-AER differences at 33-35 weeks CA between early and late preterm born infants and also between normal and abnormal neurological/neuropsychological outcome at age 5-7 years. Finally, the individual BMC-AER results for infants with an abnormal neurodevelopmental outcome at age 5-7 years were analysed.

This study has been approved by the Ethics Committee of the University Hospital Nijmegen. Informed consent was obtained from all parents of infants in this study.

Material and methods

Patients

Eighty-one randomly selected preterm infants (GA 25-34 weeks) were included in this prospective study. This group consisted of inborn and outborn infants who were admitted to the Neonatal Intensive Care Unit of the University Hospital Nijmegen. Infants with dysgenetic brain lesions, major congenital anomalies or well-defined clinical syndromes were excluded from the study.

In the neonatal period the infants were classified as high-risk or low-risk according to the semi-quantitative Neonatal Neurological Inventory (NNI). The NNI assessment was performed in the first two weeks after birth. The NNI is

based on four items 1) clinical neurological examination, 2) echoencephalography, 3) arterial or capillary blood pH, and 4) Apgar score The neurological examination was performed according to Dubowitz *et al* [1980] Along with the items of the Dubowitz score the examination contained a qualitative analysis of spontaneous and evoked motility A similar approach has recently been described by Albers and Jorch [1994] On the basis of the clinical neurological examination, infants with neonatal seizures, cranial nerve palsies, asymmetric neurological syndromes or echoencephalographically determined brain lesions were classified as high-risk The neurological and echoencephalographic examinations were performed at least once biweekly until discharge In case of haemorrhage the echoencephalographic studies were classified according to Papile *et al* [1978] Periventricular leukomalacia was assessed as present or absent The NNI assessment was also based on blood pH and Apgar score In low-risk infants the blood pH had to be above 7 10 (arterial) or 7 00 (capillary) and the Apgar score had to be above seven at five minutes Based on the NNI, 65 of the 81 preterm infants were classified as low-risk and 16 as high-risk (i e , having one or more of the four NNI high-risk criteria) Five of the 65 low-risk infants and seven of the 16 high-risk infants died in the neonatal period Forty-four of the surviving low-risk infants (73%), and all of the nine surviving high-risk infants (100%) had a complete follow-up The other infants were not available to follow-up because of migration or withdrawal by the parents

BMC-AER recordings

BMC-AERs were obtained every two weeks during the preterm period, at 40 weeks CA, 52 weeks CA and at 5-7 years of age as described elsewhere [Pasman *et al* 1991] In the analyses, ABR latencies and amplitudes of ipsilateral components I, II, III and V and contralateral components IIc and Vc, next to interpeak latencies (IPLs) III-I, V-III, V-I and Vc-IIc and amplitude ratio V/I were used For the MLR latencies and amplitudes of components P0 and Na, IPL Na-P0 and peak-peak amplitude (PPA) P0-Na were analysed The latencies and amplitudes of ACR components Na, PbP1, P2p, N2p, IPL N2p-P2p and(PPA) P2p-N2p were also analysed, but at 33-35 weeks only the latencies Na and N2p were considered Detectability of individual BMC-AER components was determined for infants with registrations obtained both during 30-34 weeks CA and 35-41 weeks CA The last registration during 30-34 weeks CA and the first registration during 35-41 weeks CA were considered Differences in detectability (30-34 weeks CA) or cumulative detectability (30-34 and/or 35-41 weeks CA) of BMC-AER components between several subgroups were studied

Neurological and neuropsychological follow-up

At the age of 5-7 years a follow-up investigation was performed consisting of a neurophysiological, neurological and neuropsychological evaluation. The clinical neurological examination was carried out by an experienced child neurologist using standard pediatric neurological examination methods. The neurological abnormalities were classified, using the WHO classification of Impairments, Disabilities and Handicaps [WHO 1980]. Neurological abnormalities were classified as minor if they did not result in disability and/or handicap and they were classified as major if they did. Based on the neurological examination, the infants were divided into two groups: 1) the neurologically normal group consisting of infants with no or minor neurological abnormalities and, 2) the neurologically abnormal group consisting of infants with major neurological abnormalities.

The neuropsychological diagnostic work-up consisted of standardized tests: the Visual-Motor Integration Test, the 'Leiden Diagnostic Test' or the Revised Wechsler Intelligence Scale for Children, the Bourdon-Wiersma-Vos concentration test for infants and the Auditory Discrimination Test [Haassen *et al.* 1974, Schroots and Alphen de Veer 1976, Crul and Peeters 1976, Vos 1988, Beery 1989].

Based on the NNI and the neurological evaluation at 5-7 years of age four subgroups were determined: 1) low-risk infants without major neurological abnormalities, 2) low-risk infants with major neurological abnormalities, 3) high-risk infants without major neurological abnormalities, 4) high-risk infants with major neurological abnormalities. Based on the NNI and the neuropsychological evaluation at 5-7 years of age four analogous subgroups were determined.

Statistics

The statistical analyses for examining differences between low-risk and high-risk preterm infants, between early (25-30 weeks GA) and late (31-34 weeks GA) preterm infants and between normal and abnormal neurological respectively neuropsychological outcome at 5-7 years, for the (cumulative) detectability of the various BMC-AER components, were performed using Fisher's exact test for 2 x 2 tables. The BMC-AER differences between the group of early low-risk infants and early high-risk infants with neurological or neuropsychological abnormalities at age 5-7 years were analysed for the recordings at 30 weeks (or 29 to 31 weeks) and 34 weeks (or 33 to 35 weeks) for averaged left-right observations (including incomplete observations) with two-sample Student's *t*-tests. To analyse the BMC-AER differences at 34 weeks CA (33 to 35 weeks CA) between early and late low-risk preterm infants and between normal and abnormal neurological or neuro-

psychological outcomes, two-way analyses of variance were used for averaged left-right observations (including incomplete observations)

Any difference was considered to be statistically significant if a p-value ≤ 0.05 was found. In case $0.05 < p \leq 0.10$ it was said that a trend to differences could be shown. The individual BMC-AER results were assessed using reference values obtained by the authors [Rotteveel *et al.* 1987a, 1987b, 1987c, Pasman *et al.* 1991, Pasman *et al.* 1992]. The statistical analyses were carried out using the SAS statistical package [1985].

Results

In Table 1 gestational age, birth weight and head circumference at birth of the preterm subgroups are given. The distributions of neurological and neuropsychological abnormalities at age 5-7 years for the early/late and low-risk/high-risk preterm subgroups are given in Table 2. Previous results showed that the effect of prematurity on the BMC-AERs in the low-risk and high-risk groups had to be taken into account, which meant that some groups were too small for statistical analysis [Pasman *et al.* 1996].

Detectability of BMC-AER components

Table 3 shows the absence of the complete BMC-AER recording in the preterm infants with a normal long-term neurodevelopment, and in the preterm infants with an abnormal long-term neurodevelopment. No important differences with respect to the presence or absence of the complete ABR, MLR or ACR were found. The majority of the absent ABR, MLR or ACR recordings were obtained between 25 and 30 weeks CA.

The effect of risk category was assessed by analysing the differences in (cumulative) detectability between the low-risk and high-risk subgroups, irrespective of outcome or degree of prematurity.

The detectability at 30-34 weeks CA for ABR components I, III and Vc, MLR component Na and ACR component Na is significantly higher in the low-risk subgroup than in the high-risk subgroup for at least one stimulation side and/or derivation. For MLR component Pa and for ACR component P2p the detectability was significantly lower in the low-risk subgroup than in the high-risk subgroup for one stimulation side and/or derivation. For the cumulative detectability the differences between the high-risk and low-risk subgroup were smaller than for the detectability at 30-34 weeks CA.

Table 1. *Patient characteristics*

	n		Age at birth (GA) mean ± sd (weeks)		Birth weight mean ± sd (grams)		Head circumference mean ± sd (cm)	
Outcome	Neurol	Psychol	Neurol	Psychol	Neurol	Psychol	Neurol	Psychol
Early preterm	28		29 1 ± 1 5		1113 ± 254		26 2 ± 2 2	
Low-risk	21		28 9 ± 1 5		1071 ± 269		26 0 ± 2 4	
Normal	15	16	28 8 ± 1 6	28 9 ± 1 5	1025 ± 222	1059 ± 236	25 3 ± 1 8	25 7 ± 2 4
Abnormal	6	5	29 7 ± 1 4	29 2 ± 1 3	1185 ± 360	1110 ± 388	27 7 ± 3 2	26 8 ± 3 4
High-risk	7		29 5 ± 1 2		1240 ± 159		26 9 ± 1 1	
Normal	1	2	27 3	28 1 ± 1 2	1230	1375 ± 205	27	28 0 ± 1 4
Abnormal	6	5	29 9 ± 0 8	30 1 ± 0 7	1242 ± 174	1186 ± 120	26 9 ± 1 3	26 4 ± 0 8
Late preterm	25		32 5 ± 1 0		1570 ± 359		29 5 ± 2 6	
Low-risk	23		32 6 ± 1 0		1568 ± 351		29 6 ± 2 7	
Normal	21	18	32 6 ± 1 0	32 5 ± 1 0	1579 ± 343	1567 ± 342	29 7 ± 2 8	29 9 ± 2 9
Abnormal	2	5	32 6 ± 1 6	32 8 ± 1 2	1458 ± 576	1573 ± 425	28 4 ± 1 6	28 6 ± 1 1
High-risk	2		32 0 ± 1 4		1585 ± 615		28 5 ± 2 1	
Normal	1	0	33	-	2020	-	30	-
Abnormal	1	2	31	32 0 ± 1 4	1150	1585 ± 615	27	28 5 ± 2 1

Neurol neurological outcome at 5-7 years of age

Psychol neuropsychological outcome at 5-7 years of age

Table 2. *Frequency distributions of long-term neurological and neuropsychological outcome for different preterm subgroups*

	Neurological outcome			Neuropsychological outcome		
	normal	abnormal	total	normal	abnormal	total
Low-risk preterm (25-30 weeks GA)	15 (71%)	6 (29%)	21 (100%)	16 (76%)	5 (24%)	21 (100%)
Low-risk preterm (31-34 weeks GA)	21 (91%)	2 (9%)	23 (100%)	18 (78%)	5 (33%)	23 (100%)
High-risk preterm (25-30 weeks GA)	1 (14%)	6 (86%)	7 (100%)	2 (29%)	5 (71%)	7 (100%)
High-risk preterm (31-34 weeks GA)	1 (50%)	1 (50%)	2 (100%)	0 (0%)	2 (100%)	2 (100%)
Total preterm	38 (72%)	15 (28%)	53 (100%)	36 (68%)	17 (32%)	53 (100%)

Table 3. *Absence of the complete ABR, MLR and ACR in (low-risk and high-risk) preterm infants*

	Normal outcome			Abnormal outcome		
	Absent responses obtained between			Absent responses obtained between		
	n*	25-34 weeks CA	25-30 weeks CA†	n*	25-34 weeks CA	25-30 weeks CA†
ABR	33	7 (21%)	7/7	20	3 (15%)	2/3
MLR	33	5 (15%)	4/5	20	3 (15%)	2/3
ACR	33	5 (15%)	2/5	20	2 (10%)	0/2

* total number of infants/recordings

† number of absent responses obtained between 25-30 weeks CA/number of absent responses obtained between 25-34 weeks CA

Table 4. *Effect of risk category on detectability of ABR, MLR and ACR components irrespective of outcome and prematurity*

	Detectability rate 30-34 weeks CA			Cumulative detectability rate 30-34 and/or 35-41 weeks CA		
	Low-risk	High-risk		Low-risk	High-risk	
ABR	n=31	n=9	*p*-value	n=31	n=9	*p*-value
I	1	0 78	0 05	-	-	-
III	0 94	0 56	0 02	1	0 67	0 009
IIc	0 94	0 67	0 07	1	0 78	0 05
Vc	0 97	0 67	0 03	1	0 78	0 05
MLR	n=30	n=9		n=30	n=9	
Pa*	0 33	0 75	0 05	-	-	-
ACR	n=31	n=9		n=31	n=9	
Na†	0 74/0 65	0 22/0 25	0 008/0 06	0 87/-	0 56/-	0 06/-
	n=24	n=9		n=24	n=9	
P2p‡	0 33	0 78	0 05	-	-	-

ABR and MLR after left-sided stimulation and ACR for left lateral derivation

Only significant ($p < 0\ 05$) or trends to differences ($0\ 05 < p \leq 0\ 10$) have been given

* derivation C4-A1A2

† derivation Cz-A1, C3-A1 resp

‡ derivation Cz-A2

Generally, the results for detectability and cumulative detectability pointed in the same direction. Because no large differences in (cumulative) detectability between left-sided stimulation and right-sided stimulation (ABR and MLR) and different derivations/electrodes (ACR) were found, we give only the significant differences or trends to differences after left-sided stimulation, with respect to left derivation. See Table 4.

The effect of prematurity on the detectability of BMC-AER components was studied by analysing the differences in (cumulative) detectability between early low-risk and late low-risk preterm groups with a normal neurologically outcome. The size of the other early and late subgroups did not permit analogous analyses. For the ABR and ACR no clear differences were found between these subgroups.

The detectability of MLR component Pa was significantly lower in the early low-risk subgroup with a normal outcome after left-sided stimulation for two derivations.

The relation between the detectability of BMC-AER components and the long-term outcome was determined by analysing the differences in (cumulative) detectability between the neurologically normal and the neurologically abnormal late low-risk group. For ACR component P2p a significantly higher cumulative detectability was found for the left lateral derivation in neurologically normal infants. The size of the other subgroups did not permit analogous analyses.

BMC-AER differences related to neonatal risk category

The significant differences or trends to differences for BMC-AERs obtained at 29-31 weeks CA and 33-35 weeks CA between early low-risk infants and early high-risk infants with neurological or neuropsychological abnormalities at 5-7 years of age are given in Table 5a and 5b.

For abnormal neurological outcomes, the mean ABR latencies I and Vc, ABR IPL Vc-IIc, MLR latency P0 and ACR latencies Na (lateral derivation) and P2 (central derivation) obtained between 29-31 weeks CA were significantly longer in the early high-risk infants than in the early low-risk infants. For the contralateral derivation the PPA P0-Na was significantly lower in high-risk infants. For abnormal neuropsychological outcomes, the same holds for ABR latencies I and Vc, and ABR IPL Vc-IIc, MLR latency P0 and ACR latency Na (central derivation).

At 33-35 weeks CA, for abnormal neurological outcomes, significant differences were found between early high-risk and low-risk infants with respect to ABR IPL V-III, ABR IPL ratio V-III/III-I and MLR latency P0, with higher means in the early high-risk infants.

Table 5a. *Effect of risk category on BMC-AERs**

ABR	29-31 weeks CA			33-35 weeks CA		
	Early low-risk	Early high-risk	*p*-value	Early low-risk	Early high-risk	*p*-value
	n = 3	n = 4		n=3	n=5	
Latency I (ms)	3 35 ±0 37	4 09±0 20†	0 02	-	-	-
Latency Vc (ms)	9 00±0 62	10 83±1 10	0 04	-	-	-
IPL V-III (ms)	-	-	-	2 03±0 12	2 79±0 46	0 03
IPL Vc-IIc (ms)	4 23±0 45	5 20±0 47	0 04	4 32±0 25	5 12±0 51‡	0 06
Amplitude ratio V\I	1 55±0 70	0 48±0 33	0 06	-	-	-
IPL ratio V-III/III-I	-	-	-	0 69±0 18	0 93±0 09	0 04
MLR	n=4	n=3		n=3	n=5	
Latency P0 central§ (ms)**	9 8±0 7	12 9±0 8	0 003	8 4±0 7	11 9±0 8	<0 001
PPA P0-Na contalateral¶ (μV)††	1 07±0 32	0 40±0 05	0 02	-	-	-
ACR	n=3	n=3				
Latency Na lateral‖ (ms)‡‡	28±3‡	35±5	0 05	-	-	-
Latency P2p central§ (ms)§§	191±5	222±16	0 03	-	-	-
PPA P2p-N2p lateral‖ (μV)	3 1±1 1	1 0±1 1	0 07	-	-	-

* Subgroup means (± sd) of BMC-AERs for early low-risk and high-risk infants with neurological abnormalities at 5-7 years, in case of significant differences or trends to difference, according to two sample Student's *t*-tests

† n = 5

‡ n = 4

§ Central MLR - derivation Cz-A1A2, ACR- derivation Cz-A1 or Cz-A2

¶ Contralateral MLR - derivation C4-A1A2 (left-sided stimulation), C3-A1A2 (right-sided stimulation)

‖ Lateral ACR - derivation C3-A1 or C4-A2

** Similar results were found for the ipsi- and contralateral derivations

†† Similar results were found for the ipsilateral derivation (p = 0 08)

‡‡ Similar results were found for the central derivation (p = 0 10)

§§ Similar results were found for the lateral derivation (p = 0 09)

For abnormal neuropsychological outcomes significant differences were found for ABR latencies IIc and MLR latency P0, in which early high-risk infants also showed higher means than early low-risk infants. The MLR IPL Na-P0 was significantly lower in early high-risk infants.

Relation between outcome, degree of prematurity and BMC-AER measures.
In a two-way analysis of variance, the effect gestational age on the BMC-AERs

obtained between 33-35 weeks CA, as well as the effect of outcome on these BMC-AERs in low-risk infants was evaluated. Generally, the means of the BMC-AER variables of the four subgroups were similar. See Table 6a and 6b for significant differences or trends to differences. Averaged over neurologically normal and abnormal the mean MLR PPA Na-P0 (contralateral) was significantly higher for late preterm infants. Averaged over early and late the mean ACR Na latency was significantly higher in neuropsychological abnormal infants. In general, the estimated effects of gestational age were of the same magnitude as the effects of neurodevelopmental outcome.

Table 5b. *Effect of risk category on BMC-AERs**

ABR	29-31 weeks CA			33-35 weeks CA		
	Early low-risk	Early high-risk	*p*-value	Early low-risk	Early high-risk	*p*-value
	n=5	n=3		n=4	n=3	
Latency I (ms)	3 27±0 42	4 09±0 20	0 02	-	-	-
Latency III (ms)	-	-	-	5 71±0 28	6 32±0 45	0 08
Latency V (ms)	8 73±0 69	10 28±1 23	0 06	8 09±0 56	9 25±0 74	0 06
Latency IIc (ms)	-	-	-	4 11±0 24	4 61±0 28	0 05
Latency Vc (ms)	9 01±0 81	10 83±1 10	0 04	8 48±0 55	9 60±0 71	0 06
IPL V-III (ms)	2 13±0 35	2 63±0 19	0 07	-	-	-
IPL Vc-IIc (ms)	4 24±0 42	5 20±0 47	0 02	-	-	-
MLR	n=5	n=3		n=4	n=3	
Latency P0 central† (ms)‡	10 2±1 0	12 9±0 8	0 01	8 6±0 7	11 5±0 8	0 004
IPL Na-P0 central† (ms)‡	-	-	-	10 5±1 8	7 2±1 3	0 04
ACR	n=3	n=3				
Latency Na central§ (ms)	26±2	35±4	0 04	-	-	-
Latency P2p central§ (ms)	199±8	222±16	0 08	-	-	-

* Subgroup means (± sd) of BMC-AERs for early low-risk and high-risk infants with neuropsychological abnormalities at 5-7 years, in case of significant differences or trends to difference, according to two sample Student's *t*-tests

† Central MLR - derivation Cz-A1A2

‡ Similar results were found for the ipsi- and contralateral derivations

§ Central ACR - derivation Cz-A1 or Cz-A2

Table 6a. *Subgroup means (± sd) of BMC-AERs for low-risk preterm infants, classified by prematurity and neurological outcome at 5 years, in case of significant differences or trend to differences at 33-35 weeks CA according to two-way analyses of variance*

ABR			Early low-risk		Late low-risk	
			n	mean ± sd	n	mean ± sd
IPL III-I (ms)		normal	12	2 89±0 31	19	2 87±0 32
	[2] p=0 08	abnormal	3	3 07±0 69	2	3 33±0 04
IPL V-I (ms)		normal	12	5 31±0 49	19	5 23±0 34
	[3] p=0 07	abnormal	3	5 10±0 58	2	5 80±0 28
Amplitude ratio V/I		normal	11	1 06±0 69	18	0 92±0 45
	[1] p=0 053	abnormal	3	1 39±0 64	2	0 42±0 42
MLR						
IPL Na-P0 (ms)		normal	12	9 3±1 6	18	9 8±1 8
contralateral*	[2] p=0 08	abnormal	3	11 7±1 9	2	10 4±3 1
PPA P0-Na (μV)		normal	12	0 38±0 19	17	0.55±0 28
ipsilateral†	[1] p=0 06	abnormal	3	0 40±0 13	2	0 70±0 42

[1] (Nearly) significant for differences between early preterm and late preterm For PPA Po-Na similar results were found for the central en contralateral derivations (p = 0 06, resp P = 0 05)

[2] Nearly significant for differences between normal and abnormal outcome

[3] Nearly significant interaction between early\late and normal/abnormal

* MLR contralateral derivation C4-A1A2 after left-sided stimulation, C3-A1A2 after right-sided stimulation

† MLR ipsilateral derivation C3-A1A2 after left-sided stimulation, C4-A1A2 after right-sided stimulation

Individual BMC-AERs and abnormal neurodevelopmental outcome

The individual BMC-AER results of high-risk and low-risk infants with neurological and/or neuropsychological abnormalities at 5-7 years of age are tabulated in Table 7 (high-risk infants) and Table 8 (low-risk infants). Applying available references values, five of the eight surviving high-risk infants (63%) and two of 12 low-risk infants (17%) showed an abnormal ABR. The abnormalities consisted of the absence of all components (three high-risk infants), one or more components (one low-risk infant) or increased (inter-peak) latencies (two high-risk infants and one low-risk infant). One low-risk infant showed the absence of ABR components IIc and Vc at 27 weeks CA. However, at this CA-level the absence of these components cannot be considered as abnormal. Three surviving high-risk (38%) and

nine low-risk (75%) infants with an abnormal outcome had normal ABRs at the first recording.

For the MLR, six of eight surviving high-risk infants (75%) and none of 12 low-risk infants (0%) with an abnormal neurodevelopmental outcome, had abnormal MLR responses. None of the surviving high-risk (0%) and 10 of the low-risk (83%) had a normal MLR. At this CA-level the absence of one or more MLR components in two surviving high-risk and two low-risk infants cannot be considered as abnormal.

Table 6b. *Subgroup means (± sd) of BMC-AERs for low-risk infants, classified by prematurity and neuropsychological outcome at 5 years in case of significant differences or trend to differences at 33-35 weeks CA according to two-way analyses of variance*

MLR			early low-risk		late low-risk	
Latency P0 (ms)	[1] p=0 08	normal	n=11	9 4±0 9	n=15	9 2±0 7
contralateral*	[3] p=0 03	abnormal	n=4	8 4±0 5	n=5	9 7±1 1
PPA P0-Na (μV)		normal	n=11	0 36±0 18	n=14	0 65±0 30
central†	[3] p=0 08	abnormal	n=4	0 61±0 22	n=5	0 55±0 26
ACR						
Latency Na (ms)		normal	n=10	22±2	n=14	22±2
lateral‡	[2] p=0 008	abnormal	n=4	24±3	n=3	26±2

[1] Nearly significant for differences between early preterm and late preterm

[2] Significant for differences between normal and abnormal outcome Similar results were found for the central derivation (p = 0 04)

[3] (Nearly) significant interaction between early\late and normal/abnormal For latency Po similar results were found for the central and ipsilateral derivations (p = 0 06, resp 0 03)

* MLR contralateral derivation C4-A1A2 after left-sided stimulation, C3-A1A2 after right-sided stimulation

† MLR central derivation Cz-A1A2

‡ ACR lateral derivation C4-A2 or C3

The second follow-up MLR registration in these infants showed MLR abnormalities in one of the two surviving high-risk infants and none of the two low-risk infants.

For the ACR, four of the eight surviving high-risk infants (50%) and one of the 12 low-risk infants (8%) showed an abnormal ACR response.

Table 7. *Individual BMC-AER results obtained in high-risk preterm infants with neurological and/or neuropsychological abnormalities at age 5-7 years. Also the results of the high-risk preterm infants who died in the neonatal period are given**

Deceased infants	Neurological/neuro-psychological (ab)normal	Recording (weeks CA)	**ABR**	**MLR**	**ACR**
1	+/+	26	I†, III†, V†, IIc† and Vc† absent	P0†, Na† absent	Na†, PbP1†, P2† and N2† absent
2	+/+	26	I†, III†, V†, IIc† and Vc† absent	P0†, Na† absent	Na†, PbP1†, P2† and N2† absent
3	+/+	28	I†, III†, V†, IIc† and Vc† absent	P0†, Na† absent	Na† absent
4	+/+	26	I†, III†, V†, IIc† and Vc† absent	P0†, Na† absent	Na†, N2† absent
5	+/+	29	V-I, V-III and Vc-IIc increased	normal	normal
6	+/+	31	normal	P0 increased	Na increased
7	+/+	31	III†, IIc† and Vc absent	P0†, Na absent	Na increased, PbP1†, P2†, N2† absent
Surviving infants					
1	+/-	33	normal	Na and P0-Na increased	Na† absent
2	+/+	29	I, III†, V, IIc† and Vc absent	P0†, Na† absent	normal
3	+/+	29	I, III†, V, IIc† and Vc absent	P0† absent	P2† absent
4	+/+	32	normal	P0 increased	PbP1 increased, P2† absent
5	+/+	31	V, Vc, V-I and Vc-IIc increased	P0 increased	Na increased
6	+/+	31	Vc-IIc increased	P0 increased	Na† absent, P2 increased
7	+/+	33	I, III†, V, IIc† and Vc absent	P0†, Na absent	Na†, PbP1†, P2† and N2† absent
8	-/+	33	normal	P0 increased	Na† absent, PbP1 increased

* The results are compared with the available normative data for each CA-level

† at this specific postconceptional age the absence of this component can not be considered as abnormal

Table 8. *Individual BMC-AER results obtained in low-risk preterm infants with neurological and/or neuropsychological abnormalities at age 5-7 years**

Infant	Neurological/neuro-psychological (ab)normal	Recording (weeks CA)	ABR	MLR	ACR
1	+/+	27	IIc† and Vc† absent	P0†, Na† absent	Na†, PbP1†, P2† and N2† absent
2	+/+	30	normal	normal	Na† and N2† absent
3	-/+	30	Vc-IIc increased	normal	Na†, PbP1†, P2† and N2† absent
4	+/+	31	normal	P0† absent	P2† and N2† absent
5	+/-	32	IIc† and Vc absent	normal	P2 increased, N2† absent
6	+/+	30	normal	normal	N2† absent
7	+/-	30	normal	normal	PbP1† and N2† absent
8	-/+	36	normal	normal	N2† absent
9	+/+	32	normal	normal	Na†, P2† and N2† absent
10	-/+	36	normal	normal	P2†, N2† absent
11	-/+	34	normal	normal	P2†, N2† absent
12	+/+	34	normal	normal	Na†, P2† and N2† absent

* The results were compared with the available normative data for each CA-level

† at this specific postconceptional age the absence of this component can not be considered as abnormal

One of the surviving high-risk (13%) and none of the low-risk (0%) infants showed a normal ACR. Because of the CA-level at time of registration the ACRs of three of the surviving high-risk (38%) and 11 of the low-risk (92%) infants cannot be considered as abnormal. We also analysed the AERs of the high-risk preterm infants who died in the neonatal period. Two of the seven infants (29%) showed ABR abnormalities, one infant (14%) had a normal ABR and four infants (57%) had one or more absent ABR components but because of the CA-level at time of registration this does not necessarily imply abnormality. The same holds for the MLR and the ACR.

Discussion

Changes in BMC-AERs can be related to normal and abnormal functional and/or structural alterations of the auditory system. In preterm infants BMC-AERs reflect the functional and structural maturation of the auditory system. The appearance of BMC-AERs in preterm infants born between 25 and 29 weeks CA implies a certain degree of maturation of the auditory system [Starr *et al.* 1977, Despland and Galambos 1980, Rotteveel *et al.* 1987b, 1987c, 1987e, Ponton *et al.* 1993]. Myelination of the auditory pathway is considered to be a requisite for function of the auditory system. Indeed, several studies have shown that myelination of the cochlear nerve and auditory structures in the brainstem starts between 26 and 29 weeks CA or even as early as 24 weeks CA [Yakovlev and Lecour 1967, Gilles *et al.* 1983, Moore 1985, Inagaki *et al.* 1987]. For the majority, the myelination of the auditory brainstem pathways is completed between 40 and 44 weeks CA [Yakovlev and Lecour 1967, Doobing and Sands 1973, Gilles *et al.* 1983, Moore 1985]. Other factors besides myelination, such as increasing synaptic efficiency, dendritic growth and the summation, synchronization and phase-locking capabilities of the auditory system, are also important in determining the central auditory conduction [Javel 1980, Moore 1985, Romand 1992]. The functional maturation of the auditory pathway is reflected by the changes in detectability, latencies and amplitudes of BMC-AER components [Rotteveel *et al.* 1987b, 1987c, 1987e].

Prematurity predisposes infants to a variety of neurodevelopmental and educational sequelae [Cox *et al.* 1992]. The early identification of infants who will exhibit long-term neurodevelopmental abnormalities is difficult, and there are frequent false-negative results, i.e., a substantial number of infants classified as low-risk will show neurodevelopmental impairments in infancy or childhood.

Several neuropathological studies have demonstrated that, in the preterm period, in particular auditory structures in the brainstem, such as the cochlear nuclei, superior olivary complexes and inferior colliculi, are vulnerable to perinatal anoxic-ischemic insults, but BMC-AER measures are not thoroughly evaluated as neonatal risk factors [Griffiths and Laurence 1974, Leech and Alvord 1977]. Some authors have suggested that ABRs may predict long-term neurobehavioural development in preterm and low birth weight infants [Stockard *et al.* 1983, Majnemer *et al.* 1988, Cox *et al.* 1992].

To determine if BMC-AERs in high-risk infants differ from those obtained in low-risk infants we compared the BMC-AER results of high-risk and low-risk subgroups. For both detectability and cumulative detectability differences were found between low-risk and high-risk infants for ABR, MLR and ACR. Generally, the high-risk group showed lower (cumulative) detectability rates than the low-risk group. Differences between low-risk and high-risk infants were found also for BMC-AER latencies, IPLs and amplitude measures (PPA and amplitude ratio). Because some of the groups were small, this could only be analysed for the early preterm infants with an abnormal neurological/neuropsychological outcome. In general, the latencies and IPLs were longer and the PPAs were smaller in early high-risk infants than in early low-risk infants. The individual recordings showed also more ABR-abnormalities in high-risk preterm infants than in low-risk infants. Much the same holds for the analysis of the individual MLR and ACR recordings. These longer latencies, longer IPLs and lower PPAs can be the result of de\dysmyelination or delayed myelination and synaptic evolution of the central auditory pathway [Yakovlev and Lecour 1967, Javel 1980]. Because the BMC-AER differences were generally more clear for recordings obtained at 29-31 weeks CA than for recordings obtained at 33-35 weeks CA a delayed myelination seems more likely than a de/dysmyelination [Pasman *et al.* 1992, 1996].

In previous studies we have shown that preterm birth affects the maturation of BMC-AERs, even in preterm infants with a normal neurodevelopmental outcome at 5 years of age [Pasman *et al.* 1992, 1996]. Therefore, the degree of prematurity has to be taken into account when the relation between BMC-AERs and neurodevelopmental outcome in preterm infants is studied. Generally, we found no clear differences in (cumulative) detectability for the degree of prematurity and for neurological/neuropsychological outcome. Furthermore, a complex pattern of BMC-AER differences was found between the various preterm subgroups (related to outcome and taking the degree of prematurity into account). The differences consisted not only of longer mean latencies and IPLs for early and abnormal low-risk infants, but concerning some BMC-AER measures also of

shorter means Based on the individual BMC-AER recordings of the preterm infants no clear distinction could be made between preterm infants with and preterm infants without an abnormal neurodevelopmental outcome These complex pattern of (generally small) BMC-AER differences might be due, in part, to potentially counteracting (patho)physiological effects on the maturation of BMC-AERs Whereas, delayed myelination results in longer latencies and IPLs and lower PPAs, other mechanisms, such as a disturbed synaptic efficacy or reduced dendritic growth, may result in less complex auditory relay centers and, accordingly, to shorter latencies and IPLs Some of these counteracting effects might be related to prematurity alone, whereas others might be related to pathophysiological mechanisms or combinations of prematurity and pathophysiological mechanisms These opposing effects might result in smaller BMC-AER differences than expected, masking functional and/or structural changes in the auditory system

This study shows that neonatally obtained BMC-AERs in preterm infants are influenced by risk category (high-risk/low-risk) as well as degree of prematurity, and that BMC-AERs are, to some extent, also related to neurodevelopmental outcome However, the effect of risk category is more clear than the effect of the degree of prematurity, or the effect related to neurodevelopmental outcome These results imply that low-risk preterm infants with a later abnormal neurodevelopmental outcome are barely detectable in the neonatal period using BMC-AERs Because delayed myelination is likely to be an important factor in the BMC-AER differences found between low-risk and high-risk infants, prenatal emerging cerebral lesions may account for these differences Recently, Burke and Tannenberg reported that placental infarctions are associated with prenatal cerebral ischemic lesions [Burke and Tannenberg 1995] These prenatal cerebral ischemic lesions consist primarily of periventricular white-matter lesions These white-matter lesions might be related to disturbed myelination and result in transient BMC-AER abnormalities Furthermore, it has been suggested that the maturation of the ABR can be faster in growth-retarded newborn infants than in appropriately grown infants The faster maturation might be the related to raised levels of steroid hormones and catecholamines caused by placental dysfunction It is known that steroid hormones and catecholamines have a variety of effects on neural maturation [Amiel Tison and Pettigrew 1991]

From the present study we conclude that neonatally obtained BMC-AERs in preterm infants cannot be used to generate a simple neonatal risk factor, because there is no strong relationship between BMC-AERs obtained in low-risk preterm infants, and later neurodevelopmental outcome These results, however, do not

preclude the use of BMC-AERs as an additional indicator of risk, to strengthen the validity and/or predictive value of (current) neonatal risk scores. Furthermore, BMC-AERs obtained in preterm infants can be useful in maturational studies, in preterm infants at risk for hearing disorders, and in infants clinically suspected of central (or peripheral) dysfunction of the auditory system.

Chapter 7

Neonatal risk factors and risk scores including auditory evoked responses.

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(submitted)

Summary

In a prospective study 81 preterm infants and 25 healthy term infants were neurologically and neurophysiologically evaluated in the neonatal period. At 5-7 years of age the neurological and neuropsychological outcome was assessed. In this study the validity and predictive value of the Neonatal Neurological Inventory (NNI) and the Neurobiologic Risk Score (NBRS) in preterm infants with respect to neurodevelopmental outcome were assessed. Furthermore, the predictive value of a number of neonatal risk factors, including a gestational age factor (GAF) and an auditory evoked response factor (AERF), was determined. Three of the 53 surviving preterm infants with a complete follow-up (6%) showed major neurological abnormalities at 5-7 years. Five infants (9%) showed neuropsychological abnormalities. Twelve infants (23%) showed neurological and neuropsychological abnormalities. An important subgroup of preterm infants can be identified as high-risk using the NNI and NBRS. However, the relatively low sensitivity and negative predictive value (NPV) eventuate in a considerable number of false negative results. The validity and predictive value of the NNI were comparable with that of the NBRS. Logistic regression showed that intraventricular haemorrhage and bilirubin levels contributed highly to the prediction of neurological outcome. For neuropsychological outcome these factors were: intraventricular haemorrhage and assisted ventilation. Addition of the GAF and AERF as separate items to the NBRS did not affect the predictive power. However, combined addition of the GAF and AERF showed a substantial improvement of the validity and the predictive value. This study shows that intraventricular haemorrhage, bilirubin and assisted ventilation contribute most to the validity and predictive value of the NBRS. Furthermore, regarding neurological outcome addition of a gestational age factor (GAF) in combination with an auditory evoked response factor (AERF) resulted in a substantial improvement of the validity and predictive value of the NBRS. However, the shortcomings of the current neonatal risk scores require a careful interpretation of clinical perinatal data regarding the prediction of neurodevelopmental outcome in preterm infants.

Introduction

Over the last few decades survival of preterm infants born between 25 and 34 weeks gestational age (GA) has substantially improved [Drillien *et al.* 1980, Kitchen *et al.* 1980, Michelsson *et al.* 1984, Vohr *et al.* 1989, Veen *et al.* 1991, Robertson *et al.* 1992]. Nevertheless, in surviving preterm infants the incidence of neurodevelopmental disturbances remains high. The incidence of major handicaps varies from 5% to 22%, depending on the maturity of the patient population, the classification of neurological and neuropsychological abnormalities and the duration of follow-up [Drillien *et al.* 1980, Brazy *et al.* 1991, Ornstein *et al.* 1991, Scheiner and Sexton 1991, Collin *et al.* 1991, Veen *et al.* 1991, Fazzi *et al.* 1992, Graziani *et al.* 1992].

Early prediction of neurodevelopmental outcome is important. For that purpose, two perinatal risk scores were developed recently. In 1991 Brazy *et al.* [1991] introduced the NBRS for infants less than 1500 gram and Scheiner and Sexton [1991] introduced the Perinatal Risk Inventory (PERI).

We designed the NNI to identify preterm infants as low-risk or high-risk infants using a simple combination of a restricted number of neonatal risk factors. Because of the limited predictive power of the available risk scores, we added a gestational age factor (GAF) and an auditory evoked response factor (AERF) to the 13 items of the NBRS. The aim of the present study was to assess the validity and predictive value of the NBRS and the NNI with respect to the long-term neurodevelopmental outcome of preterm infants born between 25 and 34 weeks GA.

Materials and methods

Eighty-one preterm infants (GA 25-34 weeks) and 25 healthy, term infants (GA 38-42 weeks) were included in this prospective study. The preterm group consisted of randomly selected inborn and outborn preterm infants who were admitted to the Neonatal Intensive Care Unit of the University Hospital Nijmegen. The term group consisted of healthy term infants born in same hospital in the same period and served as a control group. Infants with dysgenetic brain lesions, major congenital anomalies or well-defined clinical syndromes were excluded.

The preterm infants were classified as high-risk or low-risk infants according to the semi-quantitative NNI, performed in the first two weeks after birth. The NNI is based on four items: 1) clinical neurological examination, 2) echoencephalo-

graphy, 3) arterial or capillary blood pH and 4) Apgar score. The NNI items and criteria are summarized in Table 1.

With respect to the clinical neurological examination infants with neonatal seizures, cranial nerve palsies, asymmetric neurological syndromes or persistent abnormalities at neurological examination according to Dubowitz *et al.* [1980] were classified as high-risk infants. The neurological examination also contained a qualitative analysis of spontaneous and evoked motility. A similar approach was recently described by Albers and Jorch [1994]. To determine structural ischemic and/or haemorrhagic brain lesions transfontanellar echoencephalographic studies were performed daily in the first week of life and after that at least once biweekly until discharge. In case of haemorrhage the echoencephalographic results with respect to intracranial haemorrhages were classified according to Papile *et al.* [1978]. Periventricular leukomalacia (PVL) was assessed as present or absent. The NNI assessment was also based on blood pH and Apgar score. In low-risk infants the blood pH had to be above 7.10 (arterial) or 7.00 (capillary) and the Apgar score had to be above seven at five minutes. Based on the NNI 65 of the 81 preterm infants were classified as low-risk and 16 were classified as high-risk (i.e., presence of at least one of the four NNI high-risk criteria).

During the preterm period auditory evoked responses (AERs) were obtained every two weeks. Based on previous studies we selected ABR interpeak latency (IPLs) V-I and Vc-IIc, MLR latencies P0 and Na and MLR IPL Na-P0 for further analyses [Pasman *et al.* 1991, 1992, 1996]. Test conditions, instrumentation, test parameters and nomenclature are reported previously [Rotteveel *et al.* 1987b, 1987c, 1987e]. Based on previous reports the preterm infants were divided into an early (25-30 weeks GA) and late (31-34 weeks GA) group [Rotteveel *et al.* 1987b,1987c, 1987e, Pasman *et al.* 1996].

Five of the 65 low-risk preterm infants and seven of the 16 high-risk preterm infants died in the neonatal period. Forty-four of the surviving low-risk preterm infants (73%), all of the surviving high-risk preterm infants (100%) and 18 of the 25 term infants (72%) had a complete follow-up. The other infants were not available to follow-up because of migration or withdrawal by the parents. GA, birth weight and head circumferences of these infants are summarized in Table 2.

The NBRS and revised NBRS were conceived for the preterm infants in our study. The NBRS assessment was based on data obtained within the first four weeks after birth. The NBRS consists of 13 risk factors for brain injury in preterm infants [Brazy *et al.* 1991]. The revised NBRS is based on the seven most predictive NBRS items: intraventricular haemorrhage, assisted ventilation, periventricular leukomalacia, infection, blood pH, seizures, and hypoglycemia [Brazy *et al.* 1991].

Table 1. *Neonatal Neurological Inventory (NNI)*

	Item	Low-risk	High-risk[a]
1	Clinical neurological examination	absence of neonatal seizures, cranial nerve palsies, asymmetric neurological syndromes, structural brain lesions[b]	presence of neonatal seizures, cranial nerve palsies, asymmetric neurological syndromes, structural brain lesions[b]
2	Echoencephalography	IVH grade I and II[c], PVL absent	IVH grade III and IV[c], PVL present
3	Blood pH[d]	> 7 10 (art) or > 7 00 (cap)	< 7 10 (art) or < 7 00 (cap)
4	Apgar score	> 7 after 5 min	< 7 after 5 min

[a] Infants meeting one or more of these criteria are considered as high-risk

[b] I e , persistent abnormalities at neurological examination according to Dubowitz *et al* Brain Dev 1980, 2 3-14

[c] According to Papile *et al* J Pediatr 1978, 92 529-534

[d] In the first hour after birth

Table 2. *Patient characteristics*[a]

		Gestational age in weeks	Birth weight in grams	Head circumference in cm
	n	mean ± sd	mean ± sd	mean ± sd
Term infants (38-42 weeks GA)	18	39 4 ± 1 5	3144 ± 516	34 2 ± 1 3
Low-risk preterm infants (25-30 weeks GA)	21	28 9 ± 1 5	1071 ± 269	26 0 ± 2 4
Low-risk preterm infants (31-34 weeks GA)	23	32 5 ± 1 1	1568 ± 351	29 6 ± 2 7
High-risk preterm infants (25-34 weeks GA)	9	30 1 ± 1 6	1317 ± 299	27 0 ± 1 4

[a] Only the characteristics of infants with a complete follow-up are given

The items of the NBRS and revised NBRS are summarized in Table 3. In the NBRS zero points are given if a risk factor is absent. If present, the item is graded as 1, 2, or 4. The results were analysed for neurological and neuropsychological outcome.

Based on ABR and MLR an auditory evoked response factor (AERF) was designed. The first and second recording were assessed separately for each infant If the AER components were detectable and the (interpeak) latencies were within the normal range, the AER was qualified as normal. If one AER component (V, I, IIc, Vc, P0, Na) was not detectable or outside the normal range the AER was qualified as slightly abnormal; moderately abnormal if two AER components were not detectable or outside the normal range; severely abnormal if three or more AER components were not detectable or outside the normal range. Next, for each recording a raw score was conceived The raw score was graded 'zero' if the AER was qualified as normal or slightly abnormal and was graded 'one' if the AER was qualified as moderately or severely abnormal. The final AERF was based on these raw scores. If only the first recording had a raw score 1, the AERF was also graded as 1. If the second recording had a raw score 1, the AERF was graded as 2. If the first and the second recording had a raw score of 1, the AERF was graded as 3. If both recordings had a raw score zero, the AERF was graded as 0.

Furthermore, we introduced a gestational age factor (GAF) as a separate item within the NBRS. A GA of 38-42 weeks was graded as 0, a GA of 31-34 weeks as 1 and a GA of 25-30 weeks as 2.

Table 3. *Neurobiological Risk Score (NBRS)*[a]

	Item		Item		Item
1	Apgar score	6	Hypotension	11	Infection[b]
2	PaO_2	7	Patent ductus arteriosus	12	Hypoglycemia[b]
3	Assisted ventilation[b]	8	Seizures[b]	13	Bilirubin
4	Blood pH[b]	9	Intraventricular haemorrhage[b]		
5	Apnea with Bradycardia	10	Periventricular leukomalacia[b]		

[a] According to Brazy *et al* J Pediatr 1991, 118 783-792

[b] Items included in the revised NBRS

At the age of 5-7 years the infants were invited to participate in a follow-up investigation consisting of a neurological and neuropsychological evaluation Clinical neurological examination was performed by an experienced child neurologist using standard pediatric neurological examination methods To classify the neurological abnormalities we used the WHO classification of Impairments, Disabilities and Handicaps [WHO 1980] Neurological abnormalities were classified as minor if they did not result in disability and/or handicap and they were classified as major if they did Based on the neurological examination the infants of both the preterm and the term group were divided into two subgroups 1) the neurologically normal group consisting of infants with no or minor neurological abnormalities and, 2) the neurologically abnormal group consisting of infants with major neurological abnormalities

The neuropsychological diagnostic work-up consisted of standardized tests Visual-Motor Integration Test (VMI), 'Leiden Diagnostic Test' (LDT) or the Revised Wechsler Intelligence Scale for Children (WISC-R) depending on the test age of the child, Bourdon-Wiersma-Vos concentration test for infants (BWVK) and Auditory Discrimination Test (ADIT) [Haassen *et al* 1974, Crul and Peters 1976, Schroots *et al* 1976, Vos 1988, Beery 1989] Since for the VMI, LDT and WISC-R age-norms are available performances on these tests could be transformed to standard scores For the BWVK and ADIT group performances were compared based on raw scores

Analyses of variance and a χ^2-test of homogeneity were used to determine the neuropsychological differences between different low-risk groups Stepwise forward logistic regression was used to determine NBRS items that significantly predicted neurological or neuropsychological outcome at 5-7 years of age No differences between the socioeconomic status of the various groups were found Therefore, socioeconomic status was not used as a neonatal risk factor in the statistical analyses The statistical analyses were carried out using the SAS

statistical package, except the logistic regression, which was carried out using SPSS for Windows version 6.0 [SAS Institute Inc. 1985].

This study has been approved by the Ethics Committee of the University Hospital Nijmegen. Informed consent was obtained from all parents.

Results

Neurodevelopmental outcome

Twelve of the 81 preterm infants died during the first four weeks after birth, resulting in a neonatal mortality rate of 15%. The term infants showed no major neurological abnormalities at 5-7 years, whereas major neurological abnormalities were found in 15 of the 53 surviving preterm infants. These neurological deficits consisted of mental retardation, epilepsy, infantile encephalopathy with diplegia, hemiplegia, quadriplegia or extrapyramidal movement disorders and visual, auditory or sensory disturbances. The neurological deficits are summarized in Appendix 1. The infants with minor neurological abnormalities showed, among others, attention deficit disorders, reflex asymmetries and clumsiness.

In Table 4 the neuropsychological test results are presented. Overall, low-risk neurologically abnormal preterm infants showed a poorer performance than the term infants. One of the eight low-risk infants who exhibited major neurological abnormalities was not able to perform the neuropsychological tests.

According to an analysis of variance the theoretical means of the groups (term, normal low-risk preterm 31-34 weeks, normal low-risk preterm 25-30 weeks, neurological abnormal low-risk preterm) were not equal to each other for PIQ ($F(3,56) = 3.45$, $p = 0.02$), and VMI ($F(3,56) = 7.12$, $p < 0.001$). Some normal preterm infants, and six out of eight abnormal preterm infants failed on the BWVK-concentration test, as compared to none of the term infants.

Inspection of individual test scores suggested that the lower averages of the preterm groups were caused by a few neuropsychological 'poor-performers', whereas the remaining infants obtained test scores within the normal range. Therefore, based on the two tests that yielded significant group differences, the following criteria were used to identify neuropsychologically poor-performers: 1) A score in the lowest 10% range on the VMI (i.e., VMI: < 7) and/or the performance IQ (i.e., PIQ < 80), or 2) a moderately poor VMI score of 7 combined with a below average (< 100) score on the performance part of the intelligence test (LDT or WISC-R).

Table 4. *Neuropsychological test results (mean ± sd or ratio of positive results)*

Group	Term infants	Normal low-risk preterm infants[a]		Neurologically abnormal low-risk preterm infants[b]	Analysis of variance[c]	High-risk preterm infants[a]
Gestational age	38-42 weeks	31 - 34 weeks	25 - 30 weeks	25 - 34 weeks		25 - 34 weeks
Number of infants	n = 18	n = 21	n = 15	n = 8[d]	*p*-value	n = 9[e]
Total IQ	114 ± 17	113 ± 15	108 ± 15	99 ± 12	ns[f]	78 ± 20
Verbal IQ	113 ± 18	114 ± 18	107 ± 16	104 ± 12	ns	79 ± 19
Performance IQ	111 ± 14	107 ± 10	106 ± 11	93 ± 14	0.02	81 ± 19
VMI	10.4 ± 1.9	9 0 ± 2.1	10.2 ± 2 3	6.2 ± 2.4	< 0.001	8.6 ± 2.5
ADIT	28.1 ± 1.4	28 7 ± 1.4	27.5 ± 1.9	28.0 ± 1.0	ns	-
BWVK-N	18/18	18/21	13/15	2/8	ns[g]	-
Neuropsychological poor-performers	n = 0	n = 3	n = 1	n = 6		n = 7

[a] The preterm infants were divided in low-risk and high-risk infants according to the NNI.

[b] Six of the eight neurological abnormal low-risk preterm infants were within the 25-30 weeks gestational-age-range.

[c] The high-risk infants were excluded from analysis.

[d] One infant was neuropsychologically not testable

[e] Four infants were neuropsychologically not testable

[f] ns = not significant ($p > 0.10$).

[g] Chi-squared test.

All term control infants had a VMI score of 8 or higher, and a PIQ score above 80 Eight of the low-risk preterm infants had a poor VMI score (< 7), and two had a moderately poor VMI score (= 7) combined with a below average PIQ These 10 low-risk preterm infants were identified as poor-performers Six of these 10 poor-performers were also classified as neurologically abnormal, four from the 25-30 GA-range, and two from the 31-34 GA-range

Four of the nine high-risk preterm infants were not testable and were classified as poor-performers Three other high-risk infants had an IQ below 80 (two of them combined with a moderately poor (VMI = 7) to poor (VMI < 7) VMI-score) These three infants were also classified as poor-performers As a result seven of the nine high-risk infants were classified as poor-performers The remaining two infants had a VMI score of 10 or higher, combined with a slightly below average WISC-R IQ, in the 90 - 100 range The long-term neurological and neuropsychological outcome of the surviving preterm infants is summarized in Appendix 2

Comparison of neonatal risk scores

The analyses were performed for neurological outcome and neuropsychological outcome separately The validity and predictive value (i e , sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)) of the NNI was compared with those of the NBRS and revised NBRS for both the long-term neurological and neuropsychological outcome using the data of the present study The evaluations were performed according to the methods and criteria of Brazy *et al* [1991] For the neurological outcome the NNI, NBRS and revised NBRS showed almost similar results except a lower sensitivity for the revised NBRS Regarding the neuropsychological outcome no clear differences between the NNI, NBRS and revised NBRS were found

Furthermore, the results based on our data were compared with the NBRS results described by Brazy *et al* [1991] They found a slightly higher sensitivity and PPV, a somewhat lower NPV and almost the same specificity The results are summarized in Table 5

Determination of neonatal risk factors

Logistic regression analysis entering all 13 NBRS items was performed to determine those factors contributing most to the prediction of outcome The analyses were performed for neurological outcome and neuropsychological outcome separately The results of the logistic regression analyses are summarized in Table 6 and 7

Table 5. *Validity and predictive value of neonatal risk scores (n=53)*

	Sensitivity	Specificity	PPV	NPV
		Neurological outcome		
NNI	7/15 = 0 47	36/38 = 0 95	7/9 = 0 78	36/44 = 0 82
NBRS	7/15 = 0 47	37/38 = 0 97	7/8 = 0 88	37/45 = 0 82
NBRS revised	5/15 = 0 33	37/38 = 0 97	6/7 = 0 83	37/46 = 0 79
NBRS[a]	0 60	1 00	1 00	0 68
		Neuropsychological outcome		
NNI	7/17 = 0 41	34/36 = 0 94	7/9 = 0 78	34/44 = 0 77
NBRS	7/17 = 0 41	35/36 = 0 97	7/8 = 0 88	35/45 = 0 78
NBRS revised	7/17 = 0 40	34/36 = 0 94	7/9 = 0 78	34/44 = 0 77

[a] Results from the literature Brazy *et al* NBRS and neurodevelopmental abnormalities at 24 months (MDI < 85, PDI < 85 and/or abnormal neurologic examination)

With respect to neurological outcome a forward stepwise approach (probability stepwise 0 05 (entry) and 0 10 (removal)) yielded intraventricular haemorrhage and bilirubin as significant factors With respect to neuropsychological outcome the forward stepwise approach revealed next to intraventricular haemorrhage, assisted ventilation and hypotension as significant factors Under a model with these two, respectively three variables the regression coefficients, standard errors and *p*-values of the Wald test are given in Table 6 The combination of these two, respectively three items is almost as powerful as the combination of all 13 NBRS items and the combination of the seven items of the revised NBRS See Table 7 The analyses yielded high specificity (0 94-1 00) and PPV (0 80-1 00), a slightly lower NPV (0 74-0 84), and a rather low sensitivity (0 40-0 53) When a gestational age factor (GAF) was added as a neonatal risk factor and all 14 items are entered in a stepwise logistic regression analysis, the same risk factors (i e , intraventricular haemorrhage and bilirubin) were determined as relevant for neurological outcome However, sensitivity rose to 0 67 (13 items + GAF) or 0 73 (7 items + GAF) NPV rose to 0 88 and 0 90 respectively, whereas specificity (respectively 0 95 and 0 95) and PPV (respectively 0 83 and 0 85) showed a slight decrease Regarding the neuropsychological outcome the results of the analyses using only the original 13 or 7 NBRS items showed no differences if compared with the results of the analyses after adding GAF to the original (13 or 7) NBRS items Furthermore, the auditory evoked response factor (AERF) was added to the various models used in the logistic regression analyses After adding the AERF to

the items of the (revised) NBRS no clear changes in validity and predictive value were found for neurological outcome or neuropsychological outcome However, after both AERF and GAF were added to the complete NBRS (13 items) sensitivity and negative predictive value improved to 0 87 and 0 95, respectively, whereas specificity (1 00) and PPV (1 00) for the neurological outcome remained unchanged

Table 6 *Predictive neonatal factors for neurodevelopmental outcome in surviving preterm infants*[a]

Variable (grading risk factors)	Regression coefficient	Standard error	*p*-value Wald test	*p*-value model χ^2-test
13 NBRS items		Neurological outcome[b]		
Constant	-1 9	0 5	0 0001	
Intraventricular hemorrhage (0-1-2-4)	1 3	0 6	0 02	$p = 0\ 003$
Bilirubin (0-1-2)	1 3	0 7	0 05	
13 NBRS items		Neuropsychological outcome[c]		
Constant	-0 7	0 4	0 07	
Intraventricular haemorrhage (0-1-2-4)	1 9	0 8	0 02	
Assisted ventilation (0-1-2-4)	-1 2	0 6	0 04	$p = 0\ 003$
Hypotension (0-1-2-4)	9 7	27 6	0 73	
13 NBRS items + GAF + AERF				
Constant	-0 4	0 4	0 4	
Intraventricular haemorrhage (0-1-2-4)	4 5	2 2	0 03	
Assisted ventilation (0-1-2-4)	-1 7	0 7	0 02	$p = 0\ 03$
Hypotension (0-1-2-4)	14 7	41 5	0 7	
AERF (0-1-2-3)	-3 6	2 5	0 2	

[a] Results of forward stepwise logistic regression The results for the 13 NBRS items and the 13 NBRS items extended with GA are the same

[b] 38 neurologically normal preterm infants and 15 neurologically abnormal infants

[c] 36 neuropsychologically normal preterm infants and 17 neuropsychologically abnormal infants

Table 7. *Validity and predictive value of neonatal risk factors in surviving preterm infants*[a]

	Sensitivity	Specificity	PPV	NPV
Model variables		Neurological outcome		
Intraventricular hemorrhage + bilirubin	0 47	0 97	0 88	0 82
NBRS (13 items)	0 53	1	1	0 84
NBRS + GAF	0 67	0 95	0 83	0 88
NBRS + AERF	0 53	0 97	0 89	0 84
NBRS + GAF + AERF	0 87	1	1	0 95
NBRS revised (7 items)	0 4	1	1	0 81
NBRS revised + GAF	0 73	0 95	0 85	0 9
NBRS revised + AERF	0 47	0 97	0 88	0 82
NBRS revised + GAF + AERF	0 73	0 97	0 92	0 9
		Neuropsychological outcome		
Intraventricular haemorrhage + Assisted ventilation + hypotension	0 42	0 97	0 89	0 75
Intraventricular haemorrhage + Assisted ventilation + hypotension + AERF	0 42	0 92	0 89	0 75
NBRS (13 items)	0 53	0 97	0 91	0 79
NBRS + GAF	0 53	0 97	0 91	0 79
NBRS + AERF	0 68	0 91	0 91	0 84
NBRS + GAF + AERF	0 74	0 91	0 82	0 86
NBRS revised (7 items)	0 42	0 94	0 8	0 74
NBRS revised + GAF	0 42	0 94	0 8	0 74
NBRS revised + AERF	0 37	0 97	0 88	0 73
NBRS revised + GAF + AERF	0 42	0 94	0 8	0 74

[a] Using logistic regression models

Inclusion of GAF and AERF in the revised NBRS regarding neurological outcome also resulted in an improved sensitivity. For neuropsychological outcome the differences were less distinct. For neuropsychological outcome the logistic regression analyses using a stepwise forward approach intraventricular hemorrhage,

assisted ventilation, AERF and hypotension were identified as a powerful combination of risk factors With respect to neurological outcome AERF did not influence the combination of the most powerful risk factors See Table 6 and 7

Discussion

In this study neonatal mortality was considerably lower than reported in the literature, whereas the incidence of neurological and/or neuropsychological abnormalities was somewhat higher than in recent studies [Drillien *et al* 1980, Brazy *et al* 1991, Scheiner and Sexton 1991, Collin *et al* 1991, Veen *et al* 1991, Fazzi *et al* 1992, Graziani *et al* 1992, Robertson *et al* 1992] However, these results need to be handled with caution, because the study was not designed to yield epidemiological information as to mortality and morbidity Furthermore, stressing that no differences in socioeconomic status were found between the preterm subgroups is important

The results of the neuropsychological examination revealed significant differences for VMI and PIQ between the low-risk groups and the term group These differences are due to a subgroup of neuropsychological poor-performers and not to a slightly lower performance of all low-risk preterm infants The high-risk preterm group, as could be expected, showed the poorest results with respect to a neuropsychological outcome This is more obvious if one takes into account that more high-risk infants than low-risk infants were not testable

Studies on long-term neurodevelopmental outcome of preterm infants have identified several neonatal risk factors, such as low birth weight and fetal growth retardation [Zubrick *et al* 1988, Abel Smith and Knight-Jones 1990] Especially the combination of these factors with early, abnormal neurological signs results in an unfavourable prognosis regarding neurodevelopmental and motor outcome, learning capabilities, and language acquisition [Kitchen *et al* 1980, Michelsson *et al* 1984, Powell *et al* 1986, Stewart *et al* 1989, Vohr *et al* 1989] Gestational age, intraventricular haemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, socioeconomic status, assisted ventilation and hyperbilirubinaemia are reported to be important neonatal risk factors for neurodevelopmental outcome of preterm infants [Litmann and Parmalee 1972, Bozynski *et al* 1987, van de Bor *et al* 1989, Stewart *et al* 1989, den Ouden *et al* 1990, Brazy *et al* 1991, Scheiner and Sexton 1991, Graziani *et al* 1992] However, with respect to socioeconomic status, assisted ventilation and hyperbilirubinaemia these studies are equivocal Based on logistic regression analyses Brazy *et al* reported that only seven of the 13 items of their neonatal risk score (NBRS) demonstrated a strong correlation

with neurodevelopmental outcome Despite the number of items included in the (revised) NBRS the sensitivity (0 60) and the negative predictive values (0 68) remained relatively low Our results for the (revised) NBRS and NNI are largely in agreement with the results reported by Brazy *et al* [1991], except that our results showed a slightly better NPV and somewhat lower sensitivity After addition of GAF and/or AERF to the (revised) NBRS intraventricular haemorrhage remained the most important risk factor for long-term neurological outcome and also neuropsychological outcome This also is according to the findings of Brazy *et al* [1991] Moreover, for neurological outcome next to intraventricular haemorrhage the factor bilirubin contributed most to the variation These findings agree with those of Van de Bor *et al* [1989] For neuropsychological outcome, next to intraventricular haemorrhage, assisted ventilation and hypotension were important factors Although hypotension, as a single factor, was not identified as a significant factor, in combination with other NBRS factors it strengthened the predictive power However, in this combination its p-value on the Wald test was not significant This is because hypotension had usually a zero-value in the score and therefore led to unstable results

Addition of GAF to the (13 or 7) NBRS items in the logistic regression for neurological outcome increased sensitivity and NPV, but slightly decreased specificity and PPV The score for auditory evoked responses (AERF) alone did not enhance the predictive value of the (revised) NBRS However, after appending both GAF and AERF to the NBRS for neurological outcome, sensitivity (0 87) and NPV (0 95) substantially improvement, whereas specificity (1 00) and PPV (1 00) remained high In other words, the combination of AERF and GAF added to the NBRS had an important effect on the predictive value and the validity of this neonatal risk score

For prediction of long-term neurodevelopmental outcome it is important that neonatal risk scores reach a high sensitivity and specificity False negative results due to low sensitivity and/or NPV may lead to unjustified withdrawal from treatment modalities False positive results may lead to parental disappointments Based on these considerations the clinical importance of current neonatal risk factors and risk scores is limited because of a considerably high percentage of false negative results This is due to pathophysiological mechanisms that cannot be detected in the perinatal period by clinical and BMC-AER measures included in the current risk scores The pathophysiological factors leading to 'non-predictable' handicaps need to be identified Our results show that an AERF based on AERs obtained in the neonatal period in preterm infants in combination with a GAF related to the degree of prematurity contribute to predictive power of current neonatal risk scores Few studies also showed that neurophysiological methods,

such as electroencephalography and/or evoked potentials, might contribute to the diagnostic approach in preterm infants at risk for neurodevelopmental abnormalities [Tharp *et al.* 1989, Holmes and Lombroso 1993, Lombroso and Holmes 1993].

From this study can be concluded that:

1) Since the validity and the predictive value of neonatal risk scores (NNI, NBRS and revised NBRS) with respect to the neurodevelopmental outcome in preterm infants show comparable results, risk scores with a reduced number of risk factors are largely as powerful as more elaborate risk scores.
2) The neonatal risk factors contributing most to the validity and predictive value are intraventricular haemorrhage, high bilirubin levels and assisted ventilation.
3) Regarding neurological outcome, addition of a gestational age factor (GAF) in combination with an auditory evoked response measure (AERF) to the 13 NBRS items led to a substantial improvement of the validity and predictive value of NBRS.
4) The shortcomings of the current neonatal risk scores require a careful appraisal of available perinatal clinical data for prediction of the (long-term) neurodevelopmental outcome.

Further research is needed to confirm the present results. Neurophysiological methods, such as electroencephalography and/or evoked responses, should be evaluated more extensively for their contribution in future neonatal risk scores.

Appendix 1. *Neurological deficits in 15 preterm infants at age 5-7 years*

		Low-risk
25-30 weeks CA	1	Mental retardation, epilepsy, hemiplegia, vision loss
	2	Epilepsy, hemiplegia
	3	Mental retardation, epilepsy
	4	Hemiplegia, ataxic gait
	5	Mental retardation, quadriplegia, epilepsy
	6	Quadriplegia
31-34 weeks CA	1	Mental retardation, dyspraxia
	2	Quadriplegia
		High-risk
25-30 weeks CA	1 2	Diplegia, vision loss
	3	Mental retardation, diplegia, attention deficit disorder
	4	Attention deficit disorder, diplegia, hearing loss
	5	Mental retardation, diplegia, hydrocephalus (VP-drain), retinopathy
	6	Mental retardation, quadriplegia, epilepsy
		Mental retardation, quadriplegia, vision loss
31-34 weeks CA	1	Mental retardation, quadriplegia, hydrocephalus (VP-drain), epilepsy

Appendix 2. *Frequency distribution of long-term neurological and neuropsychological outcome for different preterm subgroups*

	Total	Normal outcome	Only neurologically abnormal outcome	Only neuropsychologically abnormal outcome	Neurologically and neuropsychologically abnormal outcome
Low-risk preterm (25-30 weeks GA)	21 (100%)	14 (67%)	2 (9%)	1 (5%)	4 (19%)
Low-risk preterm (31-34 weeks GA)	23 (100%)	18 (78%)	0 (0%)	3 (13%)	2 (9%)
High-risk preterm (25-30 weeks GA)	7 (100%)	1 (14%)	1 (14%)	0 (0%)	5 (71%)
High-risk preterm (31-34 weeks GA)	2 (100%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)
Total preterm	53 (100%)	33 (62%)	3 (6%)	5 (9%)	12 (23%)

General discussion and conclusions

Although the survival rate of preterm born infants has gradually improved over the past twenty years, the rate of preterm infants with neurodevelopmental disabilities has remained stable. Consequently an increasing number of surviving preterm infants will show major disabilities such as cerebral palsy, mental retardation, epilepsy, visual and hearing impairments in early life. Early detection of handicap in preterm infants is an important factor in deciding whether or not to continue intensive care treatment. Furthermore, early identification of high-risk preterm infants allows early therapeutic intervention and adequate perinatal management. Effective neonatal developmental screening would also allow a more efficient planning of necessary follow-up for infants born prematurely. In view of these considerations, there is a need for a neonatal risk score combining neonatal risk factors resulting in a sufficient validity and predictive value. Furthermore, if neonatal risk scores are to be of practical use in a neonatal intensive care unit, they must be simple, quick and objective.

Several factors such as gestational age, intraventricular haemorrhage, periventricular leukomalacia and bronchopulmonary dysplasia have been identified as factors relating to an unfavourable long-term neurodevelopmental outcome in preterm infants. Recently, two neonatal risk scores were presented including various neonatal risk factors. The Neurobiologic Risk Score (NBRS) consists of 13 variables based on data recorded in the neonatal period. The Perinatal Risk Inventory (PERI) contains 18 variables. However, these risk scores have a limited predictive value, mainly because of a relatively low sensitivity and negative predictive value (NPV). A low sensitivity and NPV can result in a number of preterm infants being falsely identified as low-risk.

So there is a need for neonatal risk factors which can be added to current risk scores to improve the validity and predictive value. Early physiologic indices can be used to predict long-term developmental trends. Furthermore, neurophysiological methods are suitable as noninvasive techniques for evaluating brain function at the bedside in newborn infants.

Aim of the study

- The aim of this study has been to establish the clinical value of BMC-AERs obtained in the neonatal period in preterm infants. The more specific aim was to assess the validity and predictive value of BMC-AERs with respect to the long-term neurodevelopmental outcome in these infants.
- In order to answer this key question, a study of two specific developmental

aspects of BMC-AERs in preterm infants was necessary. First, the (cumulative) detectability for all BMC-AER components in low-risk preterm infants (i.e., preterm infants expected to show a normal long-term neurodevelopmental outcome) had to be determined. A sufficient detectability of BMC-AER components during the preterm period is needed, before BMC-AERs can be used in clinical practice. Secondly, the effects of preterm birth on the maturation of BMC-AERs in low-risk preterm infants had to be established before the effects of perinatal pathology on BMC-AERs could be assessed.

- In order to assess of the predictive value of BMC-AERs, it was necessary to establish the long-term neurological and neuropsychological outcome in the preterm infants. In this evaluation it was appropriate to investigate whether neuropsychological impairments in low-risk preterm infants are due to moderate-severe impairment in a few preterm infants, or to slight impairment in the majority.
- The clinical and predictive value of BMC-AERs as a single neonatal risk factor in relation to long-term neurodevelopmental outcome was determined, taking into account the results of the developmental studies. First the clinical and predictive value for subgroups of preterm infants (high-risk/low-risk, early/late preterm and normal/abnormal outcome) was determined. This was then done for the individual preterm infants.
- The predictive power of neonatal risk factors can be improved combining separate neonatal risk factors in a neonatal risk score. In this study, therefore, two neonatal risk scores were evaluated with respect to long-term neurological and neuropsychological outcome. In order to improve the predictive power of one of these risk scores (NBRS) a BMC-AER factor and a GA (gestational age) factor were added to the 13 items combined in the NBRS.

Developmental aspects of BMC-AERs in preterm infants

Detectability. The clinical utility of evoked responses is primarily based on the latencies, interpeak latencies and absence/presence of evoked response components. To a lesser extent amplitudes and peak-peak amplitudes are useful in the clinical application of evoked responses. During the ontogenesis the first BMC-AER components emerge between 25 and 29 weeks CA. In the following period more BMC-AER components become detectable. Consequently, for the clinical applicability of BMC-AER in preterm infants, it is essential to determine normative data for the detectability of BMC-AER components.

Our study showed that between 30 and 34 weeks CA the detectability rates of ABR components I, IIn, V and Vc and MLR component Na were high enough to be clinically useful in preterm infants. The detectability rates of ACR components were generally too low to be useful in clinical practice. However, the clinical applicability could be improved if two separate registrations (at least four weeks apart) resulting in a so-called cumulative detectability rate are taken into account. These cumulative detectability rates showed that ABR components I, II, IIN, III, V, IIc, IIINc and Vc, MLR components Na and P0, and ACR components PbP1 and N2p are sufficient to serve as diagnostic measures in preterm infants.

Effect of preterm birth. The effect of preterm birth on the maturation of BMC-AERs has not been thoroughly reported in the literature. Nevertheless, it is necessary to understand the possible effects of preterm birth on the maturation of BMC-AERs because these effects may interfere with pathophysiological effects. Our study showed BMC-AER differences between low-risk preterm infants (i.e., preterm infants expected to show a normal neurodevelopmental outcome) and term infants at 40 and 52 weeks CA. In preterm infants longer ABR latencies were found, in particular for components III, V and Vc and interpeak latency I-V. These ABR results support the hypothesis of a delayed myelination, partly in combination with conductive hearing loss (middle ear effusions). For the early MLR components Na and P0 too, longer latencies in preterm infants were found. However, for the late MLR components no differences were found. Therefore, other mechanisms apart from delayed myelination must be involved, since developmental studies have shown that normal myelination progresses in a centripetal direction. Enhanced synchronization due to decreased dendritic complexity is one such possible mechanism. For the ACR longer latencies were found for components Na, N1 and P2 in term infants compared with preterm infants at 40 weeks CA. However, at 52 weeks CA the latencies of these ACR components were, on the other hand, shorter in term infants. Furthermore, our study showed that the ACR waveform in preterm infants at 40 and 52 weeks continues to exhibit an immature waveform morphology, whereas a more mature waveform morphology was found in term infants. Because ACR waveform morphology is closely related to the cortical generators of the ACR, changes in these generators result in changes in waveform morphology and consequently also result in latency and interpeak latency differences. The shifting of localization and orientation of ACR sources is the result of complex interactions between various mechanisms such as myelination, synaptic efficacy and dendritic growth. There-

fore, pathophysiological alterations in these mechanisms influence both the ACR waveform morphology and the (cortical) ACR sources.

The follow-up study at 5-7 years of age showed that a substantial number of the preterm infants neonatally classified as low-risk showed neurodevelopmental impairments. The classification of preterm infants as low-risk or high-risk infants therefore produced false-negative results. These false-negative results meant that it was appropriate to reanalyse the data on the effect of preterm birth on the maturation of ABR and ACR relevant. In order to evaluate the effect of preterm birth in more detail the preterm group was divided in two age groups: 25-30 weeks CA and 30-34 weeks CA. We also analysed the ABRs and MLRs obtained at five years of age in order to establish whether the effects of preterm birth were transient or more permanent. The results showed that preterm birth affects the maturation of ABR and MLR, even in preterm infants with a normal neurodevelopmental outcome. These results are largely consistent with the previous results for the low-risk preterm infants. This shows that abnormal neurodevelopmental outcome at five years of age is not clearly related to an altered maturation of ABR and MLR in a low-risk preterm population. We also found that the degree of prematurity influenced the maturation of the ABR. This might be due to the time-dependent vulnerability of the auditory pathway during the preterm period. Furthermore, the effect of preterm birth on the maturation of the middle latency auditory evoked responses might be explained by differential maturation of the primary and non-primary MLR components.

Follow-up study

The results from this part of the study show that, as a group, preterm infants had a more unfavourable neurodevelopmental outcome than term infants. For the high-risk infants this was the case for all except one. For the low-risk infants the unfavourable outcome was due to a subgroup of infants with a combination of neurological abnormalities and a poorer neuropsychological outcome at age 5 years. The remaining low-risk preterm infants showed no neurological and/or neuropsychological abnormalities when compared with the term infants. We concluded that the unfavourable outcome of the low-risk preterm group as a whole was due to moderate-severe impairment of the few, rather than slight impairment of the majority. The neuropsychological test results showed that the subgroup of low-risk preterm infants with an unfavourable neuropsychological outcome performed less well on performance tasks, visual-motor performance, concentra-

tion and auditory memory in combination with integrative functions. This neuropsychological profile largely corroborates the data in the literature.

Clinical and predictive value of BMC-AERs as a single risk factor

First, we established the clinical and predictive value of BMC-AERs between various preterm subgroups (high-risk/low-risk, early-preterm-born/late-preterm-born, normal/abnormal outcome). We then studied the BMC-AER results for the individual preterm infants in relation to the high-risk/low-risk classification, the degree of prematurity (early/late) and the neurodevelopmental outcome.

The results showed that BMC-AERs obtained neonatally in preterm infants are influenced by risk category (high-risk/low-risk) as well as degree of prematurity and, to a certain extent, are also related to neurodevelopmental outcome. However, the influence of the risk category is clearer than the influence of the degree of prematurity, or the effect related to neurodevelopmental outcome. These results imply that low-risk preterm infants with a later abnormal neurodevelopmental outcome are difficult to identify in the neonatal period using BMC-AERs as a single neonatal risk factor. However, despite the insufficient predictive power of BMC-AERs, they remain important in maturational studies, in preterm infants at risk of hearing disorders, and in infants clinically suspected of central and/or peripheral auditory abnormalities.

Predictive value of neonatal risk scores including a BMC-AER and GA factor

In this part of the study we assessed the validity and predictive value of two neonatal risk scores (NNI and NBRS) in relation to neurological and neuropsychological outcome. We then added a BMC-AER factor (AERF) and a gestational age factor (GAF) in order to improve the predictive power of the NBRS. The results showed no clear differences between the NNI and NBRS. For the validity and predictive value of the NBRS and NNI based on our data a somewhat lower sensitivity and PPV and a slightly higher NPV were found when compared with the results for the NBRS reported by Brazy *et al.* [1991]. We also compared the results of these two risk scores with a revised NBRS proposed by Brazy *et al.* [1991]. With the exception of a lower sensitivity concerning neurological outcome, the revised NBRS showed similar results.

We performed logistic regression analyses in order to establish which risk factors contribute the most to the prediction of neurodevelopmental outcome. The analyses were carried out for various combinations of risk factors based on the NBRS and an AERF and GAF. For neurological outcome the regression analysis yielded intraventricular haemorrhage and bilirubin as significant factors. For the neuropsychological outcome these factors were: intraventricular haemorrhage, assisted ventilation and hypotension. Although hypotension in combination with the two other factors strengthened the predictive power the addition of hypotension led to unstable results, because the factor hypotension usually had a zero-value. After the addition of the AERF and GAF, the same two relevant factors, i.e., haemorrhage and bilirubin, were identified for neurological outcome. However, for neuropsychological outcome in addition to intraventricular haemorrhage, assisted ventilation and hypotension AERF was identified as a significant neonatal risk factor.

The validity and predictive value of the NBRS and revised NBRS showed a clear improvement after both AERF and GAF were added. The most powerful combination relating to neurological outcome consisted of the 13 NBRS items in combination with AERF and GAF (sensitivity 0.87, specificity 1.00, PPV 1.00 and NPV 0.95). However, for the seven items of the revised NBRS in combination with AERF and GAF the results were almost the same. For neuropsychological outcome the results were almost the same, although the improvement was less distinct.

Conclusions

1. The detectability rates of ABR components I, IIn, V and Vc and MLR component Na obtained between 30 and 34 weeks CA are high enough to be clinically useful. Improvement could be achieved if cumulative detectability rates were assessed. The cumulative detectability rates of ABR components I, II, IIN, III, V, IIc, IIINc and Vc, MLR components Na and P0, and ACR components PbP1 and N2p were high enough to serve as diagnostic measures in preterm infants.
2. Preterm birth effects the maturation of ABR and MLR, even in preterm infants with a normal neurodevelopmental outcome. The effect on the ABR is probably the result of a delayed myelination, partly in combination with conductive hearing loss (middle ear effusions). The delayed myelination

might be due to the time-dependent vulnerability of the auditory pathway during the preterm period.

3. The effect of preterm birth on the maturation of the middle latency auditory evoked responses might be explained by differential maturation of the primary and non-primary MLR components.
4. Complex pathophysiological interactions between various mechanisms such as myelination, synaptic efficacy and dendritic growth might account for the effect of preterm birth on the ACR.
5. The unfavourable neuropsychological outcome of the low-risk preterm group as a whole is due to moderate-severe impairment of a few infants and not to slight impairment in nearly all infants. Low-risk preterm infants with an unfavourable neuropsychological outcome show particular impairment on visual-motor integration, concentration and auditory memory in combination with integrative functions.
6. BMC-AERs applied as a single neonatal risk factor are hardly able to identify low-risk preterm infants with a later abnormal neurodevelopmental outcome.
7. Despite the insufficient predictive power of BMC-AERs as a single risk factor, they remain important in maturational studies, in preterm infants at risk of hearing disorders, and in infants clinically suspected of central and/or peripheral auditory abnormalities.
8. The neonatal risk factors contributing most to the predictive power of the NBRS are for neurological outcome: intraventricular haemorrhage and bilirubin. For neuropsychological outcome these factors are: intraventricular haemorrhage and assisted ventilation.
9. Although the current neonatal risk scores relating to long-term neurodevelopmental outcome achieve a sufficient specificity and positive predictive value, sensitivity and negative predictive value are relatively low. In other words, some preterm infants will be falsely identified as low-risk infants, notwithstanding an unfavourable neurodevelopmental outcome at school age.
10. The predictive power of the NBRS in relation to neurological outcome can be improved substantially if an auditory evoked response factor and a gestational age factor are added. The same is true to a lesser extent for neuropsychological outcome.

During the past few decades many neonatal risk factors have been found and several neonatal risk scores were proposed. These neonatal risk factors combined in neonatal risk scores contributed to an improvement of the predictability of long-term neurodevelopmental outcome in newborn infants. However, despite this improvement the current risk scores are still inadequate, because of the substantial number of false-negative results. In view of these findings it is necessary to make a careful appraisal of available clinical perinatal data relating to prediction of (long-term) neurodevelopmental outcome in order to overcome the shortcomings of the current neonatal risk scores. Neurophysiological methods, such as electro-encephalography and/or evoked responses, should be evaluated more extensively in order to determine their contribution in future neonatal risk scores. These future neonatal risk scores should be composed of a limited number of powerful clinical, echoencephalographic and neurophysiological factors. With respect to the neuro-physiological methods electroencephalography is an underestimated diagnostic tool in preterm infants. However, the introduction of commercially available digital EEG systems now allows continuous monitoring and online computer analysis of the neonatal EEG. These new EEG techniques need to be evaluated thoroughly in order to determine their potential contribution to neonatal risk scores. This research should focus in particular on the background activity of the preterm EEG and on the evolution of the background activity in the first days after birth. Furthermore, new echoencephalographic techniques, such as echographic image processing, characterization of echographic texture and on-line parametric ultrasound imaging might become important in the early detection of cerebral lesions leading to periventricular leukomalacia.

In this study we have established the effect of preterm birth on the maturation of BMC-AERs. The results show that the MLR and ACR in particular underwent complex waveform morphology changes. In order to understand these complex changes more research must be done into ACR (and MLR) source characterisation in (preterm) infants. For adults and older children the current source characterisation techniques are sufficient. However, for (pre)term infants these techniques are not yet suitable, because no appropriate head models exist, the head size is too small for an adequate number of electrodes to be applied, and because the signal-to-noise-ratio of the MLR and ACR in neonatal recordings is generally low.

Although the assessment of the BMC-AER maturation after birth was not a primary objective of this study, the BMC-AERs obtained at 5 years of age

indicated that the ACR maturation is not completed in the first two years after birth, but continues until at least 7 years of age.

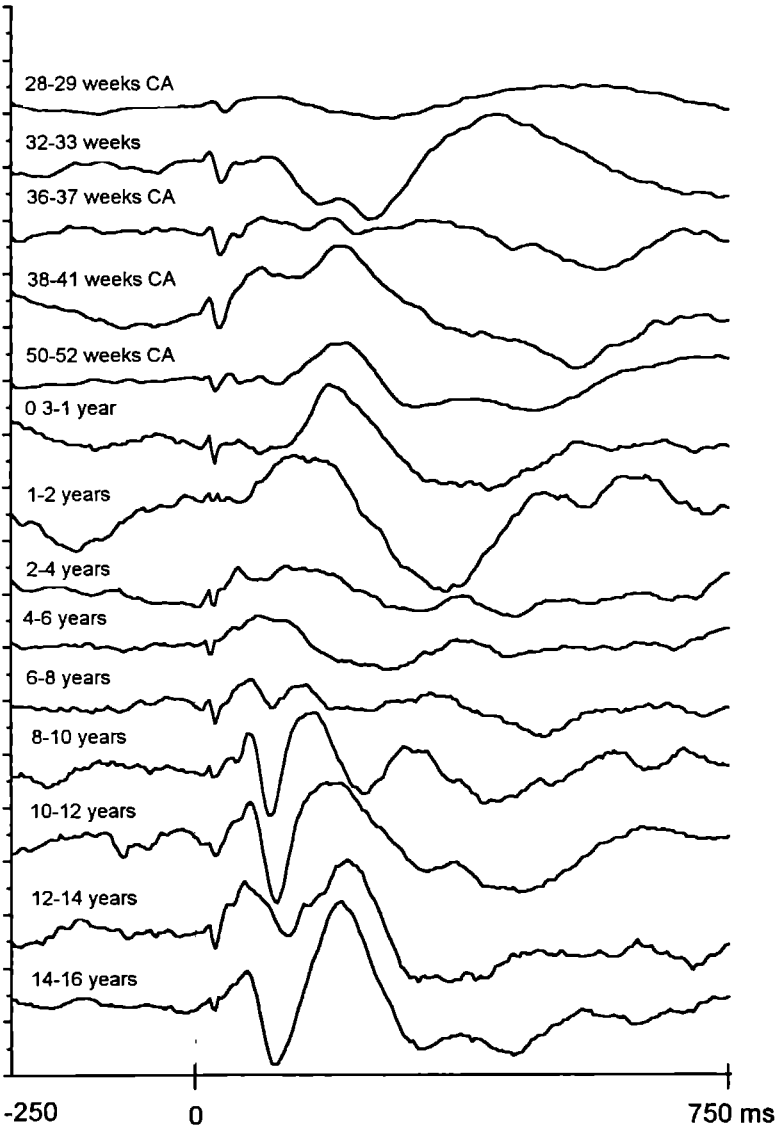

Fig. 1. *Maturation of the ACR waveform between 28 weeks CA and 12 years of age.*

In order to support this hypothesis we performed a preliminary study on the maturation of the ACR from 30 weeks CA until 14 years of age. The results showed a clear development of the ACR during childhood, reaching the mature waveform between 8 and 10 years of age. Furthermore, two clear transitional periods were found for ACR waveform morphology, the first transitional period between 37 and 40 weeks CA, and the second around 5 years of age. See Figure 1.

Further research is needed to determine whether these transitional periods in the maturation of ACRs correspond with important functional changes of the central auditory system. Brain-electric source characterisation of auditory evoked responses and of event-related potentials might both be useful tools in this research.

Summary

The aim of this thesis was to study the clinical and predictive value of BMC-AERs obtained in the neonatal period in preterm infants. In order to answer these key questions it was necessary to study two specific developmental aspects of BMC-AERs in preterm infants. The long-term neurodevelopmental outcome of the preterm infants was assessed at 5-7 years of age. It was also relevant to investigate whether neuropsychological impairments in low-risk preterm infants are due to moderate-severe impairment in a few preterm infants, or to slight impairment in the majority. We also attempted to establish the neuropsychological profile in preterm infants. The clinical and predictive value of BMC-AERs as a single neonatal risk factor was determined. Two neonatal risk scores (NNI and NBRS) were then evaluated with respect to long-term neurological and neuropsychological outcome. We added a BMC-AER factor and a GA factor to the items of the NBRS in order to improve the predictive power of the NBRS.

Chapter 1 gives a general introduction, and describes the aim of the study and the outline of the prospective longitudinal follow-up study from birth to 7 years of age in a cohort of 81 preterm infants and 25 term infants.

In *Chapter 2* the (cumulative) detectability of individual BMC-AER components in low-risk preterm infants was determined. The BMC-AERs were obtained between 30 and 41 weeks CA. The results demonstrate that the detectability rates of BMC-AER components, determined between 30 and 34 weeks CA, are too low for the absence or presence of these components to be useful for clinical purposes, except ABR components I, IIn, V and Vc and MLR component Na. Improvement could be achieved by determining the cumulative detectability rates after two recordings for all BMC-AER components. The cumulative detectability rates of ABR components I, II, IIN, III, V, IIc, IIINc, Vc, and MLR components Na and P0 are high enough to serve as a diagnostic tool. This is also true of the fast ACR component PbP1 and the slow ACR component N2p. However, after 37 weeks CA the ACR components show a noticeable loss of (cumulative) detectability due to the transition from premature waveform to infantile waveform. In the preterm period, BMC-AERs are not significant unless at least two recordings (spaced at least a month apart) are obtained.

In *Chapter 3* the effect of preterm birth on the maturation of auditory evoked responses in low-risk preterm infants (28-36 weeks conceptional age) was assessed. The ABR showed a consistent trend towards longer latencies and interpeak latencies in preterm infants. Longer latencies were also found in preterm infants for MLR component P0. The ACR showed at 40 weeks CA longer latencies for components Na and P2 in term infants, whereas at 52 weeks CA the latencies of

the same ACR components were longer in preterm infants. These results support the hypothesis that retarded myelination is partially responsible for ABR and MLR differences found between preterm infants and term infants. It is possible that, in addition to retarded myelination, mild conductive hearing loss in preterm infants might also be (partly) responsible for the differences between term and preterm infants. The differences between term and preterm infants for MLR component Na and ACR components Na and P2 are the result of a more complex mechanism.

In *Chapter 4* the neurodevelopmental profile of a group of low-risk preterm infants was determined. As a group the low-risk preterm infants had a more unfavourable neurological and neuropsychological outcome than the term infants. The group differences were largely attributable to neurological abnormalities and/or a poorer neuropsychological outcome in 12 of the 44 low-risk preterm infants. The remaining low-risk preterm infants, however, showed quite similar test scores when compared with the term infants. These results showed that the unfavourable neurodevelopmental outcome of low-risk preterm infants when compared with the outcome of term infants is due to moderate to severe impairment in a few low-risk preterm infants, rather than slight impairment in the majority. The low-risk preterm infants with an unfavourable neurodevelopmental outcome showed particular impairment in measurements of visual-motor integration, concentration and auditory memory in combination with integrative functions.

In *Chapter 5* the effect of preterm birth on the maturation of the ABR and MLR in preterm infants with a normal neurodevelopmental outcome was studied. The results are largely consistent with the previous results. This concordance may imply that there is no strong association between neurological and neuropsychological abnormalities resulting in an abnormal neurodevelopmental outcome at 5 years of age, and disturbed maturation of ABR and MLR in a low-risk preterm population. Furthermore, the results made it clear that prematurity also influenced the maturation of the ABR. This can be explained by a time-dependent vulnerability of the auditory pathway during the early and late preterm periods. The effect of preterm birth on the maturation of the MLR might be due to a differential maturation of the primary and non-primary MLR components.

In *Chapter 6* the diagnostic and predictive value of brainstem, middle latency and cortical auditory evoked responses (BMC-AERs) was assessed in relation to neurodevelopmental outcome. The results showed that BMC-AERs obtained neonatally in preterm infants are influenced by risk category (high-risk/low-risk) as well as degree of prematurity and neurodevelopmental outcome. As a result, BMC-AERs relating to infants with abnormal neurodevelopmental outcomes are

barely distinguishable from the BMC-AERs for infants with normal neurodevelopmental outcomes. Therefore, BMC-AERs are of limited clinical value in predicting neurodevelopmental outcome in preterm infants. However, BMC-AERs obtained in preterm infants have proved useful in maturational studies and with infants showing symptoms suggesting lesions or dysfunction of the peripheral and/or central auditory system.

In *Chapter 7* the validity and predictive value of neonatal risk scores with and without a gestational age factor (GAF) and an auditory evoked response factor (AERF) were determined with respect to neurodevelopmental outcome. The validity and predictive value of the NNI were comparable with that of the NBRS. Intraventricular haemorrhage and bilirubin levels contributed substantially to the prediction of neurological outcome. For neuropsychological outcome these factors were: intraventricular haemorrhage and assisted ventilation. In relation to neurological outcome, the addition of a gestational age factor (GAF) in combination with an auditory evoked response factor (AERF) resulted in a substantial improvement in the validity and predictive value of the NBRS.

Samenvatting

De overlevingskansen van te vroeg geboren kinderen (prematuren) zijn in de loop van de laatste decennia toegenomen Toch blijft het percentage prematuren dat neurologische en/of neuropsychologische stoornissen ontwikkelt min of meer constant Dit resulteert in een toenemend aantal prematuren met neurologische stoornissen zoals diplegieen, tetraplegieen, mentale retardatie, epilepsie, visuele stoornissen en gehoorstoornissen Vroegtijdige ontdekking van ernstige neurologische stoornissen bij prematuur geboren kinderen is belangrijk bij het nemen van behandelingsbeslissingen op de afdeling neonatale intensieve zorg Verder kan vroege identificatie van high-risk premature kinderen bijdragen aan vroegtijdige therapeutische interventie Voor een effectieve neonatale screening is er behoefte aan een neonatale risicoscore, gebaseerd op combinaties van neonatale risicofactoren met een toereikende validiteit en predictieve waarde Voor de dagelijkse praktijk dient een dergelijke risicoscore eenvoudig, makkelijke toepasbaar en objectief te zijn

Van verschillende klinische factoren, zoals intraventriculaire bloedingen, periventriculaire leucomalacie en bronchopulmonale dysplasie, is vastgesteld dat zij een voorspellende waarde hebben voor neurologische en/of neuropsychologische stoornissen op latere leeftijd bij te vroeg geboren kinderen Recent zijn in de literatuur twee neonatale risicoscores beschreven waarin verschillende risicofactoren zijn gecombineerd De neurobiological risk score (NBRS) is opgebouwd uit 13 neonatale variabelen De perinatal risk inventory (PERI) is gebaseerd op 18 variabelen Deze beide risicoscores hebben een beperkte predictieve waarde vanwege een relatief lage sensitiviteit en negatieve voorspellende waarde Een lage sensitiviteit en negatieve voorspellende waarde resulteren beiden er toe dat een aantal kinderen ten onrechte als low-risk worden aangemerkt Er is dus behoefte aan neonatale risicofactoren, die toegevoegd aan bestaande risicoscores of in combinatie met andere risicofactoren resulteren in een betere validiteit en een hogere voorspellende waarde Het is bekend dat vroege (neuro-)fysiologische indices predictieve waarde kunnen hebben ten aanzien van ontwikkelingsstoornissen bij premature kinderen Daarbij zijn neurofysiologische technieken uitermate geschikt als niet-invasieve methoden voor de evaluatie van het (centrale) zenuwstelsel bij pasgeborenen

In dit proefschrift zijn de resultaten beschreven van het onderzoek naar de klinische relevantie en voorspellende waarde van auditieve evoked responses (BMC-AERs) vervaardigd in de neonatale periode bij te vroeg geboren kinderen Een groep a term geboren kinderen fungeerde als controle groep Om de klinische relevantie en voorspellende waarde van BMC-AERs te kunnen bepalen, was het noodzakelijk eerst enkele ontwikkelingsaspecten van BMC-AERs te bestuderen

Allereerst werden de (cumulatieve) opkomstpercentages van de afzonderlijke BMC-AER-componenten, geregistreerd in de neonatale periode bij low-risk kinderen, geanalyseerd. Een hoog opkomstpercentage van de afzonderlijke BMC-AER-componenten is noodzakelijk om het al dan niet opwekbaar zijn van deze componenten te gebruiken voor klinische doeleinden. Vervolgens moest het effect van prematuriteit op de ontwikkeling van de BMC-AERs bepaald worden, alvorens de effecten van perinatale pathologie op neonataal geregistreerde BMC-AERs te kunnen analyseren.

Om de voorspellende waarde van BMC-AERs op de neurologische en neuropsychologische ontwikkeling te kunnen bepalen werden tussen het vijfde en zevende levensjaar de a term geboren kinderen en de prematuur geboren kinderen opnieuw onderzocht. Dit onderzoek bestond uit het registreren van de BMC-AERs, een neurologische onderzoek en een neuropsychologische evaluatie. Bij dit vervolgonderzoek was het van belang na te gaan of eventuele neurologische/neuropsychologische stoornissen in de groep low-risk prematuren terug te voeren waren op milde afwijkingen bij vrijwel alle kinderen of op matige tot ernstige stoornissen bij een beperkt aantal kinderen. Daarop volgend werd de klinische relevantie en de voorspellende waarde van BMC-AERs vervaardigd in de neonatale periode onderzocht. Allereerst werd dit gedaan voor BMC-AERs als enige neonatale risicofactor. Vervolgens werden twee neonatale risicoscores (NNI en NBRS) geëvalueerd in relatie tot de neuropsychologische ontwikkeling en de neurologische ontwikkeling. Om de voorspellende waarde van de NBRS te verbeteren werd een auditieve evoked response factor (AERF) en een zwangerschapsduurfactor (GAF) toegevoegd aan de 13 factoren die deel uitmaken van de NBRS.

Hoofdstuk 1 bevat een algemene introductie en een omschrijving van het doel van het onderzoek. Daarnaast wordt de opzet van het prospectieve, longitudinale onderzoek bij 81 prematuren en 25 a term geboren kinderen van de geboorte tot het zevende levensjaar beschreven.

In *Hoofdstuk 2* worden de (cumulatieve) opkomstpercentages van de afzonderlijke BMC-AER-componenten bij premature kinderen met een gering risico op hersenbeschadigingen, de zogenaamde low-risk prematuren, vastgesteld. De BMC-AERs werden vervaardigd tussen 30 en 41 weken postconceptie (PC). Uit de resultaten blijkt dat de opkomstpercentages van de afzonderlijke BMC-AER-componenten geregistreerd tussen 30 en 34 weken PC over het algemeen te laag zijn om de aan/afwezigheid van deze componenten te gebruiken in de klinische praktijk, met uitzondering van de ABR-componenten I, IIn, V en Vc en MLR-component Na. De klinische bruikbaarheid van 'de aan/afwezigheid' van BMC-

AER-componenten kan echter verbeterd worden als gebruik wordt gemaakt van cumulatieve opkomstpercentages. De cumulatieve opkomstpercentages voor de ABR-componenten I, II, IIN, III, V, IIc, IIINc en Vc, MLR-componenten Na en P0 zijn voldoende om als diagnostische test te kunnen dienen. Dit geld ook voor de ACR-componenten PbP1 en N2p. Hierbij dient echter opgemerkt te worden dat de opkomstpercentages van de ACR-componenten na 37 weken PC afnemen omdat de premature ACR-golfvorm tussen 37 en 42 weken PC overgaat in een vroegkinderlijke golfvorm. Geconcludeerd kan worden dat in de premature periode de aan/afwezigheid van de meeste BMC-AER-componenten alleen dan gebruikt kan worden voor klinische toepassingen als gebruik wordt gemaakt van twee opeenvolgende BMC-AER-registraties die met een interval van minimaal een maand vervaardigd zijn.

In *Hoofdstuk 3* wordt het effect van vroeggeboorte op de ontwikkeling van BMC-AERs bij low-risk prematuren (28-36 weken zwangerschapsduur) geanalyseerd. De ABR toont langere latentietijden en interpieklatentietijden voor prematuur geboren kinderen in vergelijking met a term geboren kinderen. In de premature groep werden tevens langere latentietijden gevonden voor de MLR-component P0. Op 40 weken PC werden voor de ACR-componenten Na en P2 langere latentietijden gevonden bij a term geboren kinderen in vergelijking met prematuur geboren kinderen, daarentegen zijn de latentietijden van deze componenten op 52 weken juist korter in de a term geboren groep. Deze resultaten ondersteunen de hypothese dat de gevonden ABR en MLR verschillen tussen prematuren en a term geboren kinderen deels verklaard kunnen worden door een vertraagde myelinisatie van de hersenstam, mogelijk in combinatie met een gering conductief gehoorverlies. De verschillen ten aanzien van MLR-component Na en ACR-componenten Na en P2 tussen prematuur geboren en a term geboren kinderen zijn echter niet alleen het resultaat van een vertraagde myelinisatie, maar het resultaat van meer complexe mechanismen.

In *Hoofdstuk 4* wordt het neuropsychologische profiel van de groep low-risk prematuur geboren kinderen beschreven. Uit de resultaten blijkt dat de low-risk premature kinderen als groep een minder gunstige neurologische en neuropsychologische ontwikkeling hebben doorgemaakt dan de groep voldragen kinderen. De verschillen tussen deze twee groepen berusten grotendeels op neurologische en/of neuropsychologisch afwijkingen in 12 van de 44 low-risk premature kinderen. Tussen de resterende 32 low-risk premature kinderen en de a term geboren kinderen werden geen duidelijke verschillen gevonden. Deze resultaten geven aan dat de minder gunstige neuropsychologische ontwikkeling van de premature groep als geheel terug te voeren is op een beperkt aantal low-risk kinderen met matig tot

ernstige neuropsychologische stoornissen en niet op milde neuropsychologische stoornissen bij vrijwel alle low-risk premature kinderen. De low-risk premature kinderen met neuropsychologische ontwikkelingsstoornissen scoorden in vergelijking met de andere kinderen lager met betrekking tot de visueel-motore integratie, auditief geheugen in combinatie met integrerende functies en concentratie.

In *Hoofdstuk 5* wordt het effect van vroeggeboorte op de ontwikkeling van de ABR en MLR bij prematuur geboren kinderen met een normale neurologische en neuropsychologische ontwikkeling op vijf-jarige leeftijd bestudeerd. De resultaten komen grotendeels overeen met de resultaten beschreven in hoofdstuk 3. Dit impliceert dat een gestoorde neonatale ontwikkeling van de ABR en MLR bij low-risk premature kinderen vastgesteld kan worden, zonder duidelijke associatie met neurologische en/of neuropsychologische ontwikkelingsstoornissen op latere leeftijd. Daarnaast wordt in dit onderzoek vastgesteld dat de neonatale ontwikkeling van de ABR in low-risk premature kinderen wordt beïnvloed door de mate van prematuriteit. Dit laatste kan verklaard worden door een tijds-afhankelijke kwetsbaarheid van het auditieve systeem in de premature periode. Het effect van vroeggeboorte op de ontwikkeling van de MLR kan deels toegeschreven worden aan een gedifferentieerde ontwikkeling van de primaire en niet-primaire MLR-componenten.

In *Hoofdstuk 6* wordt de diagnostische en voorspellende waarde van BMC-AERs met betrekking tot neurologische en neuropsychologische ontwikkelingsstoornissen bestudeerd. Op grond van de resultaten kan gesteld worden dat neonatale BMC-AERs vervaardigd bij premature kinderen zowel door risicocategorie (low-risk/high-risk) als mate van prematuriteit worden beïnvloed. Daarnaast bestaat er een relatie tussen de neonataal vervaardigde BMC-AERs en de neurologische en neuropsychologische ontwikkeling van prematuur geboren kinderen. Hierdoor zijn neonataal vervaardigde BMC-AERs van premature kinderen die later een gestoorde neurologische en/of neuropsychologische ontwikkeling doormaken nauwelijks te onderscheiden van neonataal vervaardigde BMC-AERs van premature kinderen die zich neurologisch/neuropsychologisch normaal ontwikkelen. Derhalve zijn BMC-AERs van een beperkte klinische waarde als het gaat om het voorspellen van neurologische en neuropsychologische ontwikkelingsstoornissen. Ondanks het feit dat neonatale BMC-AERs niet gebruikt kunnen worden voor het vroegtijdig differentiëren tussen deze twee categorieën kunnen, BMC-AERs van belang zijn in neurofysiologische ontwikkelingsstudies. Daarnaast blijven BMC-AERs van belang bij premature kinderen bij wie er mogelijk sprake is van disfunctie van het perifeer en/of centraal auditieve systeem.

In *Hoofdstuk 7* wordt de validiteit en voorspellende waarde van neonatale risk scores met en zonder prematuriteitsfactor en AER-factor geanalyseerd in relatie met neurologische en/of neuropsychologische ontwikkelingsstoornissen. Uit dit onderzoek blijkt dat de validiteit en de voorspellende waarde van Neonatal Neurological Inventory (NNI) grotendeels overeenkomen met die van de NeuroBiologic Risk Score (NBRS). De factoren intraventriculaire bloeding en bilirubine droegen in hoge mate bij aan het voorspellen van neurologische ontwikkelingsstoornissen bij prematuur geboren kinderen. Ten aanzien van het voorspellen van neuropsychologische ontwikkelingsstoornissen waren de factoren intraventriculaire bloeding en beademing van belang. Toevoegen van een prematuriteitsfactor in combinatie met een auditieve evoked response factor resulteerde wel in een verbetering van voorspellende waarde van de NBRS met betrekking tot neurologische ontwikkelingsstoornissen.

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Curriculum vitae

De auteur van dit proefschrift werd op 13 februari 1956 geboren te Doesburg. In 1974 behaalde hij het diploma Atheneum-B aan het Baudartius College te Zutphen. In 1974 begon hij met de studie Geneeskunde aan de Katholieke Universiteit te Nijmegen, alwaar hij in augustus 1981 het artsexamen behaalde. Van september 1981 tot en met december 1982 was hij als dienstplichtig luchtmachtarts werkzaam op de vliegbasis Deelen. Van 1 januari 1983 tot 1 januari 1987 volgde hij de opleiding tot neuroloog in het Instituut voor Neurologie van het Academisch Ziekenhuis Nijmegen St Radboud (opleider: Prof. Dr. B.P.M. Schulte †). In 1987 was hij als neuroloog werkzaam op de polikliniek van het Instituut voor Neurologie van het Academisch Ziekenhuis Nijmegen St Radboud. Van 1 januari 1988 tot 1 januari 1989 volgde hij, eveneens in het Instituut voor Neurologie van het Academisch Ziekenhuis Nijmegen St Radboud (afdeling Klinische Neurofysiologie), de opleiding in het kader van de aantekening Klinische Neurofysiologie (opleider: Prof. Dr. S.L.H. Notermans). Sedert 1 januari 1989 is hij werkzaam als klinisch neurofysioloog op de afdeling Klinische Neurofysiologie van het Instituut voor Neurologie van het Academisch Ziekenhuis Nijmegen St Radboud. De auteur is gehuwd en heeft twee kinderen.

STELLINGEN

horende bij het proefschrift

AUDITORY EVOKED RESPONSES IN PRETERM INFANTS
developmental aspects and clinical value

In het openbaar te verdedigen
op vrijdag 23 mei 1997
des namiddags om 1 30 uur precies
door

Jaco W. Pasman

1 De meeste auditieve evoked response-componenten zijn op een conceptieleeftijd van 30-34 weken klinisch diagnostisch onbruikbaar wegens te lage opkomstpercentages Door gebruik te maken van cumulatieve opkomstpercentages neemt het aantal bruikbare componenten toe *Dit proefschrift*

2 Vroeggeboorte als zodanig beinvloedt de ontwikkeling van auditieve evoked responses, ook bij zich normaal ontwikkelende kinderen Dit is meetbaar tot op de leeftijd van 5-7 jaar *Dit proefschrift*

3 De neuromorbiditeit bij ex-prematuren als groep wordt waarschijnlijk veroorzaakt door matige tot ernstige ontwikkelingsstoornissen bij een beperkt aantal van hen, en niet door milde stoornissen bij vrijwel allen Deze waarneming volgt het principe low incidence, high morbidity *Dit proefschrift*

4 Door de invloed van "prematuriteit" en "risk category", hebben auditieve evoked responses als enkelvoudige risicofactor prognostisch nauwelijks waarde *Dit proefschrift*

5 De huidige neonatale risicoscores hebben slechts een beperkte klinische waarde vanwege een te lage sensitiviteit en negatieve voorspellende waarde Door het toepassen van deze risicoscores worden er ten onrechte premature kinderen als low-risk geclassificeerd *Dit proefschrift*

6 Corticale auditieve evoked responses bereiken de volwassen vorm pas tussen het achtste en tiende levensjaar Twee transitiefasen kunnen worden herkend de eerste rond de uitteldatum, de tweede rond het vijfde levensjaar *Dit proefschrift*

7 Serial EEG recordings are a useful prognostic tool in preterm infants *Tharpe et al - Neuropediatrics 1989, 20 64-72*

8 The formulation of statistical analysis as a test with two possible outcomes - significant or not significant - has had harmful effects on the medical literature *Altman - Practical statistics for medical research, 1991*

9 Wat vandaag algemeen bekend is, was gisteren wetenschap *Niels Bohr*

10 Grote hersenen kunnen, evenals een groot bestuurlijk apparaat, niet in staat blijken eenvoudige dingen op een eenvoudige manier uit te voeren *Donald O Hebb*

11 Het is wenselijk dat de opvolger van een hoogleraar in een klinisch vak ruimschoots voor het vertrek van de zittende hoogleraar wordt benoemd

12 Het is van groot belang dat dyslexie bij kinderen op de basisschool vroegtijdig wordt onderkend en behandeld

13 Het samenbrengen van openbaar basisonderwijs en basisonderwijs op godsdienstige grondslag in een zgn ontmoetingsschool heeft zowel een positief effect op het godsdienstonderwijs als het vormingsonderwijs

14 Elk politiek systeem toont kenmerken van 'deterministische chaos' alhoewel door beginselen en regels bepaald blijkt het systeem (principieel) onvoorspelbaar

15 Wintersporters zouden verplicht moeten worden om 's zomers terug te keren naar hun wintersportoord om de nadelige milieu-effecten van hun sportieve gedragingen met eigen ogen te aanschouwen

16 Het schrijven van een proefschrift over auditieve evoked responses toont overeenkomsten met bergbeklimmen In beide gevallen krijgt men met pieken en dalen te maken

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